School of Physiotherapy and Exercise Science

Acute Lung Injury (ALI): Evaluating and Improving Functional Outcomes in Survivors

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Declaration

This thesis contains no material which has been accepted for the award of any other degree or diploma in any university. To the best of my knowledge and belief this thesis contains no material previously published by any other person except where due acknowledgement has been made.

Signature:

Date: 10th August 2019

Abstract

Background, research questions and purposes

This program of research comprises 3 studies, each of which examines successive phases of recovery in a cohort of people who have survived an admission to an intensive care unit (ICU) for acute lung injury (ALI).

The following research questions were addressed in Study 1 and 2:

i. Do adults who have survived an ICU admission for acute lung injury (ALI), when assessed within 7 days of discharge from an ICU, demonstrate impairments in peripheral muscle strength (primary outcome), balance, ability to stand from supine, walking speed and peak and submaximal exercise responses measured during a functional exercise test (secondary outcomes), relative to those who survived an ICU admission for a critical illness other than ALI?

ii. In adults who have survived an ICU admission for ALI or another critical illness, does the 10-metre walk speed (10MWS) explain more than 50% of the variance in 6-minute walk distance (6MWD), when both outcomes are measured within 7 days of discharge from the ICU?

iii. In adults who have survived an admission to an ICU for ALI or another critical illness, can the 6MWD measured within 7 days of discharge from the ICU, separate those who: (a) require a longer ward length of stay versus those who require a shorter ward length of stay; and (b) are discharged home versus discharged to another care facility?

iv. Do adults who have survived an admission to an ICU for ALI, at 6 weeks after discharge from an acute care facility demonstrate differences in peak exercise (primary outcome) or submaximal exercise responses measured during an incremental cycle ergometry test (ICET), when compared with a healthy group? If so, what is the underlying cause of their exercise limitation?

v. Do adults who have survived an admission to an ICU for ALI, at 6 weeks after discharge from an acute care facility demonstrate differences in daily physical activity (PA) and sedentary time (ST), peripheral muscle strength, health-related quality of life (HRQL) and fatigue, when compared with a healthy group?

The purpose of Study 3 was:

vi. In adults who have survived an admission to an ICU for ALI, to examine the adherence to, as well as tolerance and progression of, a high intensity exercise-based rehabilitation program (EBRP) initiated 8 weeks after discharge from an acute care facility.

vii. In adults who have survived an admission to an ICU for ALI, to examine within participant changes in resting lung function and submaximal and peak physiological responses during an ICET and 6-minute walk test (6MWT) as well as PA and ST, peripheral muscle strength, HRQL and fatigue following a program of high intensity EBRP initiated 8 weeks after discharge from an acute care facility.

Study 1

Study 1 answers research questions i, ii and iii.

Study 1 Methods

This cross-sectional and observational study included 22 people who were admitted to ICU with a diagnosis of ALI, and 33 people who were admitted to ICU with a diagnosis other than ALI. Within 7 days of discharge from ICU to the ward, the following measures were made: (i) peripheral muscle strength via a custom-designed fixed force gauge, hand-held dynamometer or a hand grip dynamometer; (ii) balance via the Berg Balance Scale (BBS); (iii) ability to stand from supine via the time-to-stand from supine test (TTS); (iv) walking speed via the 10-metre walk test (10MWT); and (v) functional exercise tolerance via the 6MWT. Additional variables were recorded to describe the characteristics of the participants, including details of their ICU admission, height and measures of spirometric lung function measured on

the ward, ICU and hospital length of stay and discharge destination. Between-group comparison of data were conducted. Associations and relationships between variables were explored and modelled. Data are presented as median [interquartile range] unless otherwise stated.

Study 1 Results

The participants with ALI and critical illness were of similar age (median [IQR], 50.0 [42.0 to 66.6] vs. 57 [52.0 to 63.3] yr, $p = 0.09$) and sex proportion (males n [%], 10 [45] vs. 19 [58], $p = 0.59$). Compared with the participants with critical illness, the participants with ALI were characterised by less hand grip (mean ± SD, 18 ± 9 vs. 13 ± 8 kg, $p = 0.018$) and shoulder flexion strength (10 ± 4 vs. 7 ± 3 kg, $p = 0.047$), slower 10MWS (1.03 [0.78 to 1.14] vs. 0.78 [0.67 to 0.94] m/s, $p = 0.039$) and shorter 6MWDs (265 [71 to 328] vs. 165 [53 to 220] m, $p = 0.037$). Throughout the 6MWT, the submaximal pattern of response in heart rate (HR), arterial oxygenation (SpO_2), blood pressure and symptoms was similar between groups. Three participants in both the ALI and critical illness groups demonstrated desaturation to < 85% resulting in an enforced rest. For all participants, SpO_2 increased to > 85% within one minute of an enforced rest. No other adverse events were recorded during the 6MWT. Leg/general fatigue was the main symptom limiting performance in all participants. The BBS and TTS were similar in both groups. With both participant groups considered together, the proportion of variance in the 6MWD explained by the 10MWS was not significant (adjusted $R^2 = 0.049$, $p = 0.13$). With both participant groups considered together, the 6MWD was prognostic of ward length of stay and discharge destination. When compared with those who achieved a 6MWD ≥ 100m, those who achieved a 6MWD < 100m had both greater odds of staying on a hospital ward for ≥ 14 days (OR [95% CI], 12.9 [2.8 to 59.7]) and being discharged to a destination other than home (OR [95% CI], 10.6 [2.4 to 46.8]).

Study 1 Discussion and conclusion

This study identified that compared with survivors of critical illness other than ALI, those with ALI demonstrated greater impairment in peripheral muscle strength, and a lower 6MWD and 10MWS when measured within one week of discharge from the

ICU. These differences were not the result of disparities in age, gender proportion and severity of illness as these characteristics were balanced between the two groups. Taken together, these results suggest that those who survive an ICU admission for ALI, are on average, likely to have greater physical impairment when measured shortly after discharge to the ward. Identification of those discharged from ICU who are most profoundly affected may be beneficial. Clinicians should suspect profound physical impairment in survivors of ALI with the aim of providing targeted rehabilitation to ameliorate the impairment.

This study has demonstrated that using a 6MWT in survivors of critical illness shortly after discharge from ICU to the ward appears to be safe and feasible. The test itself was not onerous in duration and provides useful information regarding the patient's trajectory of recovery. Specifically, data collected in this study demonstrated that a 6MWD < 100m when measured on the ward shortly following discharge from the ICU increased the odds of a ward length of stay > 2 weeks and discharge to another care facility. These findings can be used by the patient and their family during discharge planning and can guide expectations of recovery for both the patients and their carers.

Study 2

Study 2 answers research questions iv and v.

Study 2 Methods

This cross-sectional and observational study included 10 people who were admitted to ICU with a diagnosis of ALI and 21 healthy people. Participants with ALI were invited to attend 2 assessment sessions, 6 weeks after discharge from hospital, and separated by 7 days. Healthy participants were also invited to attend 2 assessment sessions. The following measures were collected on both the participants with ALI and the healthy participants: (i) peak and submaximal exercise responses during a symptom-limited ICET; (ii) peripheral muscle strength via a custom-designed fixed force gauge, hand-held dynamometry or a hand grip dynamometer; (iii) HRQL via the Medical Outcomes Study Short Form 36 General Health Survey Version 2 (SF36); and (iv) fatigue via the fatigue severity score 7-item version (FSS)

questionnaire. Participants were also required to wear a portable metabolic monitor (SenseWear® armband [SAB]) for 7 days, to measure PA and ST. Over the course of these 2 assessment sessions, demographic and anthropometric information were collected. For the participants with ALI only, descriptive measures were collected of: (i) 6MWD, using the best value from 2 6MWTs; and (ii) resting lung volumes, gas transfer and maximal respiratory pressures. Data are presented as mean ± standard deviation and median [interquartile range]. Individual ALI participant physiological responses during the ICET were averaged over 30-second intervals and plotted on a 9-panel graphical array.

Study 2 Results

The participants with ALI and the healthy participants were of similar age (50.9 ± 13.9 vs. 49.9 ± 6.2 yr, $p = 0.77$) and sex proportion (n [%] 5 [50] vs. 11 [52] males, $p = 1.00$). The 6MWD measured in the participants with ALI only was 507 [460 to 619] m, and the difference between the first and second test was 30 [17 to 56] m ($p = 0.020$). Compared with the healthy participants, the participants with ALI achieved lower measures of maximum work rate (WR) (180 [135 to 250] vs. 90 [76 to 120] W, $p < 0.001$) and peak rate of oxygen uptake (VO_2) (31.80 [26.60 to 41.73] vs. 17.80 [14.85 to 20.85] mL/kg/min, $p < 0.001$), and peak rate of carbon dioxide production (VCO_2) (2.81 [2.25 to 4.05 vs. 1.75 [1.57 to 2.13] L/min, $p < 0.001$), peak minute ventilation (VE) (102.1 ± 38.3 vs. 75.9 ± 16.9 L/min, $p = 0.049$), peak oxygen pulse (15 [11 to 20] vs. 9 [8 to 12] mL/beat, $p = 0.003$), and peak HR (166 ± 8 vs. 151 ± 21 bpm, $p = 0.009$). All other peak responses were similar between groups. Compared with the healthy participants, the participants with ALI had a lower anaerobic threshold (AT) ($p = 0.001$) and a higher VE/VCO_2 at AT ($p < 0.001$). At test completion, compared with the healthy participants, the participants with ALI reported similar levels of dyspnoea on the 0 to 10 modified Borg scale (5 [3 to 7] vs. 4 [2 to 6], $p = 0.27$) but greater leg fatigue (5 [3 to 8] vs. 7 [5 to 8], $p = 0.049$). Eight (80%) participants with ALI had a decreased peak VO_2. Although no participant was limited by his or her respiratory capacity, an elevated minute ventilation was present in 6 (60%) participants. One participant desaturated during the ICET, which was not associated with an elevated minute ventilation response. The cause of limitation in the participants who had a decreased peak VO_2 appeared

to be impairment in pulmonary diffusion (n = 7), deconditioning (n = 7) and cardiac impairment, evidenced by signs of non-symptomatic cardiac ischemia (n = 2).

Compared with the healthy participants, the participants with ALI demonstrated lower peripheral muscle strength for all actions ($p < 0.009$). When presented as a proportion of normative reference values, knee extension in the participants with ALI demonstrated the greatest impairment in strength at < 70% predicted, with the remaining actions being > 75% predicted. Compared with the healthy participants, the participants with ALI spent a lower proportion of their waking hours in moderate and vigorous PA (MVPA) (17 [10 to 25] vs. 5 [2 to 13] %, $p = 0.001$) and a greater proportion in ST (58 [48 to 70] vs. 72 [63 to 80] %, $p = 0.008$). The proportion of waking hours spent in light PA (LPA) was similar between groups being 21 [16 to 26] % in the healthy participants and 20 [11 to 28] % in the participants with ALI ($p = 0.86$). Furthermore, compared with the healthy participants, the participants with ALI accumulated a lower proportion of the total time spent in MVPA in unbroken bouts ≥ 10 minutes (30 [20 to 44] vs. 14 [0 to 27] %, $p = 0.018$) and a greater proportion of ST in unbroken bouts ≥ 30 minutes (38 [23 to 50] vs. 51 [43 to 66] %, $p = 0.031$). Compared with the healthy participants, the participants with ALI recorded lower values for all measures of peripheral muscle strength ($p < 0.01$) and domains in the SF36 ($p < 0.005$), and greater fatigue as measured using the FSS ($p < 0.001$).

Study 2 Discussion and conclusion

In the participants with ALI, the difference between the 2 6MWTs performed 6 weeks after hospital discharge, exceeded the minimal important difference reported in those recovering from acute respiratory failure, of 20 to 30 m. This implies that in this population, the 6MWD increases significantly with test familiarization. This needs to be considered by studies of ICU survivors when the 6MWD is used to evaluate changes over time and/or in response to a training program.

The impairments in exercise capacity identified in the participants with ALI during the ICET appeared largely related to deconditioning. There was also evidence of abnormalities of pulmonary gas exchange and cardiac dysfunction. While deconditioning may be improved through exercise training programs, it is unlikely

that such programs will change abnormalities in pulmonary gas exchange and cardiac dysfunction. Knee extension strength was shown to be the most affected when compared with upper limb and respiratory muscle strength. Therefore, exercise training which aims to condition the quadriceps, would appear to be a priority. Given 2 of the 10 participants with ALI had evidence of non-symptomatic cardiac ischemia during exercise, clinicians should suspect cardiac dysfunction as a possible contributor to exercise impairment.

The results suggest that both the total time spent in MVPA and ST, as well as the way in which time is accumulated may be targets for therapy. In order to increase participation in MVPA, it would seem sensible to first increase peak VO_2, thereby optimise functional reserve. Increasing participation in LPA, which requires a lower proportion of aerobic reserve, may assist in ameliorating the risk of prolonged ST and is likely to be a more achievable goal for people following ALI who are characterised by low exercise capacity.

Study 3

Study 3 addresses the research purposes vi and vii.

Study 3 Methods

Ten participants were invited to participate in Study 3 which was designed as part of a randomised controlled trial. Recruitment to this study commenced in 2011 and halted in 2014, due to profound difficulty in recruiting participants. As a result, a pragmatic approach has been taken in which data are reported on the 2 participants (Annie and James [aliases]) who completed measures before and after the EBRP.

The assessments of resting pulmonary function, peak and submaximal exercise responses during a symptom-limited ICET and 6MWD, peripheral muscle strength, PA and ST, HRQL, and fatigue, which were completed in Study 2 were used as the baseline measures in Study 3. These measures were repeated following the 8-week EBRP.

Regarding the EBRP, participants attended 2 supervised training sessions of 60 minutes in duration each week which were prescribed in conjunction with an

unsupervised home-based walking program on the remaining days of the week. Adherence and progression of the exercise prescription were recorded.

Each supervised exercise session comprised aerobic training (walking and cycling) and resistance training (upper and lower limbs). Participants were asked to walk for 10 min at 80% of the average speed achieved during their pre-training 6MWT, and to complete 15 minutes of interval, high intensity exercise prescribed at 60% of the maximum WR achieved during the ICET and 5 minutes of continuous cycling training prescribed at 40% of the maximum WR achieved during the ICET. Training intensity was titrated and progressed with the goal of evoking symptoms that were perceived to be between 4 and 5 on the modified Borg score for dyspnoea or 12 to 16 on the rating of perceived exertion scale (RPE). Resistance training was undertaken for muscles of the upper and lower limb. The initial weight for upper limb training was prescribed at 1.5 kg for women and 2 kg for men. Participants also performed functional lower limb resistance exercise comprising step ups and half squats. Each exercise was performed in 2 sets of 5 repetitions. Upper limb and lower limb resistance exercises were progressed when the participant was able to achieve 10 continuous repetitions with tolerable symptoms (RPE < 12). On each day that the participants did not attend supervised exercise training, they were encouraged to walk for 20 min at home.

Study 3 Results

Annie was a 43-year-old female, who was previously active and worked full-time. She was admitted to ICU with faecal peritonitis secondary to a bowel perforation after a laparoscopic tubal ligation with resulting sepsis. On admission to the ICU, she had an acute physiologic and chronic health evaluation II (APACHE II) score of 12 and a sequential organ failure assessment (SOFA) score of 10. She was mechanically ventilated for 9 days with an ICU length of stay of 9 days and total hospital length of stay of 16 days. James was a 63-year-old man, who was retired. He was admitted to ICU with community acquired pneumonia with resulting sepsis. On admission to the ICU, he had an APACHE II score of 25 and a SOFA score of 10. He was mechanically ventilated for 9 days with an ICU length of stay of 11 days and a total hospital length of stay of 20 days.

Regarding adherence to the EBRP in the current study, both participants completed all sessions although for James, a holiday had been previously planned and a 4-week hiatus in the program occurred as a result between session 9 and 10 (Week 5). Neither participant completed the home exercise diary.

Regarding progression of the EBRP, for both Annie and James, all modes of exercise, except walk-work during the walking training for Annie, were progressed. Annie achieved moderate to high intensity exercise during both the interval and continuous cycling regimes. The intensity of James' cycling programs was lower than that achieved by Annie and constituted predominantly moderate intensity exercise.

Both Annie and James demonstrated increases in peak VO_2 (+5.17 and +5.01 mL/kg/min, respectively) and AT (+5.6 and +1.15 mL/kg/min, respectively). The change in the remaining outcomes of functional exercise capacity (6MWD), strength, PA and ST, and HRQL and fatigue were notably different between the 2 participants. The improvements noted in peripheral muscle strength, participation in PA, the perception of physical function and the reduction in fatigue were consistent with the proposed benefits of an exercise training program. In contrast, changes in these outcomes were variable for Annie.

Study 3 Discussion and conclusion

While recruitment into this study was suboptimal, retention of participants in the intervention group once they commenced the program, was excellent. The excellent retention is likely related to in part the specific prescription based on objective measures of performance and the close supervision provided by the same physiotherapist.

The EBRP elicited an increase in peak VO_2 which exceeded that expected as part of natural recovery, was clinically meaningful, and which has not been demonstrated previously in large intervention studies examining the effect of exercise in survivors of critical illness after hospital discharge. An EBRP consisting of moderate to high intensity training was safe and appeared to convey optimal physiological gains in exercise capacity. Further study is required to identify the factors that contributed to the varied response to the EBRP.

Statement of Originality

This thesis is presented for the degree of Doctor of Philosophy at Curtin University, Western Australia. Studies were undertaken between November 2009 and August 2019, through the School of Physiotherapy and Exercise Science at Curtin University, Western Australia in association with the Department of Intensive Care and the Department of Sleep and Respiratory Medicine at John Hunter Hospital, Newcastle, the Department of Intensive Care and the Physiotherapy Department at Calvary Mater Newcastle, and the School of Health Sciences, The University of Newcastle, New South Wales.

This research project was developed in association with my supervisors who have been involved in editing both this thesis and all associated publications. All material presented in this thesis is original.

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Publications arising from this thesis

Peer reviewed journals

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Manuscripts in preparation

Mackney J, Harrold M, Jenkins S, Wrench G, Reid C, Fehlberg R, Thomas L, Havill K, Hill K. The 6MWD measured at ICU discharge as a predictor of health care use and mortality.

Mackney J, Harrold M, Jenkins S, Fehlberg R, Thomas L, Havill K, Hill K. Impairment in strength and functional exercise capacity in survivors of ALI as measured on ICU discharge is greater than the general ICU population.

Abstracts presented at conferences

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Mackney JH, Jenkins S, Fehlberg R, Thomas L, Havill K, Hill K. The six-minute walk distance: a useful metric for inpatient rehabilitation. Paper presented at: Bi-annual Australian Physiotherapy Association Conference; October 18, 2013. Melbourne, Australia.

Mackney JH, Jenkins S, Fehlberg R, Thomas L, Havill K, Hill K. The distribution of muscle weakness in patients recently discharged from intensive care. Paper presented at: Bi-annual Australian Physiotherapy Association Conference; October 18, 2013. Melbourne, Australia.

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List of abbreviations

10MWS	10-metre walk speed
10MWT	10-metre walk test
4MWS	4-metre walk speed
6MWD	6-minute walk distance
6MWT	6-minute walk test
ALI	acute lung injury
APACHE	acute physiology and chronic health evaluation
ARDS	Acute Respiratory Distress Syndrome
AT	anaerobic threshold
BBS	Berg Balance Scale
BP	blood pressure
CMN	Calvary Mater Newcastle hospital
COPD	chronic obstructive pulmonary disease
CPAx	Chelsea Critical Care Physical Assessment tool
CPET	cardiopulmonary exercise test
D_LCO	diffusion capacity of the lung for carbon monoxide
EBRP	exercise-based rehabilitation program
FCI	Functional co-morbidity index
FEV_1	forced expiratory volume in one second
FFG	fixed force gauge
FRC	functional residual capacity
FSS	Fatigue Severity Scale 7-item
FVC	force vital capacity
HHD	hand held dynamometer
HR	heart rate
HRQL	health related quality of life
IC	inspiratory capacity
ICET	incremental cycle ergometry test
ICU	intensity care unit
ICUAW	intensity care acquired weakness
JHH	John Hunter Hospital
LIS	lung injury score
LOS	length of stay
LPA	light intensity physical activity
MEP	maximal expiratory pressure
MET	metabolic equivalent
MIP	maximal inspiratory pressure
MMT	manual muscle testing
MPA	moderate intensity physical activity
MRC-SS	Medical Research Council Sum Score

MVPA	moderate and vigorous physical activity
MVV	maximal voluntary ventilation
MWS	maximal walk speed
NOK	next of kin
O_2	oxygen
PA	physical activity
PaO_2/FiO_2	ratio of partial pressure of arterial oxygen to fraction of inspired oxygen
PCS	Physical component score
PEEP	positive end expiratory pressure
$PETCO_2$	partial pressure of end tidal carbon dioxide
$PETO_2$	partial pressure of end tidal oxygen
PF	physical functioning
PFIT	Physical Function in Intensive care Test scored
PhD	Doctor of Philosophy
PICS	Post intensive care syndrome
R	respiratory exchange quotient
RCT	randomised controlled trial
RPE	rating of perceived exertion
RR	respiratory rate
RV	residual volume
SAB	Sensewear armband
SF36	Medical Outcomes Study Short Form 36 General Health Survey Version 2
SOFA	Sequential Organ Failure Assessment
SOMS	Surgical Intensive Care Unity Optimal Mobilisation Score
SpO_2	arterial oxygen saturation
ST	sedentary time
TLC	total lung capacity
TTS	time to stand from supine
TUG	timed up and go
VCO_2	rate of carbon dioxide production
VE	minute ventilation
VO_2	rate of oxygen uptake
VPA	vigorous intensity physical activity
VT	tidal volume
WR	work rate

CHAPTER 1 Introduction

1.1 Overview

This program of research comprises 3 studies, each of which examines successive phases of recovery in a cohort of people who have survived an admission to an intensive care unit (ICU) for acute lung injury (ALI). The first study collects several measures, including peripheral muscle force and 6-minute walk distance (6MWD) in these adults shortly after discharge from ICU to the ward and compares them with the same measures collected in adults who have survived a different critical illness. With participants from these 2 groups combined (i.e. ALI and critical illness survivors), analyses are also presented that show the value of the 6MWD, measured on the ward, to predict care needs, expressed as both ward length of stay and discharge destination. The second study explores the effect of familiarisation on 6MWD as well as examines the submaximal and maximal responses during exercise, accumulation of physical activity and sedentary time and strength, HRQL and fatigue shortly after hospital discharge in survivors of ALI. These measures are compared with the same measures collected in a healthy cohort of similar age and sex-proportion. The third study examines, the adherence, progression and within-participant response to a supervised high intensity exercise training program in survivors of ALI.

The following section provides a brief overview of the literature that resulted in the development of this program of research. Research questions and hypotheses are provided. The significance of this program of research is discussed.

1.2 Background to the program of research

The term ALI and the more severe subset, acute respiratory distress syndrome (ARDS), represents a constellation of clinical signs resulting from acute systemic inflammation, and causes acute respiratory failure. The diagnostic criteria for ALI specified in the 1994 Consensus Conference[1] was used in this program of research and comprise an illness that: (i) is acute in onset; (ii) results in arterial hypoxaemia

with a partial pressure of oxygen in arterial blood to fraction of inspired oxygen ratio (PaO_2/FiO_2) of less than 300 mmHg; (iii) results in bilateral opacities on chest x-ray and (iv) has no evidence of left atrial hypertension.[1] Acute respiratory distress syndrome is defined by similar criteria with the exception of a more profound hypoxaemia ($PaO_2/FiO_2 < 200$ mmHg). Approximately 85% of patients diagnosed with ALI will progress to meet the criteria for ARDS.[2]

In 2011, the diagnostic criteria for this syndrome were modified (i.e. Berlin criteria).[3] While the criteria for ARDS according to the Berlin criteria were largely similar to the 1994 definition, the PaO_2/FiO_2 ratio was used to further categorise the severity of ARDS into mild ($PaO_2/FiO_2 = 200$ to 300 mmHg), moderate (PaO_2/FiO_2 100 to 199 mmHg) and severe illness ($PaO_2/FiO_2 < 99$ mmHg). The Berlin definition also: (i) eliminated the term ALI (this was captured in the criteria for mild ARDS); (ii) defined the timeframe between injury and onset of symptoms as 7 days; (iii) required the PaO_2/FiO_2 ratio to be assessed on $\geq 5cmH_2O$ positive end expiratory pressure (PEEP); and (iv) permitted a diagnosis of ARDS to be made in the presence of cardiogenic pulmonary oedema.[3]

The current program of research was commenced in 2009, prior to the publication of the Berlin definition.[3] As a result, the term ALI as it is used throughout the thesis, describes the participants who met the criterion as per the 1994 consensus definition and therefore comprises participants with ALI and ARDS.[1] Any reference to ARDS in the thesis when describing other research, will refer to the 1994 consensus definition of ARDS.[1] Clarification has been provided when studies have used the Berlin definition.[3]

The incidence of ALI within ICU, has been identified as 7% of all ICU admissions in a large cohort of European ICUs and rising to between 16% and 20% in those who are mechanically ventilated.[2,4,5] The management of ALI in the critical care setting has evolved over the last 15 years. Early identification of sepsis, a causative factor in ALI in a large proportion of patients, together with the implementation of lung protective ventilation strategies,[6,7] and general enhancement in patient care within the ICU has led to a decrease in mortality. The National Institutes of Health - National Heart, Lung, and Blood Institute (NIH-NHLBI) ARDS network, showed

through its clinical trials a clear decline in mortality from 40% in 1997[8,9] to 25% in 2009.[10,11] It is clear that there are more ALI survivors living in the community.

Herridge et al[12,13] first identified that people surviving an admission to ICU with a diagnosis of ARDS exhibited prolonged and notable impairments in physical function and health-related quality of life (HRQL). A large body of literature now exists since these papers were first published and demonstrate impairment which exists after hospital discharge.[12-24] These survivors have been shown to experience pronounced reductions in 6MWD and strength,[12-17] impairments in cognition,[18,19] symptoms of anxiety and post-traumatic stress,[20,21] and impaired HRQL for up to 5 years after discharge from hospital.[22-24]

However, physical impairment following an admission to ICU has not been fully described, with a paucity of data related to strength and functional exercise capacity after discharge from ICU to the ward. Further, contributors to the impairment in physical capacity after hospital discharge, as identified using laboratory-based studies, have not been reported. Programs initiated after ICU discharge with the aim to ameliorate these impairments have shown nil or minimal effect.[25-30]

The overarching aim of this program of research was to increase the knowledge regarding the extent and contributors to these impairments during the acute hospital admission and after hospital discharge and to examine the adherence to and effect of a high intensity exercise-based rehabilitation (EBRP) program on these impairments.

1.3 Study 1

This was an observational, cross-sectional study in which 2 groups of participants (ALI and critical illness) were recruited during an admission to ICU and where assessments of physical function were performed within 7 days after ICU discharge to the ward.

1.3.1 Research questions

(i) Do adults who have survived an ICU admission for ALI, when assessed within 7 days of discharge from an ICU, demonstrate impairments in peripheral muscle strength (primary outcome), balance, ability to stand

from supine, walking speed and peak and submaximal exercise responses measured during a functional exercise test (secondary outcomes), relative to those who survived an ICU admission for a critical illness other than ALI?

(ii) In adults who have survived an ICU admission for ALI or another critical illness, does the 10-metre walk speed (10MWS) explain ≥ 50% of the variance in 6MWD, when both outcomes are measured within 7 days of discharge from the ICU?

(iii) In adults who have survived an admission to ICU for ALI or another critical illness, can the 6MWD measured within 7 days of discharge from the ICU, separate those who: (a) require a longer ward length of stay versus those who require a shorter ward length of stay; and (b) are discharged home versus discharged to another care facility?

1.3.2 Hypotheses

(i) When assessed within 7 days of discharge from an ICU, adults who have survived an ICU admission for ALI, will demonstrate greater impairments in peripheral muscle strength (primary outcome), balance, functional ability, functional ambulation and peak and submaximal exercise responses measured during a functional exercise test (secondary outcomes), relative to those who survived an ICU admission for a critical illness other than ALI.

(ii) In adults who have survived an ICU admission for ALI or another critical illness, the 10MWS will explain more than 50% of the variance in 6MWD, when both outcomes are measured within 7 days of discharge from the ICU.

(iii) In a group of adults who have survived an ICU admission for ALI or another critical illness, the 6MWD measured within 7 days of discharge from the ICU, will separate those who: (a) require a longer ward length of stay versus those who require a shorter ward length of stay; and (b) are discharged home versus discharged to another care facility.

1.3.3 Background

A number of studies in people surviving an admission to ICU with a diagnosis of ALI, have demonstrated profound impairment after hospital discharge and extending up to 5 years, in measures of: (i) peripheral muscle strength; (ii) 6MWD, walking speed and the Rivermead Mobility Index; and (iii) HRQL.[12-17,31] While much of the research reporting disability after an admission to ICU has recruited those with ALI/ARDS, the research examining the effect of an EBRP during and after the ICU admission has been in a general population with critical illness. However, the degree of physical disability in survivors of ALI when compared to a general population of critical illness survivors is unclear.

Few studies have compared outcomes in those surviving ALI with outcomes in survivors of other critical illnesses. Davidson et al[32] demonstrated that, when compared with critical illness survivors with a similar severity of illness, survivors of ALI have greater reduction in HRQL. The difference between these groups was clinically important and predominantly related to poorer physical functioning reported by the survivors of ALI. There have been no studies which have compared outcomes such as strength, 6MWD and walk speed in survivors of ALI and survivors of other critical illnesses shortly after ICU discharge to the ward. Targeted rehabilitation for those who, on average show greater impairment after an ICU admission is likely to be important to optimise both patient outcomes and resource use. Further, while 6MWD has been measured in survivors of critical illness after discharge from hospital, and found to be prognostic of readmission,[33] HRQL,[34] mortality[14] and the participant living in their own home,[14] the prognostic value of the 6MWD when measured during the hospital admission, has not been examined.

1.4 Study 2

This was an observational, cross-sectional study in which participants with ALI were recruited on discharge from hospital. Peak and submaximal exercise responses, physical activity (PA) and sedentary time (ST), strength, HRQL and fatigue were measured and compared with a group of healthy participants.

1.4.1 Research questions

(i) Do adults who have survived an admission to an ICU for ALI, at 6 weeks after discharge from an acute care facility demonstrate differences in peak exercise (primary outcome) or submaximal exercise responses measured during an incremental cycle ergometry test (ICET), when compared with a healthy group? If so, what is the underlying cause of their exercise limitation?

(ii) Do adults who have survived an admission to ICU for ALI, at 6 weeks after discharge from an acute care facility demonstrate differences in daily PA and ST, peripheral muscle strength, HRQL and fatigue, when compared with a healthy group?

1.4.2 Hypotheses

(i) Adults who have survived an admission to an ICU for ALI, when measured 6 weeks after discharge from an acute care facility, will demonstrate differences in peak or submaximal exercise responses measured during an ICET, when compared with a healthy group of similar age and sex-proportion. The mechanism of limitation will be decreased peripheral muscle force and impairment in lung function.

(ii) Adults who have survived an admission to an ICU for ALI, when measured at 6 weeks after discharge from an acute care facility, will demonstrate impaired daily PA and ST, peripheral muscle strength, HRQL and fatigue, when compared with a healthy group of similar age and sex-proportion.

1.4.3 Background

Given the promising results of rehabilitation commencing within the ICU, and the known positive effect of an EBRP in many populations with pathologies such as chronic obstructive pulmonary disease (COPD),[35] coronary artery disease,[36] and diabetes mellitus,[37] it has been hypothesised that an EBRP following discharge from ICU, would also achieve improvements in strength and exercise capacity in survivors of critical illness. To date, this has not been reflected in the literature.[25-

[28,30,38,39] A number of studies investigating the effect of EBRP in survivors of critical illness initiated following hospital discharge have shown no effect on the perception of physical function, the timed up and go, 6MWD or peak exercise capacity.[25-28,30,38,39]

While field-based assessments such as the 6-minute walk test (6MWT) are used to quantify the magnitude of functional impairment seen in survivors of critical illness, these tests offer very little information regarding the mechanism of limitation to exercise. Studies that have attempted to identify mechanisms have often focused on peripheral causes of limitation such as the development of muscle atrophy during the ICU admission and changes in skeletal muscle structure seen via biopsy, such as the rapid decline in muscle cross sectional surface area and a sustained cellular change in muscle structure.[40,41] No studies have attempted to elucidate the causes of impairment in exercise capacity in survivors of ALI via laboratory-based exercise tests. Lung volume and spirometric measures appear to normalise within 6 months of the illness, although prolonged impairment in diffusing capacity has been demonstrated in survivors of ALI.[42] There is a paucity of data quantifying the exercise capacity of ALI survivors using a laboratory-based exercise test such as an ICET and subsequently a paucity of data using an ICET to identify the physiological basis for any limitation. Knowledge of the mechanism of limitation to exercise in survivors of ALI will add to the knowledge base regarding the impairments reported in strength and exercise capacity experienced by this population and also provide information to guide the prescription with which to optimise exercise-based rehabilitation.

1.5 Study 3

This study was planned as an interventional study. However, the study is presented as an observational study in which the adherence, progression and effect of a high intensity EBRP in survivors of ALI after discharge from hospital was examined.

1.5.1 Research purposes

(i) In adults who have survived an admission to an ICU for ALI, to examine the adherence to, as well as tolerance and progression of, a high intensity EBRP initiated 6 weeks after discharge from an acute care facility.

(ii) In adults who have survived an admission to an ICU for ALI, to examine within participant changes in resting lung function and submaximal and peak physiological responses during an ICET and 6MWT as well as PA and ST, peripheral muscle strength, HRQL and fatigue following a program of high intensity EBRP initiated 6 weeks after discharge from an acute care facility.

1.5.2 Background

Given that ALI survivors appear to be characterised by substantial and prolonged disability, rehabilitation strategies are likely to be helpful in optimising their functional recovery.[13,43] In people with COPD[44] and chronic heart failure,[45] there is convincing evidence that supervised exercise programs improve exercise capacity and HRQL. Further, in these populations, an EBRP which is prescribed at a high proportion (i.e. ≥ 60%) of an individual's maximum exercise capacity appears to optimise physiologic benefit.[46-48] Of note, these improvements are mediated, at least in part, by peripheral muscle conditioning which serves to increase the skeletal muscle oxidative capacity, reduce the early reliance on anaerobic energy systems and minute ventilation requirements at sub-maximal exercise intensities.[46-48] That is, exercise training has no effect on lung function. A corollary of this is that high-intensity, supervised exercise training may optimise peak exercise capacity in survivors of ALI and that these changes will be achieved through conditioning of the peripheral muscles, and do not require improvements in lung function. While, exercise training appears to be both safe and feasible in patients who survive a critical illness,[27] the lack of effect of EBRP initiated after hospital discharge may be related to the type and intensity of exercise prescribed. That is, unsupervised and low-moderate intensity which has been trialed in previous work, may not be sufficient to elicit training–related gains in peripheral muscle condition in these patients.[26,27] The adherence to, and effect of, a supervised high-intensity exercise

training program in patients who survive an admission to ICU for ALI on exercise capacity and functional impairment, is unknown.

1.6 Significance and novelty of the research

There are several novel components to the studies presented in this thesis. First, the comparison of physical function of 2 different participant groups who have survived an admission to ICU. Second, the methodology of quantification of an integrated systems response to exercise i.e. ICET, in examination of the mechanism of limitation to exercise in survivors of ALI after hospital discharge. Thirdly, the implementation of a high intensity program of exercise in survivors of ALI after hospital discharge.

Comparison of impairments in survivors of ALI with that in survivors of a critical illness other than ALI has not been described at any time point along the trajectory of recovery. Early identification of groups such as those admitted with ALI who are potentially at greater risk of experiencing impairments in physical ability such as strength or exercise capacity, and are likely to require more resources and represent a notable ongoing burden on the healthcare system,[49] may enable targeted rehabilitation, early discharge planning and collaborative care planning with the patient and family. The safety and feasibility of objective measures such as the 6MWT, to evaluate exercise capacity during the acute hospital admission and which may aid in early identification of those who have greater impairment, has not been explored to date. Further, description of the response to exercise in survivors of ALI, using an ICET has not been reported and will enable identification of the mechanisms of limitation of exercise. These data will add to the knowledge regarding the factors contributing to the functional impairments observed following a critical illness and provides a basis for optimisation and individualisation of an EBRP to ameliorate the impairments. Finally, the adherence to, and effect of, a high intensity EBRP has not been described in survivors of a critical illness. This information may inform further programs of research aiming to improve exercise capacity and physical function after a critical illness.

CHAPTER 2 Literature Review

2.1 Overview

This chapter provides a review of the literature regarding intensive care medicine and the issues surrounding survivorship following a critical illness. It is divided into 4 parts. Part 1 will describe the evolution of intensive care medicine and the costs related to an intensive care admission. Part 2 will define and describe acute respiratory distress syndrome (ARDS) and acute lung injury (ALI). Part 3 will investigate survivorship following critical illness specifically related to physical function, such as exercise capacity, strength, health related quality of life (HRQL) and fatigue, and the measures used to describe physical function in these people. Finally, Part 4 will describe and synthesise information related to interventions that have aimed to ameliorate the ongoing impairments in physical function observed in survivors of critical illness. Due to the broad scope of the topics covered in this chapter, a narrative review based on a broad search of the literature was performed. A summary is provided at the end of each of the individual parts.

2.2 Part 1 - Intensive care

This part will address the definition, evolution of intensive care medicine, the costs associated with an intensive care admission, mortality and issues related to survivorship.

2.2.1 Intensive care in Australia

The Australian College of Intensive Care Medicine describes 3 levels of adult intensive care within Australia, where Level 1 represents the lowest care level unit, and Level III represents the highest care level unit.[50] These levels have been defined according to the size of the region and population that the intensive care unit (ICU) services, the services and resources available within the hospital and hence the capability to provide invasive cardiovascular monitoring and ongoing multi-system and complex support.[50] For example, an ICU situated within a hospital in a rural area e.g. Taree Hospital, New South Wales (NSW), which houses a level II ICU, will be

able to provide mechanical ventilation but are limited in other support they can provide, while a unit within a large metropolitan hospital such as Liverpool Hospital, NSW which is a level III ICU will be able to provide mechanical ventilation as well as complex support and monitoring such as extracorporeal membrane oxygenation and intracranial pressure monitoring.

2.2.2 The evolution of intensive care medicine in Australia

The concept of critical care has developed over time. Intensive care as we know it today developed from a recognition that in order to care for the critically ill, a unit offering specific medical and nursing skills was required.[51] The concept of intensive care has since been transformed by an explosion in the availability and complexity of technology and the growing body of critical care research, particularly in the last 2 decades. The evidence for critical care medicine has expanded with well conducted, large, multi-centre trials. The findings of these trials and the clinical application of these findings have both improved mortality and debunked interventions thought to previously be effective. For example, when compared with the use of higher tidal volumes, the use of low tidal volumes in those with ALI was shown to improve mortality;[8] routine insertion of the pulmonary artery catheter was associated with no benefit in survival or organ function and increased complications and costs;[10] and excess sedation was associated with increased mortality and longer ICU and hospital length of stay (LOS).[52] The care of the patient in ICU has also moved from an autocratic medical model to a more patient-centred approach. This is seen with initiatives such as unrestricted visiting hours in many ICUs worldwide[53] and consideration of the effect of ICU on mortality as well as the ongoing physical and psychological function and quality of life of those who survive an ICU admission.[54]

2.2.3 Growth in both utilisation and cost associated with intensive care

The evolution of intensive care medicine is also reflected in the increased need and usage of this branch of medicine. Within Australia, there are currently 9.04 ICU beds per 100 000 population and 261 adult intensive care units.[55] There has been enormous growth observed in the number of funded beds within Australia over the past decade and the number of admissions to the ICUs. This growth has been reported by the Australia New Zealand Intensive Care Society Centre for Outcome

and Resource Evaluation (ANZICS CORE) at both a national and state level.[55] Admissions to ICU within Australia and New Zealand, have increased to 149,691 in 2016 from approximately 90,000 in 2007. The growth in units and admissions is particularly evident in NSW where the number of units has increased from approximately 60 in 2011 to 70 in 2016 and ICU admissions have increased from 35,000 in 2011 to approximately 40,000 in 2016.[55]

2.2.4 Healthcare utilisation in survivors of critical illness is high and continues after hospital discharge

The care of a critically ill patient requires significant resources. The cost of a single bed day in an Australian ICU was calculated to $2,670 in 2005,[56] $4,028 in 2010[57] and $4,657 in 2017.[55] A comparison of cost in 2009/2010 between a single ICU patient day and an entire acute care hospital admission (excluding ICU, emergency care) was $4,028 and $3,840, respectively. In total in 2017, delivery of ICU care within Australia is estimated to be $2.7 billion based on average cost per ICU bed of $4,657 and the number of ICU bed days as reported through the annual ANZICS Critical Care Resources survey (2015/16).[55] The costs associated with the provision of critical care services is accrued largely by a small proportion of patients requiring particularly high levels of care for prolonged periods. Within Australia, in a 12-month period across 2015/16, 471,282 ICU bed days were recorded for adult care. Of the people who accrued these bed days, 2.4% had a LOS of more than 14 days and accounted for 20.6% of the total ICU bed days.[55]

Internationally, over the same time period, the increase in ICU beds has exceeded the increase in general hospital beds. That is, between 2000 and 2005, the number of ICU beds in the United States of America (USA) increased by 7% in contrast to a 4% decrease in hospital beds. Also, during this period ICU bed days increased by 10% in contrast to a 5% increase in non-ICU bed days.[58] As a result, annual intensive care medicine costs have increased by 44% during this time.[58]

The largest proportion of costs for provision of care within ICU is staff-related with approximately 60 to 70% of all resources attributed to staffing.[56] Within Australian ICUs, the high allocation of cost to staffing is related to the high ratio of staff to patients specified by professional bodies.[50] In an Australian Level III ICU the nurse-

patient ratio is 1:1, and the availability of medical staff is recommended as at least one staff specialist, and one other medical officer per pod of 8-15 beds. These staff are required to have post graduate ICU training.[50] Allied health staff such as physiotherapists and social workers are also required to be available.[50] Consumables, include specialised equipment such as mechanical ventilators and extra-corporeal membrane oxygenation devices, contribute approximately 20% of the cost of ICU care delivery.[56]

The ward stay following an ICU admission can also be lengthy. In comparison to the average LOS reported for acute care in Australia in 2014/15 of 2.7 days,[59] the ward LOS following discharge from a prolonged ICU admission, defined as an ICU LOS > 5 days, has been reported as between 13 and 15 days.[60] The lengthy ward stay also contributes to the health care costs with a figure of $800 per day attributed to health care offered on the wards.[61] The health care utilisation of survivors of critical illness also continues past hospital admission. Data pertaining to discharge destination and cost within Australia is sparse, and not provided in the reports published by ANZICS. However, a study of Australian survivors of critical care, reported that just 40% of participants who were mechanically ventilated for > 7 days in a Perth hospital were discharged home, with the remaining proportion of patients receiving inpatient rehabilitation (43%) or other hospital care (approximately 14%).[62] Internationally, Cheung and colleagues[49] identified that in a group of Canadian survivors of ARDS, recruited during their ICU admission between 1998 and 2001, costs were great for the initial hospitalisation, both ICU and ward admission ($CAD 97,810; 95% confidence interval [CI] $83,640 to $115,130 and $31,649 95%; CI $24,470 to $43,450, respectively) and continued for 2 years following hospital discharge to a mean total of $28,350. The engagement of allied health services, rehabilitation and home care contributed $3,210, $8,790 and $3,570 to the total costs (55% of total post discharge health care costs) following hospital discharge. The use of health care services by those who have experienced a critical illness is ongoing.

2.2.5 Mortality

In-hospital mortality for those admitted to ICU has decreased between 2007 and 2016, from 13% to 8%.[63] This may be related to a change in case mix and increasing numbers of low risk elective surgical admissions, such as elective cardiac surgery,

influencing the raw mortality data.[55] However, the risk adjusted mortality based on the Australian and New Zealand Risk of Death model, a mortality prediction model developed by ANZICS,[64] has decreased over time, and is most likely due to improvements in care both within the ICU and outside it.[55]

2.2.6 Increased focus on survivorship

As a result of an increased number of ICU beds and a lower mortality rate, it is logical that the number of survivors of critical illness living within the community is also increasing. While data reporting the number of people who have survived an intensive care admission within Australia are not available, these data have been reported in the USA. Those who have survived for more than 3 years following ICU admission for severe sepsis have increased by over 200% between 2003 and 2008.[65] As a result, the scope of care for those working and researching within ICU has now extended past the 28-day survivorship, that has historically been used as the primary outcome of interest.[66] The number of publications reporting on survivorship following an ICU admission (as reported in a search via PubMed using the terms 'survivor' and 'critical care') has increased from 954 between 2000 and 2010 to 1,941 between 2011 and 2018. These publications report on long term outcomes that include not only survival but morbidity as well.[66]

Much of the research examining the short- and long-term impacts of a critical illness on survivors have done so in a population with a homogenous disease process. The diagnostic group is most commonly of ARDS or ALI[12,13,23,32,49,67,68] with a diagnosis of sepsis used less frequently as an inclusion criterion.[69-71]

2.2.7 Summary

The role of intensive care medicine within health care has evolved over time. The number of available ICU beds has increased significantly, and the mortality associated with an ICU admission has decreased. The health care utilisation of these people who experience a critical illness extends well after the ICU admission. As a result, the number of survivors of critical illness living within the community has increased and is reflected in the growth of research examining this population.

2.3 Part 2 - Acute respiratory distress syndrome and acute lung injury

This part will define ARDS and ALI and discuss the pathophysiology, incidence, risk factors, and mortality associated with this syndrome.

2.3.1 Definition of acute respiratory distress syndrome and acute lung injury

The original description of ARDS was published in 1967 by Ashbaugh and colleagues,[72] who described a specific set of clinical and pathological features which included a rapid onset of tachypnea and hypoxaemia, loss of lung compliance and bilateral infiltrates on chest x-ray. These features were common regardless of differences in precipitating illnesses. In 1994 the American-European Consensus Conference (AECC)[1] proposed a definition to aid consistency in diagnosis and enhance research regarding ARDS. The diagnostic criteria for ARDS were defined as: (i) acute onset; (ii) arterial hypoxaemia with a partial pressure of oxygen in arterial blood to fraction of inspired oxygen ratio (PaO_2/FiO_2) of less than 200 mmHg; (iii) bilateral opacities on chest x-ray; and (iv) no evidence of left atrial hypertension. The definition also specified criteria for ALI. This comprised the same criterion as that for ARDS, except it encompassed a broader range of hypoxaemia, that of $PaO_2/FiO_2 < 300$ mmHg.

The definition proposed in 1994[1] has been recognised to have limitations. Specifically, it specified neither the time frame from injury to presentation nor the amount of positive end expiratory pressure (PEEP) to be used when assessing the PaO_2/FiO_2 ratio. Radiographic interpretation of the ARDS criteria also lacked sensitivity and specificity when used by critical care physicians. In 284 patients with risk factors for ARDS, sensitivity and specificity determined when comparing critical care physician recognition of ARDS diagnosis with autopsy findings was 76% (95% CI, 67% to 83%) and 75% (95% CI, 68% to 81%), respectively.[73]

In an attempt to overcome these limitations with the AECC definition of ARDS and ALI, a Delphi consensus statement was produced.[1,74] In this statement, a time frame of 72 hours was suggested between injury and presentation and the PaO_2/FiO_2 ratio was to be assessed with a PEEP of > 10cmH_2O.[74] Regarding the other criteria, the

Delphi consensus statement identified that bilateral airspace disease should be present that involved at least 2 quadrants on frontal chest x-ray.[74] Also, as the use of pulmonary artery catheters is now rare, it was difficult to definitively exclude left atrial hypertension. Therefore, the Delphi consensus statement suggests that a lack of clinical evidence of congestive cardiac failure is adequate to exclude left atrial hypertension.

The Berlin definition published in 2011 further refined the criterion for ARDS. The PaO_2/FiO_2 ratio categorises the severity of ARDS into mild (PaO_2/FiO_2 = 200 to 300 mmHg), moderate (PaO_2/FiO_2 100 to 199 mmHg) and severe illness (PaO_2/FiO_2 < 99 mmHg). The Berlin definition also: (i) eliminated the term ALI (this was captured in the criteria for mild ARDS); (ii) defined the timeframe between injury and onset of symptoms as 7 days; (iii) required the PaO_2/FiO_2 ratio to be assessed on ≥ 5cmH_2O positive end expiratory pressure (PEEP); and (iv) permitted a diagnosis of ARDS to be made in the presence of cardiogenic pulmonary oedema.[3]

2.3.2 Pathophysiology

Acute lung injury and ARDS are caused by an insult to the alveolar-capillary membrane that results in increased permeability and subsequent interstitial and alveolar oedema.[75] The pathogenesis is the result of a direct insult on lung cells (pulmonary), most commonly pneumonia or aspiration, and/or an indirect insult as a result of an acute and overwhelming systemic inflammatory response (non-pulmonary), most commonly sepsis.[76,77] Although the understanding of cellular and humoral components of the inflammatory responses in the lung has improved since this syndrome was first described in 1967,[72] the exact mechanisms by which such a wide variety of insults can lead to this syndrome, and the precise sequence of events leading to lung damage remains unclear.

While the exact pathogenesis of ALI/ARDS is unclear, the central concepts to the development of ALI include dysregulated inflammation,[75,78] inappropriate accumulation and activity of platelets and leukocytes which release harmful mediators e.g. tumor necrosis factor and interleukin 1, 6 and 8, leading to further cell damage,[79] uncontrolled activation of coagulation pathways and altered permeability of alveolar endothelial and epithelial barriers.[75,78,80] In the initial or acute phase there

is alveolar flooding with protein-rich fluid secondary to the increased vascular permeability. Alveolar epithelial injury of type I cells contributes to pulmonary oedema and the breakdown of this epithelial barrier exposes the underlying basement membrane. Injury to type II alveolar cells leads to impaired surfactant synthesis resulting in increased alveolar surface tension and alveolar collapse.[81] The acute phase is followed by a fibro-proliferative phase in some patients with varying degrees of fibrosis, neovascularisation and later resolution.[82] These stages may, however, overlap.

Vascular injury and remodeling may lead to pulmonary arterial hypertension which may lead to right ventricular dysfunction,[83,84] contributing to circulatory failure and exacerbating hypoxaemia. This circulatory failure is often further exacerbated by the processes inherent in sepsis, whereby uncontrolled dysregulation of the proinflammatory and anti-inflammatory mediators leads to systemic vasodilation and decreased oxygen supply to working organs.[85] The profound hypoxaemia inherent in ARDS also contributes to organ dysfunction and failure.[86]

2.3.3 Epidemiological features of ALI and ARDS

The prevalence of ARDS varies considerably between studies. An international multi-centre prospective cohort study using point prevalence to determine the incidence of ARDS in ICU, reported that patients admitted to ICU with ARDS represented 10.4% (95% CI, 10.0 to 10.7) of total ICU admissions and 23.4% (95% CI, 21.7 to 25.2) of all patients requiring mechanical ventilation.[87] While examination of the entire cohort showed that over 4 weeks, ARDS represented 0.42 cases/ICU bed, there was some geographic variation, with Oceania including Australia reporting the highest prevalence of ARDS (0.57 cases/ICU bed). The lowest prevalence was reported by Asia (0.27 cases/ICU bed).[87]

The prevalence of ALI within ICU, which encompasses patients who have a broader range of hypoxaemia as defined by the PaO_2/FiO_2, has been identified by the European-based Acute Lung Injury Verification of Epidemiology group, as 7%.[2] When examination of the prevalence is restricted to the mechanically ventilated population in intensive care, the incidence of ALI rises to between 16%[4] and 20%.[5] Similarly the incidence of ALI, using the time to newly diagnosed cases as a

proportion of total time all of the individuals in the cohort contributed to the study i.e. person-years, varies between reports. An Australian study, which explored the incidence of ALI across 3 states reported ALI to be present in 34 cases per 100,000 person-years.[88] Rubenfeld and colleagues,[76] adjusting for age, found a substantially higher incidence of 86 per 100,000 person-years.

The variation in the prevalence and incidence may be due to factors such as the intercountry differences in the availability of ICU beds. For example, the higher incidence of ARDS reported in a single USA study (33.8 new ARDS cases/100,000)[89] compared with that reported in Europe (5 to 7.2/100,000)[77,90] is likely due to the greater number of ICU beds in USA as a ratio of total hospital beds compared with Europe (20/100,000 population in the USA vs. approximately 2.5/100,000 in Europe).[91] The variation may also be related to the way the data was collected (retrospective estimates vs. prospective reporting). Nevertheless, these disparities may also reflect true variation in the incidence of the syndrome, which arise in relation to genetic predisposition and the level of the hospital and ICU.[92] Moving forward, the incidence of ALI is likely to increase as a consequence of an aging population (see next paragraph on risk factors), and the improved management of the acutely ill patients, who are susceptible to the development of ALI.

Regarding causative and risk factors, the pathologies leading to the development of ALI are numerous with the most common being sepsis. In a cohort of 1,113 patients with ALI, 46% of the group presented with sepsis from a suspected pulmonary source and 33% with sepsis from a non-pulmonary source.[76] Age also impacts on the incidence of ALI resulting from sepsis. In the same cohort the incidence of ALI was lowest in the 15 through 19 years age group (16 cases per 100,000 person-years), and increased with age, peaking in the 75 through 84 years age group (306 case per 100,000 person-years). In a smaller cohort of 255 patients with a diagnosis of ARDS, both pneumonia and sepsis were identified as the primary cause of the diagnosis in 42% and 31% of patients, respectively.[77] Other causative factors for ALI, albeit with a significantly lower incidence, include trauma, aspiration, and pancreatitis.[77]

Environment and genetic factors have also emerged as a potent contributor to the susceptibility and severity of ARDS and ALI. Environmental factors such as chronic alcohol abuse increases the risk of both ALI and ARDS and multi-organ dysfunction.[77,93] Active and passive cigarette exposure, have been independently associated with the development of ALI after severe blunt trauma.[94] Genetic variations have been associated with developing ALI and/or ARDS and with clinical outcomes.[95] These variations have involved genes that regulate inflammation, coagulation, endothelial cell function, reactive oxygen radical generation and apoptosis.[93,95-99]

2.3.4 Mortality following ARDS

The rate of mortality following ARDS/ALI varies widely, and has been described as between 25% and 58%.[5,9,76,77,88,100] A pooled estimate of published data evaluating ARDS mortality in the 20 years to 2006, suggested a mortality of between 36 and 44% with little change over that time.[101] Conversely, the National Institutes of Health - National Heart, Lung, and Blood Institute (NIH-NHLBI) ARDS network, a clinical network created to carry out multi-centre trials of ARDS treatments in the USA, showed through its clinical trials a clear decline in mortality from 40% in 1997[8,9] to 25% in 2009.[10,11] This decline was observed even though over the same time period people presented with a higher acuity of illness and were more likely to have premorbid chronic disease, as defined by the acute physiology and chronic health evaluation (APACHE) III score. The decreasing mortality in those diagnosed with ARDS is likely to be the result of early identification of sepsis, together with the implementation of lung protective ventilation strategies,[6,7] the use of prone positioning[102] and lung recruitment manoeuvres.[103]

In those diagnosed with ARDS, higher mortality has been associated with higher severity of arterial hypoxaemia (PaO_2/FiO_2 < 100 mmHg), older age (> 60 years), higher severity of illness scores, higher plateau and driving inspiratory pressure requirements,[87,104] and multi-system organ dysfunction including shock, liver dysfunction and kidney injury.[86,105,106] Only a small proportion of patients (19.3%) with ARDS die from hypoxaemia.[77] Lung injury, however, does appear to predispose patients to the development of a systemic inflammatory response, if not

already present, as well as the development of multi-system organ dysfunction.[107] The most frequent cause of death reported in an ARDS cohort (n = 255) was multi-system organ dysfunction (46% of the cohort who died) and the greater number of organs involved, the greater the mortality.[77]

2.3.5 Summary

Over the past 25 years, there have been several iterations of the criteria used to diagnose ARDS. The AECC definition of ALI published in 1994 was inclusive of a more hypoxaemic subgroup of ARDS.[1] While most recently the Berlin definition of ARDS has been proposed, consistent with much of the research published to date, this program of research has used the AECC definition. The knowledge relating to the pathophysiology of ARDS is growing and supports essentially an overwhelming insult to the capillary-alveoli barrier causing flooding and damage to the lining of the alveoli. The mortality as a result of ARDS is decreasing.

2.4 Part 3 - Sequelae of critical illness

This part will examine the sequelae of critical illness and focuses on outcomes of peripheral muscle strength, exercise capacity, participation in PA, accumulation of ST as well as health-related quality of life. Where possible, the impact, pathophysiology and considerations when evaluating impairments in these outcomes are addressed.

2.4.1 Overview

The seminal work in ICU survivorship was published by Herridge and colleagues[12] who, in 2003, reported a composite of outcomes measures collected in ARDS survivors 1 year following their ICU admission. This publication was followed by reports of data collected 2-years and 5-years following the ICU admission.[13,49] Consistent with this earlier work, the studies included within the current program of research also use a diagnosis of ALI as an inclusion criterion as this allows for the recruitment of a relatively homogenous patient population within an otherwise remarkably heterogeneous ICU population.[15,108-111] Those surviving ARDS or ALI are likely to represent some of the most severely affected survivors of critical illness as ARDS is characterised by a very high acuity of illness.[112]

The data reported in these earlier studies of survivors of ARDS show pronounced reductions in 6-minute walk distance (6MWD) and peripheral muscle strength,[12-17] impairments in cognition,[18,19] symptoms of anxiety and post-traumatic stress,[20,21] and impaired HRQL.[22-24] This spectrum of sequelae has been termed 'post intensive care syndrome' (PICS) and extends to include not only those experiencing these sequelae who are diagnosed with ARDS but as a result of any admission to ICU.[113]

The following section will focus predominantly on the physical sequelae described in PICS.

2.4.2 Peripheral muscle weakness

It is well established that survivors of a critical illness demonstrate impairments in peripheral muscle strength. This peripheral muscle weakness that develops during the ICU admission has been identified as a factor which contributes significantly to the impairments observed in functional exercise capacity after discharge in survivors of critical illness.[12] Longitudinal data collected in ARDS survivors have shown that impairments in peripheral muscle strength are still evident 24 months following discharge from ICU.[15]

Muscle changes rapidly in the early days of critical illness with rectus femoris cross-sectional area in a cohort of 63 critically ill patients with a mean age of 55 (95% CI, 22 to 25) years and APACHE II score of 24 (95% CI, 22 to 25) decreasing between days 1 and 7 of an ICU admission (mean difference [95% CI], -12.5 [-35.4 to 24.1] %, $p = 0.002$).[40] Using ultrasound, a loss of cross-sectional area of the quadriceps femoris muscle in the critically ill was quantified as 18% within 10 days of admission to ICU.[40,114]

Regarding the distribution of weakness observed during critical illness, proximal muscle strength appears to be more impaired than distal muscle strength in both upper and lower limbs.[115] Specifically, in 24 patients who were mechanically ventilated for > 7 days, and who were diagnosed via electrophysiologic evaluation with weakness of peripheral neuromuscular origin, the mean score achieved during manual muscle testing for the shoulder was 2.1 ± 1.5 out of 5 while the wrist was 3.1 ± 1.5 out of 5 (higher scores represent greater strength). Similarly the mean manual

muscle testing score for the hip was 2.1 ± 1.3 and the ankle 3.3 ± 1.3.[115] The loss of muscle strength also appears to be more evident in the extensors, or antigravity muscle groups, which support upright posture.[116] In addition to peripheral muscle weakness, the pressure-generating capacity of the respiratory muscles is often also reduced, which may delay weaning.[117]

It is important to note that impairment in the force-generating capacity of peripheral muscles has also been demonstrated using non-volitional muscle contractions, which are independent of patient effort. Specifically, compared with a healthy group, less peak torque was generated by the ankle dorsiflexors during peroneal nerve stimulation group in a group of 19 mechanically ventilated patients with an ICU LOS > one week, (median [IQR], 11.6 [7.8] vs. 7.3 [6.4] Nm, p = 0.006).[118] This suggests that the reduction in strength cannot be attributed solely to a reduction in effort or central drive to the muscle. It must therefore result, at least in part, from contractile dysfunction at the level of the muscle.

In a proportion of patients admitted to the ICU, a syndrome named intensive care unit acquired weakness (ICUAW) has been shown to develop. This syndrome is characterised by profound, symmetrical weakness caused by a polyneuropathy and/or myopathy.[117] It often affects the lower limbs more than the upper limbs, and may include the respiratory muscles leading to failure to wean from mechanical ventilation.[119] The prevalence of ICUAW has been estimated to be approximately 40% in the general ICU population who have been mechanically ventilated for between 48 hours and 4 days.[120] The incidence when diagnosed clinically via manual muscle testing is lower (32%, 95% CI 30 to 35 %) than when diagnosed using electrophysiological techniques such as somatosensory evoked potentials (47%, 95% CI 45 to 50).[120] When explored in only those patients who require prolonged mechanical ventilation and have sepsis or multi-organ dysfunction, the incidence of ICUAW has been shown to exceed 50%.[121]

The presence of ICUAW impacts several patient centred outcomes.[119] In a systematic review examining outcomes associated with neuromuscular dysfunction acquired in critical illness, 12 of the 13 studies demonstrated an association between ICUAW and prolonged ventilation.[122] Specifically, the presence of ICUAW

increased the probability of prolonged weaning from mechanical ventilation after awakening (hazard ratio [HR] [95% CI], 2.4 [1.4 to 4.2]),[119] was associated with a prolonged hospital LOS when compared with those admitted to ICU without ICUAW ($p = 0.007$).[122] The presence of ICUAW also appears to increase the odds of hospital mortality (odds ratio [95% CI], 7.1 [1.5 to 32.8], $p < 0.001$) as well as mortality measured at 90 days and 12 months following ICU admission.[71,121,123] Further, ICUAW has been associated with impaired functional status 2 years after discharge. That is, when compared with patients with normal strength, patients with persistent ICUAW had reduced 6MWDs ($p \leq 0.01$).[15]

The understanding of the pathology of the disease and the impact the weakness has during the acute illness is growing. The reason for the weakness and the subsequent impairments in physical capacity which is apparent after resolution of the critical illness is unclear. These impairments extend past an acceptable period of recovery that might be observed in the healthy population and continue after factors contributing to the original muscle catabolism e.g. inflammatory markers, have returned to normal levels.[41]

2.4.2.1 Causes and risk factors for peripheral muscle weakness in survivors of critical illness

The main factors that contribute to the development of peripheral muscle weakness in the ICU relate to the use of sedation, leading to prolonged periods of bed rest and mechanical unloading of skeletal muscle, and the processes inherent in critical illness including the presence of increased circulating inflammatory mediators and dysfunctional microcirculation.[124] Regarding sedation, the conventional model of ICU care for patients with severe illness, used in the 1980's and 1990's, included heavy sedation in order to minimise pain and anxiety, optimise synchrony with mechanical ventilation and to manage physiological responses that are inherent to the multisystem pathologies.[125] The use of heavy sedation promotes bed rest and subsequent mechanical unloading of skeletal muscle which contribute to physical debilitation (see the next paragraph). Low levels of physical activity in the first 5 days of admission to ICU have been reported using a triaxial accelerometer in patients mechanically ventilated for more than 48 hours.[126] Sedation, as reported by the treating physiotherapists, was the main barrier to the promotion of activity with

activity levels associated with the highest level of mobility reported on day 5 of data collection using the Intensive care unit Mobility Scale.[126] Sedation was also the main barrier to mobilisation in a cohort of Australian and Scottish ICUs.[127] The American College of Critical Care medicine (ACCCM) now recommend an evidence based institutional-specific pain and analgesia protocol which assesses, treats and prevents pain, agitation and delirium, rather than maintaining a deep level of sedation for all patients.[128] Nevertheless, sedation is still required in many cases.

Patients in the ICU are largely immobile and often spend the entirety of their day and night resting in bed.[129] This results in prolonged mechanical unloading, particularly of the anti-gravity trunk and peripheral muscles. The effects of mechanical unloading resulting from immobility have been described extensively in healthy adults, with the muscles unloaded using limb suspension and cast immobilisation, but also using space flight, enforced bed rest and microgravity simulated by a head down position.[117,130,131] Several studies have shown a reduction in strength in a healthy cohort of almost 10% within 5 days of mechanical unloading, which increases to at least 20% within 2 weeks of unloading.[132,133] Similar trends have been shown in the reduction of cross sectional muscle area. Beyond the initial 2 weeks, it appears further loss of strength and muscle mass occurs at a slower rate.[134,135,136] Regarding histology, mechanical unloading causes a slow-to-fast shift in fibre type, and may be accompanied by preferential atrophy of type 1 slow twitch fibres.[137-139]

Although all patients in the ICU who are sedated and undergo prolonged mechanical unloading of their antigravity muscles are likely to develop muscle weakness, it appears that some people are at greater risk than others. Earlier work has shown that risk factors associated with the development of ICUAW include the presence of a systemic inflammatory response (OR [95% CI], 3.75 [1.59 to 8.86]), sepsis (OR [95% CI], 2.20 [1.30 to 3.71])[140] and severe illness as represented by an APACHE II score of > 15 (OR [95% CI], 2.03 [1.22 to 3.4]).[141,142] Other modifiable contributors to muscle weakness within the ICU, although controversial, include the use of neuromuscular blocking agents, glucocorticoids, and the development of hyperglycaemia.[71,143,144] However, aiming to reduce these risk factors within the ICU environment is complex, because in some studies, the reduced use of neuromuscular

blocking agents and tight intensive gylcaemic control has been shown to compromise survival.[145]

Interest in the cause of the ongoing impairment in peripheral muscle strength in survivors of critical illness has led to a small number of studies utilising ultrasound, computed tomography and muscle biopsies to identify changes in the size and cellular composition of the muscle during the ICU admission and up to 6 months following discharge. In muscle biopsies, on days 1 to 7 of a critical illness, a reduced ratio of protein to deoxyribonucleic acid (mean difference [95% CI], -29.5 [13.4 to 45.6] %) has been demonstrated.[40] Further, depressed rate of muscle protein synthesis compared with healthy controls has been demonstrated on day 1 (mean [95% CI], 0.035 [0.023 to 0.047] vs. 0.039 [0.029 to 0.048] %/hr), and although the rates increased to that observed in a healthy fed state by day 7, the net balance of proteolysis remained catabolic at day 7.[40] Electrolyte disturbances, such as decreased phosphate, potassium and calcium along with deranged magnesium levels can also contribute to the weakness seen in those with critical illness.[146,147]

Muscle atrophy observed within 10 days of admission to ICU was greater in those with a higher acuity of illness and with multiple system organ dysfunction and associated with necrosis and macrophage infiltrate identified via muscle biopsy.[40] At 6 months after discharge from ICU, muscle atrophy was present despite normalisation of autophagy and mitochondrial content, and in the absence of markers of muscle proteolysis and inflammation.[41] The patients with sustained atrophy, however, presented with a decrease in progenitor cells indicating that the regenerative capacity of the injured muscle had been impaired.[41] The changes within the muscles structure appear to be heterogeneous and ongoing.

2.4.2.2 Methods used to quantify peripheral muscle strength in survivors of critical illness

Several methods have been used to quantify peripheral muscle strength in survivors of critical illness. The most common methods used both in research and clinical practice include manual muscle testing using the MRC sum score and dynamometry - both hand-held dynamometry (HHD) and hand grip dynamometry. Used

infrequently, particularly in the clinical setting, are techniques which assess the non-volitional twitch force elicited during peripheral nerve stimulation.

In clinical practice, the assessment of force generated by peripheral muscles is contingent on volitional muscle contraction. Measurement of volitional force generation assesses the function of the entire motor unit extending from the motor cortex, along the neural pathways and to the contractile properties of the muscle. The advantage to using volitional contractions to measure muscle strength relate to the often minimal or uncomplicated equipment required. The examination of the volitional muscle force is typically performed using the MRC Manual Muscle Test (MMT).[148,149] This scale grades muscle strength on a 6 point scale with a score ranging from 0 (no muscle contraction) to 5 (full strength). The MRC sum score (MRC-SS) is the total score of 3 upper limb and 3 lower limb muscle grades which are assessed bilaterally.[115] A MRC-SS of < 48/60 represents a clinical diagnosis of ICUAW.[119]

Despite its popularity, the MRC has limitations. The range of grades 0 to 3 may provide an objective score for strength assessment in patients with more profound weakness.[150,151] The scale however is limited by its sensitivity at the higher grades, as shown by the MRC of 4 to 5 encompassing a large range of hand-grip strength values (0 to > 80% predicted).[152,153] In survivors of critical illness with weakness that is mild yet ongoing, impairments may not be consistently identified with the MRC. Conflicting evidence exists regarding the reliability of performing manual muscle testing using the MRC in critically ill patients. Excellent inter-rater reliability for the overall MRC-SS was demonstrated in 19 healthy volunteers and survivors of critical illness (intraclass correlation coefficient [ICC] [95% CI], 0.99 [0.98-1.00]).[154] When measuring individual muscle groups however, the inter-rater agreement was much lower (weighted kappa < 0.56).[149]

Another method used in the ICU to quantify muscle force generated during a volitional muscle contraction is dynamometry in the form of a hand-grip, hand-held or a chair mounted device.[150,153] This technique requires the dynamometer to be secure and to meet the force applied.[155,156]

Portable dynamometers are simple to use, and generally sensitive to small changes in muscle force generation.[157] Hand-grip dynamometry, specifically using a Jamar® dynamometer, has been shown to be an accurate measure of grip strength (+/- 3% of known suspended weights), possess high inter-rater reliability (Pearson's product correlation coefficient [r] = 0.99) and excellent test-retest reliability (r = 0.82).[158] Hand-held dynamometry has been shown to provide measures of strength in the upper limb in healthy participants, which have a moderate to strong association with that measured using the gold standard of isokinetic dynamometry (r = 0.52 and r = 0.78 on 2 separate days).[159] The use of HHD to measure quadriceps femoris muscle strength however is problematic. In a population of 20 healthy people over the age of 60 years, quadriceps femoris muscle strength as measured by the HHD while correlated with the value obtained via the isokinetic machine, tended to underestimate the strength by an average of 14.5 (95% CI, 8.5 to 20.6) Nm.[160] Differences became increasingly apparent amongst the stronger paricipants.[160] Strength assessment using hand-held devices may be limited by the examiner's ability to meet the force generated by stronger individuals. This can be of particular note when measuring isometric knee extension strength. For this reason, fixed devices such as chair mounted dynamometers have been used, whereby the chair itself matches the patient's force. When used in this way, the measures obtained from the fixed dynamometer demonstrate are similar to that measured with an isokinetic device for knee extension.[161]

Dynamometry is a particularly attractive option when assessing the strength range of MRC grades 4 and 5 where small changes in strength of muscles might be missed using MMT. In contrast, however, interpretation of change in profoundly weak patients such as those diagnosed with sepsis and admitted to ICU is challenging as an approximate 20% change in force is needed to exceed measurement error. This is compared with between 2 and 7.5% change in healthy people.[151] Unsurprisingly, the equivalent absolute values for the 2 groups recruited, that of critically ill and healthy, in order to overcome measurement error were similar. For example, for right knee extension, the absolute values to overcome measurement error were 7.1 kg and 6.5 kg which equated to 20% and 2% change in force, respectively. Finally, a consideration when examining muscle strength specifically in the critically ill is the

extended time to peak force generation which was shown to exceed 5 seconds in some patients assessed within ICU.[151]

Techniques which assess evoked muscle force stimulate the motor nerve supply of the muscle and in doing so, remove the influence of patient cooperation and enabling reliable measure of muscle force in unconscious or confused patients. In ICU, evoked muscle force and fatigue of the adductor pollicis muscle has been used to measure strength in 13 patients with sepsis and multi-organ dysfunction.[162] Peak torque and rate of force development of the ankle dorsiflexors has been reported in a case series of long-term critically ill patients.[118] Magnetic stimulation of the ulnar nerve to generate adductor pollicis twitch tension was reported in a mixed group of ICU, surgical patients and healthy controls.[163] While assessment of evoked muscle force is considered superior in regard to objectivity, and particularly in uncooperative patients, it is rarely suitable for clinical routine. This method of assessment requires intricate set up and is time consuming.

2.4.2.3 Summary

Muscle strength is an outcome measure that has been utilised extensively in survivors of critical illness. The measurement of peripheral muscle strength has been shown to be safe and feasible from the ICU admission throughout the recovery process.[15,16,151] Dynamometry is a simple, valid and reliable measure of muscle strength which allows for differentiation at higher forces. The validity of measures of knee extension strength using a dynamometer is improved with the use of a fixed device.

2.4.3 Exercise capacity and physical function

Exercise capacity is defined as the maximal amount of physical exertion a person can sustain.[164] When referring to the critically ill, the tools that are utilised to safely and effectively measure exercise capacity vary depending on the time point of measurement within the trajectory of recovery.

In patients admitted to ICU, during the ICU admission, composite measures of physical function have been developed and reported specifically for this group of patients at this time point. These include the Physical Function in Intensive care Test

scored (PFIT),[165] the Chelsea Critical Care Physical Assessment tool (CPAx),[166] ICU Mobility Scale,[167] and the Functional Status Score for the ICU.[168,169] These measures are useful for quantification of global impairments in physical strength and ability, using criterion such as step cadence and number of bilateral shoulder lifts.[165] However, there are no normative data available for these tools, and no data derived in other populations using these tools. The magnitude of impairment reported in survivors of critical illness using these tools is therefore difficult to compare with other populations that may present with significant debilitation and weakness.

On discharge from ICU to the ward, exercise capacity has been reported using the 6-minute walk test (6MWT). Unsurprisingly, at ICU discharge, impairments in 6MWD have been reported. In 2 separate cohorts of survivors of critical illness the 6MWD was 179 ± 101m (n = 23)[170] and 188 ± 126m (n = 60).[60] At hospital discharge, the 6MWD in a group of survivors of critical illness remained low at (median [IQR]) 143 [37 to 226] m.[171] Impaired function as a result of weakness and reduced exercise capacity can also be described by the increased risk of falls in survivors of critical illness during the initial hospital admission. Approximately 17% of a cohort of 190 survivors of critical illness (mechanical ventilation > 7 days) fell at least once during their ward admission following ICU discharge.[172] Notable impairments have also been reported in survivors of critical illness using the Berg Balance Score whereby the proportion of patients achieving a score ≥ 2 on the Berg Balance Scale at ICU and hospital discharge was 34% and 85%, respectively.[171] Nevertheless, this risk of falls appears to reduce over the first 3 months following hospital discharge.[29] Further, at hospital discharge, the Functional Independence Measure has been reported with a median of between 3 and 4 for bed mobility, transfers and gait,[173] and the Barthel Index with a median [IQR] score of 75 [8 to 95].[174]

In survivors of critical illness following discharge from hospital, quantification of impairments in exercise capacity have been reported using predominantly the 6MWT,[12,15,27,43,60,175] and in 3 studies using cardiopulmonary exercise testing.[27,38,176] In those studies that measured functional exercise capacity using the 6MWT in the first year following ICU discharge, the 6MWD was notably below that of a healthy reference population.[12,14,15,60] Fan and colleagues,[15] reported in a cohort of survivors of ALI with aged (median [IQR]) 52 [42 to 63] years at 12 months after discharge, a

6MWD of approximately 60% of that predicted in a healthy population. The 6MWD collected in a cohort of survivors of ALI at 12 months after discharge by Needham and colleagues[14] was a mean of 67% of that predicted in healthy people. The recovery of functional exercise appears to plateau at approximately 12 months[13] which is likely to define the period of natural recovery for this outcome measure.

In the 2 studies that measure exercise capacity in survivors of ICU after discharge from hospital using laboratory-based exercise testing, the peak rate of oxygen uptake (VO_2) reported in 2 studies was markedly below that of a healthy population.[27,176] These studies conducted a cardiopulmonary exercise test (CPET) in groups of critical illness survivors who had been mechanically ventilated for > 5 days, and who were assessed 6 weeks after hospital discharge. The peak VO_2 reported in these studies were 13.8 mL/kg/min[176] and 13.4 mL/kg/min,[27] respectively which is similar to that reported in other populations exhibiting profound functional disability. For instance, in a cohort of 1,620 participants with heart failure (New York Heart Association class II-IV) a median peak VO_2 of 15.0 mL/kg/min was reported,[177] and a peak VO_2 of 13.4 mL/kg/min was reported in a cohort of participants with severe COPD (classification III-IV according to the Global initiative for Chronic Obstructive Lung Disease).[178] When compared with the previously described studies examining VO_2 in survivors of critical illness, a slightly higher mean peak VO_2 of 21 mL/kg/min was reported in a cohort of survivors of critical illness measured at between 8 and 16 weeks after hospital discharge. When compared with the previously mentioned studies,[27,176] the higher peak VO_2 in this study was likely related to the longer timeframe between discharge and performance of the CPET (6 vs. 8 to 16 weeks) which represents a greater time for natural recovery.[38] A number of studies have suggested a cut point in peak VO_2 whereby physical function becomes suboptimal.[179-181] The cut points range from 17.7 mL/kg/min[180] to 20 mL/kg/min[181] whereby a peak VO_2 lower than these values is associated with impaired ability to perform activities of daily living (ADL) and where assistance with these activities may be required. The peak VO_2 reported in survivors of critical illness at 6 weeks, falls below these levels and is likely to represent an impairment in the ability to perform activities of daily living.

Multiple measures of global function have also been used in studies of ICU survivorship following discharge from hospital. The 4-metre walk speed (4MWS) was reported in 2 studies of survivors of ARDS.[14,15] A mean 4MWS of 1 m/s was reported both at 6 months (n = 183)[15] and 36 months (n = 62)[14] following ICU discharge in separate cohorts of survivors of ARDS. A 4MWS lower than 1m/s was associated with a cognitive decline in 5 years and, increased risk of hospitalisations and dependence with ADLs in community dwelling older people and those living in residential care.[34] Other tests used to measure functional capacity following hospital discharge include the Rivermead Mobility Index (RMI)[182] which appears to have limited responsiveness in this population given 25% of a population of survivors at 3 months achieved 14 of a possible maximum 15 points.[31,183]

2.4.3.1 Causes and risk factors for impaired exercise capacity in survivors of critical illness

The impairments in exercise capacity in survivors of critical illness are likely to relate to both the impairments in peripheral muscle function and the effects of bed rest on the cardiovascular system. As previously described, changes in the structure and size of peripheral muscles and microvascular dysfunction as a result of immobility, the acute systemic illness and management of the pathology within ICU are all likely to impact on exercise capacity following discharge from ICU (see section 2.3.2). The effect of bed rest on the cardiovascular system, which is well established in healthy individuals, also further impacts exercise capacity in survivors of critical illness. An acute but ongoing decline in blood volume, decrease in stroke volume, increase in resting heart rate,[184] and decreased capillary density of skeletal muscle[185] are all associated with prolonged bed rest and are likely to contribute to the impairment in oxidative capacity.

The effect of a critical illness on the respiratory system and cardiac function may also contribute to the limitation in exercise capacity after hospital discharge. Respiratory impairment shown in survivors of critical illness is comprised of a mixture of both restrictive and obstructive patterns at 2 months after hospital discharge.[67,176] In survivors of ARDS and ALI, a predominantly restrictive respiratory pattern has been reported to occur at 3 and 6 months while at 12 months it has been shown to normalise.[12] Impaired pulmonary diffusion, measured as

diffusion capacity of carbon monoxide (D_LCO), has been demonstrated previously in survivors of ARDS at 3 and 12 months (median [IQR]), 63 [54 to 77] % and 72 [61 to 86] % of that predicted in a healthy population).[12,186] This impairment observed in survivors of ARDS appears to have largely resolved by 2.5 years when D_LCO was measured to be 94 ± 14 % of that predicted in a healthy population.[42] The ongoing significant impairment to muscle strength and exercise capacity, however, has been demonstrated to be inconsistent with the largely normalised respiratory function from 12 months onwards. Therefore, these respiratory impairments while initially considered to contribute to exercise impairment, are now thought to be largely superfluous as a cause of the impairment exercise capacity observed in survivors of critical illness.

Cardiac dysfunction, which is further to that explained by bed rest alone, has been reported as occurring during the acute illness. Sepsis related depressed intrinsic myocardial performance[187-191] and circulatory failure secondary to ARDS-related pulmonary hypertension and right ventricle failure[83,84] which occur during the acute illness may also contribute to the impairments in exercise capacity observed after hospital discharge. The contribution of cardiac dysfunction to exercise capacity after a critical illness, however, has not been examined. Although, the cause of impairments in exercise capacity in survivors of critical illness have been postulated to be largely related to the peripheral muscle impairments, the mechanisms of limitation to exercise, particularly after hospital discharge have not been investigated.

2.4.3.2 Methods used to quantify exercise capacity and physical function in survivors of critical illness

The methods used to quantify and describe exercise capacity and physical function in survivors of critical illness vary depending on the time point at which it is measured. In those patients in ICU, as previously mentioned, composite measures of exercise capacity and physical function have been developed. Six of these measures have undergone clinimetric testing. These include the PFIT,[165] CPAx,[166] Perme mobility scale,[192] Surgical intensive care unit Optimal Mobilisation Score (SOMS),[193] ICU Mobility Scale,[167] and the Functional Status Score for the ICU.[168] Excellent reliability of all tools have been established, and construct and criterion

predictive validity established for the PFIT (predictive of discharge home, ICUAW and hospital LOS, $p < 0.01$),[165,194] CPAx (predictive of discharge home, $p < 0.0001$)[166] and SOMS (predictive of ICU and hospital LOS and mortality, $p < 0.004$).[193,195]

The utility of these tools following ICU discharge is not as clear. For the majority of these tools, both floor and ceiling effects have been described during the ICU admission.[169] Of particular interest as the patient regains function is the ceiling effect whereby a high proportion of patients achieve a maximal or near maximal score.[196] For example, a ceiling effect when using the PFIT on ICU discharge, was demonstrated in 7 of the 66 participants (11%).[169] This is the case for the majority of the composite measures developed for use in ICU.[197] The presence of floor and ceiling effects are particularly important when examining the recovery trajectories of patient compromises responsiveness.

Regarding the assessment of exercise capacity, just one study has reported 6MWD at ICU discharge.[60] Denehy and colleagues[60] as part of a randomised controlled trial (RCT) examining the effect of exercise based rehabilitation measured 6MWD on discharge from ICU. However, the timeframe from ICU discharge to the actual performance of the 6MWT was not reported. An earlier report regarding the protocol by Denehy and colleagues, clarified that the 6MWT was performed once the participant was able to ambulate 10m unassisted.[198] Given the low proportion of patients discharged from ICU who are independently ambulant,[170] and the high prevalence of delirium in those who are mechanically ventilated (reported as 82% in a cohort of 224 patients mechanically ventilated in ICU)[199] which makes informed consent difficult, performance of a 6MWT on the exact day of ICU discharge in the majority of the study population is unlikely.[60] Regarding the assessment of exercise capacity at hospital discharge, the 6MWD has been reported by 2 studies, and the 3-minute walk distance by one study.[171,200,201] All of these studies reported ongoing reductions in exercise capacity.[171,200,201] Similar to the study by Denehy and colleagues,[60] the exact time point at which the test was performed in these studies was not specified, except that it was performed at hospital discharge.[171,200]

The 6MWT, a commonly used field based walking test, has been utilised widely to describe impairments in exercise capacity in survivors of critical illness.[12,13,15,16,60,202] When compared with laboratory based exercise test, the 6MWT has many advantages. These relate to the ease of administration, the need for minimal equipment and low cost. The 6MWT has been shown to be safe and feasible in survivors of critical illness both during the initial hospitalisation after ICU discharge to the ward[170] and at hospital discharge.[171] The test is a valid measure of functional capacity for survivors of acute respiratory failure and ARDS. The 6MWD when measured at 6 months after ICU discharge, has been shown to influence the odds of mortality (OR [95% CI], 0.84 [0.77 to 0.91]) and re-hospitalisation (OR [95% CI], 0.91 [0.86 to 0.96]) and is related to HRQL (β [95% CI], 3.9 [3.3 to 4.4]) at 12 months after discharge.[203] A clinically important difference of 20 to 30m has been identified in survivors of acute respiratory failure and ARDS.[203] The utility of the 6MWT is evident in its extensive and safe use in survivors of critical illness.

The 6MWT, and field-based walking tests generally, however, have limitations. There is a floor effect in those who are severely physically debilitated and who cannot stand. Measures collected during the test are limited to distance and HR, SpO_2 and symptoms. The 6MWT provides limited information regarding the specific physiological responses underlying altered exercise capacity. Furthermore, the 6MWT has been shown to elicit sub-maximal exercise responses in survivors of critical illness when compared with a symptom limited cardiopulmonary exercise test.[204]

Laboratory-based CPET has had limited use in the quantification of exercise capacity limitation of survivors of critical illness. A single study by Benington and colleagues[176] reported the feasibility of conducting a CPET 4 weeks after hospital discharge in this population and quantified the peak VO_2 and AT as 56% and 41% of predicted values in a healthy population respectively. Two further RCTs examining outpatient based exercise training initiated within 6 weeks of hospital discharge, for survivors of prolonged critical illness utilised a CPET to quantify change in exercise capacity.[27,38] One further study utilised a CPET, in addition to pulmonary function testing, to examine pulmonary function in survivors of severe ARDS at between one and 4 years after hospital discharge.[42]

The value of a CPET lies in its ability to provide detailed evaluation of exercise intolerance and quantification of factors limiting exercise.[205] The CPET provides a measure of peak rate of oxygen uptake and also describes the interaction and response of the cardiovascular, pulmonary, neuropsychological and skeletal muscle systems during submaximal and peak exercise.[205] Cardiopulmonary exercise testing is typically performed using a cycle ergometer or a treadmill. Both allow an incremental increase in workload and are reproducible. However, cycle ergometry, in comparison to the treadmill, is less likely to produce noise (i.e. motion) artefact in the physiological variables. This is because testing performed on a cycle ergometer has the person in a supported and seated position whereas testing performed on a treadmill involve the person undertaking whole body movement including that of the head and arms. Notwithstanding this consideration, the main advantage of cycle ergometry tests over treadmill tests lies in the capacity to precisely control external work imposed by the bike. Measures of peak VO_2 reported during a maximal treadmill test are higher as compared to cycle ergometry,[206] which has been attributed to the larger exercising muscle mass.[207] Incremental cycle ergometry testing (ICET) has been successfully utilised in a wide variety of patient groups and has been shown to be both feasible and safe in survivors of critical illness.[176,205,208-211]

Interpretation of the results of the ICET, requires quantification of normal responses in a comparative population. Published normative values are available and used widely when examining individual responses during an ICET.[205] However, the generation and use of a database of responses generated within the respective laboratory from a healthy local population is recommended.[205] This is as a result of variation in the geographical area the population is drawn from including the type of activity, vocation and exercise usually performed, and differences in laboratory processes.[205]

Regarding the assessment of physical function at ICU and hospital discharge, several tools have been used which are summarised in Table 2-1 and Table 2-2.

Table 2-1 Tools used to assess physical function at ICU discharge and/or during the ward stay

ASSESSMENT	Bailey et al[212]	Dantas et al[213]	Winkelman et al[214]	Denehy et al[60]	Walsh et al[31]	Yosef-Brauner et al[215]	Morris et al[216]
STRENGTH							
MRC		✓	✓				
Hand grip dynamometer						✓	✓
Hand-held dynamometer							✓
MIP/MEP		✓				✓	
EXERCISE CAPACITY							
6MWT				✓			
FUNCTIONAL ASSESSMENT							
RMI					✓		
Katz ADL			✓				
SPPB							✓
PFIT				✓			
TUG				✓			
Stolov sitting balance						✓	
Activity level†	✓						

Katz ADL: Katz activities of daily living scale; MEP: maximal expiratory pressure; MIP: maximal inspiratory pressure; MRC: Medical research council scale for grading muscle strength; PFIT: Physical function intensive care test; RMI: Rivermead Mobility Index; SPPB: Short performance physical battery; TUG: timed up and go; 6MWT: 6-minute walk test; ✓: Yes; †: identified a priori as one of three levels of activity.

Table 2-2 Tools used to assess physical function at hospital discharge

ASSESSMENT	Nava et al[201]	Burtin et al[171]	Schweickert et al[174]	Hanekom et al[217]	Jackson et al[29]	Brummel et al[218]	Kayambu et al[219]	Gruther et al[200]
STRENGTH								
MRC			✓				✓	✓
Hand grip dynamometer		✓	✓					
Hand held dynamometer		✓						
EXERCISE CAPACITY								
6MWT	✓	✓						
3MWT								✓
FUNCTIONAL ASSESSMENT								
Walking distance†			✓					
Barthel			✓	✓				✓
Katz					✓	✓		
Berg		✓						
PFIT							✓	
TUG					✓	✓		
FACS		✓			✓			
D-K Tower test					✓			
ACIF							✓	

ACIF: acute care index of function; D-K Tower test: Delis-Kaplan Tower test; FACS: Functional ambulation categories score; Katz ADL: Katz activities of daily living scale; MEP: maximal expiratory pressure; MIP: maximal inspiratory pressure; MRC: Medical Research Council scale for grading muscle strength; PFIT: Physical function intensive care test; RMI: Rivermead Mobility Index; SPPB: Short performance physical battery; TUG: timed up and go; w/o A: without assistance; 3MWT: 3-minute walk test; 6MWT: 6-minute walk test; †: distance walked without assistance.

Evaluation of physical function and especially long-term function in survivors of critical illness is an acknowledged challenge.[220-223] A scoping review by Turnbull and colleagues[220] reported a total of 250 unique outcome instruments used in the 425 eligible articles reviewed which described functioning following discharge from ICU. In this review, the outcome instruments identified were grouped into the World Health Organisation's International classification of functioning, disability and health framework.[224] Impairments in the criterion of physical structure or function were commonly reported using pulmonary function and neuromuscular function with the latter measured predominantly via electromyography/nerve conduction studies, MMT and grip strength. The criterion of physical activity was reported using 8 unique outcome instruments although 80% of the studies used the 6MWT to quantify this domain.[220] No single tool has been identified to discriminate and evaluate the breadth of changes in physical function known to occur during a critical illness.

2.4.3.3 Summary

Measures of exercise capacity and physical function have been utilised extensively in survivors of critical illness. Composite measures of physical function of survivors of critical illness have been developed to be used during the ICU admission. Following discharge from ICU, field walking tests have been shown to be safe and feasible from the ICU admission throughout the recovery process.[15,16,151] There is a paucity of data derived from laboratory-based exercise testing for survivors of critical illness.

2.4.4 Participation in physical activity and accumulation of sedentary time

Physical activity (PA) is defined as any bodily movement that is produced by contraction of skeletal muscles that results in energy expenditure.[225] While exercise may be included in the measurement of PA, the definition of exercise is separate from that of PA. Exercise refers to planned, structured and repetitive movements to improve or maintain physical fitness, and may include aerobic exercise training, resistance exercise training and flexibility stretches. Sedentary time (ST) is defined as any waking behaviour with an energy expenditure of ≤ 1.5 MET accumulated in a sitting or lying posture.[226]

The benefits of regular participation in PA for the general population has been widely described. Guidelines had been published identifying the minimum amount of PA, to confer health benefits to be 150 minutes of moderate intensity physical activity (MPA) per week. While previous guidelines have recommended PA be accumulated in bouts > 10 minutes,[227-230] recent research has identified that reduction in mortality risk associated with PA was independent of patterns of accumulation.[231,232] Furthermore, emerging research studying the effect of ST on health, is suggesting that increased time spent in sitting is associated with an adverse cardio-metabolic risk profile and an elevated all-cause mortality risk, with prolonged bouts of ST further increasing the risk.[233-238] Accumulating the recommended amount of PA of 30 minutes per day is also unlikely to mitigate the deleterious effects of high ST.[239]

In those surviving a critical illness, there is a paucity of literature examining the amount of time spent participating in PA and sedentary time (ST).[240] The barriers to PA within the ICU are numerous and include the capacity of the patient to mobilise, which is influenced by sedation levels, delirium and illness severity, attachments and cultural influences within the unit.[241] Low levels of PA in ICUs have been associated with poor functional outcomes, as measured by the P-FIT upon ICU discharge.[126]

Regarding participation PA during the ICU admission, activities performed by the patient in bed, in sitting or standing, and walking, was shown to be performed in only 13% of patients mechanically ventilated > 48 hours in Australian ICUs during a specified 24-hour period in 2013.[242] No patient who was mechanically ventilated sat out of bed or walked.[242] Physical activity measured via direct observation within the ICU has shown that PA outside specific rehabilitation sessions is minimal with 14.5 hours of a 15 hour observational period spent sitting in bed.[243] In an observational cohort study examining mobility practices in Australian and Scottish ICUs published in 2015,[127] 60% of patients admitted to ICU in Australia participated in a mobilisation activity which comprised of sitting on the edge of the bed through to standing and walking. While more patients mobilised in the Australian cohort than the Scottish cohort (60% vs. 40% respectively), the proportion of mobilisation episodes performed with patients intubated with an endotracheal tube or tracheostomy was low in both groups (2.1% and 2.7%, respectively).

In spite of the increasing efforts to implement rehabilitation during the ICU admission, the time spent in PA (defined as any activity performed at an intensity ≥ 1.5 metabolic equivalents [MET]) during the ICU admission, has been reported as being as low as (median [IQR]) 6 [0 to 22] minutes in an Australian cohort of 60 patients aged (mean ± SD) 60 ± 14 years with an APACHE II score of 21 ± 6.[126] These data were collected via an accelerometer worn between 0800 and 1900 hours each day from day 7 (median time to enrollment) of mechanical ventilation until the patient was discharged home from the ward.[126] Of 2,050 observations collected every 10 minutes across 8 days in a major Australian ICU, participants spent (median [IQR]) 100 [69 to 100] % of the day in bed and 96 [76 to 96] % of the day participating in little or no activity.[129]

The time spent in PA by survivors of critical illness once discharged to the ward remains low.[126,244] In the same Australian cohort in which PA was measured in ICU via accelerometry, compared with the time spent in PA in ICU, that amount of PA recorded once discharged to the ward increased (median [IQR], 6 [0 to 22] vs. 29 [9 to 74] min/d).[126] In contrast, a retrospective notes audit of 72 patients discharged from a North American ICU to the ward, showed that activity level as defined as the number of sessions of ambulation with a physiotherapist or nurse that had been documented in the participants notes, decreased in 55% of participants on the first full ward day when compared with that achieved in the ICU.[244] While the number of ambulation sessions with a staff member may not accurately reflect the time spent in PA, the decreased ambulation sessions are likely to accurately reflect the number of times the patient ambulated each day. At this time point it is unlikely that the patients were engaging in independent ambulation. It appears that patients admitted to ICU participate in very low levels of PA and that these levels on discharge to the ward, remain suboptimal.

Physical activity performed after hospital discharge by survivors of critical illness has been reported in 2 cohorts of adults who had survived a prolonged intensive care admission. Daily PA following hospital discharge was measured using accelerometers and demonstrated that, at 2 months after ICU discharge, survivors participated in low levels of walking (> 20 steps in a row or 3% of waking hours) and accumulated a low daily step count (4,894 ± 3,070 steps).[240] The proportion of

participants who achieved the recommended 10,000 steps per day was also low (6%).[240] Borges and colleagues[70] demonstrated that, at 3 months following discharge from ICU, when compared with a healthy group, their sample spent a lower proportion of their waking hours walking (6.3 ± 3.0 vs. 10.1 ± 4.4 %, $p < 0.05$). Time spent in PA in survivors of critical illness remains low following discharge from hospital.

Regarding accumulation of ST during the ICU admission, specific data has not been reported to date. However, in the studies that have reported participation in PA in those admitted to ICU, the time spent either in lying or sitting in bed is likely to constitute ST and indicate that accumulation of ST is high. As mentioned previously, of 200 patients who were mechanically ventilated > 48 hours in an Australian ICU, no patient who was mechanically ventilated sat out of bed or walked suggesting 100% of waking hours of these patients were spent in ST.[242] An Australian cohort of 60 patients accumulated just (median [IQR]) 6 [0 to 22] minutes in PA suggesting the remainder of waking hours was spent in ST.[126] Approximately 14.5 hours of a 15 hour observational period in 47 patients mechanically ventilated within ICU was spent sitting in bed.[243] Finally, of 2,050 observations collected in a major Australian ICU, participants spent (median [IQR]) 100 [69 to 100] % of the day in bed.[129]

On discharge to the ward, participation in PA remains low (29 [9 to 74] min/d), again suggesting ST remains high.[126] On discharge from hospital the proportion of waking hours spent in sitting and lying has been reported as 26 ± 14 % and 63 ± 20 %, respectively. Three months after discharge from hospital, the proportion of waking hours spent in sitting increased (45 ± 12 %) while the proportion spent in lying decreased (13 ± 8 %).[70] At 2 months after discharge from hospital, approximately 90% of waking hours was spent in the inactive category (mean ± SD, 12:17 ± 1:33 hr:min).[240] Sedentary time in survivors of critical illness, after discharge from hospital, remains high.

2.4.4.1 Methods used to quantify physical activity and sedentary time in survivors of critical illness

Measures of PA and ST can be collected by direct observation, questionnaires (including diaries, recall questionnaires and interviews), and physiological markers

such as calorimetry and motion sensors.[245,246] As PA is a multi-dimensional construct, including components such as intensity, duration and mode of activity, obtaining accurate measures of PA and ST over long periods can be complex.

Both self-report questionnaires and self-report activity diaries are commonly used and useful at a population level. However, both rely on the ability of participants to recall activity, and can be burdensome, particularly for individuals with cognitive dysfunction as observed in survivors of critical illness[16] and if not completed regularly, can be susceptible to recall bias. These tools are useful when reporting vigorous intensity exercise, but is less accurate at reporting lower intensity activities, as has been shown to be performed in those surviving a critical illness.[126] Pedometers are widely used in the general population because they are simple, and inexpensive. They record vertical movements by recording the number of times the horizontal spring-suspended lever arm within the pedometer shifts with vertical movement. Limitations to these simple devices are therefore related to the mechanism of the device in that horizontal movement, intensity and duration of PA are not measured.[247] Further, the sensitivity of the set vertical acceleration required for a step to be registered means that slow walking may not be detected.[248]

In the literature describing measures of PA and ST in survivors of critical illness, accelerometers are the most commonly employed devices.[70,126,240] Accelerometers often provide minute-by-minute monitoring, the ability to capture intensity, accuracy with both static and dynamic behaviours and possess large memory capacities.[249,250] They are however, expensive and require technical expertise, specialised hardware, software, and individual programming.[251] In order to optimise the accuracy of the data collected via an accelerometer, a standard protocol for managing or reducing data is required, and a sufficient number of days and hours per day collected in order to account for any reactivity bias that may be induced by the wearing of the device.[252] Furthermore, the cut-points applied to the data to group intensities of PA should be clearly specified and considered when comparing with data collected in other research.[253]

2.4.4.2 Summary

There is a paucity of literature reporting PA and ST in survivors of critical illness during the ICU admission, after discharge from ICU to the ward, and after hospital discharge. The measurement of PA, and subsequently ST, using accelerometers at each of these time points however has been shown to be feasible.[70,126,240]

2.4.5 Health-related quality of life and fatigue in survivors of critical illness

Health-related quality of life is a multi-dimensional concept which aims to describe the impact that health status has on quality of life. Evaluation of the HRQL aims to describe the perceived impact of an individual's health status on their physical function, mental health, emotional wellbeing, and social functioning. It is a recognised key outcome measure in evaluating recovery in survivors of critical illness, and is often a component of the core outcome set for survivors of critical illness.[22,23,254,255] Survivors of critical illness have impaired HRQL versus age- and sex-matched population norms, and these impairments can persist for months to years.[13,22,256] Greater deficits are observed in the physical domains when compared to the mental health domains in both survivors of ARDS and heterogeneous groups of survivors of critical illness.[12,23,110,257-259]

The measurement of HRQL in survivors of critical illness provides additional information regarding survivorship above objective measures of function such as the 6MWD. Domains that reflect the impact of health status on physical function such as the Physical Function (PF) domain in the Medical Outcomes Study Short Form 36 General Health Survey Version 2 (SF36), does not reflect directly the actual physical functioning of the individual. In survivors of critical illness at 3 months after ICU discharge, a discordance between the SF36 physical domain and 6MWD was evident whereby only 14% of the variance in the PF domain ($p < 0.001$) and 30% of the variance in the physical component score (PCS) ($p < 0.001$) were explained by the concomitant low 6MWD.[260] Measures of HRQL and objective measures of exercise capacity are not interchangeable but provide complementary insight into the recovery of survivors of critical illness.

Preadmission measures of HRQL for those admitted to ICU provides information regarding function prior to the critical illness. Comorbidity has been identified as an

important determinant of outcome, and the trajectory of recovery following critical illness.[261,262] As a result preadmission HRQL is a useful prognostication tool.[263] Because of the often emergent and acute nature of critical illness, preadmission HRQL cannot be prospectively measured in most ICU patients. In these circumstances, proxies such as the patients' next of kin, may estimate patient HRQL, or ICU survivors may be asked to retrospectively assess their HRQL.[264-267] Both of these HRQL assessment methods are subject to bias.

Proxy assessment of HRQL has been shown to have fair to moderate agreement with patient assessments, largely due to lower proxy responses when compared with patient responses, in all 8 SF36 domains.[264] In one study of ALI patients, the average difference between paired patient and proxy responses was trivial in 5 of 8 domains of the SF36, but patient-proxy agreement was still only fair (kappa statistic = 0.30 to 0.40).[265] Survivors own recall of their preadmission HRQL has also been used. While this may be affected by recall bias,[266] the severity of illness does not appear to influence the recall of physical function. Provision of added caution with results has been suggested for those with low education levels, since retrospective recall in this subgroup appears to be more strongly affected by ICU severity of illness.[267]

Severe fatigue has been described in survivors of critical illness,[268] who reported that fatigue contributed to the impaired HRQL and ability to perform ADLs at 3 and 12 months that survivors of ARDS experienced.[12] Fatigue has also been reported as contributing to the severe physical and cognitive dysfunction which survivors of critical illness experience.[269] In spite of these subjective descriptions, measurement of fatigue has not been strongly advocated for use routinely in assessment of survivors of critical illness.[222,254] This is largely due to the paucity of research examining fatigue in large populations of survivors of critical illness.[270]

2.4.5.1 Summary

Health-related quality of life is an outcome measure reported extensively in survivors of critical illness.[12,23,110,257-259] Use of a proxy to report preadmission HRQL provides information regarding comorbidities which may impact on both mental and physical functioning prior to the admission. There is a paucity of literature reporting fatigue in survivors of critical illness.

2.5 Part 4 – Amelioration of the physical sequelae described in survivors of critical illness

This part will examine and critique the literature examining the effect of exercise-based rehabilitation programs (EBRP) implemented to ameliorate the sequelae of an admission to ICU.

2.5.1 Overview

Although much of the research describing the physical sequelae of critical illness has been performed in those diagnosed with ALI and ARDS, all of the work published on ameliorating or improving these sequelae has been conducted in a heterogeneous group of survivors of critical illness with the main inclusion criterion being 2 to 5 days of mechanical ventilation.[43,271-275] Much of this research can be divided into 2 subgroups: (i) rehabilitation within the ICU; and (ii) rehabilitation commencing after discharge from ICU. This part will focus on participation in exercise training and as such literature pertaining to neuromuscular electrical stimulation have not been included here.[276]

2.5.2 Rehabilitation within the intensive care unit

Research investigating the effect of an EBRP commencing within the ICU, gained attention in 2009 with the publication of seminal studies by Schweickert and colleagues[174] and Burtin and colleagues.[171] Schweickert and colleagues[174] showed that when compared with standard care, interruption of sedation and whole-body rehabilitation initiated within 72 hours of mechanical ventilation, led to improved physical outcomes at hospital discharge (mean Barthel index, 55 [0 to 85] vs. 75 [8 to 95], $p = 0.05$), a shorter period of delirium (median [IQR], 4 [2 to 8] vs. 2 [0 to 6] days, $p = 0.02$) and higher number of ventilator-free ICU days (median [IQR], 21 [0 to 24] vs. 24 [7 to 26] days, $p = 0.05$). This research highlighted the importance of sedation vacations in order to optimise the opportunity to ameliorate the decline in strength and ability to ambulate, and also suggested that rehabilitation commencing in ICU was safe, as described by the low incidence of adverse events at the time of the intervention (one serious adverse event, desaturation < 80%, during 498 therapy sessions).[174] Burtin and colleagues,[171] reported that when compared with standard

care, cycle-based rehabilitation commencing within the ICU in patients mechanically ventilated for > 5 days, lead to improved functional exercise capacity measured by the 6MWD (median [IQR], 143 [37 to 226] vs. 196 [126 to 329] m, $p < 0.05$) and quadriceps strength at hospital discharge (mean ± SD, 1.86 ± 0.78 vs. 2.03 ± 0.75 N/kg, $p = 0.11$ and 1.83 ± 0.91 vs. 2.37 ± 0.62 N/kg, $p < 0.01$; for the standard care and rehabilitation group, respectively).

Both of these early studies had limitations which have shown to be idiosyncratically problematic of research in this arena. Both studies screened a large number of patients for a small proportion who met inclusion criterion and consented - of 1,161[174] and 3,213[171] patients admitted to ICU over a one to 2 year period, 104 (9%) and 58 (2%) patients were randomised, respectively. The inclusion criteria of a Barthel Index of > 70 denoting independence prior to ICU admission makes extrapolation of the data from Schweickert and colleagues[174] study, to those with preadmission comorbidities limited. The identification of comorbidities which may contribute to impairments in strength and exercise capacity, or enhance the risk of these impairments, after the critical illness, has since become a notable consideration when recruiting and analysing prediction models for impairment following an ICU admission.[277] In the study by Burtin and colleagues,[171] in spite of the positive outcome, the description of the training protocol was limited and makes replication in future studies or clinical practice challenging. Specifically, the intensity of the cycling performed by the participants was determined by the participant or the therapists' perception of intensity, which was individually adjusted. Furthermore, the amount and type of rehabilitation the participants in both the treatment and the control group received on the ward was not recorded. It is also notable that the cycling commenced was late at 10 and 14 days in the control and treatment group respectively, particularly when compared with the onset of rehabilitation in the study by Schweickert and colleagues, being 72 hours.[174]

The lack of published details of the interventions prescribed in studies examining rehabilitation in ICU has been noted most recently in a systematic review and meta-analysis by Tipping and colleagues.[271] This review is one of 5 systematic reviews examining the effect of exercise including functional activity, resistance exercises and cycle ergometry (excluding neuromuscular electrical stimulation) within ICU

and considered 15 controlled trials.[43,271-274] While the most recently published review papers have concluded that improvements in strength on ICU discharge and functional capacity on hospital discharge result from rehabilitation commencing within the ICU,[271-274] the description of the intervention in many of these trials was suboptimal. For example, Tipping and colleagues[271] who investigated the effect dose of intervention had on days alive and out of hospital, was unable to include data from 11 of the 15 studies.

Examination of the dose of EBRP commencing in the ICU has to date considered timing of initiation, intensity, frequency and program duration of the rehabilitation. A meta-analysis conducted by Tipping and colleagues,[271] which included 3 studies that specified the timing and quantity of the intervention,[217,278,279] showed that compared with late and high does rehabilitation (mean difference [95% CI], 5.00 [-8.79 to 18.79] d, $p = 0.48$, I^2 = not applicable), early and low dose rehabilitation resulted in a significant mean difference in days alive and out of hospital at 180 days after ICU discharge, favouring the rehabilitation group (mean difference [95% CI], 12.04 [2.27 to 21.81] d, $p = 0.02$, I^2=0%). Compared with usual care, early goal-directed rehabilitation prescribed according to the SOMS score and commencing at 48 hours after initiation of mechanical ventilation in patients who were previously functionally independent, resulted in a higher SOMS (mean ± SD, 1.5 ± 0.8 vs. 2.2 ± 1.0, $p < 0.0001$). Further, compared with the usual care group, the intervention group had a greater proportion of patients who were able to walk at ICU discharge (25% vs. 52%), who were functionally independent at hospital discharge (28% vs. 51%) and who were discharged home (27% vs. 51%, $p < 0.0007$).[280] A similar pilot feasibility RCT of a rehabilitation intervention conducted in Australia and New Zealand and commencing within the ICU, showed that a goal directed functional rehabilitation intervention based on the ICU mobility scale and implemented at the highest level of activity possible (intensity) was feasible, lead to no adverse events, and when compared with usual care, may increase the proportion of patients who walked in ICU (38% vs. 66%, $p = 0.05$).[278]

Although the initiation of early intervention in ICU (< 72hr after initiation of mechanical ventilation) appears to be safe and feasible, and lead to improved outcomes at ICU and hospital discharge, the effect of this intervention on outcomes

past hospital discharge has been questioned. In the goal-directed intervention implemented by Schaller and colleagues,[280] compared with usual care, in-hospital and 3-month mortality appeared slightly higher, albeit non statistically, among the intervention group (8% vs. 16% in hospital, $p = 0.09$; 17% vs. 22% at 3 months, $p = 0.35$). This was despite a similar APACHE II score. Similar cautionary data exist in the area of stroke rehabilitation. That is, A Very Early Rehab Trial (AVERT) investigated exercise commencing within 24 hours of stroke, and showed a somewhat higher mortality and higher disability at 3 months in the intervention group when compared with the control group.[281,282] A RCT of rehabilitation commencing during the hospital admission of an acute exacerbation of COPD resulted in a higher one year mortality in the early rehabilitation group compared with the control group.[283] It appears that when using safety criteria such as those reported by Hodgson and colleagues,[284] serious adverse events occurring in the ICU as a result of rehabilitation in the critically ill are extremely low.[174,271] However, more data on the longer-term outcomes of commencing rehabilitation in ICU in a large cohort are needed. That is, consideration of the effect of an increased physiological demand elicited by rehabilitation in the acute illness and its impact on longer term functional outcomes and mortality is needed.[285]

Regarding the frequency of EBRP implemented in ICU, 2 North American studies by Moss et al[286] and Morris et al[216] compared usual physiotherapy care with an intervention of rehabilitation provided 7 days/week until hospital discharge or for 4 weeks, respectively. Moss and colleagues[286] implemented a single intervention exercise session of 39 ± 11 minutes each day compared with a usual care of 22 ± 4 minutes and while usual care was not defined it was reported that the number of sessions performed as part of the usual care group was half that of the intervention group (6.1 ± 3.8 vs. 12.4 ± 6.5, $p < 0.001$). Morris and colleagues[216] implemented 3 intervention sessions per day comprising passive range of motion, physical therapy and resistance exercises compared with usual care. The number of days of delivery of physical therapy to the usual care group was (median [IQR]) 9 [5 to 14] d and to the intervention group was 1 [0 to 8] d for passive range of motion, 5 [3 to 8] d for physical therapy and 3 [1 to 5] d for progressive resistance exercise. Neither study demonstrated a positive effect of the intervention as defined by the Continuous Scale Physical Functional Performance Test short form score ($p = 0.73$)[286] at hospital

discharge or hospital LOS (median difference [95% CI], 0 [-3 to 1.5] d, $p = 0.96$).[216] The lack of effect of these interventions could be related to the timing of intervention initiation. As previously described, EBRPs implemented within 72 hr of mechanical ventilation specifically, appear to be consistently effective.[271] The protocol defined by Moss and colleagues[286] commenced the intervention (median [IQR]) 8 [6 to 11] d after initiation of mechanical ventilation. While Morris and colleagues[216] initiated the physical rehabilitation and progressive resistance components of the intervention 3 [1 to 6] d and 4 [2 to 7] d after initiation of ventilation, there was a large variability around the median suggesting more than half of the sample commenced the EBRP after 72 hours of mechanical ventilation.

Only one study has implemented a continuum of exercise starting from ICU, continuing on the ward and then onto an outpatient rehabilitation program following discharge from hospital.[60] Prescription of EBRP was individualised and based on results of the physical function tests performed, that of PFIT in the ICU, 6MWD on ICU discharge, and 5 repetition maximum for upper and lower limbs. Compared with the control group, the primary outcome of 6MWD was significantly lower in the intervention group on ICU discharge (mean difference [95% CI], -44.7 [-82.3 to -7.1], $p = 0.02$), and thereafter no significant difference between groups was noted at any time point. The rationale as to why this intervention showed no effect likely lies with the participant selection. Specifically, comorbidity as a determinant of response to exercise training following a prolonged admission to ICU, is likely to have contributed to the lack of effect of the intervention.[261,262] A secondary analysis of this cohort was conducted.[287] This secondary analysis stratified the 2 cohorts by the presence or absence of chronic disease.[287] The trajectory of improvement in 6MWT was upward for all groups except the control group with pre-existing chronic conditions which plateaued at 3 months after hospital discharge.[287] Comorbidity has been identified as an important determinant of outcome, and specifically the trajectory of recovery following critical illness. In 2 studies using national administrative databases in Scotland and Canada, the strongest predictors of hospital readmission and ongoing resource use were preadmission factors such as prior illness and resource use rather than the actual acuity of the illness leading to the ICU admission.[261,262] Pre-existing comorbidities may attenuate the effect of programs aimed to improve functional capacity.

2.5.3 Rehabilitation commencing after discharge from the intensive care unit

Given the promising results of rehabilitation commencing early within the ICU, and the known positive effect of EBRP in many populations with pathologies such as COPD,[35] coronary heart disease,[36] and diabetes mellitus,[37] it has been hypothesised that an EBRP following discharge from ICU, would also achieve improvements in strength and exercise capacity in survivors of critical illness. This however has not, to date, been reflected in the literature. Table 2-3 and Table 2-4 describe the studies published to date which have investigated the effect of EBRP for survivors of a critical illness and implemented after discharge from ICU. Criteria for a study to be included in Table 2-3 and Table 2-4 were that it needed to be a RCT or controlled clinical trial of adult patients who had been mechanically ventilated in ICU. For Table 2-3, to be included, the trials needed to have compared rehabilitation commencing on the ward to usual care, and to present outcomes at hospital discharge. For Table 2-4, to be included, the trials needed to have compared rehabilitation commencing after hospital discharge to usual care.

A Cochrane review published by Connolly and colleagues[288] in 2015 examined 6 trials conducted on adult survivors who had been mechanically ventilated for more that 24 hours and examined an EBRP commencing at a point after discharge from ICU. Two of the trials reported the effect of an intervention that was commenced upon cessation of mechanical ventilation and discharge from ICU to the ward,[183,289] and 4 of the trials reported the effect of an intervention implemented after hospital discharge.[29,30,38,39] This review found overall, the quality of the evidence was very low, and while an overall effect on functional exercise capacity was unable to be determined, 3 studies showed a small effect and the remaining 3 no effect. Of those studies which showed an effect, a greater increase in the exercise capacity as represented by the maximum work rate on a symptom limited incremental arm cycle ergometer test, was reported following an inpatient training program comprising of supported arm exercise in a group recently liberated from mechanical ventilation.[289] A supervised program of cycle-based training commencing 8 to 16 weeks after ICU discharge had a small beneficial effect on functional exercise capacity, when compared with the control group, as measured by the anaerobic threshold (AT).[38] This benefit however was not sustained at follow up at 26 weeks. Finally, an

improvement in the PF domain of the SF36 was identified after a 6 week rehabilitation program implemented after hospital discharge and using a manual.[39] In the remaining studies included in the review, there was no effect on strength or exercise capacity.

Since the Cochrane review has been published, a further 4 studies have been published showing no effect of EBRP on the specified primary outcome. Two studies, by McWilliams et al[27] and McDowell et al,[26] have reported the effect of implementation of an outpatient EBRP. Both reported no benefit in the intervention group as determined by peak VO_2 and AT,[27] and the PF domain of the SF36,[26] respectively. Two further studies, by Walsh et al[31] and Gruther et al,[200] showed that there was no additional benefit gained from EBRP commencing on ICU discharge over and above the natural course of recovery. It should be noted however, that the outcomes reported by Gruther and colleagues[200] reflected no difference using an intention to treat analysis, while the per protocol analysis showed a positive outcome. Table 2-4 details the interventions for each of these studies and provides a critique of the intervention.

The lack of effect observed of EBRP initiated after ICU discharge, may be related to a number of factors including the point at which the intervention is commenced as previously described. Rehabilitation commencing early in the ICU admission appears to ameliorate the rapid loss in muscle mass and strength associated with the acute illness, and mechanical unloading. As previously described, in survivors of critical illness, the recovery of muscle mass and strength is slow, and the structure of the muscle in some patients appears to remain altered still at 6 months.[41] The implementation of EBRP interventions commencing after the ICU admission may be at best, suboptimal in its timing where prevention is key, and ineffective at worst where muscle structure is altered by the illness and management provided. Notwithstanding this consideration, there are a number of limitations to the studies published to date on EBRP implemented after ICU discharge, which may potentially attenuate the degree of physiological adaptation the interventions implemented in these studies were likely to convey.

Similar to the research examining EBRP within ICU, adequate description of the intervention used in studies examining EBRP after discharge from ICU is lacking (Table 2-3 and Table 2-4).[25,29,31,39,183] Much of the research examining EBRP in survivors of critical illness was conducted and published prior to the publication of the template for intervention description and replication (TIDieR) checklist.[290] This checklist was devised in an effort to improve the completeness of reporting of interventions within the healthcare literature and to enable replication of the interventions. However a number of factors have been reported which may contribute to the lack of effect observed. Regarding the factors which relate to the intervention, suboptimal exercise prescription and specifically failing to use high intensity exercise which has been shown to generate the greatest change in exercise capacity in health and cardiometabolic disease,[48] may have impacted on the neutral effect of EBRP reported in survivors of critical illness. Further, the use of unsupervised training programs may produce suboptimal outcomes particularly when implementing a program of high intensity exericse.[291] The one study which employed both supervised training and optimal prescription of intensity was that by Gruther and colleagues.[200] However while the intention-to-treat analysis produced no difference between groups, the per-protocol analysis indicated a shorter ward LOS in those enrolled in the intervention group.[200] Compared with those who were allocated to the standard care group, those who were allocated to the intervention group and participated fully in the intervention, demonstrated a decreased ward LOS (median [IQR], 21 [13 to 34] vs. 14 [12 to 20] d, $p = 0.033$).

Regarding the patient population recruited for these groups, and their impact on the neutral outcomes reported following EBRP in survivors critical illness, as previously described, the presence of comorbidities has been suggested to contribute to the response to EBRP.[287] Regarding the sample size recruited in the studies, a lack of statistical power to detect a change in the primary outcome is a limitation to some of the studies investigating EBRP after ICU discharge.[28,183,289] Further, a number of studies utilised outcomes which are indirect measures only of physical capacity. These include the RMI[31,183] and the PF domain of the SF36.[25,26,28,30,38,39] While these outcomes may be obtained remotely i.e. via phone consultation, as described earlier specifically related to the SF36, they are not direct surrogates for measures of

exercise capacity.[260] It is unlikely changes in exercise capacity in response to EBRP will be detected using these tools.

Table 2-3 Details and critique of published randomised controlled trials investigating the effect of exercise-based interventions commencing on ICU discharge and completed prior to hospital discharge in survivors of critical illness

Author	Inclusion criterion	Delivery of intervention	Outcomes and timing of assessments[†]	Effect of intervention when compared with usual care	Critique
Porta[289]	I+V > 48 hr and liberated from mechanical ventilation for > 48-96 hr	S: Supervised M: Upper limb ergometry F: Daily D: 20 min/session I: commenced at 0 W and increased according to Borg score (increase of 2.5 W per 1-point decrease in Borg scale) P: 15 sessions	Peak work rate and endurance time via an incremental upper limb exercise test (i) within 48 hr of successful weaning (ii) intervention completion or hospital discharge	Greater increase in the intervention group for peak work rate (p = 0.003) and endurance time (p = 0.021)	Sample size calculations were not specified. No primary outcome identified. Multiple outcomes were used for a modest sample size (25 in each group) Functional benefit of upper limb training is unclear.
Salisbury[183]	I+V > 4 d	S: Supervised by generic rehabilitation assistance M: Passive, active and resistance exercises/functional F: Daily D: Individualised NS I: Individualised NS P: Ward admission	RMI TUG 10m walk test Grip strength Mortality Loss to follow up (i) ICU discharge (ii) 3 mth after ICU discharge	No difference between groups.	Not powered to identify a difference between groups. Detail of the exercise prescription was not provided.

Author	Inclusion criterion	Delivery of intervention	Outcomes and timing of assessments†	Effect of intervention when compared with usual care	Critique
Walsh[31]	I+V > 48 hr	S: Supervised M: Passive, active and resistance exercises/functional F: Daily D: Individualised NS I: Individualised NS P: Ward admission	RMI (i) ICU discharge (ii) 3 mth after ICU discharge	No difference between groups	Detail of the exercise prescription was not provided. The functional exercises were likely insufficient intensity to elicit a physiological training response. Detail of usual care were not provided. The delivery of therapy in the usual care group may be similar to that in the intervention group.
Gruther[200]	APACHEII ≥ 20 and ERBI -150 and SOEOB > 1min	S: Supervised M: Breathing techniques/ mobilisation/resistance training/aerobic training /NMES F: 2-5 sessions /wk (aerobic training 5 d/wk) D: 10-30 min/session I: 50-80% maximum heart rate P: Ward admission	Ward length of stay	Intention to treat analysis: No difference between groups Per protocol analysis: Shorter ward length of stay in intervention group, p = 0.033	The inclusion criteria eliminated those who were profoundly impaired (SOEOB > 1 minute). The intervention may convey added benefit to patients with more profound disability. Difference in effect between intention to treat and per protocol analysis suggests a positive effect of the intervention and the difficulty of implementing training in this population.

APACHE II: acute physiology and chronic health evaluation version 2 score; ERBI: early rehab Barthel index; ICU: intensive care unit; I+V: intubated and ventilated; NMES: neuromuscular electrical stimulation; RMI: Rivermead mobility index; SOEOB: sitting on edge of bed; NS: not specified; TUG: timed up and go. S: supervision; M: modality; F: frequency; D: duration; I: intensity; P: program duration. †: the baseline and follow up assessments are denoted using (i) and (ii) respectively. The studies were not reviewed using a specific study quality assessment tool, and this may be seen as a limitation.

Table 2-4 Details and critique on published randomised controlled trials investigating the effect of exercise-based interventions commencing on hospital discharge in survivors of critical illness

Author	Inclusion criterion	Delivery of intervention	Outcomes and timing of assessments†	Effect of intervention when compared with usual care	Critique
Cuthbertson[25]	Any admission to ICU	S: Unsupervised, self-monitored M: a physio developed exercise rehab manual introduced by a nurse. Details not specified F: NS D: NS I: NS P: 3 mth	SF36 – physical component score and mental component score (i) prior to hospital discharge (ii) 12 months after hospital discharge	No difference between groups	Primary outcome does not objectively measure physical function. The intervention consisted of unsupervised training. Compliance with the program was not reported. Detail of the exercise prescription was not provided. Mean APACHE II score was 19 and mean ICU length of stay was 3d in both groups denoting a moderate acuity of illness. The intervention may convey added benefit to patients with more profound disability reflected by higher APACHEII scores and a longer ICU admission.
MacDowell[26]	I+V > 96 hr	S: Supervised x 2 + Unsupervised x 1 /wk M: Strength/conditioning, circuit, aerobic training F: 3 sessions /wk D: < 1 hour per session I: Moderate breathlessness P: 6 wk	SF36 physical functioning domain (i) within 2 wk of hospital discharge (ii) 6-8 wk after hospital discharge	No difference between groups	Primary outcome does not objectively measure physical function. The specified target intensity may not be sufficient to elicit a physiological training response.

Author	Inclusion criterion	Delivery of intervention	Outcomes and timing of assessments[†]	Effect of intervention when compared with usual care	Critique
McWilliams[27]	I+V > 5 d	S: Supervised x 1 + Unsupervised x 2 /wk M: Circuit – 1min per station involving major muscle groups F: 3 sessions /wk D: 20 minutes per session I: 50-60%HRR (high risk) or 60-70%HRR (low risk)/target Borg 3-4 P: 7 wk	Peak VO_2 and AT (i) within 6 wk of hospital discharge (ii) 8-10 wk after first assessment	No difference between groups	The intervention largely consisted of unsupervised training. Compliance with the program not reported. Exercise prescription (intensity and duration) likely not sufficient to elicit a physiological change.
Connolly[28]	I+V > 48 hr and diagnosis of ICUAW	S: Supervised x 2 + Unsupervised x 1 /wk M: Cardiovascular training (cycling, treadmill, elliptical); Strength training F: 2 sessions /wk D: 40 minutes per session I: Borg for perceived exertion 3-5 (mod to severe); Walking speed NS; Strength 80% 10RM P: 16 sessions	(Primary outcome not specified, core outcome set identified) ISWT 6MWT SF36 (Physical component and mental component score) HADS (i) hospital discharge (ii) 3 mth after hospital discharge	Greater increase in the intervention group for the ISWT ($p = 0.047$) No difference between groups in other outcome measures	Not powered to identify a difference between groups. Exercise prescription (intensity, duration and frequency) likely sufficient to elicit a physiological change.

Author	Inclusion criterion	Delivery of intervention	Outcomes and timing of assessments†	Effect of intervention when compared with usual care	Critique
Jackson[29]	I+V of any period with a TUG >1SD below the norm reference mean on hospital discharge	S: Unsupervised with second wkly tele-video sessions and motivation telephone calls every other wk M: Cognitive/physical/functional rehabilitation – physical rehabilitation consisted of lower limb functional exercises e.g. steps, walking F: NS D: NS I: Dosed according to functional status, no further detail specified P: 12 wk	TUG (i) hospital discharge (ii) 12 wk after hospital discharge	No difference between groups	The intervention consisted of unsupervised training. Compliance with the program not reported. Detail of the exercise prescription was not provided. Exercise prescription, using functional status to prescribe intensity, was possibly not sufficient to elicit a physiological change.
Batterham[38]	I+V > 3 d	S: Supervised x 2 + unsupervised x 1 session /wk M: Individually or in pairs - Cycle ergometry (supervised); Walking F: 3 sessions /wk D: 40 minutes I: 12-14 on RPE P: 8 wk	SF36 physical functioning domain AT (i) 8-16 wk after hospital discharge (ii) completion of intervention (week 9) and 26 wk after intervention	Small beneficial effect in the intervention group on both primary outcomes present at Week 9 but not sustained at Week 26	Exercise prescription (intensity using RPE) likely not sufficient to elicit a physiological change. Loss to follow up whereby only 30 of enrolled 59 participants had AT recorded.

Author	Inclusion criterion	Delivery of intervention	Outcomes and timing of assessments†	Effect of intervention when compared with usual care	Critique
Jones[39]	I+V and ICU length of stay > 48 hr	S: Unsupervised M: Self-help rehabilitation manual including self-directed exercise program + advice (psychological, psychosocial and physical problems) F: 3 wkly phone calls D: NS I: NS P: 6 wk	(Primary outcome not specified) SF36 physical functioning domain HADS Impact of events scale (i) one wk after ICU discharge (ii) 8 and 26 wk after ICU discharge	Greater increase in the intervention group for the SF36 physical functioning domain at 8 and 26 wk after hospital discharge (p = 0.006) No difference in other outcomes	Primary outcome does not objectively measure physical function. The intervention consisted of unsupervised training. Compliance with the program was not reported. Detail of the exercise prescription was not provided. Trajectory of recovery between groups appears similar in the graphical representation of data.
Elliott[30]	I+V > 24 hr and ICU length of stay > 48hr and specific geographical region	S: Unsupervised M: Home-based with home visits from a qualified trainer at 1,3 and 6 wk, telephone support on other wks M: Walking/Strength training with an illustrated exercise manual F: 5 sessions /wk D: 20-30 min I: Walking 80% baseline peak walking speed; Strength 1-3 sets of 8RM P: 8 wk	SF36 physical functioning domain (i) one wk after hospital discharge (ii) 8 and 26 wk after hospital discharge	No difference between groups	Primary outcome does not objectively measure physical function. The intervention consisted of unsupervised training. Compliance with the program was not reported.

AT: anaerobic threshold; HADS: hospital anxiety and depression score; HRR: heart rate reserve; ICU: intensive care unit; ICUAW: intensive care unit acquired weakness; I+V: intubated and ventilated; ISWT: incremental shuttle walk test; NS: not specified; RM: repetition maximum; RPE: rating of perceived exertion; SF36: Medical Outcomes Study Short Form 36 General Health Survey Version 2; TUG: timed up and go; VO_2: rate of oxygen uptake; 6MWT: 6-minute walk test. S: supervision; M: modality; F: frequency; D: duration; I: intensity; P: program duration. †: the baseline and follow up assessments are denoted using (i) and (ii) respectively. The studies were not reviewed using a specific study quality assessment tool, and this may be seen as a limitation.

2.5.4 Summary

Rehabilitation commencing in ICU and EBRP commencing after ICU and hospital discharge, have aimed to ameliorate the physical impairments that result from a prolonged ICU admission. Rehabilitation commencing in ICU has shown promising results related to improvements in physical function when compared with usual care, specifically when rehabilitation is initiated within 72 hours of mechanical ventilation. Exercise based rehabilitation programs implemented after discharge from ICU have to date not shown any benefit.

2.6 Synopsis

The number of available ICU beds has increased significantly, and the mortality associated with an ICU admission has decreased. The health care utilisation of survivors of a critical illness and specifically ARDS extends well after the ICU admission. The data reported in earlier studies of survivors of ARDS show pronounced reductions in peripheral muscle strength and 6MWD,[12-17] and impaired HRQL.[22-24] The current knowledge related to fatigue, PA and ST in survivors of critical illness during the ICU admission, after discharge from ICU to the ward, and after hospital discharge is scarce.[70,126,240]

Although much of the research describing the physical sequelae of critical illness has been performed in those diagnosed with ALI and ARDS, all of the work published on ameliorating or improving these sequelae has been conducted in a heterogeneous group of survivors of critical illness.[43,271-275] Those surviving ARDS or ALI are likely to represent some of the most severely affected survivors of critical illness.[112] The uncontrolled widespread inflammation inherent in both ARDS,[75,78] which leads to depressed protein synthesis, reduced ratio of protein to deoxyribonucleic acid (DNA) in skeletal muscle, and subsequent muscle catabolism,[40] may lead to increased physical impairment in survivors when compared with a similar cohort surviving and ICU admission but without a diagnosis of ARDS. Previous reports using small cohorts suggest an association between a low PaO_2/FiO_2 ratio, and increased loss in peripheral muscle strength and cross-sectional muscle area when compared with patients admitted to ICU for other pathologies.[40,140] However, the impact that an admission for ALI has on strength, exercise capacity and physical

function in survivors when compared with a general cohort of ICU survivors has not been examined.

Rehabilitation commencing in ICU has shown promising results related to improvements in physical function when compared with usual care, specifically when rehabilitation is initiated within 72 hours of mechanical ventilation.[271] Knowledge pertaining to those who may experience greater physical impairment after discharge from ICU may enable early identification for targeted rehabilitation. Exercise based rehabilitation programs implemented after discharge from ICU, however, have to date not shown any benefit.[26,27,31,200,288] The rationale for the lack of benefit demonstrated to date is unclear and may be multifactorial. Knowledge related to the mechanism of limitation in those surviving an ICU admission, use of appropriate outcome measures to identify physiological adaptation to EBRPs and consideration regarding the delivery of the intervention, specifically high intensity supervised exercise, may be of benefit.

CHAPTER 3 Study 1

3.1 Overview

This chapter presents Study 1, which answers the following research questions:

(i) Do adults who have survived an ICU admission for ALI, when assessed within 7 days of discharge from an ICU, demonstrate impairments in peripheral muscle strength (primary outcome), balance, ability to stand from supine, walking speed and peak and submaximal exercise responses measured during a functional exercise test (secondary outcomes), relative to those who survived an ICU admission for a critical illness other than ALI?

(ii) In adults who have survived an ICU admission for ALI or another critical illness, does the 10-metre walk speed (10MWS) explain more than 50% of the variance in 6-minute walk distance (6MWD), when both outcomes are measured within 7 days of discharge from the ICU?

(iii) In adults who have survived an admission to an ICU for ALI or another critical illness, can the 6MWD measured within 7 days of discharge from the ICU, separate those who: (a) require a longer ward length of stay (LOS) versus those who require a shorter ward LOS; and (b) are discharged home versus discharged to another care facility?

This chapter will be divided into 3 sections: Methodology, Results and Discussion.

3.2 Methodology

Section 3.2 presents information pertaining to the methodology used in Study 1. Specifically, section 3.2 presents information related to approval from the relevant Human Research Ethics Committees, recruitment of participants, outcome measures, and statistical analyses.

3.2.1 Study design and participants

This study was cross-sectional and observational in design. Two groups of participants were recruited: participants with ALI and participants with critical illness.

3.2.1.1 Approval from Human Research Ethics Committees

The study was approved by the Human Research Ethics Committees of Hunter New England Area Health (HREC 10/11/17/4.06), Curtin University (HR 27/2011) and The University of Newcastle (H-2011-0029) (Appendix 1 and Appendix 2). In response to some participants being discharged from John Hunter Hospital (JHH) or Calvary Mater Newcastle Hospital (CMN) to local private hospitals within 7 days of their ICU admission, approval for data collection at Newcastle Private Hospital (January 2012) and Hunter Valley Private Hospital (August 2011) was sought and granted under an agreement with the Human Research Ethics Committees of Hunter New England Area Health.

3.2.1.2 Recruitment and study criteria for participants with ALI and critical illness

Patients admitted to the ICU at JHH or CMN were screened on a daily basis to determine their eligibility to participate in this study. Screening was to occur between March 2011 and December 2013 to enable completion of data collection in the time frame specified by the associated PhD candidacy.

To be eligible for inclusion in the ALI group, participants needed to be aged over 18 years and meet the diagnostic criteria for ALI during an ICU admission. These criteria were:

- profound hypoxaemia defined by the ratio of partial pressure of oxygen in arterial blood to the fraction of inspired oxygen (PaO_2/FiO_2) of < 300;
- non-cardiogenic pulmonary oedema seen as bilateral infiltrates on chest xray;
- acute onset of hypoxaemia and non-cardiogenic pulmonary oedema within < 72 hours from an initial insult.[1]

Eligibility for inclusion was assessed according to these criteria and did not rely on a clinical diagnosis of ALI to be made by the treating medical team.

To answer the primary research question and explore whether or not there were differences in the magnitude of impairment in outcomes such as peripheral muscle strength between those who have survived an ICU admission for ALI versus another critical illness, a second group of adults was recruited. These participants needed to have survived an admission to the ICU for a critical illness other than ALI.

In order to optimise the likelihood that the 2 groups of participants were balanced for factors that may have influenced the outcome measures chosen for the primary research question, additional inclusion criteria were applied to this group. Specifically, to ensure that groups were balanced in terms of their requirements for mechanical ventilation, to be eligible for inclusion in the critical illness group, participants needed to have received intubation and mechanical ventilation for ≥ 4 days. This requirement was based on earlier work which reported those with ALI require a median period of mechanical ventilation of 5 days.[76] To optimise the likelihood that the 2 groups would be balanced in terms of gender proportion, separate recruitment targets for males and females were defined. Specifically, as data suggests that ALI affects more males than females (70:30),[88] males and females were recruited according to a ratio of 2:1. Finally, in order to optimise the likelihood that the 2 groups of participants were balanced in terms of age, at the beginning of recruitment, to be eligible for inclusion in the critical illness group, participants were required to be aged between 50 to 70 years. This range was selected in response to data from the Australian New Zealand Intensive Care Society (ANZICS) showing that the average age of ALI survivors across 3 Australian states was 59±19 yr.[151]

Recruitment to both the ALI and critical illness groups occurred concurrently. Once 11 participants with ALI had completed the study, the mean age was calculated and minor changes were made to the eligibility criteria related to age of the critical illness survivors to optimise the likelihood that these groups would be well balanced on study completion. These minor amendments in eligibility criteria for the critical illness survivors were approved by the relevant human research ethics committees.

Exclusion criteria applied to both groups comprised: (i) the presence of any neurological or musculoskeletal condition likely to adversely affect the ability to mobilise safely; (ii) orthopaedic injuries with mobility restrictions; (iii) non-ambulant prior to admission; (iv) documented neurological disease including traumatic brain injury; (v) treatment or diagnosis of malignant cancer within preceding 12 months; (vi) history of recent major pulmonary resection; (vii) poorly managed psychiatric disorders; (viii) an inability to follow commands; and (ix) inability to understand English.

3.2.1.3 Study protocol for participants with ALI and critical illness

The Doctor of Philosophy (PhD) candidate was responsible for obtaining consent from every participant as well as all aspects of data collection.

Variables used to describe the characteristics of the participants were collected both during the ICU admission and during the assessment period conducted on the ward. Specifically, during the ICU admission, pre-admission health-related quality of life (HRQL) and pre-admission comorbidities affecting physical function were collected via the next of kin (NOK) using the Medical Outcomes Study Short Form 36 General Health Survey Version 2 (SF36) and Functional Comorbidity Index (FCI), respectively. Information pertaining to the participants' ICU and ward admission, including measures of severity of illness and prognostic indicators were extracted from the participants' notes on a daily basis. Length of stay in the ICU was calculated on the day of discharge. Thereafter, within 7 days of discharge from ICU to the ward, participants were invited to complete 2 assessment sessions over 2 consecutive days. In order to optimise participant recruitment and data collection, the candidate was in daily contact with the relevant ward staff via telephone or by attending the ward. Measures collected during the first session comprised: (i) peripheral muscle strength via a custom-designed fixed force gauge (FFG), hand-held dynamometer (HHD) or a hand dynamometer; (ii) balance via the Berg Balance Scale (BBS); and (iii) ability to stand from supine via the time-to-stand from supine test (TTS). Measures collected during the second session comprised: (i) walking speed via the 10-metre walk test (10MWT); and (ii) functional exercise capacity via the 6-minute walk test (6MWT). During the second session, additional variables were recorded to describe the characteristics of the participants, such as height and

measures of spirometric lung function. Every feasible effort was made to complete collection of all measures prior to both planned and unexpected discharge from hospital which occurred within the 7 days of discharge from ICU. The hospital LOS and discharge destination was recorded on the day of hospital discharge. Figure 3-1 shows the measurements collected in the participants with ALI and critical illness, the order in which the assessment sessions were conducted and the assessors who collected the measurements.

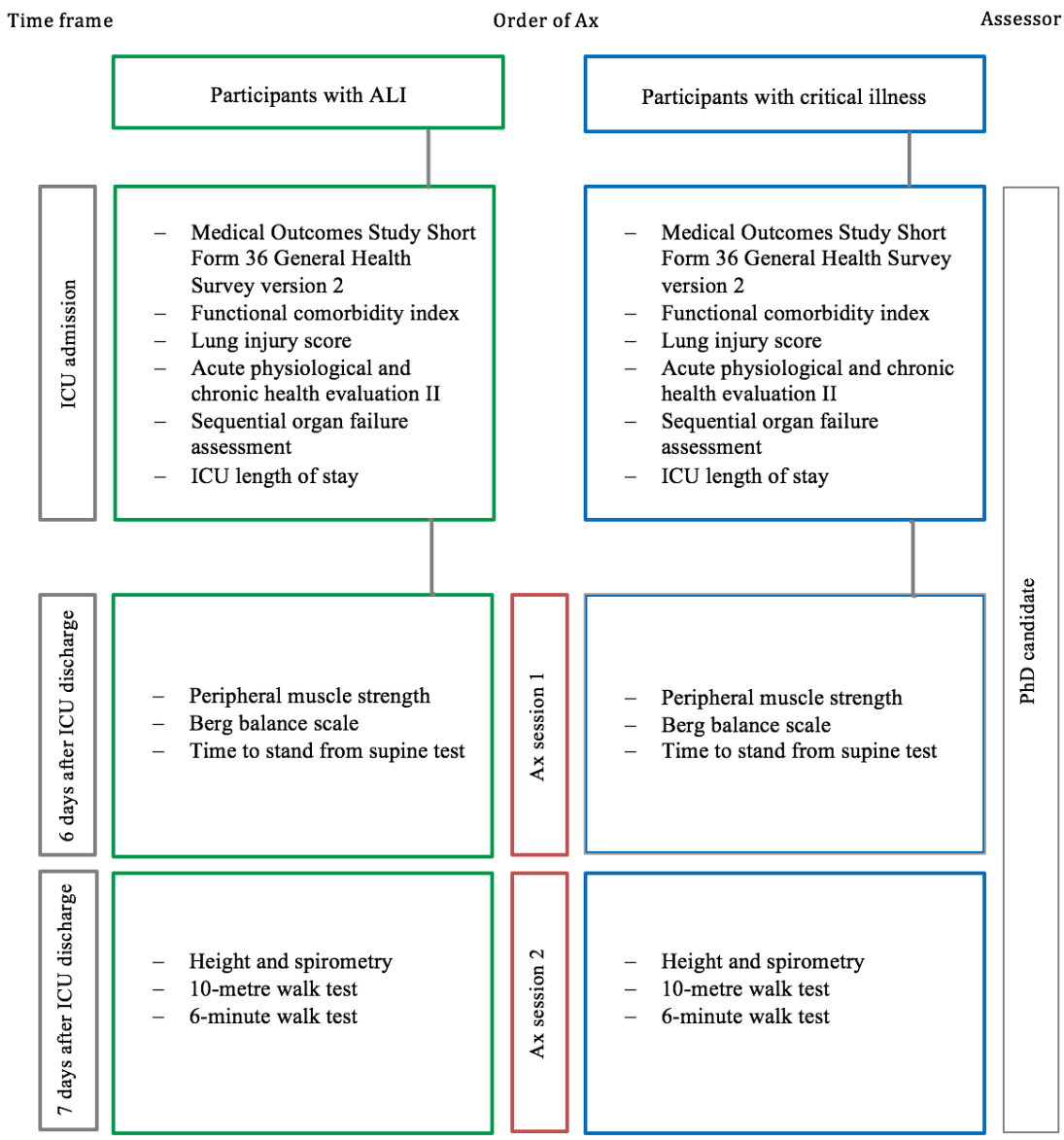

Figure 3-1 Timing of assessments, order of assessments and assessor of measurements in the participants with ALI and critical illness

ALI: acute lung injury; Ax: assessment; ICU: intensive care unit; PhD: Doctor of Philosophy.

3.2.2 Measurements

This section describes the measurements made in this study. Details are first presented regarding the collection of descriptive measures (section 3.2.2.1 to 3.2.2.4) and thereafter, details are presented regarding the collection of measures used to answer the research questions (section 3.2.2.5 to 3.2.2.9).

3.2.2.1 Age, sex, height and weight

During the ICU admission, age and sex were recorded. Body weight prior to admission was obtained from the NOK, and, as soon as possible following discharge to the ward, height was collected via a wall mounted stadiometer (seca 206, seca gmbh & co. kg, Hamburg, Germany).

3.2.2.2 Medical outcomes study short form 36 general health survey version 2 and functional comorbidity index

Preadmission HRQL was obtained from the participant's NOK using the SF36 questionnaire.[292] Similarly, the NOK also provided information pertaining to comorbidities that affected physical function prior to the ICU admission were measured using the FCI.[293] The proxy who completed the SF36 was a person who resided with the participant or should the participant have lived alone, knew the participant well.[255] The participant proxy was instructed to answer the questions as they pertained to the participant for the one month prior to the ICU admission. The SF36 was self-completed by the proxy or, when the proxy was unable to read, the responses to the questions were obtained during interview.

The SF36 is a 36-item, questionnaire that measures generic HRQL. The SF36 has established reliability, validity and sensitivity to change in a range of acute and chronic diseases,[292,294-296] and is recommended for use in critical illness.[297] Responses were scored, collated and presented in the domains of physical function (PF), role physical, pain, general health, vitality, social functioning, role emotional and mental health. The responses to the questions in each SF36 domain were weighted equally, summed and transformed to a 0 to 100 scale with a higher score indicating a better HRQL. The 2 component summary scores, PCS and MCS, were also calculated using a scoring algorithm.[298,299] Data were presented as absolute values, the domains as transformed data and the summary component scores as

normative based values. All scoring was completed by the QualityMetric Health Outcomes™ Scoring software 2.0.

The FCI was developed for use in the general population to evaluate physical function. It reports on 18 diagnoses with a score of one given if a diagnosis is present. A higher total score on the FCI denotes a higher number of comorbid illnesses.[293] The FCI has been shown to be associated with the PCS and PF scores of the SF36 in a population with acute respiratory distress syndrome (ARDS) at 3, 6 and 12 months after discharge from hospital.[109]

3.2.2.3 Acute physiologic and chronic health evaluation II score, lung injury score and the sequential organ failure assessment

During the ICU admission, details were collected regarding severity of illness and prognostic indicators. These measures comprised the acute physiologic and chronic health evaluation II (APACHE II),[300] lung injury score (LIS)[301] and the sequential organ failure assessment (SOFA).[302] Specifically, the APACHE II[300] was calculated during the first 24 hours of admission and represents a prognostication tool to establish the risk of mortality in hospital.[303-306] The scoring system comprises an acute physiological component, age and a chronic health component to calculate a score out of 71. Higher scores represent a higher severity of illness and denotes a higher risk of death.[300,307] A score of 25 represents a predicted mortality of 25% and a score of over 35 represents a predicted mortality of 80%.[307] The APACHE II score was routinely calculated in all patients admitted to the ICUs of JHH and CMN by a senior ICU medical officer using a computer program to allocate the final score.

The LIS,[301] was calculated using information recorded in the participants' notes. The LIS is a commonly utilised measure within ICU to quantify the severity of lung injury.[308] The full LIS represents an aggregate of individual scores allocated to chest x-ray changes, degree of hypoxaemia, level of positive end expiratory pressure (PEEP) requirements and static compliance of the respiratory system. The measurement of static compliance of the respiratory system, however, requires the patient to be heavily sedated or paralysed, and with the current practice within ICU which aims to maintain the patient as sedation free as possible, the static compliance of the respiratory system is difficult and often impossible to measure. Therefore, consistent with earlier work,[12,301,309,310] a modified LIS was used, whereby a final

score was determined by calculating the mean of the remaining 3 variables. The LIS was calculated daily as the modified version, for the first 7 days and then twice weekly thereafter whilst the participant remained intubated and ventilated. The maximum LIS that was recorded for the participant was used in analyses.

The SOFA[302] was calculated using information recorded in the participants' notes. The SOFA objectively and quantitatively describes the degree of organ dysfunction over time and evaluates morbidity, in a variety of different patient groups within a hospital setting.[302,311-313] The scoring scheme assigns one to 4 points to the respiratory, circulatory, renal, haematological, hepatic and central nervous system depending on the level of dysfunction.[314] A higher score denotes a greater deviation from normal. The highest SOFA score recorded on the day of admission to ICU was recorded and used in analyses.[315]

3.2.2.4 Spirometry

During the assessment session conducted on the ward, measures were made of forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) (EasyOne™ spirometer, NDD Medical Technologies, Zurich, Switzerland). Due to the difficulty associated with getting a medical officer to chart bronchodilators for all participants, bronchodilators were not administered prior to performing spirometry. Measures were collected according to published guidelines.[316] All equipment was calibrated according to manufacturer's recommendations. Data were expressed as absolute values and as a percentage of predicted normative values estimated using regression equations.[316]

3.2.2.5 Peripheral muscle strength

During the assessment sessions conducted on the ward, peripheral muscle strength was measured on the dominant limb during knee extension, shoulder flexion, elbow flexion, and handgrip using portable dynamometers. The order of muscle group testing varied between participants and was guided by participant choice and environmental logistics. That is, knee and grip strength measurements were performed first if the patient was found in sitting when the assessor attended for the first session. Conversely, shoulder flexion and elbow strength measurements were performed first if the patient was found positioned in bed. This process was

employed in order to limit unnecessary exertion in a group who were likely to be profoundly deconditioned and in turn, to optimise their ability to perform the assessments to their maximal capacity.

Participants were informed that each test required a maximal effort. For each muscle action, participants were instructed to perform a single practice contraction at 50% of their estimated maximal force. Thereafter, participants performed a minimum of 3 maximal voluntary isometric contractions, each separated by one minute of rest to allow sufficient time for muscle recovery.[317,318] The following standardised instruction was given to each participant: "on the count of 3, I want you to push against this plate as hard as you can. I'm going to stop you from moving. Remember to breathe and I will encourage you throughout." During each contraction, strong verbal encouragement was provided to facilitate a maximum performance. Participants were asked to sustain the contraction for 6 seconds to ensure enough time was allowed for the generation of peak force.[151] For each contraction, the peak force generated was recorded, regardless of how long this force was sustained. Thereafter, the peak force recorded for each action was defined as the highest force attained, that was within 10% of another measure. All equipment was calibrated according to manufacturer's recommendations. Data were expressed as absolute values and as a percentage of predicted normative values estimated using published normative reference values for each action (Appendix 3).[155,156,319]

Regarding equipment and starting positions, peak strength generated during knee extension was measured using a custom designed FFG (Mecmesin® BFG 1000, Mecmesin, West Sussex, UK), which has been demonstrated to generate valid and reliable measures for this muscle action (Appendix 4). For this assessment, participants were placed in a sitting position with the foot free from the floor and knee at 90 degrees of flexion with the dynamometer placed just proximal to the ankle (Figure 3-2).[156] The opposite foot was supported using a small portable step and a seatbelt used to stabilise the thighs against the chair.

Peak strength generated during shoulder flexion and elbow flexion was measured with a Lafayette® hand held dynamometer (HHD) (model 01163; Lafayette Instrument, Lafayette, Illinois, USA). For the assessment of peak strength during shoulder flexion, participants were placed in supine with the shoulder at 90 degrees

flexion, elbow fully extended and palm facing medially with the dynamometer placed proximal to the elbow (Figure 3-3).[155] For the assessment of peak strength during elbow flexion, participants were placed in supine with the shoulder in neutral, humerus by the body, elbow at 90 degrees flexion and forearm in the anatomical position with the dynamometer placed on the anterior aspect of the distal forearm (Figure 3-4).[156]

Peak grip strength was measured using a JAMAR™ hand dynamometer (model PC 5030J1; Therapeutic Equipment Corporation, Clifton, New Jersey, USA). For this assessment, participants were placed in a sitting position in a straight-backed chair with feet flat on the floor, shoulder in neutral, humerus by the body, elbow at 90 degrees, forearm neutral and the wrist extended between 0 and 30 degrees.[320] The dynamometer was gripped in a vertical position and the arm was left unsupported (Figure 3-5).[321]

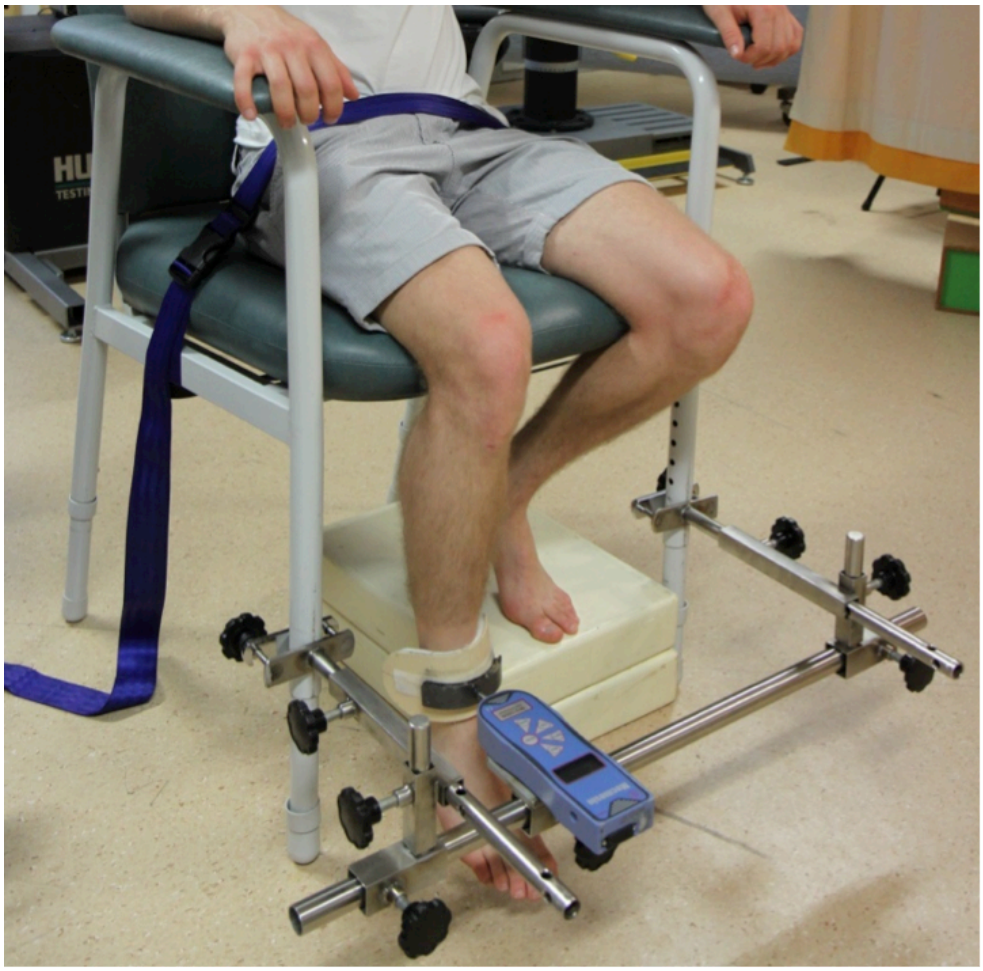

Figure 3-2 Position of participant and dynamometer for measurement of the strength of the knee extensors

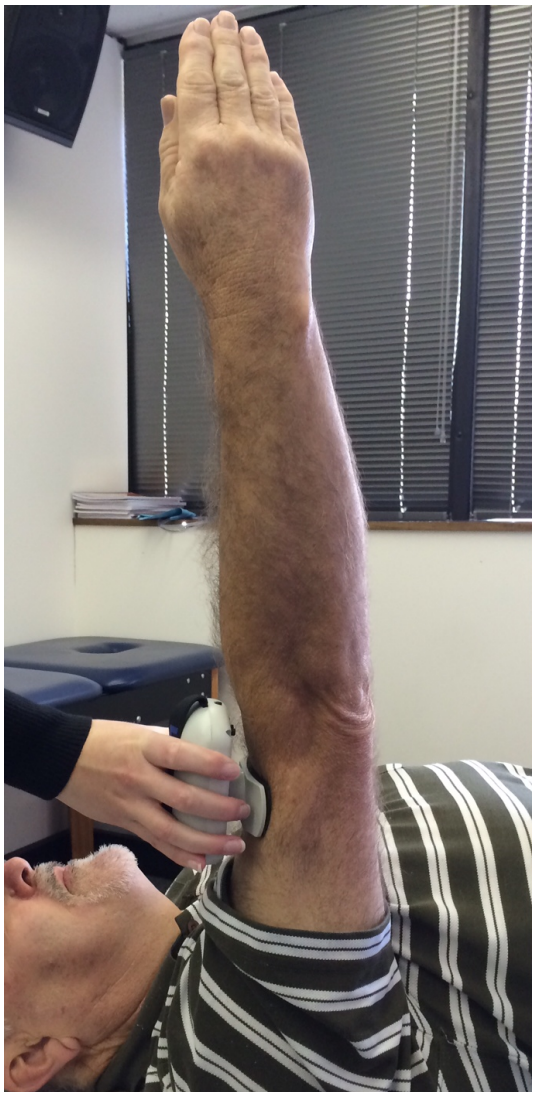

Figure 3-3 Position of participant and dynamometer for measurement of the strength of the shoulder flexors

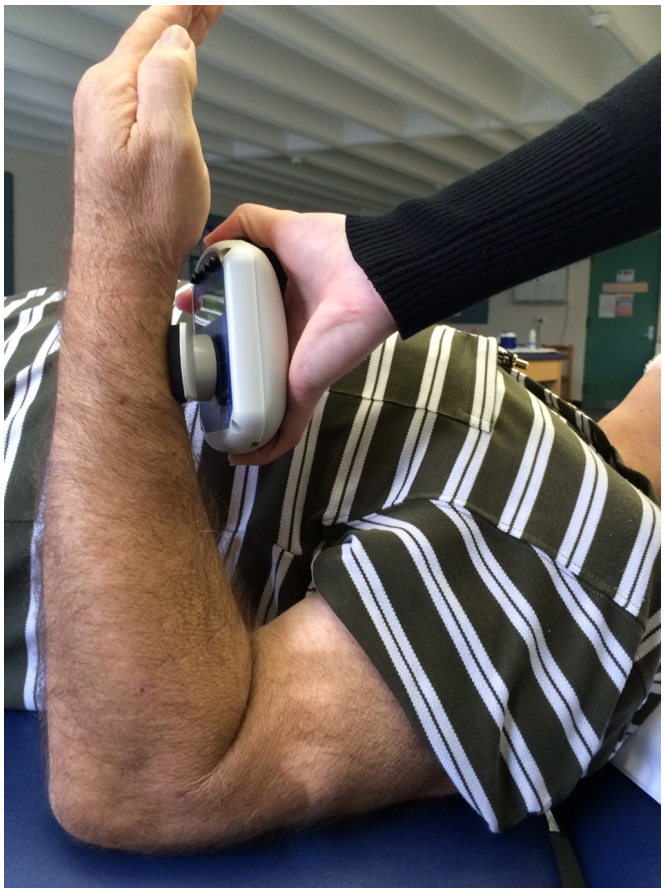

Figure 3-4 Position of participant and dynamometer for measurement of the strength of the elbow flexors

Figure 3-5 Position of participant and dynamometer for measurement of the strength of hand grip

3.2.2.6 Berg balance scale

During the assessment sessions conducted on the ward, balance was measured using the BBS. This was a 14-item test that required approximately 20 minutes to complete. Each item was scored on a 1 to 4 scale (maximum score was 56). A low score on the BBS represents impaired balance with a threshold of < 45 suggestive of an increased risk of falling.[322] The BBS has a reported high inter-rater reliability, high internal consistency and moderately good to high concurrent and predictive validity.[322,323] Data were expressed as absolute values.

3.2.2.7 Time to stand from supine test

During the assessment sessions conducted on the ward, the ability to stand from supine was measured using the TTS. This assessment measured the amount of time it took for an individual to independently achieve a standing position from supine on a bed. Time-to-stand from supine, has been shown to have high test-retest reliability and high correlation with lower limb strength in the healthy elderly population.[324]

The TTS was conducted with the participant lying supine, arms by their side, on the bed. The participant was instructed to move from lying to standing (beside the bed with their arms by their side) as quickly as possible whilst maintaining their safety. The stopwatch was started as soon as the patient began to move. This process was completed twice and the shortest time recorded as the test result. If the participant was unable to move from supine to standing without assistance, they were recorded as being unable to perform the test. Data were expressed as absolute values.

3.2.2.8 10-metre walk test

During the assessment sessions conducted on the ward, walking speed was measured using the 10MWT. This test has been shown to have excellent inter-rater and intra-rater reliability in both the healthy elderly and survivors of stroke.[156,325] Walking speed can be measured at either an individual's self-selected (SSWS) or maximal walking speed (MWS).[326,327] A 10-metre distance was marked in an enclosed corridor inside the hospital with an additional 2 m distance marked at either end for acceleration and deceleration. The participants were instructed to walk as fast as they could over the total 14-metre course, without running or feeling unsafe. A stopwatch was used to measure the time taken over the 10-metre course. This test was

conducted twice and the shortest time was recorded as the test result. Data were expressed as a speed (m/s).

3.2.2.9 6-minute walk test

During the assessment sessions conducted on the ward, functional exercise capacity was measured using the 6MWT. This test provided a measure of functional exercise capacity,[328] and has been used safely with survivors of critical illness upon discharge from ICU, hospital discharge and also during long term follow up assessments.[12,60,170,171] In adults who have chronic lung disease and heart failure, it is well recognised people improve their performance with test repetition (i.e. learning effect).[329,330] However, it is unclear whether or not this effect is seen in survivors of an ICU admission, shortly after discharge from ICU to the ward. Due to the profound debilitation which characterises this population, the battery of assessments that were conducted in this population, the relatively short timeframe in which to conduct the assessment (within 7 days of discharge from ICU) and consistent with earlier work, only a single 6MWT was conducted.[171] This decision was made after discussion with an expert clinician and researcher in the area of ICU survivorship, Dr Chris Burtin.[171] Dr Burtin commented that in his experience the performance of a second 6MWT in survivors of an ICU admission shortly after discharge from ICU was likely to elicit a lower 6MWD due to the effect of fatigue and was unlikely to be feasible in the large proportion of the sample.

The test was carried out in accordance with the protocol described by the European Respiratory Society/American Thoracic Society (ERS/ATS) over a 30-metre straight course.[331] Standardised instructions were provided to the participants prior to commencement of each test and standardised encouragement given at the end of each minute. The ERS/ATS protocol was adapted to include continuous monitoring of heart rate (HR) using telemetry (Polar A1, Polar Electro Oy, Kempele, Finland) and arterial oxygen saturation (SpO_2) via pulse oximetry (Masimo® Rad-5V, Irvine, California, USA). Both HR and SpO_2 were recorded at rest, at the end of each minute during the 6MWT and at 2-minutes following test completion. Dyspnoea was recorded at rest, on test completion and at 2 minutes following the test completion using the modified Borg scale.[332] Fatigue was recorded at rest and on test completion also using the modified Borg scale.[332] In the event that a participant rested during the

test, standardised encouragement to recommence walking was given at 15-second intervals. The number, time and duration of rests were recorded and HR, SpO_2 and dyspnoea were recorded at the beginning of any rests. Observed adverse events during the 6MWT were defined as desaturation where SpO_2 fell to below 85%, an abnormal HR response (e.g. failure of HR to rise or any fall in HR during the test), excessive tachycardia (HR > 210 - 0.65 × age), signs/symptoms of poor perfusion (e.g. sudden pallor, dizziness or fainting), development of an abnormal gait/loss of coordination, signs suggestive of mental confusion, or the onset of chest pain suggestive of ischemia.[331] The protocol mandated that in the event that SpO_2 fell below 85% during the test, a rest was enforced and the participant was encouraged to recommence walking if SpO_2 returned to ≥ 85%. For all other adverse events, the 6MWT was to be terminated immediately.

Walking aids and supplemental oxygen were used during the 6MWT as prescribed in the participants' medical notes. Any assistance that the participant required to mobilise (e.g. stand-by assistance) during the 6MWT was provided by the candidate who was positioned behind the participant in order to avoid pacing.

The 6MWD was expressed in absolute values, as a percentage of predicted normative values, estimated using regression equations that were established in an Australian population using an identical 6MWT protocol.[333]

3.2.3 Sample size calculations

Sample size calculations were based on published data available at the time the study was conceived. That is, Burtin and colleagues[171] demonstrated that isometric quadriceps force increased during the period between discharge from an ICU (1.83 ± 0.91 $N \cdot kg^{-1}$) and discharge from acute care (2.37 ± 0.62 $N \cdot kg^{-1}$) following a program of standardised passive or active movement using a bedside recumbent cycle ergometer. To determine sample size for Study 1, the gain observed in knee extension strength was postulated to be equivalent and potentially exceed the difference in knee extension strength between a group of ALI and critical illness survivors shortly after ICU discharge. This between-group difference was equivalent to an effect size of 0.7 (i.e. 0.54 $N \cdot kg^{-1}$ / pooled SD of 0.76 $N \cdot kg^{-1}$). In order to detect a difference between the participants with ALI and critical illness of similar

magnitude using a 2-tailed independent t-test, with power of 0.8 and significance inferred when $p < 0.05$, a sample size of 25 ALI and 46 critical illness survivors was required. A 2-tailed independent t-test was used for sample size calculations only and assumed equal variances.

3.2.4 Statistical analyses

Statistical analyses were performed using IBM Corporation Statistical Package for Social Sciences, version 23.0 for Macintosh (SPSS®). The distribution of the data was examined by statistical (Shapiro-Wilks) and graphical (frequency histogram and box plots) methods. Parametric data are expressed as mean ± standard deviation or mean [95% CI] and non-parametric data are expressed as median [IQR].

To answer the first research question, between-group comparison of continuous data were conducted using independent-samples t-test for parametric data or Mann-Whitney U test for non-parametric data respectively, and Chi-square test for categorical data. Analysis of sub-maximal and peak exercise responses during the functional exercise test was conducted using a linear mixed model approach. To answer the second of the secondary research questions, associations between 10MWS and 6MWD were explored using Spearman's rho for non-parametric data. The relationship between 10MWS and 6MWD was modelled using linear regression. In the presence of a non-linear relationship, an appropriate transformation was applied to the data to enable linear regression. To answer the third of the secondary research questions, the relationship between 6MWD and hospital LOS was calculated using a Kaplan Meier survival analysis and the impact of possible confounders to this relationship were explored using a Cox regression. A receiver operating characteristic (ROC) curve was used to determine the optimal operating point for the 6MWD that maximised sensitivity and specificity to predict a ward LOS of > 2 weeks. To determine whether 6MWD influenced discharge destination, grouped as discharge home versus discharged to another care facility, logistic regression was used. For all analyses, a $p < 0.05$ was considered significant.

3.3 Results

3.3.1 Overview

This section presents data to answer the research questions for Study 1. Specifically, sections 3.3.3 tot 3.3.7 presents the results of analyses that explored the first research question by comparing measures of peripheral muscle strength, the BBS, TTS, 10MWS and peak and submaximal exercise responses measured during a 6MWT, in the participants with ALI with those following critical illness. Section 3.3.8 presents the results of the second of the research question which explored the relationships between the 10MWS and the 6MWD in the participants with ALI and critical illness. Section 3.3.9 and section 3.3.10 presents the results of analyses that explored the third of the research question by presenting data pertaining to the 6MWD, ward LOS and discharge destination details in the participants with ALI and critical illness.

3.3.2 Participant recruitment and characteristics

The outcome of participant recruitment is shown in Figure 3-6. The number of participants recruited, expressed as a proportion of the target sample size, for the ALI and critical illness group was 88% and 72%, respectively. For the participants with ALI, when compared with those who contributed data, those who were lost to follow up were older (50 [42 to 66] vs. 39 [30 to 47] yr, p = 0.018] but otherwise broadly similar in terms of sex (male n [%], 10 [45] vs. 5 [71], p = 0.23) and acuity of illness as measured by the SOFA score (10 [9 to 13] vs. 8 [8 to 14], p = 0.45). For the participants with critical illness, when compared with those who contributed data, those who were lost to follow up were broadly similar in terms of age (57 [52 to 63] vs. 60 [53 to 64] yr, p=0.82), sex (19 [58] vs. 6 [55], p = 1.00) and SOFA score (10 [8 to 12] vs.11 [9 to 12], p = 0.27) (see Appendix 5). The time between discharge from ICU and the first assessment session was similar in the participants with ALI and critical illness (6 [5 to 9] vs. 6 [5 to 6] d, $p = 0.69$). Table 3-1 presents details pertaining to participant characteristics. There were no significant differences in any characteristic between the participants recruited to these 2 groups, apart from LIS which was greater in the participants with ALI ($p < 0.001$).

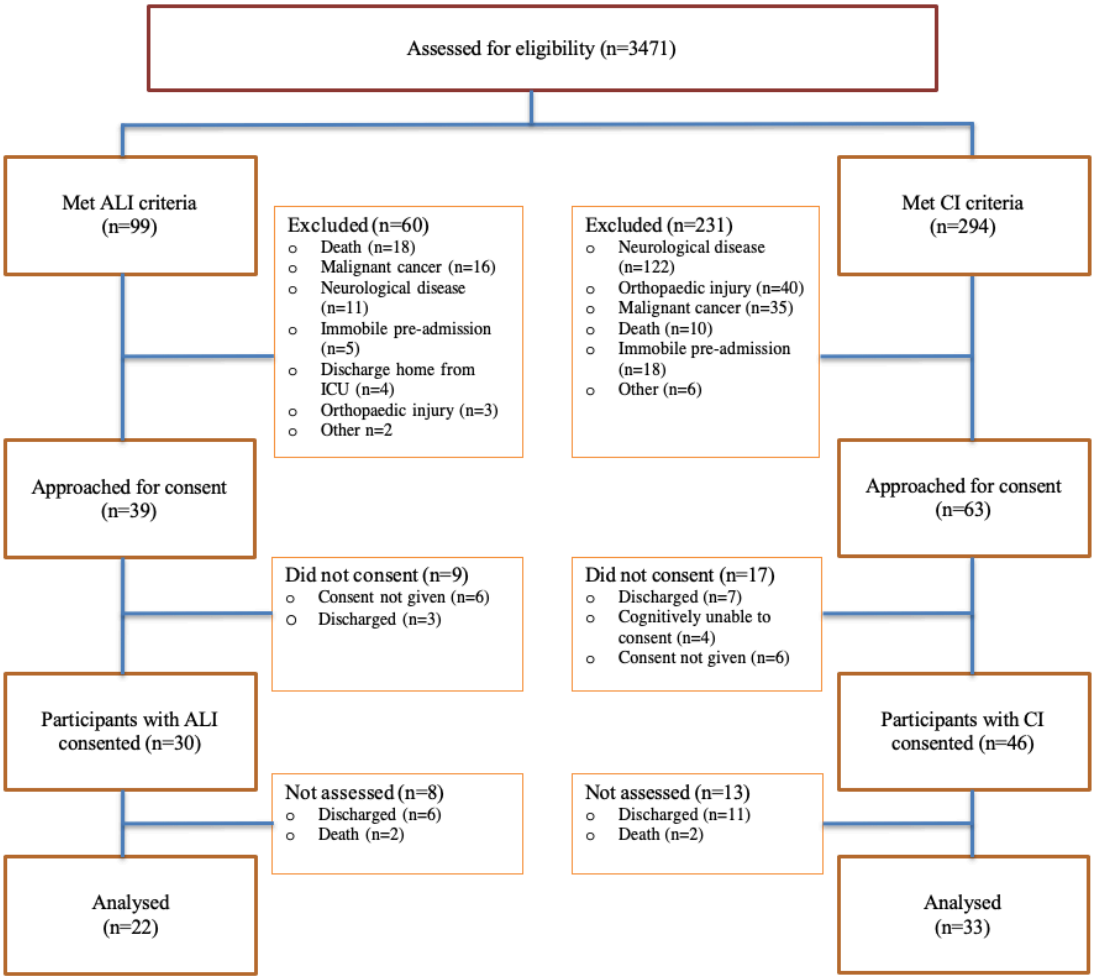

Figure 3-6 Flow of recruitment for participants with ALI and critical illness

ALI: acute lung injury; CI: critical illness; ICU: intensive care unit.

Table 3-1 Characteristics of the participants in the ALI and critical illness groups

	ALI participants (n = 22)	CI participants (n = 33)	p-value
Anthropometric / demographic data			
Age (yr)	50 [42 to 66]	57 [52 to 63]	0.09
Sex, male n (%)	10 (45)	19 (58)	0.59
Weight (kg)	78 [35 to 82]	85 [74 to 102]	0.09
Height (cm)	169 [160 to 177]	170 [160 to 177]	0.85
BMI (kg/m^2)	27.5 [23.9 to 33.6]	30.3 [25.3 to 35.2]	0.33
Pre-admission functioning			
SF36 score			
Physical functioning	65 [40 to 95]	68 [36 to 94]	0.50
Physical role	75 [44 to 89]	50 [25 to 94]	0.50
Pain	72 [27 to 84]	41 [24 to 74]	0.25
General health	59 [30 to 87]	47 [30 to 77]	0.30
Vitality	44 [31 to 72]	47 [25 to 67]	0.76
Social functioning	75 [31 to 94]	63 [38 to 97]	0.74
Emotional role	75 [48 to 100]	93 [50 to 100]	0.94
Mental health	70 [50 to 90]	70 [55 to 85]	0.95
FCI	3.0 [1.8 to 4.3]	4.0 [2.0 to 6.0]	0.09
Severity of illness and prognostic indicators			
Primary admitting diagnosis n (%)			
Sepsis	10 (45)	11 (31)	-
Pneumonia	7 (32)	5 (15)	-
Vessel rupture/blood loss	2 (9)	7 (21)	-
Perforation of GIT	1 (5)	4 (12)	-
Other respiratory	2 (9)	1 (3)	-
Other	0 (0)	6 (18)	-
APACHE II	21.5 [17.0 to 28.3]	23.0 [15.0 to 32.5]	0.74
Maximum LIS	3.3 [3.0 to 3.7]	2.0 [1.7 to 2.7]	< 0.001
SOFA	10 [9 to 13]	10 [8 to 12]	0.33
Duration of mechanical ventilation (days)	8.9 [7.8 to 11.3]	8.5 [6.5 to 11.3]	0.62
ICU length of stay (days)	11.0 [8.6 to 18.7]	12.1 [9.2 to 16.0]	0.81
Spirometry collected on the ward			
FEV_1 (L)	1.45 [1.18 to 1.92]	1.33 [1.06 to 1.94]	0.63
%predicted	53 [38 to 69]	57 [38 to 69]	0.92
FVC (L)	1.95 [1.49 to 2.35]	1.86 [1.51 to 2.61]	0.72
%predicted	55 [43 to 72]	64 [46 to 75]	0.49
FEV_1/FVC	0.81 [0.73 to 0.87]	0.76 [069 to 0.80]	0.12

Data are median [interquartile range]. ALI: acute lung injury; APACHE II: Acute Physiology and Chronic Health Evaluation II; BMI: body mass index; CI: critical illness; FCI: functional comorbidity score; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; GIT: gastrointestinal tract; ICU: intensive care unit; LIS: lung injury score; SF36: Medical Outcomes Study Short Form 36 General Health Survey Version 2; SOFA: sequential organ failure assessment.

3.3.3 Comparison of peripheral muscle strength in the participants with ALI and critical illness

Table 3-2 presents data on peripheral muscle strength for participants with ALI and critical illness. Regarding the completeness of data, 2 participants did not complete the assessment of knee extension strength; one due to fatigue and one due to discharge prior to completion of the assessments. Seven participants did not complete the assessment of shoulder flexion strength; 5 due to a recent sternotomy and 2 due to discharge prior to completion of the assessments. Two participants did not complete the assessment of elbow flexion strength; both were discharged prior to completion of the assessments. Compared with those who completed all assessments of peripheral muscle strength (ALI n = 19 and critical illness n = 27) those who contributed incomplete data (ALI n = 3 and critical illness n = 6) were broadly similar in terms of age, the proportion of males and APACHE II scores (see Appendix 5 for data).

Regarding the comparison of strength in the 2 groups, when compared with those in the critical illness group, those in the ALI group generated lower measures of force during the assessments of shoulder flexion and grip. The proportion of participants with ALI and critical illness who met the criteria for ICU-acquired weakness (ICUAW) as defined by a grip strength < 7 kg for women and < 11 kg for men,[153] was similar (n [%], 6 [27%] vs. 5 [15%], $p = 0.32$). To explore differences in the distribution of peripheral muscle strength, Figure 3-7 presents the peak strength generated by participants in the ALI and critical illness groups, expressed as a proportion of normative reference values.[155,156,319] Within the ALI group, the impairment in elbow flexion strength was less than all other muscle groups. Within the critical illness group, the impairment in elbow flexion and grip strength was less than quadriceps strength.

Table 3-2 Measures of peripheral muscle strength generated by participants with ALI and critical illness

	ALI participants	**CI participants**	***p*-value**
Knee extension (N)	124 ± 67	158 ± 83	0.13
Sample size available for analyses of knee extension	20	33	
Shoulder flexion (kg)	7 ± 3	10 ± 4	0.047
Sample size available for analyses of shoulder flexion	21	27	
Elbow flexion (kg)	10 ± 5	12 ± 4	0.06
Sample size available for analyses of elbow flexion	22	31	
Grip (kg)	13 ± 8	18 ± 9	0.018
Sample size available for analyses for grip	22	33	

Data are mean ± standard deviation. ALI: acute lung injury; CI: critical illness.

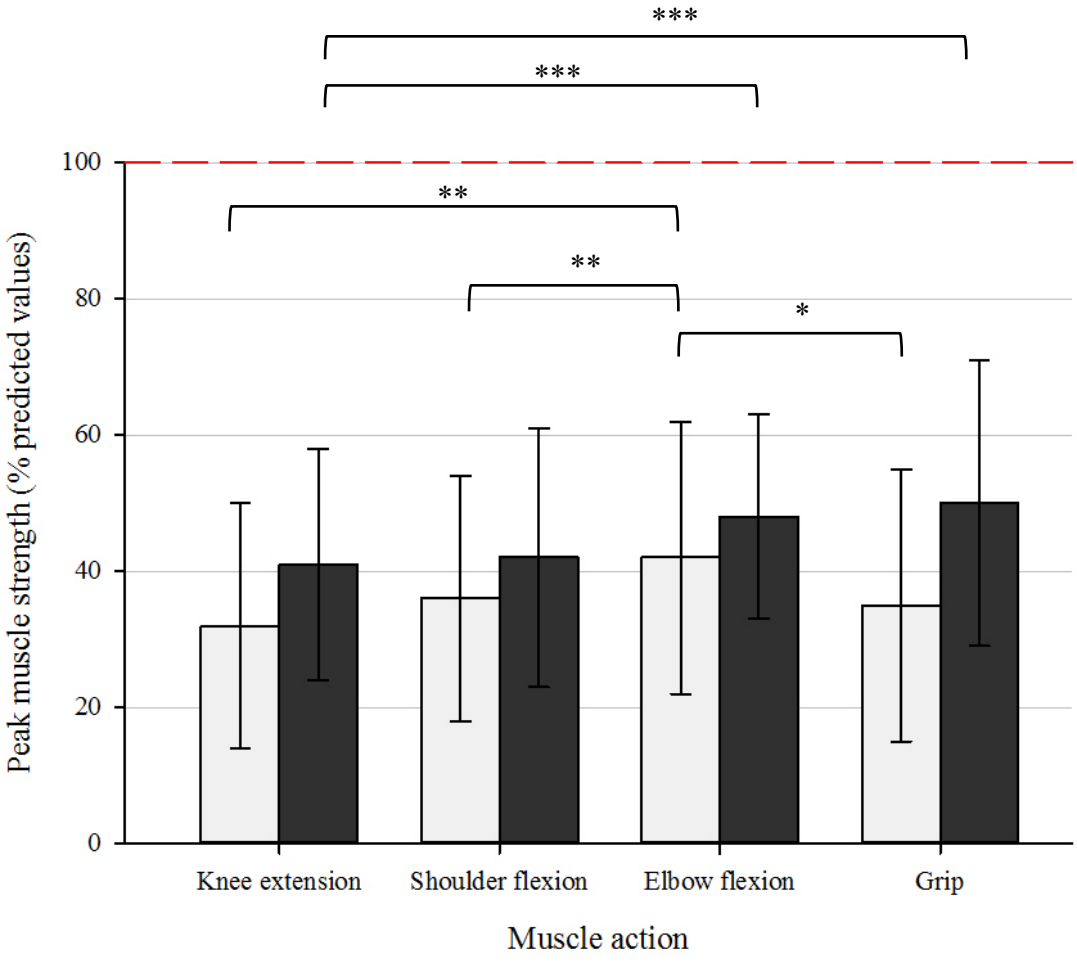

Figure 3-7 Peripheral muscle strength expressed as a proportion of normative reference values for participants with ALI and critical illness

Data are mean and standard deviation. ▭ : participants with ALI; ▬ : participants with CI. ---: Predicted normative strength value for each muscle action. * $p < 0.05$ within ALI group. ** $p < 0.01$ within ALI group. *** $p < 0.05$ within critical illness group.

3.3.4 Comparison of the Berg balance scale score in the participants with ALI and critical illness

Regarding the completeness of the data, 2 participants in the critical illness group did not complete the BBS as they were discharged prior to completion of the assessments. The number of participants with ALI and critical illness who attempted the BBS but scored 0 was similar (n [%] 2 [9] vs. 1 [6]; $p = 0.16$). With those participants who scored 0 included in the analysis, the BBS were similar for those in the ALI and critical illness groups (42 [14 to 51] vs. 43 [17 to 51], $p = 0.67$). When those with a BBS of 0 were excluded from the analysis, the BBS were similar for those in the ALI and critical illness groups (43 [21 to 51] vs. 44 [25 to 51], $p = 0.72$)

3.3.5 Comparison of the time to stand from supine in the participants with ALI and critical illness

Regarding the completeness of data, one participant with ALI and 3 participants with critical illness did not complete the TTS as they were discharged prior to completion of assessments. A further 2 participants with ALI and 8 participants with critical illness did not complete the TTS due to the fatigue and the perceived difficulty of performing this test. Compared with the participants with ALI and critical illness who attempted the TTS (n = 19 and n = 22, respectively) those with ALI and critical illness who did not attempt the TTS (n = 3 and n = 11, respectively) were broadly similar in terms of age, the proportion of males and APACHE II scores (see Appendix 5 for data).

The number of participants with ALI and critical illness who attempted the TTS but were unable to move from supine was similar (n [%] 4 [21] vs. 2 [9]; $p = 0.39$). In those who could perform the test, the participants with ALI (n = 15) and critical illness (n = 20) achieved similar times for the TTS (5.2 [3.8 to 10.1] vs. 6.9 [4.3 to 9.5] s, respectively, $p = 0.66$).

3.3.6 Comparison of the 10-metre walk speed in the participants with ALI and critical illness

Regarding the completeness of data, one participant with ALI and 5 participants with critical illness did not complete the 10MWT as they were discharged prior to

completion of assessments. A further 5 participants with ALI and 9 participants with critical illness did not complete the 10MWT due to the perceived difficulty of performing this test in the same session as the 6MWT. Compared with the participants with ALI and critical illness who attempted the 10MWT (n = 16 and n = 19, respectively) those with ALI and critical illness who did not attempt the test (n = 6 and n = 14, respectively) were broadly similar in terms of age, the proportion of males and APACHE II scores (see Appendix 5 for data).

The number of participants with ALI and critical illness who attempted the 10MWT but were unable to perform the test was similar (n [%] 4 [25] vs. 2 [11]; $p = 0.38$). In those who could perform the test, compared with the participants with critical illness (n = 17), the participants with ALI (n = 12) had a slower 10MWS (1.03 [0.78 to 1.14] vs. 0.78 [0.67 to 0.94] m/s, p = 0.039).

3.3.7 Comparison of the 6-minute walk distance and physiological variables recorded during the 6-minute walk test in the participants with ALI and critical illness

Regarding the completeness of data, one participant with ALI and 5 participants with critical illness did not complete the 6MWT, as they were discharged prior to completion of assessments. Compared with the participants with ALI and critical illness who agreed to attempt the 6MWT (n = 21 and n = 28, respectively) those with ALI and critical illness who did not agree to complete the 6MWT (n = 1 and n = 5, respectively) were broadly similar in terms of age, the proportion of males and APACHE II scores (see Appendix 5 for data).

Of the participants who attempted to complete the 6MWT, 4 participants with ALI and 2 participants with critical illness were unable to stand and/or ambulate and were therefore assigned a 6MWD of 0 m. Of the ALI and critical illness participants who were able to complete the 6MWT, a similar proportion used walking aids (n [%] 9 [53] vs.17 [65], $p = 0.53$), and ambulated with supplemental oxygen (5 [29] vs. 5 [19], $p = 0.48$). With those participants who scored 0m included in the analysis, when compared with those in the critical illness group, those in the ALI group had a lower 6MWD (265 [71 to 328] vs. 165 [53 to 220] m, $p = 0.037$). However, this difference was not significant when the 6MWD was expressed as a proportion of

normal reference values (38 [13 to 48] vs. 21 [8 to 34] %, p = 0.063). When those with a 6MWD of 0 m were excluded from the analysis, the participants with critical illness and ALI had a similar 6MWD when expressed in metres (276 [161 to 332] vs. 180 [120 to 233] m, p = 0.09) as well as a proportion of normal reference values (40 [24 to 49] vs. 32 [16 to 36] %, p = 0.16).

When those with a 6MWD of 0 m were excluded from the analysis, within the ALI and critical illness groups, a similar proportion of participants rested during the 6MWT (n [%] 8 [47%] vs. 11 [42%], p = 1.00). Further, the proportion of participants in the ALI and critical illness groups for whom a rest was enforced due to SpO_2 < 85% was similar (3 [18] vs. 3 [12], p = 0.67) as was the proportion of participants in the ALI and critical illness groups who chose to rest during the test (5 [29] vs. 8 [31], p = 1.00). The data pertaining to those participants who rested during the 6MWT, specifically the number of rests, duration of rest, HR, SpO_2 and dyspnoea at the commencement of the rest, are presented in Appendix 6.

Table 3-3 presents the resting, submaximal and peak, and recovery responses during the 6MWT for the participants with ALI and critical illness. These data excluded those with a 6MWD of 0 m. Resting values for all variables were similar for both groups of participants. At each minute during the test and recovery (minute 7 and 8), the differences between the marginal means calculated in relation to the resting values, were also similar between the ALI and critical illness groups. That is, the rate of change of HR, SpO_2, BP and dyspnoea throughout the 6MWT and during recovery, was similar between the 2 groups. The main symptom limiting performance in both the ALI and critical illness groups was leg/general fatigue with the proportion of participants in each group who experienced this symptom being similar (15 [88%] vs. 22 [85%], p = 1.00). Similarly, the severity of fatigue in both groups also similar (mean [95% confidence interval], 2 [1 to 3] and 2 [2 to 3], p = 0.58). Participants in the ALI and critical illness groups who were not limited by fatigue, reported being limited by dyspnoea (0 [0] % and 2 [8] %), or pain (1 [6] % and 0 [0] %), or had a rest enforced due to desaturation < 85% (1 [6] % and 2 [8] %), respectively. Individual participant data collected before, during and after the 6MWT are presented in Appendix 7.

Figure 3-8 presents HR (y-axis) plotted against time (x-axis). The pattern of responses shows that both the participants with ALI and critical illness had a rise in HR in the first minute of the 6MWT which then plateaued between the second and 6th minute of the test. Figure 3-9 presents SpO_2 (y-axis) plotted against time (x-axis). The pattern of responses shows that both the participants with ALI and critical illness reached nadir SpO_2 within the first 3 minutes of the 6MWT and plateaued until the end of the 6 minutes. The HR and SpO_2 at the 2^{nd} minute of recovery, returned to similar resting values in both the participants with ALI and critical illness.

Regarding observed adverse events, 3 participants with ALI (n = 17) and 3 with critical illness (n = 26) experienced a desaturation to < 85%. For all of these participants, SpO_2 had increased to ≥ 85% within one minute of an enforced rest. No other adverse events were recorded during the 6MWT.

Table 3-3 Physiological variables collected at rest, during the 6-minute walk test and during the 2-minutes of recovery in the participants with ALI and critical illness

		ALI participants, n = 17		CI participants, n = 26		
	Time	Mean	95% CI	Mean	95% CI	*p*-value
HR (bpm)	Rest	98	91 to 106	89	83 to 95	0.06†
	1	118	110 to 126	107	100 to 114	0.64
	2	119	110 to 127	112	105 to 119	0.54
	3	117	109 to 126	112	105 to 118	0.39
	4	119	111 to 127	110	103 to 117	0.96
	5	117	109 to 126	110	103 to 116	0.69
	6	120	111 to 128	111	105 to 118	0.85
	7	106	98 to 115	102	95 to 108	0.29
	8	101	93 to 110	96	89 to 103	0.34
SpO_2 (%)	Rest	96	95 to 97	97	96 to 98	0.07†
	1	93	91 to 94	94	93 to 96	0.73
	2	92	91 to 94	95	93 to 96	0.30
	3	92	91 to 94	94	92 to 95	0.87
	4	93	92 to 95	94	92 to 95	0.51
	5	93	91 to 94	95	93 to 96	0.47
	6	93	91 to 95	95	94 to 96	0.60
	7	94	92 to 96	97	95 to 98	0.20
	8	96	94 to 97	97	95 to 98	0.98
SBP (mmHg)	Rest	119	111 to 126	127	121 to 133	0.11†
	End	121	114 to 129	135	128 to 141	0.22
DBP (mmHg)	Rest	74	69 to 80	77	73 to 82	0.47†
	End	74	68 to 80	79	74 to 83	0.59
Dyspnoea (0 to10)	Rest	1	0 to 2	2	1 to 2	0.29†
	End	3	2 to 4	4	3 to 4	0.80
	8	1	1 to 2	2	1 to 2	0.76

ALI: acute lung injury; CI: critical illness; DBP: diastolic blood pressure; HR: heart rate; SBP: systolic blood pressure; SpO_2: arterial oxygen saturation. †: statistical significance of difference between resting values for participants with ALI and critical illness. All other p-values represent the between-group difference between the marginal means calculated in relation to the resting values (i.e. differences in the rate of change). Numbers 1 to 8 refer to the corresponding minute during the 6-minute walk test. Minute 7 and 8 represent recovery.

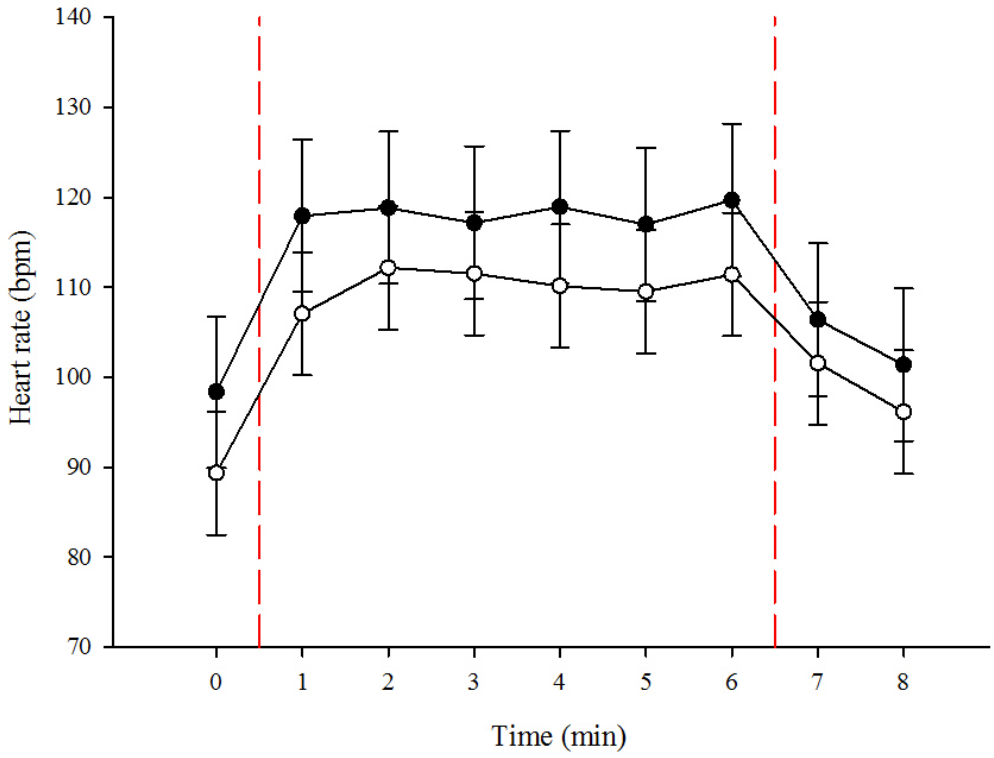

Figure 3-8 Heart rate plotted against time during the 6-minute walk test and during a 2-minute recovery for the participants with ALI and critical illness

Data are mean ± 95% confidence interval of the mean. ALI: acute lung injury; HR: heart rate. —●—: participants with ALI; —○—: participants with critical illness; — — : denotes the end of rest and the start of recovery, respectively.

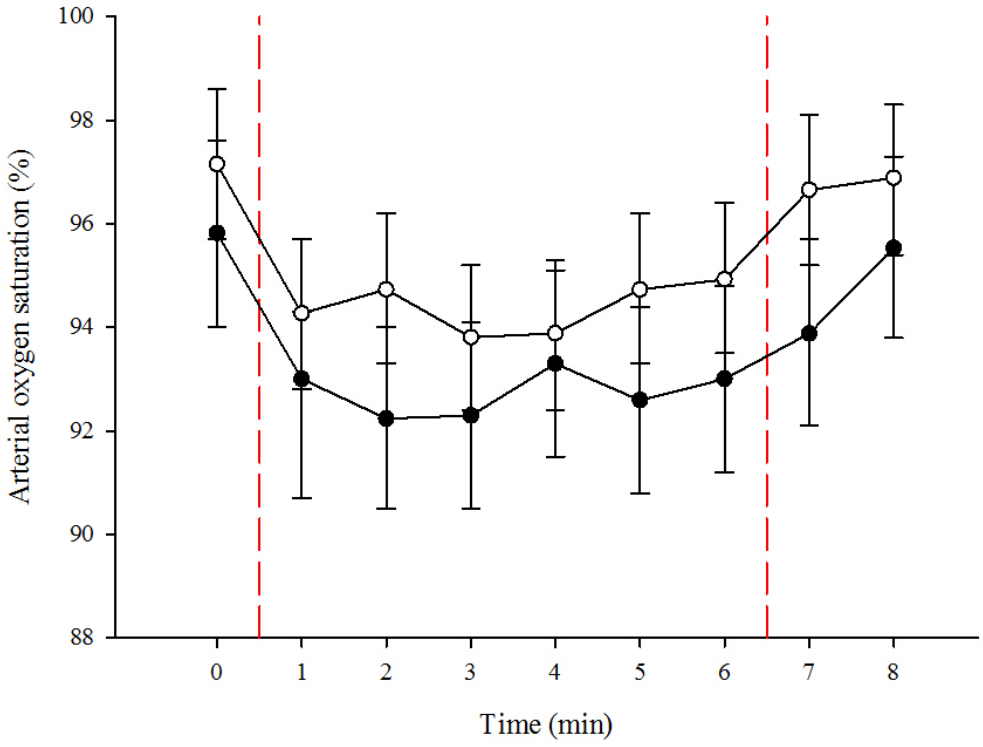

Figure 3-9 Arterial oxygen saturation plotted against time during the 6-minute walk test and during a 2-minute recovery for the participants with ALI and critical illness

Data are mean ± 95% confidence interval of the mean. ALI: acute lung injury; SpO_2: arterial oxygen saturation. —●—: participants with ALI; —○—: participants with critical illness; — — : denotes the end of rest and the start of recovery, respectively.

3.3.8 Relationship between the 10-metre walk speed and 6-minute walk distance

No relationship was found between the 10MWS and 6MWD for those in the ALI group ($r_s = 0.22$, $p = 0.49$) or critical illness group ($r_s = 0.23$, $p = 0.37$). When the participants with ALI and critical illness were examined as one group, with those who scored 0 m in the 6MWT, a weak relationship between the 10MWS and 6MWD was demonstrated ($r_s = 0.37$, $p = 0.046$).

Figure 3-10 shows the relationship between 10MWS and 6MWD. The 10MWS did not explain a significant proportion of the variance in the 6MWD (adjusted $R^2 = 0.049$, $p = 0.13$).

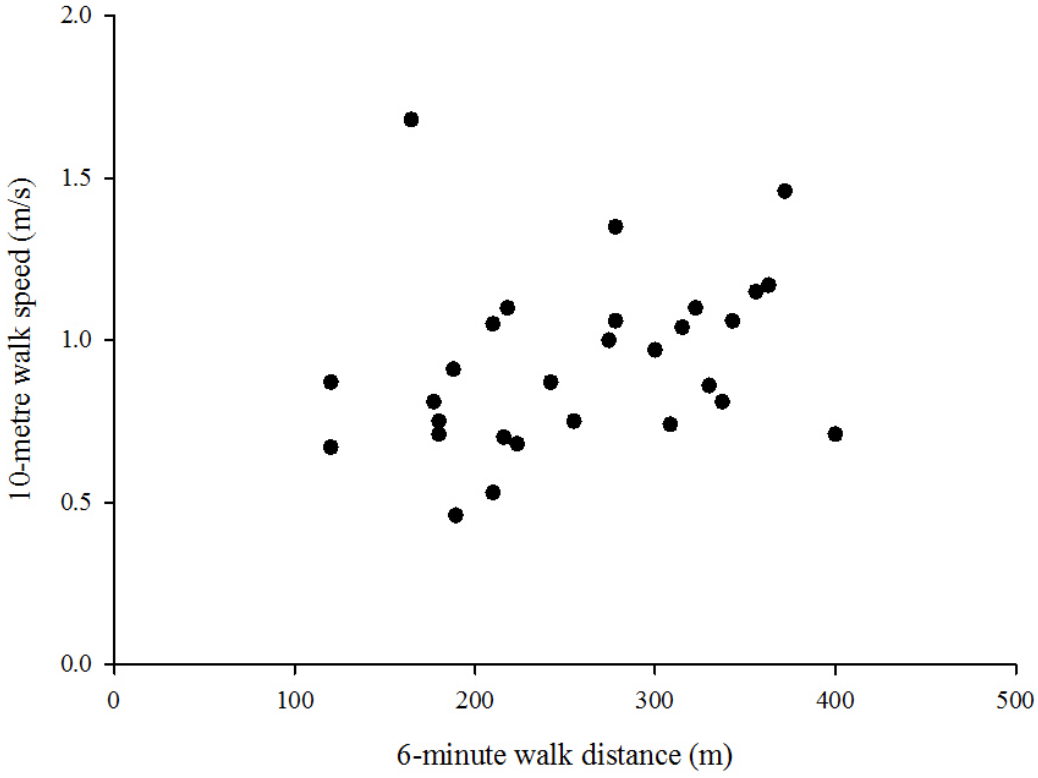

Figure 3-10 Scatterplot between 10-metre walk speed and 6-minute walk distance in the participants with ALI and critical illness

3.3.9 Determining whether the 6-minute walk distance separated those with a ward length of stay of less than, or, greater than or equal to, 2 weeks

These analyses were conducted on all participants who attempted the 6MWT, regardless of the distance achieved (i.e. participants with ALI, n = 21; participants with critical illness, n = 28).

3.3.9.1 6-minute walk distance and length of stay

The length of acute hospital admission was similar for the participants with ALI and critical illness (22.0 [18.0 to 48.0] vs. 25.5 [21.0 to 33.3] days, $p = 0.69$). Similarly, the ICU LOS and ward LOS (calculated as the difference between hospital discharge and ICU discharge) was similar for the participants with ALI and critical illness (10.5 [8.5 to 19.5] vs. 11.0 [9.1 to 15.6] days, $p = 0.93$ and 11.0 [9.1 to 17.7] vs. 11.0 [8.2 to 20.7] days, $p = 0.86$). Data from the 2 participant groups were therefore grouped for the remainder of the analyses. Statistical testing of assumptions potentially contributing to the ward LOS and discharge destination are presented in Appendix 8.

When the relationship between 6MWD (measured in metres) and the ward LOS (measured in days) was examined (using Cox regression), for every 1m decrease in 6MWD, the odds of staying longer in hospital was increased by 1.04 (95% CI, 1.0 to 1.07, $p = 0.002$). Given that this was a significant result, the analyses were re-run; first with participants grouped according to their 6MWD, which increased in 50m increments and second with participants grouped according their 6MWD, which increased in 100m increments.

Figure 3-11 presents the proportion of participants remaining in the hospital, for each 50m increase in the 6MWD measured 7 days after ICU discharge, plotted against ward LOS. The separation between curves was statistically significant ($p < 0.001$).

Figure 3-11 presents the same analysis for each 100m increase in 6MWD. The separation between the curves was again, statistically significant ($p = 0.034$). Visual analysis of Figure 3-11 suggested that lower 6MWDs were associated with a longer ward LOS. This result was more obvious in Figure 3-12, **,** with those who achieved a 6MWD < 100m having a longer ward admission. Therefore, the analyses were re-run

with participants grouped according to whether or not their 6MWD was < 100m or ≥ 100m.

Figure 3-13 presents the proportion of participants remaining in the hospital, for participants with a 6MWD of < 100m and a 6MWD ≥ 100m, plotted against ward LOS ($p = 0.003$).

Figure 3-14 presents a receiver operating characteristic (ROC) curve which was used to determine the ward LOS that a threshold of 100m had optimal sensitivity and specificity to predict. The area under this curve was 0.84 (95% CI, 0.72 to 0.95, $p < 0.001$). The ward LOS with the optimal blend of sensitivity and specificity was 13.9 days (sensitivity=0.77 and specificity=0.79). The odds of survivors of critical illness with a 6MWD < 100m to remain on a hospital ward after ICU discharge for ≥ 14 days was increased by 12.9 (95% CI, 2.8 to 59.7) fold.

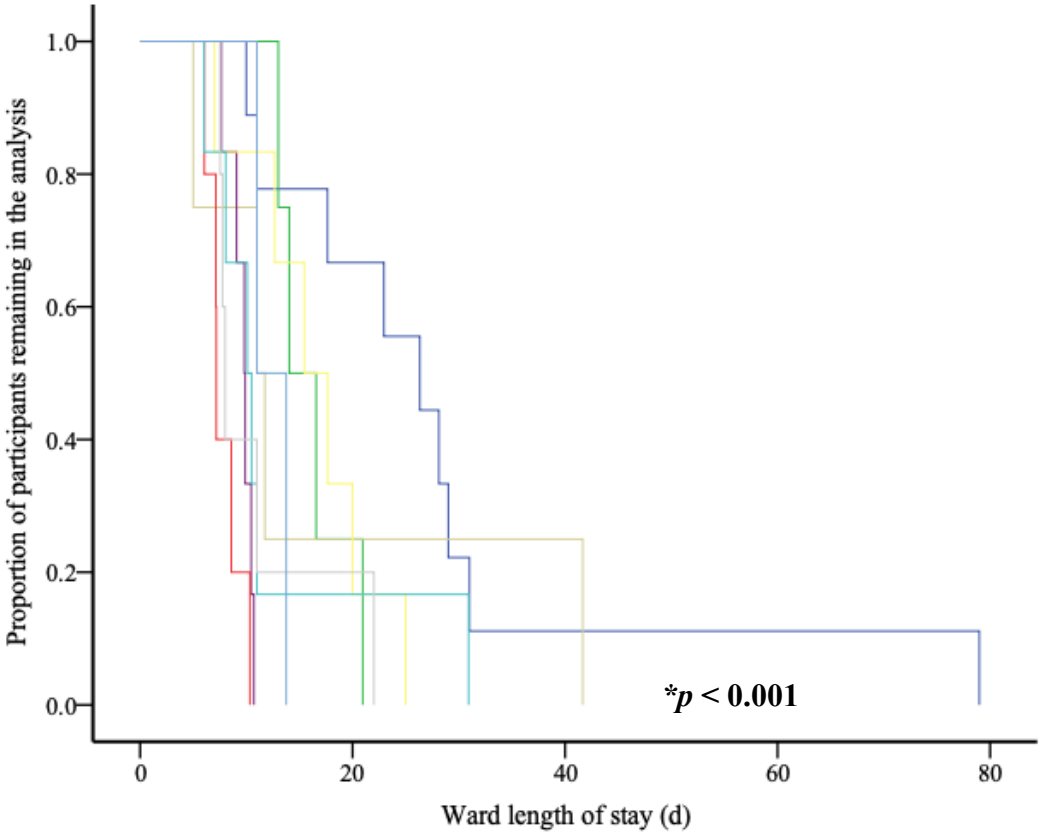

Figure 3-11 Proportion of participants remaining in the analysis plotted against the ward length of stay, with participants grouped into 6-minute walk distance categories of 50m.

0-49m; : 50-99m; : 100-149m; : 150-199m; : 200-249m; : 250-299m; : 300-349m; : 350-399m; : >400m. *Statistical significance refers to the separation between the curves.

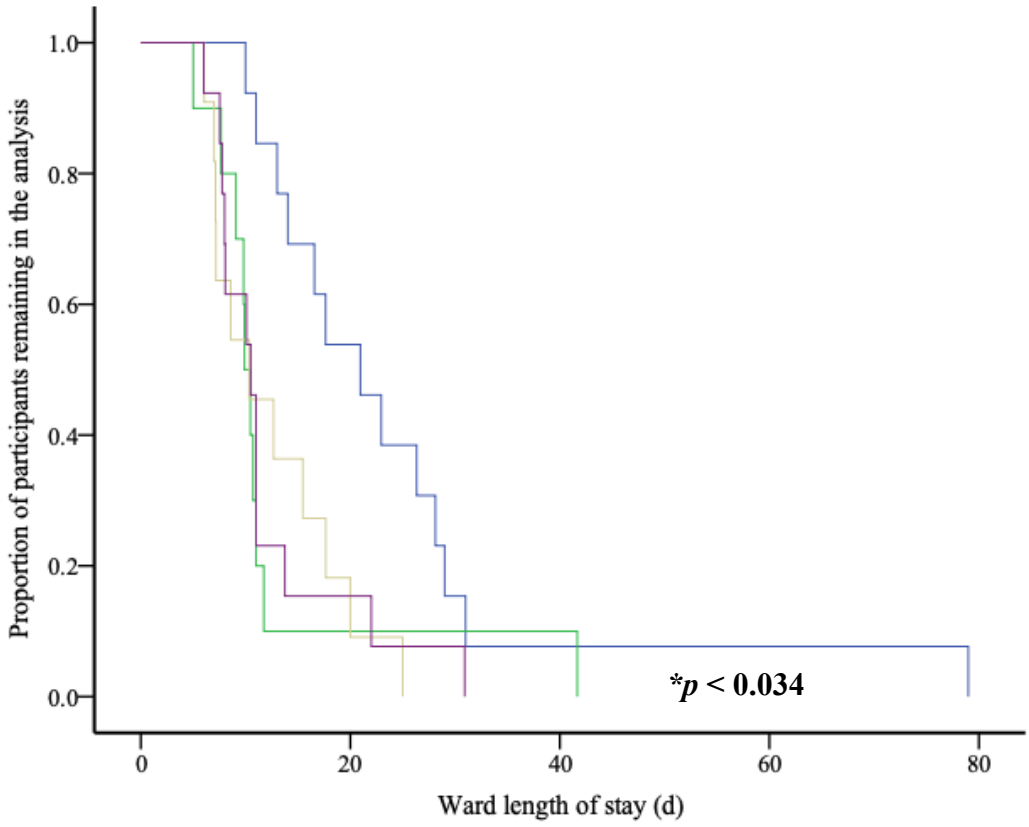

Figure 3-12 Proportion of participants remaining in the analysis plotted against the ward length of stay, with participants grouped into 6-minute walk distance categories of 100m

: < 100 m; : 100-199 m; : 200-299 m; : > 300 m. *Statistical significance refers to the separation between the curves.

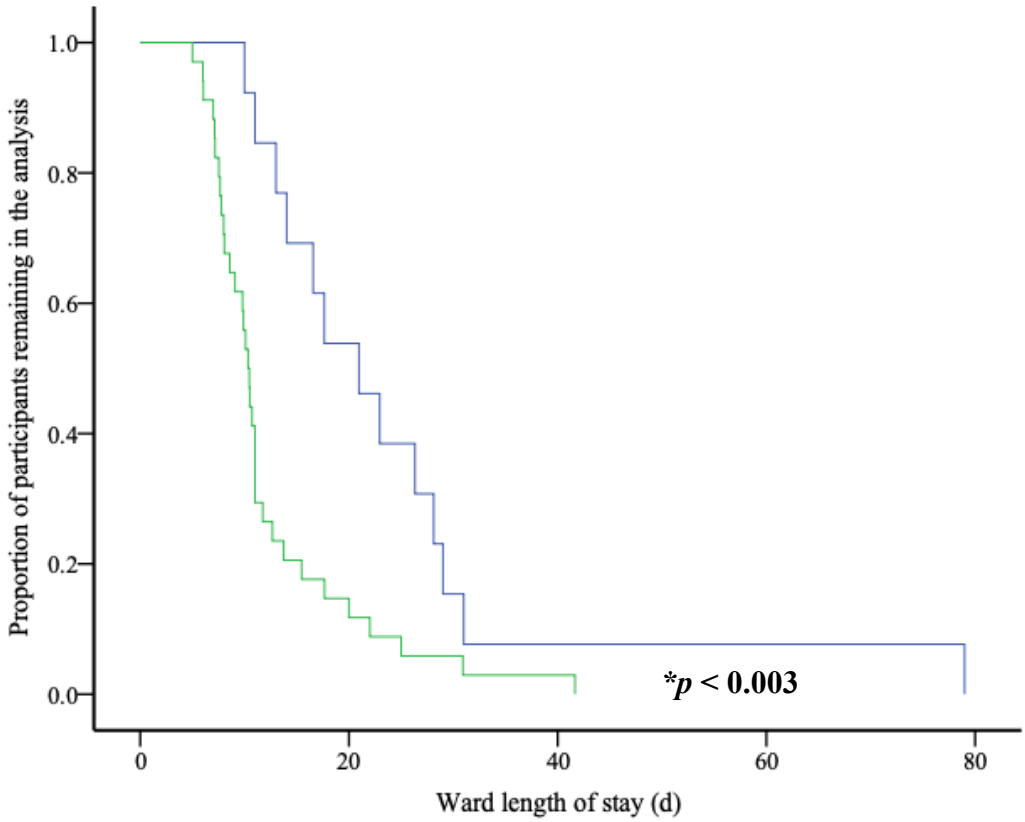

Figure 3-13 Proportion of participants remaining in the analysis plotted against the ward length of stay, with participants grouped into 6-minute walk distance categories of < 100 m and ≥ 100 m

: < 100 m; : ≥ 100 m.*Statistical significance refers to the separation between the curves.

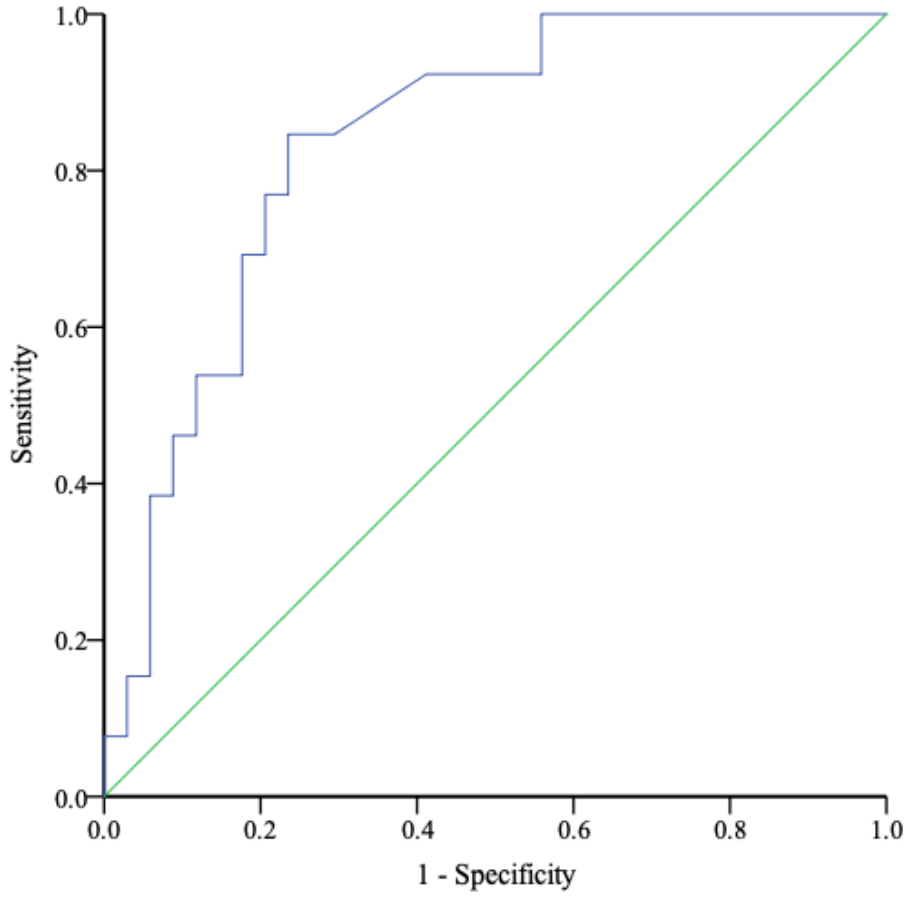

Figure 3-14 Receiver Operating Characteristic curve showing the sensitivity and specificity of a 6-minute walk distance < 100m to predict ward length of stay

3.3.10 Determining whether the 6-minute walk distance predicts discharge destination

Table 3-4 presents the destination to which participants with ALI and critical illness were discharged following their acute hospital admission. To explore whether or not a 6MWD of < 100m measured within 7 days of discharge from ICU to the ward, provided information regarding discharge destinations, these destinations were collapsed into categories of: (i) home; or (ii) another care facility. With data from the 2 participant groups considered together, compared with those participants who were discharged to another facility, the 6MWD of those who were discharged home was significantly greater (60 [8 to 189] vs. 255 [180 to 326] m, $p < 0.001$). The odds of survivors of critical illness with a 6MWD < 100m to be discharge to another facility was increased by 10.6 (95% CI, 2.4 to 46.8) fold.

Table 3-4 Discharge destination for the participants with ALI and critical illness

Transfer destination	ALI participants (n = 21), n (%)	CI participants (n = 28), n (%)
Regional hospital	1 (5)	0 (0)
Home alone with no assistance	1 (5)	0 (0)
Home alone with assistance	1 (5)	4 (14)
Home with someone who did not provide assistance	0 (0)	4 (14)
Home with someone who was providing assistance	8 (38)	11 (40)
Rehabilitation facility	9 (42)	9 (32)
Supported residential care	1 (5)	0 (0)
Hostel/Nursing Home	0 (0)	0 (0)

ALI: acute lung injury; CI: critical illness.

3.4 Discussion

3.4.1 Overview

Within 7 days of discharge from ICU, this study collected and compared a range of functional measures, including peripheral muscle strength via dynamometry, in people who survived an admission to ICU with a diagnosis of ALI, with a group who survived a critical illness other than ALI. Care was taken to ensure that these 2 groups were of similar age and gender proportion and had similar markers of disease severity. Using the data from these 2 groups considered together, the value of functional exercise capacity to estimate LOS and discharge destination was also evaluated. The main findings of this study were, compared with survivors of critical illness, those people who had survived an admission to an ICU with critical illness including ALI were characterised by greater reductions in upper limb peripheral muscle strength, exercise capacity and walk speed. The 6MWD was prognostic of both ward LOS and discharge destination.

3.4.2 Peripheral muscle strength

This study is the first to report peripheral muscle strength, measured by dynamometry, in a group of adults who survived an ICU admission for ALI compared with a group who survived an ICU admission for another critical illness shortly after discharge from ICU to the ward. The participants with ALI and critical illness were similar in terms of anthropometric and demographic data, pre-admission functioning, severity of illness and spirometric lung function. For both groups, all muscle actions demonstrated notable weakness, whereby the median value for all actions was < 50% predicted with knee extension, being the most profoundly affected. This global impairment has been noted previously in survivors of critical illness using the Medical Research Council (MRC) scoring system during ICU and at hospital discharge. Measured during the ICU admission, 2 interventional studies demonstrated total MRC scores of 22/40 and 26/40 (control and intervention groups, respectively),[214] and MRC sum scores (MRC-SS) of (mean ± SD) 40 ± 11/60 and 56 ± 4/60, respectively.[213] At hospital discharge, the MRC-SS in 3 separate interventional studies, have been demonstrated to be higher due to natural recovery but still represent weakness (median [IQR] of control and intervention groups, 48 [0

to 58] and 52 [25 to 58],[174] mean ± SD, 47 ± 14 and 52 ± 11,[219] and 56 [52 to 60] and 56 [50 to 60],[200] respectively). While the global impairment in strength values in the current study are consistent with the impairment noted in previous studies at the same time point in recovery, the current study assessed strength using dynamometry, which is more sensitive at quantifying weakness than the MRC grades reported in the earlier work, particularly in people who can move through full range against gravity.[152,153]

The specific cause of the general and profound impairment noted in the strength in all peripheral muscles in the current study is likely to involve the mechanical unloading associated with bed rest and which is further enhanced by electrolyte distrubances[146,147] and widespread inflammation inherent in ARDS,[75,78] and which leads to depressed protein synthesis, reduced ratio of protein to deoxyribonucleic acid (DNA) in skeletal muscle, and subsequent muscle catabolism.[40] The more profound impairment noted in the lower limbs is also possibly due to a detraining effect of the lower limbs, whereby low levels of ambulation have been reported in many Australian ICUs and physical activity once discharged to the ward is also low.[127,129] Comparatively, the spontaneous movement of the distal upper limbs in ICU, and the subsequent requirement to be increasingly independent in activities of daily living once discharged to the ward, such as brushing teeth and hair, may minimise the impairment in elbow flexion strength.

Regarding differences in strength between the groups, the difference is consistent with previous reports suggesting an association between sepsis and a low PaO_2/FiO_2 ratio, a criterion for diagnosis of ALI, with increased loss in peripheral muscle strength and cross-sectional muscle area when compared with patients admitted to ICU for other pathologies.[40,140] This is supported by data from a single study by Baldwin and colleagues[151] conducted in a group (n = 17) diagnosed with sepsis which reported measures of peripheral muscle strength approximately 2 weeks after admission to ICU. In this study the measure of elbow flexion strength more closely approximated those measures demonstrated in the current study for the participants with ALI rather than the participants with critical illness (median [IQR], 10.2 [5.9 to 17.6][151] vs. mean ± SD, 10 ± 5 and 12 ± 4 kg, respectively).[151] The pathological processes inherent in ALI and which are similar to that observed in sepsis, that of,

excessive inflammatory responses, endothelial and epithelial damage and disruption to the alveolar–capillary membrane,[112] appear to lead to greater impairments in strength.

The variation in degree of impairment across muscle actions suggests a heterogeneity in the distribution of muscle weakness in one or both groups. Specifically, in spite of the statistically significant difference between the ALI and critical illness participants for grip strength, the proportion of participants who met the criteria for ICU-AW in the 2 groups, using the grip strength criterion described by Ali and colleagues,[153] was similar. The distribution of muscle strength in survivors of critical illness has not been reported previously. While ICUAW is defined as a global weakness, it does not necessarily reflect a uniform impairment in each muscle action. The use of the MRC or a single hand grip strength value, while identifying the presence of ICUAW, does not adequately provide information regarding the distribution of muscle weakness. In a study with a cohort of 107 patients admitted to a surgical ICU with a median duration of mechanical ventilation of 1.5 days (25^{th}-75^{th} percentiles, 0 to 4.5d), global muscle strength measured during the ICU admission predicted mortality and LOS (OR [SE], 0.94 [0.02], $p = 0.006$) when grip strength did not (1.00 [0.03], $p = 0.74$).[334] Single measures of strength such as grip strength should therefore not be used to characterise weakness in different groups of patients within the ICU.

The data in the current study suggest that knee extensor strength was severely reduced across both groups. Given their role in functional mobility and ambulation, there has been increased interest in knee extensor strength compared with other muscles. This is likely to explain why the strength of this muscle has been measured using more sophisticated methods such as dynamometry rather than just simply reporting MRC grades. The impairment seen in this study in knee extension strength in the participants with ALI and critical illness (124 ± 67 N and 158 ± 83 N) was similar to that reported in earlier work quantifying knee extension strength during the ICU admission (117 [37 to 369] N)[151] and at ICU discharge (1.86 ± 0.78 N/kg, equivalent to 158 ± 66 N).[171]

Data reported in the current study overcomes some of the methodological limitations of these earlier studies that have reported knee extension strength using

dynamometry. Specifically, the assessment of knee extension strength undertaken in these earlier studies was performed in a suboptimal patient position (supine).[151,171] Assessments in supine will underestimate the strength of the knee extensors as these muscles need to first lift the leg against gravity; a load which is not considered in the measurement. Further, the use of HHD by the earlier studies to measure isometric knee extension strength assumes that the tester can meet and exceed the maximum force-generating capacity of the knee extensors and when this is not the case, the measurement of knee extensor force will be underestimated.[160] In comparison, the current study eliminated gravity by performing the assessment in sitting and eliminated assessor variance by using a custom designed fixed force gauge. In doing so, the current study reports values that are a more robust reflection of the participant's strength. Further, as the current study also collected measures of symptoms during exercise, these data show the impact of this weakness. Specifically, during the 6MWT a large proportion of the participants reported the limiting symptom to be leg and general fatigue rather than dyspnoea.

3.4.3 Functional ability, ambulation and exercise response

This study reported functional outcomes of BBS, TTS, and 10MWS and the functional exercise capacity outcome of 6MWD. Both the BBS and TTS were impaired but similar in the participants with ALI and critical illness. Compared with the participants with critical illness, the participants with ALI had a longer 10MWS representing a slower speed, and a lower 6MWD, although the 6MWD when presented as a proportion of predicted normative reference values was similar. The pattern of responses during the 6MWT were similar for both participant groups.

The BBS for the participants with ALI and critical illness were similar (42 [14 to 51] and 43 [17 to 51], respectively). These values are of note as a BBS of < 45-51/56 predicts an increased risk of falling.[335-338] The increased risk of falls in survivors of critical illness has been reported previously via a retrospective data analysis of 190 adults who were mechanically ventilated for > 7 d and discharged to the ward.[172] This study showed that 17% of the patients fell at least once during the ward admission. When compared with the non-fallers, fallers were younger (53.2 ± 17.9 vs. 44.1 ± 18.3 yr, $p = 0.009$), while APACHE II scores, and length of ICU and hospital admission were similar between groups.[172] Compared with the retrospective

data analysis,[172] the participants with ALI and critical illness in the current study were of a similar age (51.7 ± 18.2[172] vs. 50.0 [42.0 to 66.3] and 57.0 [52.0 to 63.3] yr, respectively), had a slightly higher APACHE II score (20 ± 8[172] vs. 21.5 [17.0 to 28.3] and 23.0 [15.0 to 32.5], respectively) and shorter duration of ICU admission (14.0 ± 9.5[172] vs. 11.0 [8.6 to 18.7] and 12.1 [9.2 to 16.0] d, respectively). The low BBS in the current study supports previous reports that survivors have impaired balance and therefore are a higher risk of falling. Ready identification of patients discharged from ICU to the ward after an admission > 4 days, through the use of coloured alert bands as is advocated by the New South Wales health service for those with an elevated falls risk, is advocated.

The TTS of the participants with ALI and critical illness was 5.2 and 6.9 s, respectively, with (n [%]) 4 [21] and 2 [9] of the respective participants who attempted the test unable to complete the task. Normative data for TTS are not available for a healthy population, but in people living with early to mid-stage Parkinson's disease a similar TTS has been reported (3.35 ± 0.92 to 6.42 ± 4.16 s).[339] The TTS test is a simple measure of the ability to perform activities of daily living and may be useful to quantify functional ability as part of a battery of tests, in the early recovery phase after an ICU admission. The psychometric properties of the TTS however, have not been examined within survivors of critical illness, with reliability testing limited to that in the geriatric population.[340] Further investigation into the utility and validity of this test in survivors of critical illness is required.

Regarding the 10MWS, compared with the participants with critical illness, the participants with ALI were slower. While SSWS as measured by the 4-metre walk speed, in survivors of ARDS has been reported at 6 months (n = 183)[15] and 36 months (n = 62)[14] following ICU discharge, walking speed during the initial hospital admission has not been reported in survivors of critical illness. Faster SSWS walk speed reported in the older population has been shown to be related to greater lower limb strength.[341] However, the 10MWS is likely to be influenced by several factors, including dynamic balance and confidence.[50] Earlier work in an elderly population aged 69 ± 4 yr, demonstrated that balance confidence correlated to the fastest speed attempted on a treadmill (Spearman's rho=0.85, $p<0.001$.[342] The slower 10MWS, using MWS, observed in those with ALI when compared with the participants with

critical illness, in the presence of similar knee extension strength may be associated with factors which were not assessed in the current study, such as dynamic balance and confidence. The MWS of those with ALI in the current study (0.78 [0.67 to 0.94] m/s) however, when compared with other populations, was similar to that reported in a meta-analysis of people aged > 70 years in an acute care hospital setting (estimate [95% CI], 0.75 [0.59 to 0.90] m/s).[343] The utility of the MWS lies in the information it provides regarding the rate of force generation in the triceps surae muscle group whereby a greater MWS has been shown to be associated with a greater rate of force development.[344] This information is complimentary to measures of strength provided by MMT and dynamometry. The 10MWS is a simple and time efficient test to perform and may provide information regarding functional performance in the community specifically for activities requiring increased and varied speed of ambulation.

Regarding the 6MWT and specifically the safety of its use in survivors of critical illness within 7 days of discharge to the ward from ICU, the pattern of response of HR during the test were similar in the participants with ALI and critical illness. The patterns of response represent an increase in HR appropriate during exercise, with a return to pre-test values at completion.[345] In the participants with ALI and critical illness, a decrease in mean SpO_2 to 92% and 95% during exercise, respectively, occurred and is consistent with impaired ventilation perfusion matching, pulmonary vascular dysfunction or cardiac dysfunction observed in 25-50% of patients with ALI or sepsis.[345-350] Additionally, all enforced rests were solely due to a SpO_2 < 85%, all of which returned to a SpO_2 > 85% within one minute of the enforced rest. There were no further adverse events during or immediately after the test. This information suggests that 6MWTs performed with survivors of ALI and critical illness shortly after discharge from ICU to the ward are safe.

The 6MWD reported in the participants with ALI and critical illness were 165 [53 to 220] m and 265 [71 to 328] m respectively representing a significant impairment in functional capacity.[351,352] One study only has reported the 6MWD in survivors of critical illness on discharge from ICU. The intervention study by Denehy and colleagues[60] demonstrated a similar 6MWD to that reported in the participants with ALI in the current study (188 ± 126 m and 146 ± 79 m, usual care and intervention

groups, respectively). However, the 6MWD for the participants with critical illness in the current study was greater than that in the study by Denehy and colleagues.[60] Given that, when compared with the sample studied by Denehy and colleagues, [60] the sample in the current study were characterised by several factors associated with greater physical impairment such as a higher APACHE II score, longer duration of mechanical ventilation and ICU LOS,[122,141,142] the higher 6MWD in the current study was somewhat surprising. When compared with the 6MWD reported by Denehy and colleagues,[60] the greater distance reported in the current study was possibly due to the somewhat younger age (60[60] vs. 50 yr) coupled with the greater opportunity for natural recovery by the sample in the current study. The 6MWT was performed in the current study a mean of 6 days after ICU discharge in comparison to 'at ICU discharge', as presented in the previous study's methodology, representing a shorter time of natural recovery. The specific timing of the test in the previous study was not reported. As previously discussed (see section 2.4.3.2), given the 6MWT was performed only once the participant was able to ambulate > 10m,[198] it is possible that this test was delayed until following ICU discharge. Considering all factors, it is unclear why the participants in the current study with critical illness present with a significantly greater 6MWD than that reported by Denehy and colleagues.[60] Further large, multi-site cohort studies are required to understand the heterogeneity present in functional exercise capacity of survivors of critical illness shortly after discharge from ICU.

When examining the differences in 6MWD between the 2 participant groups, compared with the participants with ALI, the absolute values of the 6MWD for those with critical illness were lower (265 [71 to 328] and 165 [53 to 220] m, $p = 0.037$), while a difference in the 6MWD when expressed as a proportion of the normal reference values was less clear (38 [13 to 48] vs. 21 [8 to 34] %, $p = 0.063$). The inconsistency in these between-group differences reaching $p < 0.05$ is likely to reflect, at least in part, that the regression equations used to estimate a normal 6MWD explained only 40 and 43% of the variance in the 6MWD in males and females, respectively.[333] The large degree of variance that is unaccounted for in the regression equations may have diminished the magnitude of between-group difference in 6MWD when presented as a proportion of reference values in contrast to the difference in absolute values. Nevertheless, when expressed in metres, the

difference in 6MWD between the groups is clinically important. Earlier work has demonstrated that a minimal important difference for the 6MWD in people recovering from respiratory failure is approximately 30m.[203] The difference noted between the 2 participant groups in the current study exceeded this minimal important difference. Further, the shorter 6MWD for the ALI participants is consistent with the trend for this group to have greater impairment in quadriceps strength.

With all participants grouped together, a weak association was demonstrated between the 6MWD and the 10MWS ($r_s = 0.37$, $p = 0.046$). Nevertheless, using linear regression analysis, the 10MWS was not an independent predictor of the 6MWD ($p = 0.08$). In previous reports, self-selected walking speed over 4 meters has been shown to be associated with 6MWD in a cohort of 184 survivors of ARDS at both 6 and 12 months following ICU discharge ($r = 0.56$, $p < 0.001$ and $r = 0.65$, $p < 0.001$, respectively).[15,203] Differences in these findings may reflect that the 6MWT is more likely to be undertaken as a self-selected speed, whereas the 10MWS as measured in this study is a test of maximum walking speed.

3.4.4 Predictive value of functional ambulation

This study identified that the 6MWD < 100m measured within 7 days of discharge from ICU to the ward, provides information regarding the odds of the ward LOS ≥14 days and the odds of being discharged to another facility. In survivors of critical illness, the prognostic value of 6MWD measured during the hospital admission, has not previously been investigated. In this population, during a hospital admission, other measures of physical capacity have been associated with patient outcome. Specifically, global muscle strength and handgrip strength measured during the ICU admission have been shown to predict mortality and LOS.[153,334] Further, a shorter 6MWD measured 3 months after hospital discharge has been associated with greater odds of readmission in the subsequent year.[33] The 6MWD as measured shortly after discharge from ICU, and used as a predictor of ward LOS and discharge destination is novel and adds to the small body of literature which provides information regarding recovery following a critical illness.

The cut point of a 6MWD < 100m identified in the current study is likely to reflect those survivors of critical illness whose physical function, and specifically whose functional exercise capacity, are the most profoundly affected. The ability to differentiate those patients who will require a longer hospital admission due to functional impairment and the need for further rehabilitation after discharge, is of benefit in order to provide targeted rehabilitation, discharge planning and information sharing with the patient and family. However, although the data from the current study shows that the odds of being discharged to another facility with a 6MWD < 100m is 10 times greater than if the patient had a higher 6MWD, the confidence interval around this is substantial. Further study is required to increase the precision around the estimate of the odds ratio. Nevertheless, as the lower limit of the confidence interval was 2.4, these results suggest that the true effect is at least a 2-fold increase in the odds of being discharged to another care facility (but could be as great as a 46-fold increase). In spite of the wide confidence interval, this finding is still of importance when planning discharge in this group. That is, where 6MWD is < 100m, referral to a rehabilitation facility should be anticipated.

The use of physical outcomes to predict discharge destination has been demonstrated most notably in those living with stroke whereby, a higher Barthel Index score, reflecting greater functional independence on admission, was shown to be a predictor of a more favourable discharge destination such as home, or an inpatient rehabilitation facility.[353,354] In survivors of stroke, an improvement in motor function over time during the acute admission, as measured by an increase in the Functional Independence Measure motor score from admission to discharge had no effect on the discharge destination ($p = 0.62$).[355] Further study is needed in ICU survivors, because if these data hold true in this population, it would suggest that the use of early assessment of functional ability, may be equally as sensitive at predicting discharge destination as assessment at the end of the hospital admission. Further study to explore and refine the predictive value of 6MWD in survivors of critical illness during the acute admission is warranted.

3.4.5 Limitations

The incidence of ALI in the participating ICU's was markedly lower than anticipated and recruitment was challenging. As a result, the required sample size required to

achieve adequate power was not attained. This was in spite of implementing numerous strategies to optimize both screening processes and recruitment. Further, data from the entire sample was available for only one outcome measure, that of grip strength. Incomplete data collection for the other outcomes was related to a number of factors including physical inability to perform an assessment, refusal and fatigue. However, those who completed the assessment vs. those who did not complete the assessment for each outcome measure were broadly similar in terms of age, sex and acuity of admitting illness. Finally, the order of muscle groups tested varied between participants which may have influenced the peripheral muscle strength results. The variation in testing order was considered necessary in order to limit unnecessary exertion and thereby optimise the likelihood of a maximal performance. However, given the strict and detailed protocol by which the final strength measurement was attained, it is possible, but unlikely that the lack of standardization influenced the final strength results.

3.4.6 Clinical implications and conclusions

The data presented in this study has shown that within 7 days of discharge from ICU to the ward, following an ICU admission for ALI and critical illness, people present with considerable impairments in strength, measures of balance, maximal walking speed and functional exercise capacity. Further, compared with people surviving an admission to ICU for critical illness, those with ALI experience greater impairment in upper limb strength, 10MWS and 6MWD. The 6MWD < 100m measured at this time point can be used to predict ward LOS and discharge destination.

The impairment noted for all muscle actions, and the decreased functional capacity as it potentially relates to both weakness and impaired oxygen delivery, suggest a whole-body program of rehabilitation is indicated to ameliorate the effect of a critical illness. Rehabilitation commencing in the ICU is likely to be an important component of the recovery process.[174,271,278,280] Once discharged to the ward, the dilemma of optimising the opportunity to engage in rehabilitation that continues to be performed at the highest level of the patient's function, remains challenging. In the acute care setting the availability of rehabilitation staff is often limited and rehabilitation activities have been demonstrated to occur less frequently on the ward after discharge from ICU.[244] Physical activity levels in survivors of critical illness on

the ward and after hospital discharge have also been demonstrated to be very low.[126,129,240] The BBS measured in the participants in the current study, indicate that, consistent with previous reports, survivors of critical illness are at significant risk of falling.[172] Unsupervised ambulation, with or without a walking aid, therefore may not be safe or appropriate for all patients. Identification of those at higher risk of falling using colour coded wrist bands is advocated. Prevention of the factors contributing to falls in this population are also pertinent including increasing lower limb strength, decreasing the incidence of delirium and consideration of the built environment.[356,357] For those who are identified as safe to ambulate independently, increasing the opportunity to engage safely in physical activity, will likely contribute to the optimisation of strength and functional capacity gains and prevent further functional decline. One of the strongest direct correlates of functional decline in older patients is in-hospital mobility.[358] A study examining expectations around physical activity during a ward admission indicated that 38% of the 24 participants expected to remain in bed during their hospital admission.[359] A shift in paradigm from a model of care encouraging bed rest to a model of care which encourages and normalises activity for patients in hospital is necessary.[360]

This study has demonstrated that using a 6MWT in survivors of critical illness shortly after discharge from ICU to the ward appears to be safe and feasible. The test itself is not onerous in duration and provides useful information regarding the patient's trajectory of recovery which can be used by the patient and their family during discharge planning. While many survivors of critical illness experience impairments in their physical capacity, the trajectory of recovery has not been fully characterised. Further to the prognostication value of the test in this population, it is possible that the 6MWT provides information to optimise management, potentially to provide information regarding prescription of walking training as described in the pulmonary rehabilitation literature.[361] Regarding the feasibility of use of the 6MWT in this population during the acute ward admission carries, however, it should be noted that added considerations are required when compared with its use in populations with chronic respiratory disease.[331] As mentioned, the risk of falling and the high proportion of participants in the current study requiring gait aids means that assistance may be required for patients when conducting the test and therefore increasing the requirement for resources.

This study identified that those with ALI, in spite of the similarity in characteristics with the participants with critical illness, demonstrated greater impairment in peripheral muscle strength, and a lower 6MWD and 10WS when presented as absolute values. These results suggest that the diagnosis of ALI may lead to a greater degree of physical impairment in survivors of critical illness when measured shortly after discharge to the ward. Identification of those discharged from ICU who are most profoundly affected and who will benefit from targeted management may be beneficial.[43] Indeed, one of the criticisms of rehabilitation programs implemented in survivors of critical illness is that participants are not stratified according to disability of weakness, potentially dampening the effect of the intervention by including those with minimal impairment.[43] Clinicians should suspect profound impairment in survivors of ALI with the aim of providing targeted rehabilitation to ameliorate the impairments.

CHAPTER 4 Study 2

4.1 Overview

This chapter presents Study 2, which explores the following research questions:

(i) Do adults who have survived an admission to an intensive care unit (ICU) for acute lung injury (ALI), at 6 weeks after discharge from an acute care facility, demonstrate differences in peak or submaximal exercise responses measured during an incremental cycle ergometry test (ICET), when compared with a healthy group? If so, what is the underlying cause of their exercise limitation?

(ii) Do adults who have survived an admission to an ICU for ALI, at 6 weeks after discharge from an acute care facility, demonstrate differences in daily physical activity (PA) and sedentary time (ST), peripheral muscle strength, health-related quality of life (HRQL) and fatigue, when compared with a healthy group?

This chapter is divided into 3 sections: Methodology, Results and Discussion.

4.2 Methodology

Section 4.2 presents information pertaining to the methodology used in Study 2. Specifically, section 4.2 presents information related to approvals from the relevant Human Research Ethics Committees, recruitment of participants, outcome measures, and statistical analyses.

Parts of this chapter related to the exercise responses in the survivors of ALI during the ICET, have been published:

Mackney J, Jenkins S, Havill K, Harrold M, Hill K. Abnormal exercise responses in survivors of acute lung injury measured during cardiopulmonary exercise testing: an observational study. *Journal of Cardiopulmonary Rehabilitation and Prevention.* 2019 (39):E16-E22.

4.2.1 Study design and participants

This study was cross-sectional and observational in design. Two groups of participants were recruited: participants with ALI and healthy participants.

4.2.1.1 Approval from the Human Research Ethics Committees

The study was approved by the Human Research Ethics Committees of Hunter New England Area Health (HREC 10/11/17/4.06), Curtin University (HR 27/2011) and The University of Newcastle (H-2011-0029) (Appendix 1 and Appendix 2).

4.2.1.2 Recruitment and study criteria for participants with ALI

Patients admitted to the ICU at John Hunter Hospital (JHH) or Calvary Mater Newcastle hospital (CMN) were screened on a daily basis to determine their eligibility to participate in this study. Screening was to occur between March 2011 and December 2013 to enable completion of data collection in the time frame specified by the associated PhD candidacy.

Inclusion criteria for participants with ALI comprised: (i) aged over 18 years; (ii) had an ICU admission during which they met the criteria for ALI (section 3.2.1.2)[1]; and (iii) resided within one-hour travel of the JHH (so that travel time to attend the assessments required for this study was reasonable). Exclusion criteria comprised: (i) the presence of any neurological or musculoskeletal condition likely to adversely affect the ability to mobilise safely, including documented neurological disease and orthopaedic injuries with mobility restrictions; (ii) non-ambulant prior to admission; (iii) treatment or diagnosis of malignant cancer within preceding 12 months; (iv) history of recent major pulmonary resection; (v) poorly managed psychiatric disorders; (vi) an inability to follow commands; and (vii) inability to understand English. Eligibility for inclusion was assessed according to these criteria and did not rely on a clinical diagnosis of ALI to be made by the treating medical team.

4.2.1.3 Study protocol used for participants with ALI

Consent to be included in the study was obtained via the participant's next of kin during their ICU admission, and thereafter, by the participant's themselves once they were deemed capable of doing so by a senior treating medical officer and prior to discharge from hospital. In the event that the patient was to be discharged from

hospital and a decision had not been made regarding participation, consent was obtained from the proxy or the patient to contact the patient at home in order to discuss participation. Information pertaining to the participants' ICU and ward admission, including measures of severity of illness and prognostic indicators were extracted from the patients' notes on a daily basis by the candidate. Intensive care length of stay (LOS) was recorded upon ICU discharge.

Four weeks after hospital discharge, contact was made with the participants via phone or email to arrange 2 assessment sessions with the finalised details mailed to the participants. Six weeks after discharge from an acute care facility (acute care hospital or acute rehabilitation facility), participants with ALI were invited to attend 2 assessment sessions, separated by 7 days. Over the course of these 2 assessment sessions, demographic and anthropometric information were collected, and the following measures were made: (i) 6-minute walk distance (6MWD); (ii) resting lung volumes, gas transfer and maximal respiratory pressures; (iii) peak and submaximal exercise responses during a symptom-limited ICET; (iv) peripheral muscle strength via a custom-designed fixed force gauge, hand-held dynamometry or a hand dynamometer; (iv) HRQL via the Medical Outcomes Study Short Form 36 General Health Survey Version 2 (SF36); and (v) fatigue via the fatigue severity score 7-item version (FSS) questionnaire. Participants were also required to wear a portable metabolic monitor (SenseWear® armband [SAB] [BodyMedia Inc., Pittsburgh, Pennsylvania, USA]) to measure PA and ST.

Regarding the order in which these measures were made, demographic and anthropometric data were always collected during the first assessment session and the SAB was always worn in the period between the 2 assessment sessions. The order of the other measures was determined by availability of the ICET equipment, the pulmonary function laboratory and the participant. That is, one assessment session involved completion of the ICET and pulmonary function testing and the other assessment session involved collecting measures of peripheral muscle strength, completion of the SF36 and the FSS questionnaires, and the 6-minute walk test (6MWT).

Figure 4-1 shows the measurements collected in the participants with ALI only, the order in which the assessment sessions were conducted and the assessors who collected the measurements.

4.2.1.4 Recruitment and study criteria for healthy participants

Healthy participants were recruited via word-of-mouth and the Hunter Medical Research Institute volunteer database which is a medical research division associated within the Hunter New England Area health service.

Healthy participants were eligible for inclusion if they were aged between 35 and 75 years. Exclusion criteria comprised: (i) a history of any condition that would adversely affect exercise performance or physical ability to perform cycling, walking or strength assessments, including musculoskeletal, neurological, cardiovascular and respiratory conditions; (ii) a smoking history of greater than 10 pack years; or (iii) if they participated in high level regional or competitive sport. To ensure that the participants with ALI and healthy participants were balanced for known confounders, specifically age and sex, a stratified random sampling approach was adopted. The majority of healthy participants were recruited after the participants with ALI had completed the study.

4.2.1.5 Study protocol used for healthy participants

Healthy participants gave written informed consent prior to data collection. Participants were invited to attend 2 assessment sessions, separated by 7 days. Over the course of these 2 assessment sessions, demographic and anthropometric data were collected, and the following measures were made: (i) peak and submaximal exercise responses during a symptom-limited ICET; (ii) peripheral muscle strength; (iii) HRQL via the SF36; and (iv) fatigue via the FSS questionnaire. Further, in the days between the 2 assessment sessions, participants wore a SAB to measure PA and ST.

Regarding the order in which these measures were made, demographic and anthropometric information were always collected on the first assessment day and the SAB was always worn in the period between the 2 assessment sessions. The order of the other measures was determined by availability of the ICET equipment, and the participant. That is, one assessment session involved completion of the ICET

and the other assessment day involved the collecting of measures of peripheral muscle strength, completion of the SF36 and the FSS questionnaires.

Figure 4-1 shows the measurements collected in the healthy participants, the order in which the assessment sessions were conducted and the assessors who collected the measurements.

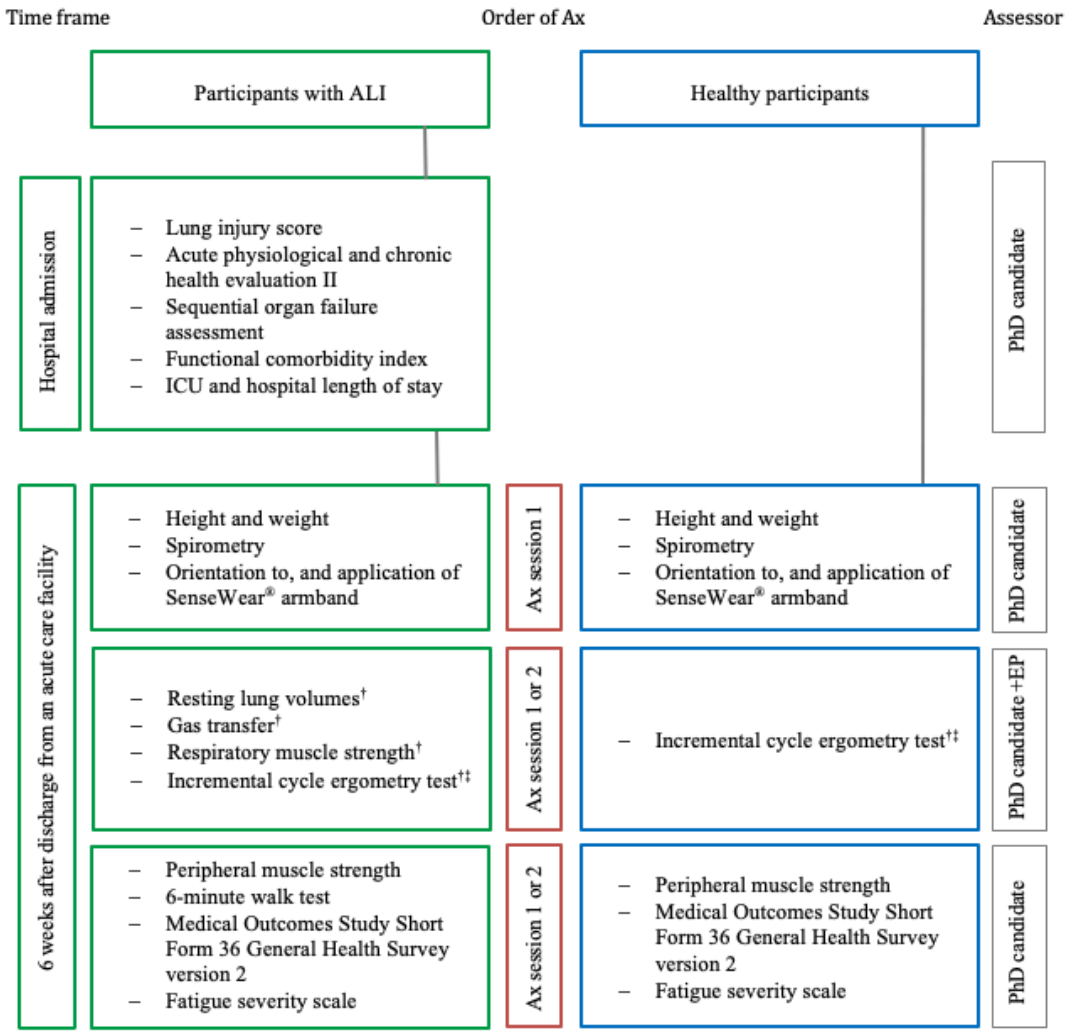

Figure 4-1 Timeframe of assessments, order of assessments and assessor of measurements in the ALI and healthy participants

ALI: acute lung injury; Ax: assessment; ICU: intensive care unit; EP: exercise physiologist; PhD: Doctor of Philosophy; †: conducted by exercise physiologist (JP); ‡: conducted by PhD candidate;

NB. The PhD candidate assisted the exercise physiologist with the ICETs for all (100%) participants with ALI and n = 8 (38%) healthy participants and independently conducted the ICETs for the remaining (n = 13, 62%) healthy participants.

4.2.2 Measurements

This section describes the measurements made in this study. Some measurements were collected in the participants with ALI only and other measurements were collected in both groups of participants. The measurements collected in the participants with ALI only were: (i) those related to the ICU admission and comprised severity of illness, prognostic indicators, and ICU and hospital LOS; and (ii) those commonly used in other studies to describe this population[12,13,42,49] and comprised resting lung volumes, gas transfer, maximal respiratory pressures, and functional exercise capacity via the 6-minute walk distance (6MWD), assessed 6 weeks after discharge from the acute care facility. These measures are described first in section 4.2.2.1 to 4.2.2.3.

All other measures were collected in both the participants with ALI and the healthy participants. These comprised collection of demographic and anthropometric information, spirometry, peak and submaximal exercise responses during a symptom-limited ICET, PA and ST, peripheral muscle strength, HRQL via the SF36 and fatigue severity via the FSS. These measures are described in section 4.2.2.4 to 4.2.2.10.

4.2.2.1 Severity of illness, prognostic indicators and length of stay (in participants with ALI only)

At the time of the ICU admission, details were collected regarding severity of illness and prognostic indicators. These measures comprised the lung injury score,[301] the acute physiologic and chronic health evaluation II (APACHE II)[300] calculated on admission, and the sequential organ failure assessment (SOFA)[302] calculated daily from the patients' notes. The pre-admission functional comorbidity index (FCI)[293] was calculated from information obtained from the participants next of kin. Both ICU LOS and hospital LOS were recorded. Details of these measures and how they were collected have been previously described in Chapter 3 (section 3.2.2.3).

4.2.2.2 Resting lung volumes, gas transfer and maximal respiratory pressures (in participants with ALI only)

Measurements were collected of resting lung volumes (functional residual capacity [FRC], residual volume [RV], total lung capacity [TLC]), gas transfer (diffusing

capacity of the lung of carbon monoxide [D_LCO] [Vmax® Encore plethysmography system, Carefusion, Hoechberg, Germany]). Haemoglobin levels were measured in a drop of venous blood obtained via a finger prick. This was then used to correct the D_LCO value in the presence of anaemia. Measures were collected of maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) from RV and total lung capacity (TLC), respectively (MicroRPM respiratory pressure metre, Vyaire Medical GmbH, Illinois, USA). A minimum of 3 maximal effort measures, during which a plateau of at least one second was achieved were collected in each participant. The greatest value that was within 20% of at least one other measurement was recorded as the test result.[362]

Measures were made according to published guidelines on the standardisation of lung function testing.[316,362,363] All equipment was calibrated according to manufacturer's recommendations. Data were expressed as absolute values and as a percentage of predicted normative values (Appendix 9) estimated using regression equations.[364,365]

4.2.2.3 Functional exercise capacity (in participants with ALI only)

Functional exercise capacity was measured using the 6MWT. To account for any increases resulting from test familiarisation, 2 6MWTs were completed. The 2 tests were separated by 30 minutes and the highest distance of the 2 tests was recorded as the test result. The details of the assessment have been previously described in Chapter 3 (section 3.2.2.9).[366]

The 6MWD was expressed in absolute values (m) and as a percentage of predicted normative values, estimated using regression equations that were established in an Australian population using an identical 6MWT protocol.[333] The difference between the first and second 6MWD was also calculated.

4.2.2.4 Demographic and anthropometric information (in participants with ALI and healthy participants)

Age and sex were recorded. Body weight and height were collected via digital scales (DS-530 MkII, Teraoka Seiko, Tokyo, Japan) and a wall mounted stadiometer (seca 206, seca gmbh & co. kg, Hamburg, Germany), respectively.

4.2.2.5 Spirometry (in participants with ALI and healthy participants)

Measures were made of forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) (EasyOne™ spirometer, NDD Medical Technologies, Zurich, Switzerland, or Vmax® Encore plethysmograph system, SensorMedics, Yorba Linda, California, USA) both pre- and post-administration of a bronchodilator (Salbutamol 100 micrograms, 4 metered actuations). The bronchodilator was delivered via a spacer and the post-administration spirometry was performed approximately 20 minutes later. Testing was performed according to published guidelines.[316] All equipment was calibrated according to manufacturers' recommendations. Data were expressed as absolute values (L) and as a percentage of predicted normative values estimated using regression equations.[316]

4.2.2.6 Peak and submaximal exercise responses during an incremental cycle ergometry test (in participants with ALI and healthy participants)

Peak and submaximal exercise responses were measured during an ICET performed on an electrically braked cycle ergometer (Ergoselect 200K; Ergoline GmbH, Bitz, Germany). Tests were conducted by an exercise physiologist or the PhD candidate in the Diagnostic Suite of the John Hunter Hospital and were supervised by a senior member of the medical staff as per American Thoracic Society/American College of Chest Physicians (ATS/ACCP) guidelines.[205]

Participants were informed prior to the commencement of the ICET that it was a maximal test. They were instructed to continue pedaling for as long as they could and were given strong verbal encouragement to facilitate a maximal performance. They were instructed to inform the person conducting the test immediately if they felt unwell or had chest pain or dizziness at any time during the test.

Participants were fitted with a mouthpiece in circuit with an expired gas analysis system (SensorMedics 2900 system, Yorba Linda, California, USA, or Ergocard Professional system, Medisoft, Sorinnes, Belgium), a 12-lead electrocardiogram (ECG) (Ergocard Professional, Medisoft, Sorinnes, Belgium), and an arterial oxygen saturation monitor with ear sensor (Massimo Radical-7®, Irvine, California, USA).

All equipment was calibrated according to the manufacturer's recommendations. Both the gas analysers and pneumotachograph were calibrated before every test.

The test commenced with 3 minutes of seated rest. The participant then commenced unloaded cycling at a cadence of 60 rpm. Work rate (WR) was incrementally increased each minute. The magnitude of incremental change was individualised and determined using a regression equation that considered age, sex and baseline respiratory function.[367] The aim of the test to was to achieve symptom-limitation within 8 and 12 minutes.[205]

During each test, using expired gas analysis, breath-by-breath measures were made of the rate of oxygen uptake (VO_2), the rate of carbon dioxide production (VCO_2), end-tidal oxygen tension ($PETO_2$), end-tidal carbon dioxide tension ($PETCO_2$), tidal volume (VT) and respiratory rate (RR). For tests conducted between 2011 and 2013, expired gas analysis was undertaken using a SensorMedics 2900 metabolic measurement cart/system (Yorba Linda, California, USA). In 2013, new equipment was acquired, and therefore, for tests performed after this time, expired gas analysis was conducted using the Ergocard Professional system (Medisoft, Sorinnes, Belgium).

During each test, heart rate (HR) and rhythm as well as arterial oxygen saturation (SpO_2) were continuously recorded (during rest, cycling and recovery). Blood pressure was measured using a manual sphygmomanometer (APLPK2 Aneroid, Paragon Care, Scoresby, Victoria, Australia) at rest, every 3 minutes during the test, on test completion, and 5 minutes after test completion. On test completion, dyspnoea and leg fatigue were measured using the modified category-ratio Borg score (0-10).[332] Data were expressed as absolute values and as a proportion of predicted normative values (Appendix 10).[345,368-371]

4.2.2.6.1 Management of data collected during the incremental cycle ergometry test

For both the participants with ALI and healthy participants, unloaded responses and peak responses for measures of VO_2, VCO_2, minute ventilation (VE), respiratory exchange quotient (R), RR, VT, oxygen pulse (O_2 pulse) (derived using 30-second averages of VO_2/HR) and HR were defined as the last 30-second average obtained

during unloaded cycling and the highest 30-second average obtained during the test respectively. A maximal test was identified by a R > 1.1.[372] Maximal voluntary ventilation (MVV) was calculated by multiplying the measured FEV_1 by 40.[371] Breathing reserve was determined as the difference between the MVV and the measured maximum VE. The nadir SpO_2 was defined as the lowest 30-second average recorded value obtained during the test. Anaerobic threshold (AT) was independently determined by investigators (i.e. the PhD candidate and another trained assessor) using the V-slope method and the ventilatory equivalent method as described by Wasserman et al.[345] Discrepancies between assessors were resolved via discussion.

To facilitate comparison of submaximal responses between the participants with ALI and healthy participants, measures of VO_2, WR, HR, VE and SpO_2 were binned into epochs equivalent to 10% of total test duration (i.e. deciles) using SigmaPlot Version 13 (Systat Software, San Jose, California, USA).

For each participant with ALI, to explore the mechanisms of exercise limitation, measures of VO_2, VCO_2, $PETO_2$, $PETCO_2$, VE, R, RR, VT, SpO_2, O_2 pulse and HR were averaged over 30-second intervals and plotted on a 9-panel graphical array previously described by Wasserman et al.[205,345]

4.2.2.7 Physical activity and sedentary time (in participants with ALI and healthy participants)

Participants were instructed to wear the SAB over the triceps brachii muscle bulk of the left arm for 7 consecutive days, removing it only for water-based activities such as bathing or swimming. The SAB is a small, light and portable metabolic monitor that uses a proprietary algorithm (SenseWear Professional 7.0; Bodymedia Inc., Pittsburgh, Pennsylvania, USA) to integrate data from a tri-axial accelerometer together with data from non-invasive physiological sensors that provide information on heat flux, skin temperature and galvanic skin response to estimate energy expenditure. It provides measures of energy expenditure, expressed as metabolic equivalents (MET) as well as step count and posture (upright vs. lying). Measures of energy expenditure derived using the SAB have been validated in a number of populations including people with chronic lung disease.[373-377]

4.2.2.7.1 Removal of overnight sleep time

As participants were instructed to wear the SAB continuously for 7 days, removing it only for water-based activities, data obtained from the SAB included both waking and sleeping time. In order to report ST, overnight sleeping time needed to be excluded from the data. To do this, data from the SAB were exported to Microsoft Excel and thereafter run through a customised filtering program (LabVIEW 2013; National Instruments Corp, Austin, Texas, USA) whereby waking hours were extracted using criteria that utilised both time of the day and posture data obtained from the SAB. Specifically, waking hours were defined to have commenced at the first point after 0500 hours where the participant accumulated a minimum of 20 consecutive minutes in an 'upright' posture, as denoted using the SAB proprietary algorithm. Waking hours were defined to have finished at the first point after 2000 hours where the participant accumulated a minimum of 20 consecutive minutes in 'lying', as denoted by the SAB proprietary algorithm. Participant data were excluded if they reported sleeping in a chair or in a supported reclined position.

Other approaches to removing overnight sleep time have been described, such as requesting the participant remove the SAB during sleep or requesting participants to diarise their sleep patterns.[378] However, requesting the participant to remove the SAB during sleep increases the risk of them forgetting to replace the SAB when they first wake, resulting in missing data. Further, requesting participants diarise their sleep time is limited by participant non-adherence and also may result in missing data.[378-381] The pragmatic approach used in this study of removing overnight sleeping time was implemented to optimise data collected during waking hours. This approach has been used previously in a cohort of people living with chronic obstructive pulmonary disease to differentiate awake time and sleep.[382]

4.2.2.7.2 Minimum wear time needed for a participant to be included in the analyses of physical activity and sedentary time

To be included in these analyses, a participant needed to contribute a minimum of 4 days of data, including at least one weekend day, with each day providing data on at least 600 minutes of waking hours (see section 4.2.2.7 for definition of waking hours). In survivors of critical illness, no data exist to guide the minimum number of days and hours per day that an activity monitor should be worn in order to accurately

represent PA and ST in a typical day. Work in other populations however, have investigated the minimum wear requirements of activity monitors. In a group of elderly people (69 ± 7 years), a minimum of 4 days of activity monitoring for at least 600 minutes per day was shown to accurately and reliably predict habitual PA defined as 21 days of PA data (intra-class correlation coefficient = 0.8).[383] Several large cohort studies involving healthy populations, have used these criteria to determine the eligibility of a participant's data to be included in analysis of PA and ST.[384-386] As PA has been shown to be less on weekend days compared with weekdays, and ST greater on weekend days compared with weekdays,[387,388] one weekend day of data was required for the participant data to be included in the analyses.

For those participants who met the minimum wear time criteria, data were averaged across days.

4.2.2.7.3 Data management

Management of data collected during waking hours using the SAB were exported to a custom computer software program in order to undertake exposure variation analysis (EVA)[389] (LabVIEW 8.6.1; National Instruments, Texas, USA). This program grouped data into 4 categories: (i) ST (defined as any time with an energy expenditure ≤ 1.5 MET; (ii) light intensity PA (LPA) (defined as any time with an energy expenditure > 1.5 and ≤ 3 MET); (iii) moderate intensity PA (MPA) (defined as any time with an energy expenditure > 3 and ≤ 6 MET; (iv) vigorous intensity PA (VPA) (defined as any time with an energy expenditure > 6 MET).[230] Time spent in each category was averaged across days. The accumulation of ST in uninterrupted bouts ≥ 30 minutes as a percentage of total ST, and of MVPA in bouts of ≥ 10 minutes as a percentage of total time spent in MVPA, was calculated for each participant. Measures of daily step count were also averaged across days.

4.2.2.8 Peripheral muscle strength (in participants with ALI and healthy participants)

Peripheral muscle strength was assessed as peak isometric force as measured on the dominant limb during knee extension, shoulder flexion, elbow flexion, and handgrip.

The details of the measurement of muscle force has been previously described in Chapter 3 (section 3.2.2.5).

The highest force value attained within 10% of the nearest value was recorded as the test result. Data were expressed as absolute values and as a percentage of predicted normative values estimated using published normative reference values for each action (Appendix 3).[155,156,319] All equipment was calibrated according to manufacturer's recommendations.

4.2.2.9 Health-related quality of life (in participants with ALI and healthy participants)

For the participants with ALI, HRQL prior to being admitted to ICU was assessed via completion of the SF36 questionnaire by a proxy (participant with ALI proxy), during the participants ICU admission. For participants in both groups, HRQL was assessed via self-completion of the SF36 questionnaire.[295] The questionnaire was completed with the PhD candidate in attendance to clarify any questions and to ensure all questions were answered.

The SF36 has established reliability, validity and sensitivity to change in a range of acute and chronic diseases,[292,294-296] and is recommended for use in critical illness.[297] Fair to moderate association has been demonstrated between patient (completed after ICU admission) and proxy SF36 scores, in a population of survivors of critical illness.[264,390,391] The properties of the SF36 and analysis of the data obtained from the SF36 have been previously described in Chapter 3 (section 3.2.2.2).

Data pertaining to the individual domains of the SF36 were presented as transformed scores using a 0 to 100 scale with a higher score indicating a better HRQL. The 2 component summary scores, physical component score (PCS) and mental component score (MCS), were calculated using a scoring algorithm and were normative based values.[298,299]

4.2.2.10 Fatigue severity (in participants with ALI and healthy participants)

Fatigue severity was assessed via completion of the FSS. The questionnaire was self-completed by the participants with the PhD candidate in attendance to clarify any questions and to ensure all questions were answered.

The original fatigue severity scale is a simple 9 item questionnaire developed to measure fatigue in neurological and medical patient groups.[392] Validity and reliability has since been established for this scale in a wide range of conditions including chronic medical patient populations such as chronic hepatitis and multiple sclerosis[392-394] people with Human Immunodeficiency Virus (HIV)[395] and in the general population.[396] A score of 1 to 7 is obtained on each of the 9 questions. While all items were completed by the participants, the final score that was presented in the current study reflect only items 3-9. These items are related to the interference of fatigue on physical functioning, work, family and social life. The 2 items that were not included in the final score were, 'My motivation is lower when I am fatigued' and 'Exercise brings on fatigue'. This reduced unidimensional 7 item version of the fatigue severity scale has been shown to have better psychometric properties than the 9 item version in people with multiple sclerosis, stroke and HIV-infected adults.[396,397] Higher scores in the FSS represent greater levels of fatigue.[392]

Data pertaining to the FSS were presented as a mean of the 7 items with a mean score of greater than 4.0 representing severe fatigue in people with multiple sclerosis and systemic lupus erythmatosus.[392]

4.2.3 Statistical analyses

Statistical analyses were performed using IBM Corporation Statistical Package for Social Sciences, version 23.0 for Macintosh (SPSS®). The distribution of the data was examined by statistical (Shapiro-Wilks) and graphical (frequency histogram and box plots) methods. Data are expressed as mean ± standard deviation or median [interquartile range].

Between-group comparison of continuous data was conducted using independent-samples t-test for parametric data or Mann-Whitney U test for non-parametric data respectively, and Chi-square test for categorical data. Linear regression was used to compare the slopes of submaximal exercise responses between the groups. For all analyses, a $p < 0.05$ was considered significant.

4.2.4 Sample size calculations

Sample size calculations were based on detecting a difference between the participants with ALI and healthy participants in peak VO_2. Neff et al[42] demonstrated that peak work capacity, expressed as work rate, measured on an ICET was 77 ± 13% of the predicted value in survivors of acute respiratory distress syndrome (ARDS) when measured 29.5 ± 8.7 months following hospital discharge. Given the strong relationship between VO_2 and WR,[205] it was likely that peak VO_2 was reduced by a similar magnitude. As this study measured peak VO_2 within 6 weeks following discharge from an acute care facility, and included participants with ALI, which, when compared with ARDS, represents a patient group with a broader severity of illness as defined by the degree of hypoxaemia (PaO_2/FiO_2), it was assumed that there would be greater variability in the difference between the groups. Therefore, in order to detect a difference between the participants with ALI and healthy participants in peak VO_2 of 23%, assuming twice the standard deviation reported by Neff et al[42] (i.e. 26%) using a 2-tailed independent t-test, with power of 0.8 and alpha set at 0.05, a sample size of 21 participants with ALI and 21 healthy participants was required. Due to the difficulty of recruiting the participants with ALI, the target sample for these participants (n = 21) was not achieved. Multiple strategies were employed to enhance recruitment, and these are described in Appendix 11. Recruitment was ceased in December 2014 with a sample of n = 10 participants with ALI and a healthy participant sample of n = 21.

4.3 Results

4.3.1 Overview

Section 4.3 presents data to answer the research questions for Study 2. Specifically, section 4.3.3 explores the first research question by presenting peak and submaximal data collected during the ICET for the ALI and healthy participants. This section also presents individual interpretation of physiological responses during the ICET for the participants with ALI only and identifies the cause of limitation to exercise capacity. Thereafter, section 4.3.4 to 4.3.7 explores the second research question by presenting data pertaining to PA and ST, peripheral muscle strength, HRQL and fatigue severity for the ALI and healthy participants.

4.3.2 Participant recruitment and characteristics

The outcome of participant recruitment is shown in Figure 4-2. All participants with ALI (n = 10) and healthy participants (n = 21) who agreed to participate, completed all assessments. The participants with ALI attended their first assessment session for this study 53 [46 to 61] days after discharge from an acute care facility. Acute care facility comprised the acute care hospital for 6 participants and an acute rehabilitation facility for 4 participants. The length of stay for the 4 participants at the acute rehabilitation facility was (range) 1 to 3 weeks. The time between the first and second assessment sessions was the same in the ALI and healthy participants (7 [7 to 7] vs. 7 [7 to 7] d, $p = 1.00$). All participants with ALI (100%) and 17 healthy participants (81%) completed the ICET in the initial assessment session. The mean age and proportion of males was similar in the ALI and healthy participants (50.9 ± 13.9 vs. 49.9 ± 6.2 yr, $p = 0.77$ and n [%], 5 [50] vs. 11 [52] males, $p = 1.00$, respectively). Descriptive data are presented across 3 tables. Specifically, Table 4-1 and Table 4-2 present data for the participants with ALI only. Table 4-1 presents data collected during the acute care admission, pertaining to disease severity, surrogates of prognosis and LOS. Table 4-2 presents data collected at the assessment performed 6 weeks following discharge from acute care, pertaining to pulmonary function and functional exercise capacity. Table 4-3 presents data collected in both the ALI and the healthy participants, pertaining to anthropometric and spirometric data.

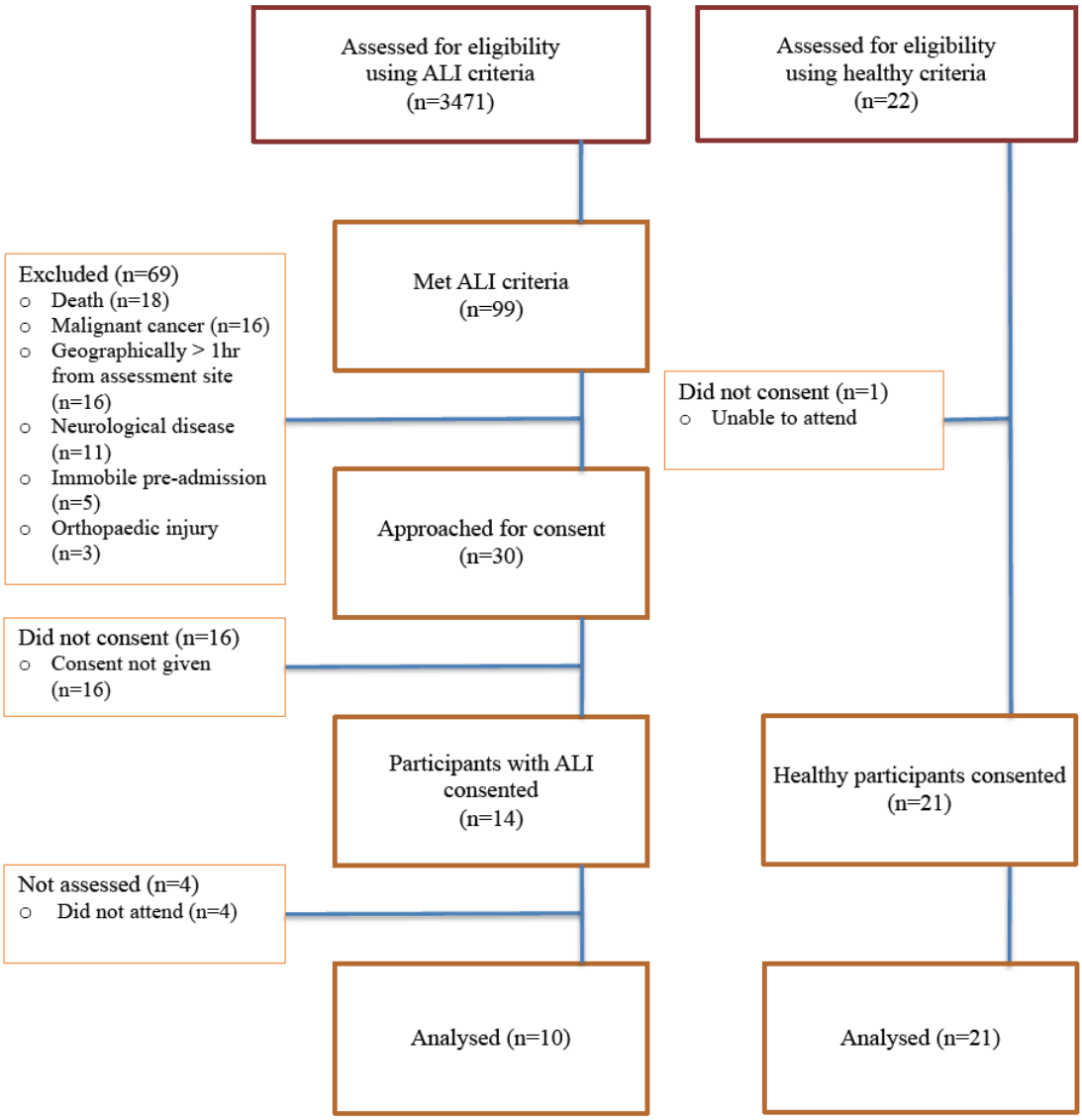

Figure 4-2 Flow of recruitment for ALI and healthy participants

ALI: acute lung injury.

Table 4-1 Disease severity, surrogates of prognosis and length of stay, collected in participants with ALI during the acute care admission

	Participants with ALI (n = 10)
Primary admitting diagnosis	
Sepsis, n (%)†	5 (50)
Pneumonia, n (%)	5 (50)
APACHE II	22.9 ± 6.5
Lung injury score	3.0 ± 0.6
SOFA	10.3 ± 2.7
Duration of mechanical ventilation (days)	8.7 ± 1.8
ICU length of stay (days)	10.4 [8.3 to 16.8]
Hospital length of stay (days)	29.3 [20.0 to 56.8]
Pre-admission FCI	4.0 ± 2.4

Data are mean ± standard deviation or median [interquartile range]. ALI, acute lung injury; APACHE II: Acute Physiology and Chronic Health Evaluation II; FCI: functional comorbidity score; ICU: intensive care unit; SOFA: sequential organ failure assessment; † sepsis as a result of pneumonia.

Table 4-2 Measures of pulmonary function and functional exercise capacity collected in the participants with ALI at the 6-week assessment

	Participants with ALI (n = 10)	%predicted
TLC (L)	4.95 ± 0.93	84 ± 14
RV (L)	1.33 ± 0.56	67 ± 27
FRC (L)	2.62 ± 0.51	85 ± 13
D_LCO (mL/min/mmHg)	16.6 ± 6.6	50 [44 - 75]
Best 6MWD (m)†	540 ± 97	75 ± 14
1st 6MWD (m)	467 [440 to 580]	-
2nd 6MWD (m)‡	507 [460 to 619]	-

Data are mean ± standard deviation. ALI: acute lung injury; D_LCO: diffusion capacity of carbon monoxide corrected for haemoglobin; FRC: functional residual capacity; RV: residual volume; TLC, total lung capacity; 6MWD: 6-minute walk distance. † the best 6MWD was the highest value recorded from the 2 tests performed. ‡ the median difference between the first and second 6MWD recorded was 30 [17 to 56] m, $p = 0.020$.

Table 4-3 Anthropometric and spirometric data collected in the ALI and healthy participants at the 6-week assessment

	Participants with ALI (n = 10)	Healthy participants (n = 21)	*p*-value
Weight (kg)	83 ± 22	77 ± 16	0.42
Height (cm)	169 ± 6	173 ± 11	0.38
BMI (kg/m^2)	26.7 [23.6 to 34.5]	24.5 [22.5 to 28.5]	0.21
FEV_1 (L)	2.56 [2.16 to 3.29]	3.35 [2.78 to 4.39]	0.017
%predicted	87 [74 to 100]	108 [101 to 114]	
FVC (L)	3.50 [2.83 to 4.06]	4.36 [3.44 to 5.41]	0.028
%predicted	95 [85 to 100]	111 [106 to 117]	
FEV_1/FVC ratio	0.81 [0.72 to 0.83]	0.80 [0.77 to 0.83]	0.66

Data are mean ± standard deviation or median [interquartile range], unless otherwise stated. ALI: acute lung injury; BMI: body mass index; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity.

4.3.3 Exercise capacity

This section presents data collected during the ICET in 2 ways. First, data collected in the participants with ALI are compared with data collected in the healthy participants. Second, data collected for each participant with ALI are presented on a case-by-case basis as: (i) measures of lung volumes, gas transfer and spirometry measured immediately prior to the ICET; (ii) key physiological responses measured during the ICET; (iii) 9-plot graphical arrays of physiological data collected during the ICET; and (iv) a narrative interpretation of these data which summarises the most likely cause of limitation for each participant. An overview is also presented of the presence and direction of abnormalities in key physiological responses during the ICET for each participant with ALI.

Three (30%) participants with ALI completed the ICET using the SensorMedics 2900 metabolic measurement cart/system (Yorba Linda, California, USA) with the remainder of the participants with ALI (70%) and all of the healthy participants (100%) using the Ergocard Professional system (Medisoft, Sorinnes, Belgium). The PhD candidate assisted the exercise physiologist with the ICETs for all (100%) participants with ALI and 8 (38%) healthy participants. The PhD candidate independently completed the remainder of the ICETs for the healthy participants (n = 13, 62%).

4.3.3.1 Comparison of data collected during the incremental cycle ergometry test between the ALI and healthy participants

4.3.3.1.1 Safety, test duration, and magnitude of incremental change in work

During the ICET, 2 (20%) participants with ALI and one (5%) healthy participant exhibited signs of asymptomatic cardiac ischaemia (ST segment depression or elevation on ECG), and one (10%) ALI participant and one (5%) healthy participant demonstrated nadir SpO_2 < 85% during the ICET (85% and 83%, respectively). The supervising medical officer allowed each of the tests to continue. All ECG changes had returned to normal within one minute of the participants voluntarily ceasing the test, and those who exhibited a nadir SpO_2 < 85% had their SpO_2 return to resting levels within 2 minutes of voluntarily ceasing the test. All 3 participants who exhibited ECG changes during the ICET were referred to their General Practitioner

with a copy of the ICET results. The participants who exhibited changes in their ECG during the ICET were not the same participants who exhibited a nadir SpO_2 < 85% and data collected in all participants were included in the final analyses. No other adverse events occurred.

Compared with the healthy participants, the participants with ALI exercised for less time (13 [11 to 15] vs. 11 [9 to 12] min, $p = 0.006$), and had a smaller magnitude of incremental change imposed each minute during the ICET (15 [10 to 20] vs. 10 [10 to 10] W, $p = 0.001$).

4.3.3.1.2 Physiological data (unloaded cycling and peak responses) and symptoms collected during the incremental cycle ergometry test

Table 4-4 presents the physiological data and symptom responses collected during the ICET in the ALI and healthy participants. During unloaded cycling, compared with the healthy participants, the participants with ALI had a lower VO_2 (expressed as mL/kg/min: $p = 0.019$) and a smaller change in VO_2 between unloaded cycling and peak work (27 [22 to 35] vs. 13 [12 to 17] mL/kg/min, $p < 0.001$). During unloaded cycling, compared with the healthy participants, the participants with ALI also had a lower SpO_2 ($p = 0.032$). All other responses during unloaded cycling were similar between the participant groups. Regarding peak responses, compared with the healthy participants, the participants with ALI achieved lower measures of work rate (180 [135 to 250] vs. 90 [76 to 120] W, $p < 0.001$) and VO_2 (2.46 ± 0.89 vs. 1.45 ± 0.37 L/min, $p = 0.006$ and 31.80 [26.60 to 41.73] vs. 17.80 [14.85 to 20.85] ml/kg/min, $p < 0.001$), and also VCO_2 ($p < 0.001$), VE ($p = 0.049$), VT ($p = 0.006$), O_2 pulse ($p = 0.003$), and HR ($p = 0.009$). All other peak responses were similar between groups. Consensus between the 2 assessors who identified the AT from the physiological responses, was achieved for all participants, with the data for one participant with ALI and one healthy participant only requiring discussion to reach consensus. Compared with the healthy participants, the participants with ALI had a lower AT ($p = 0.001$) and a higher ventilatory equivalent for carbon dioxide (VE/VCO_2) at AT ($p < 0.001$). At test completion, compared with the healthy participants, the participants with ALI reported similar levels of dyspnoea (5 [3 to 7] vs. 4 [2 to 6], $p = 0.27$) but greater leg fatigue (5 [3 to 8] vs. 7 [5 to 8], $p = 0.049$).

4.3.3.1.3 Patterns of submaximal responses during the incremental cycle ergometry test

Figure 4-3 to Figure 4-6 present the submaximal and peak responses during the ICET for the ALI and healthy participants, grouped into deciles of test duration. Figure 4-3 presents VO_2 (y-axis) plotted against WR (x-axis). Both the ALI and healthy participants had a linear submaximal pattern of VO_2 response in relation to WR. Compared with the healthy participants, the participants with ALI showed a greater slope of the plot (0.014 vs. 0.016 L/min/W, t = -635.2, $p < 0.001$). Compared with the healthy participants, the participants with ALI had a lower VO_2 at peak WR (2.64 ± 0.28 vs. 1.43 ± 0.12 L/min, $p = 0.007$). Figure 4-4 presents HR (y-axis) plotted against VO_2 (x-axis).

Both the ALI and healthy participants had a submaximal pattern of HR response in relation to VO_2 denoted by an s-shaped curve. Compared with the healthy participants, the linear portion of the curve occurring in the mid 4 deciles was characterised by a greater slope in the participants with ALI (41.0 vs. 54.9 bpm/L/min, t = 37.6, $p < 0.001$). Compared with the healthy participants, the participants with ALI also had a higher resting HR (81 ± 8 vs. 95 ± 14 bpm, $p = 0.004$).

Figure 4-5 presents VE (y-axis) plotted against VO_2 (x-axis). Both the ALI and healthy participants had a submaximal pattern of VE response in relation to VO_2 denoted by an upward sloping curve. Compared with the healthy participants, the linear portions of the curve occurring in the first 4 deciles (prior to the AT) and the last 6 deciles (following the AT), were both characterised by a greater slope in the participants with ALI (21.6 vs. 29.2, t = -5.1, $p = 0.002$ and 47.3 vs. 61.4, t = -4.0, $p = 0.003$, respectively). Compared with the healthy participants, the participants with ALI had a lower VE response (111 ± 9 vs. 80 ± 6 L/min, $p = 0.034$).

Figure 4-6 presents SpO_2 (y-axis) plotted against VO_2 (x-axis). Both the ALI and healthy participants had a submaximal pattern of SpO_2 response in relation to VO_2 denoted by a downward sloping curve. Compared with the healthy participants, the linear portion of the curve occurring in the first 3 deciles was characterised by a greater slope in the participants with ALI (-0.2 vs. -1.3 %/L/min, t = 3.3, $p = 0.029$). The slope of the linear portion of the curve across the last 7 deciles was similar in

both groups (-1.7 vs. -1.3 %/L/min, t = -1.6, p = 0.13). Nadir SpO_2 was also similar in both groups (96 ± 3 vs. 96 ± 3 %, p = 0.87).

Table 4-4 Data collected during the ICET for the ALI and healthy participants

	Participants with ALI (n = 10)		Healthy participants (n = 21)	
	Unloaded cycling	**Maximum WR**	**Unloaded cycling**	**Maximum WR**
WR (W)	0	90 [76 to 120]	0	180 [135 to 250]**
%predicted	-	64 ± 24	-	115 ± 23
VO_2 (L/min)	0.33 [0.25 to 0.37]	1.45 ± 0.37	0.40 [0.29 to 0.50]	2.46 ± 0.89**
%predicted	-	71 ± 23	-	120 ± 33
VO_2 (mL/kg/min)	3.84 [3.15 to 4.79]	17.80 [14.85 to 20.85]	4.74 [4.22 to 6.33]*	31.80 [26.60 to 41.73]**
ΔVO2 (mL/kg/min)	-	13 [12 to 17]	-	27 [22 to 35]**
VCO_2	0.28 [0.19 to 0.32]	1.75 [1.57 to 2.13]	0.36 [0.26 to 0.48]	2.81 [2.25 to 4.05]**
R	0.83 [0.74 to 0.92]	1.31 [1.21 to 1.37]	0.85 [0.81 to 0.92]	1.26 [1.18 to 1.35]
HR (bpm)	94 [81 to 100]	151 ± 21	84 [71 to 89]	166 ± 8**
%predicted	-	85 ± 13	-	93 ± 5
O_2 pulse (mL/beat)	4 [3 to 4]	9 [8 to 12]	5 [3 to 6]	15 [11 to 20]**
%predicted	-	84 [64 to 99]	-	124 [107 to 148]
VE (L/min)	11.35 [1.63 to 15.35]	75.9 ± 16.9	13.10 [9.10 to 16.85]	102.1 ± 38.3*
RR (bpm)	18 [15 to 22]	42 [38 to 52]	17 [14 to 21]	39 [36 to 46]
VT (L)	0.70 [0.58 to 0.77]	1.69 [1.52 to 2.08]	0.73 [0.55 to 1.03]	2.66 [1.93 to 3.24]**
Exercise breathing reserve (L/min)	-	32.1 ± 22.7	-	39.3 ± 22.7
VE/MVV	-	0.72 ± 0.16	-	0.72 ± 0.18
SpO_2 (%)	98 [97 to 99]	96 [94 to 98]	99 [98 to 100]*	97 [95 to 98]
Δ SpO_2 (%)	-	2 [1 to 2]	-	2 [1 to 5]
Limiting symptom (leg fatigue) n (%)	-	10 (100)	-	15 (71)
		@ AT		**@ AT**
AT (L/min)	-	0.78 [0.69 to 0.94]	-	1.20 [0.98 to 1.73]**
AT (mL/kg/min)	-	9.83 [8.52 to 11.12]	-	15.83 [13.76 to 22.40]**
VE/VCO_2		35.2 ± 4.1		25.7 ± 2.5**

Data are mean ± standard deviation or median [interquartile range]. ΔVO_2: change in rate of oxygen uptake from unloaded cycling to maximum work rate; @: at; ALI: acute lung injury; AT: anaerobic threshold; HR: heart rate; MVV: maximum voluntary ventilation; O_2 pulse: oxygen pulse; R: respiratory exchange quotient; RR: respiratory rate; SpO_2: arterial oxygen saturation measured by pulse oximetry; VE: minute ventilation; VCO_2: rate of carbon dioxide production; VO_2: rate of oxygen uptake; VT: tidal volume; WR: work rate. Statistical comparison conducted between unloaded cycling data for the ALI and healthy participants and maximum WR data for the ALI and healthy participants: * $p < 0.05$, ** $p < 0.01$. Where a statistically significant difference between groups in data collected during unloaded cycling was identified, differences in the change (i.e. peak - unloaded measures) were also explored.

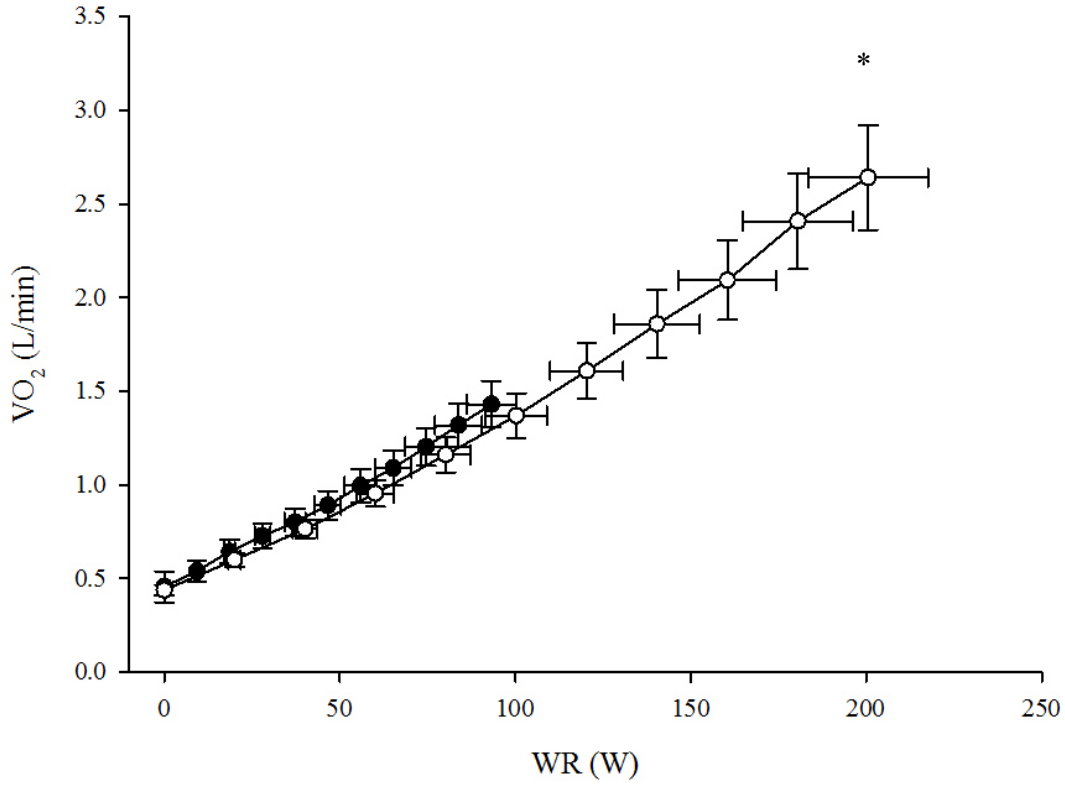

Figure 4-3 Rate of oxygen uptake plotted against work rate during the ICET for the ALI and healthy participants

Data are mean ± standard error of the mean. ALI: acute lung injury; ICET: incremental cycle ergometry test; VO_2: rate of oxygen uptake; WR: work rate. —●—: ALI participants; —○—: healthy participants. * $p = 0.007$.

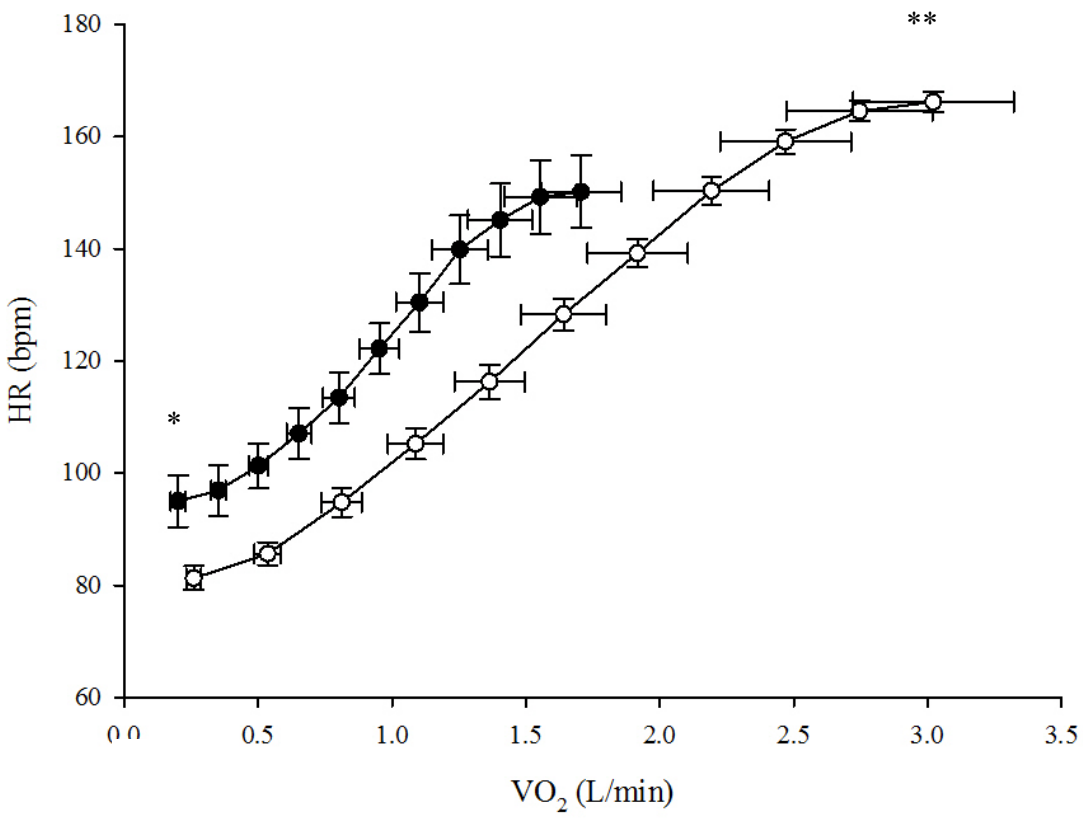

Figure 4-4 Heart rate plotted against rate of oxygen uptake during the ICET for the ALI and healthy participants

Data are mean ± standard error of the mean. ALI: acute lung injury; HR: heart rate; ICET: incremental cycle ergometry test; VO_2: rate of oxygen uptake. —●—: ALI participants; —○—: healthy participants. * $p = 0.004$; ** $p = 0.005$.

Note: When comparing the ALI and healthy participants HR during unloaded cycling, the values as presented in this figure represent the mean and standard error of the mean for the first decile of participant group data. These values were statistically different. The HR during unloaded cycling as presented in Table 1-4 however, were absolute measures and as a result, not statistically significantly different.

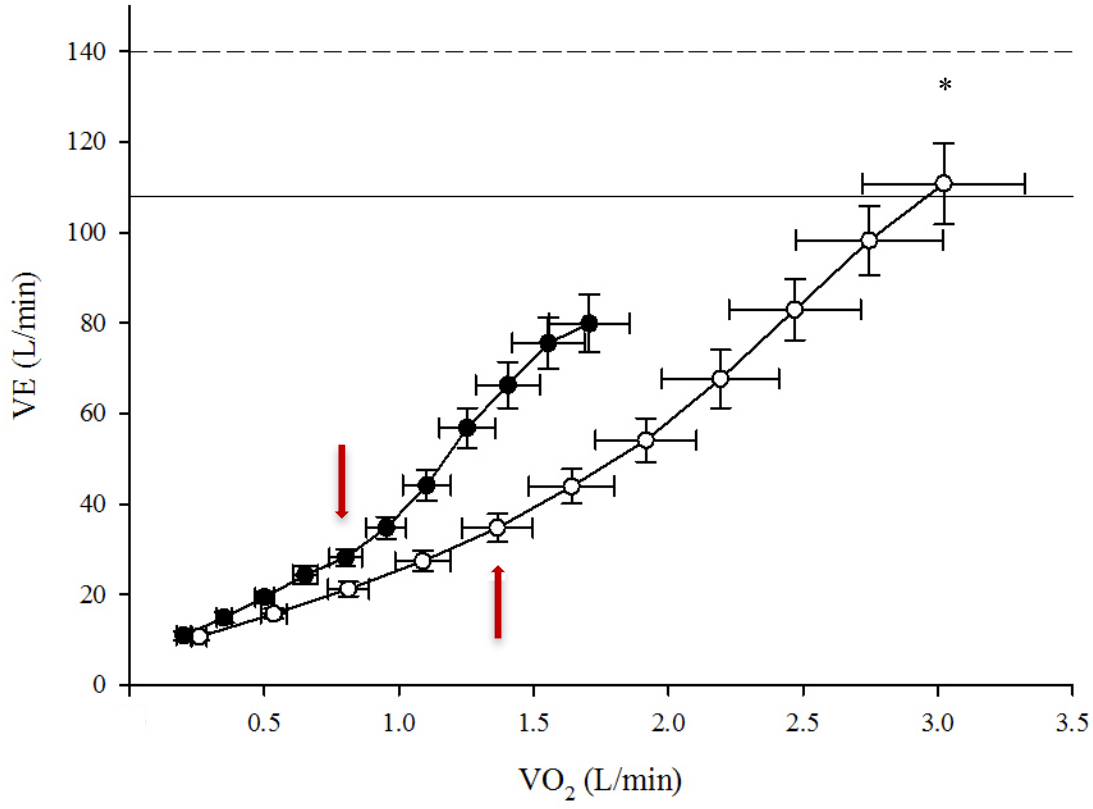

Figure 4-5 Minute ventilation plotted against rate of oxygen uptake during the ICET for the ALI and healthy participants

Data are mean ± standard error of the mean. ALI: acute lung injury; ICET: incremental cycle ergometry test; MVV: maximum voluntary ventilation; VE: minute ventilation; VO_2: rate of oxygen uptake. —●—: ALI participants; —○—: healthy participants; —— : MVV for ALI participants; - - - : MVV for healthy participants. : ➡ denotes anaerobic threshold. * p = 0.034.

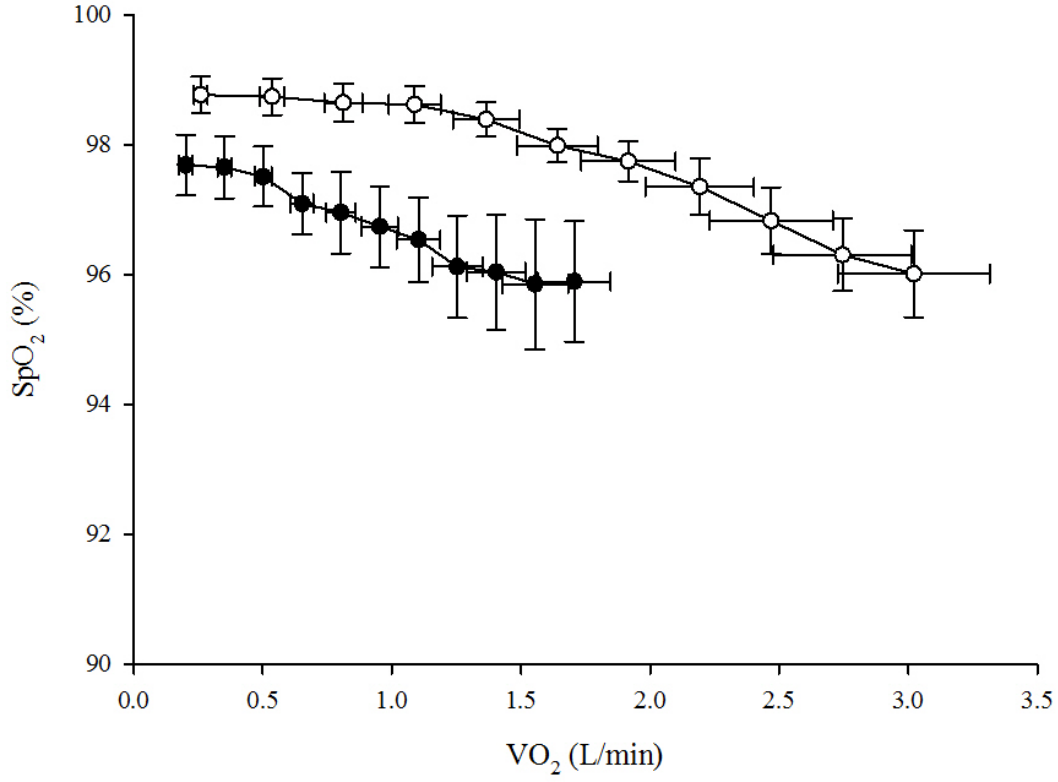

Figure 4-6 Arterial oxygen saturation plotted against rate of oxygen uptake during the ICET for the ALI and healthy participants

Data are mean ± standard error of the mean. ALI: acute lung injury; ICET: incremental cycle ergometry test; SpO_2: arterial oxygen saturation; VO_2peak: peak rate of oxygen uptake. —●—: ALI participants; —○—: healthy participants.

4.3.3.2 Presentation of individual responses to the incremental cycle ergometry test for each participant with ALI

4.3.3.2.1 Participant 1 with ALI

This was a 31-year-old male (height 161cm, weight 121 kg) who was admitted to ICU with community acquired pneumonia and sepsis. He had an APACHE II score of 25, was mechanically ventilated for 9 days with an ICU LOS of 10 days.

Table 4-5 presents the data pertaining to the resting pulmonary function collected immediately prior to the ICET, and Table 4-6 presents exercise data collected during the ICET for Participant 1 with ALI. Figure 4-7 presented the physiological responses for participant 1 with ALI during the ICET plotted as a 9-panel graphical array.

Table 4-5 Resting pulmonary function data measured in Participant 1 with ALI

Measurement	Measured	%predicted
FEV_1 (L)	3.60	93
VC (L)	3.89	81
FEV_1/VC ratio	0.90	110
IC (L)	2.66	81
TLC (L)	5.62	88
RV (L)	1.73	104
FRC (L)	2.96	94
MVV (L/min)	144	93
Hb (g/dL)	14.2	-
D_LCO (mL/min/mmHg)	26.2	70
MIP (cmH_2O)	-129	87
MEP (cmH_2O)	123	78

ALI: acute lung injury; D_LCO: diffusion capacity of carbon monoxide; FEV_1: forced expiratory volume in one second; FRC: functional residual capacity; Hb: hemoglobin; IC: inspiratory capacity; MIP: maximal expiratory pressure; MEP: maximal expiratory pressure; MVV: maximal voluntary ventilation; RV: residual volume; TLC: total lung capacity; VC: vital capacity. %predicted values calculated using published normative reference values.[156,316,319,365,371]

Table 4-6 Exercise data collected during the ICET for Participant 1 with ALI

Measurement	Measured	%predicted
Maximum work rate (W)	120	57
Peak $\dot{V}O_2$ (L/min)	2.04	65
Peak $\dot{V}O_2$ (mL/kg/min)	16.90	-
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.0	-
AT (L/min)	1.10	67
Peak heart rate (bpm)	146	77
Peak O_2 pulse (mL/beat)	14.0	84
Peak $\dot{V}E$ (L/min)	113.3	166
Exercise breathing reserve (L/min)	30.7	-
$\dot{V}E/\dot{V}CO_2$ @ AT or lowest	36.4	147
Blood pressure (rest, peak) (mmHg)	140/-, 150/-	-
Symptoms @ test end (legs, dyspnoea) (Borg)	9†, 8	-

ALI: acute lung injury; AT: anaerobic threshold; CPET: cardiopulmonary exercise test; O_2 pulse: oxygen pulse; $\dot{V}CO_2$: rate of carbon dioxide production; $\dot{V}E$: minute ventilation; $\dot{V}O_2$: rate of oxygen uptake; WR: work rate; Δ: change; @: occurring at; †: limiting symptom to continuing CPET. %predicted values calculated using published normative reference values.[345,369,370,398]

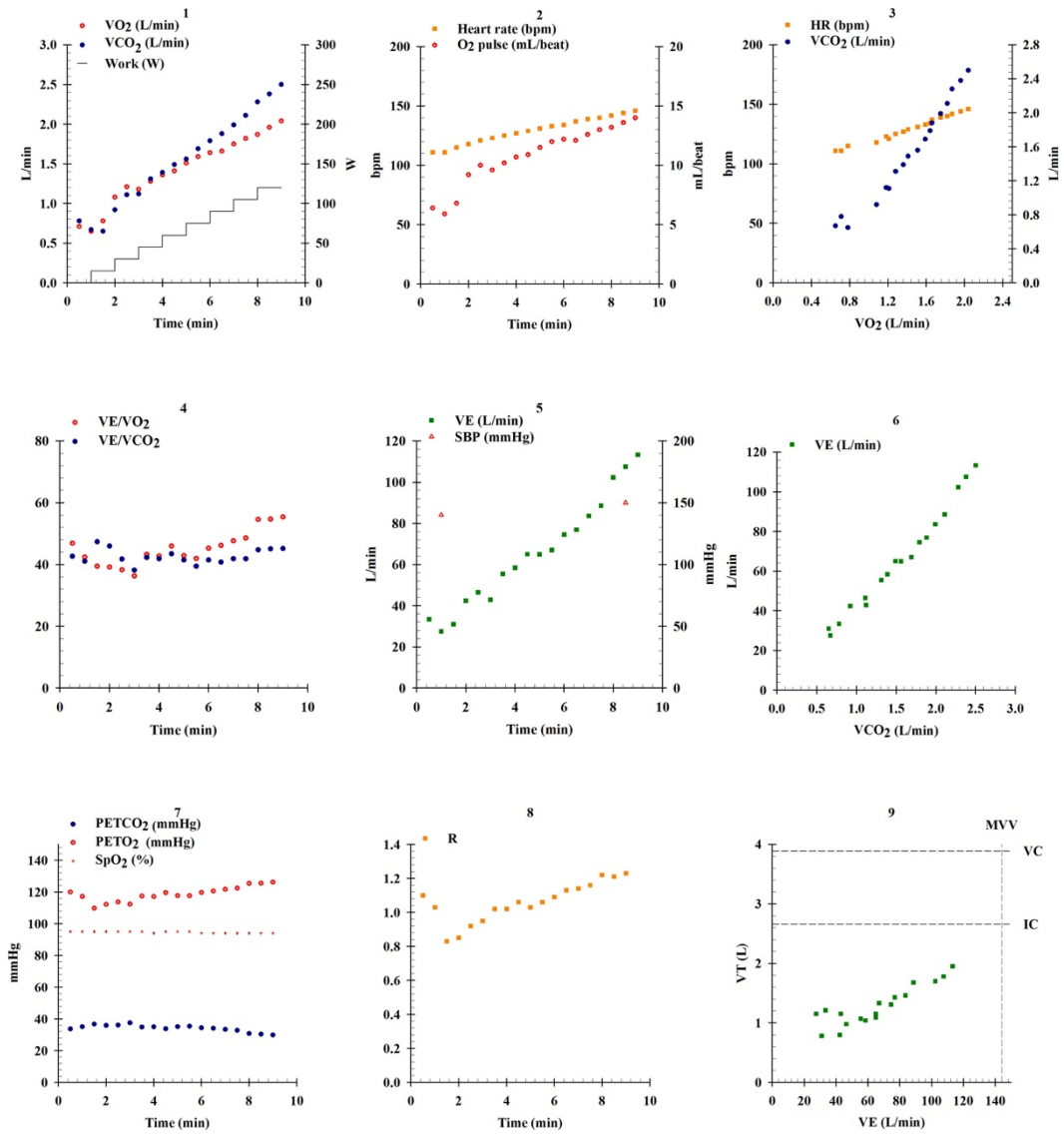

Figure 4-7 9-panel graphical array of physiological responses during the ICET for participant 1 with ALI

IC: inspiratory capacity; ICET: incremental cycle ergometry test; MVV: maximal voluntary ventilation; O_2 pulse: oxygen pulse; $PETCO_2$: end tidal carbon dioxide tension; $PETO_2$: end tidal oxygen tension; R: respiratory exchange quotient; RV: residual volume; SBP: systolic blood pressure; SpO_2: arterial oxygen saturation measured using pulse oximetry; VC: vital capacity; VCO_2: rate of carbon dioxide production; VE: minute ventilation; VO_2: rate of oxygen uptake; VT: tidal volume.

This was a maximal exercise test as the R exceeded 1.2 although there was an attenuated HR response. The change in VO_2 as a proportion of the change in WR ($\Delta VO_2/\Delta WR$) was normal. However, exercise capacity was impaired as seen by a reduction in both the maximum WR and peak VO_2. The AT was also low. Exercise was limited by leg fatigue.

At the AT, the VE/VCO_2 was elevated suggesting the ventilatory response in relation to the metabolic requirements was high. As the $\Delta VO_2/\Delta WR$ was normal and there was no evidence of arterial oxygen desaturation, the elevated VE/VCO2 at AT was unlikely to be as a result of pulmonary vascular disease related to left ventricular failure. The peak O_2 pulse was within normal limits with an appropriate progression throughout exercise, also indicating that cardiac function was normal and therefore did not contribute to the elevated ventilatory response. The cause of the elevated ventilatory response was likely due to ventilation/perfusion (V/Q) mismatching and an increased physiological dead space (V_D/V_T) possibly associated with impaired diffusion as identified in the pulmonary function testing.

The ventilatory pattern was abnormal. This was characterised by the linear relationship of VT to VE in Panel 9 of the graphs, with an absence of plateauing of the curve that occurs towards the peak of exercise. This would suggest that the test was possibly submaximal which is supported by the attenuated peak heart rate response, but in contrast to the R value. There was no ventilatory limitation to exercise as shown by the adequate breathing reserve.

The elevated HR, VE, VO_2, VCO_2 and R at the beginning of the test was likely due to anxiety.

In conclusion, participant 1 with ALI showed a reduced exercise capacity likely due to deconditioning and impaired pulmonary diffusion.

4.3.3.2.2 Participant 2 with ALI

This was a 56-year-old female (height 159 cm, weight 63 kg) who was admitted to ICU with necrotizing fasciitis and sepsis. She had an APACHE II score of 21, was mechanically ventilated for 6 days with an ICU LOS of 8 days.

Table 4-7 presents the data pertaining to the resting pulmonary function collected immediately prior to the ICET, and Table 4-8 presents exercise data collected during the ICET for Participant 2 with ALI. Figure 4-8 presented the physiological responses for Participant 2 with ALI during the ICET plotted as a 9-panel graphical array.

Table 4-7 Resting pulmonary function data measured in Participant 2 with ALI

Measurement	Measured	%predicted
FEV_1 (L)	3.13	138
VC (L)	3.98	151
FEV_1/VC ratio	0.75	96
IC (L)	2.49	119
TLC (L)	5.34	114
RV (L)	1.36	76
FRC (L)	2.85	109
MVV (L/min)	125	139
Hb (g/dL)	15.0	-
D_LCO (mL/min/mmHg)	16.8	70
MIP (cmH_2O)	- 83	112
MEP (cmH_2O)	83	95

ALI: acute lung injury; D_LCO: diffusion capacity of carbon monoxide; FEV_1: forced expiratory volume in one second; FRC: functional residual capacity; Hb: hemoglobin; IC: inspiratory capacity; MIP: maximal expiratory pressure; MEP: maximal expiratory pressure; MVV: maximal voluntary ventilation; RV: residual volume; TLC: total lung capacity; VC: vital capacity. %predicted values calculated using published normative reference values.[156,316,319,365,371]

Table 4-8 Exercise data collected during the ICET for Participant 2 with ALI

Measurement	Measured	%predicted
Maximum work rate (W)	100	109
Peak $\dot{V}O_2$ (L/min)	1.63	114
Peak $\dot{V}O_2$ (mL/kg/min)	25.87	-
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.1	-
AT (L/min)	0.90	107
Peak heart rate (bpm)	176	101
Peak O_2 pulse (mL/beat)	9.3	112
Peak $\dot{V}E$ (L/min)	74.1	105
Exercise breathing reserve (L/min)	51.1	-
$\dot{V}E/\dot{V}CO_2$ @ AT or lowest	30.8	107
Blood pressure (rest, peak) (mmHg)	120/-, 120/80	-
Symptoms @ test end (legs, dyspnoea) (Borg)	$9^{\dagger}$, 8	-

ALI: acute lung injury; AT: anaerobic threshold; CPET: cardiopulmonary exercise test; O_2 pulse: oxygen pulse; $\dot{V}CO_2$: rate of carbon dioxide production; $\dot{V}E$: minute ventilation; $\dot{V}O_2$: rate of oxygen uptake; WR: work rate; Δ: change; @: occurring at; †: limiting symptom to continuing CPET. %predicted values calculated using published normative reference values.[345,369,370,398]

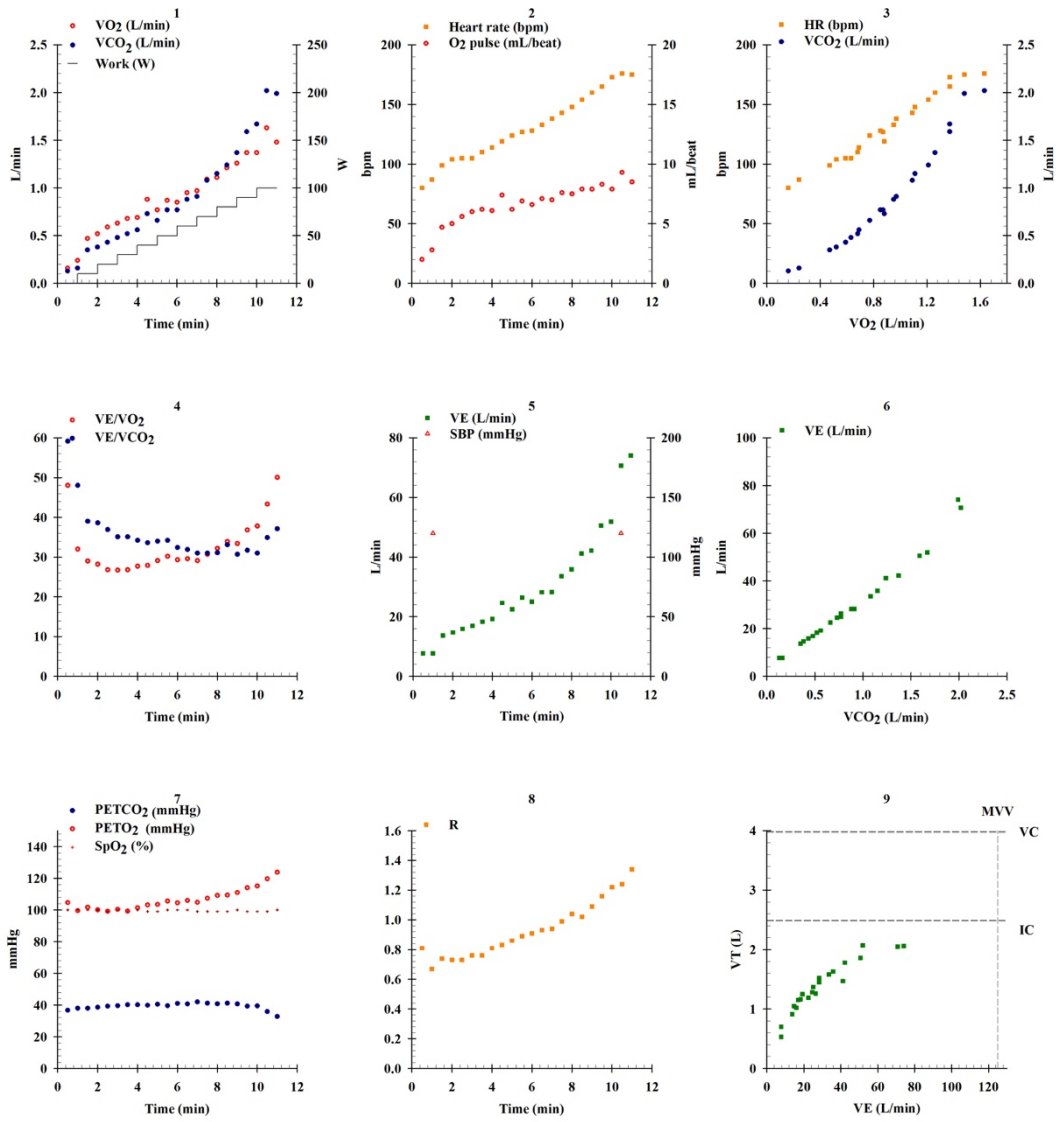

Figure 4-8 9-panel graphical array of physiological responses during ICET for participant 2 with ALI

IC: inspiratory capacity; ICET: incremental cycle ergometry test; MVV: maximal voluntary ventilation; O_2 pulse: oxygen pulse; $PETCO_2$: end tidal carbon dioxide tension; $PETO_2$: end tidal oxygen tension; R: respiratory exchange quotient; RV: residual volume; SBP: systolic blood pressure; SpO_2: arterial oxygen saturation measured using pulse oximetry; VC: vital capacity; VCO_2: rate of carbon dioxide production; VE: minute ventilation; VO_2: rate of oxygen uptake; VT: tidal volume.

This test was a maximal exercise test as the R exceeded 1.3 and the peak HR response was maximal. The $\Delta VO_2/\Delta WR$ was normal. Exercise capacity was normal as seen by a normal maximum WR and peak VO_2. The AT was also normal. Exercise was limited by leg fatigue.

The peak O_2 pulse was within normal limits with an appropriate progression throughout exercise.

The ventilatory response was appropriate, characterised by the linear relationship of VT to VE which plateaued toward the peak of exercise. There was no ventilatory limitation as shown by the adequate breathing reserve.

In conclusion, participant 2 with ALI showed a normal exercise response and capacity.

4.3.3.2.3 Participant 3 with ALI

This was a 43-year-old female (height 165cm, weight 73 kg) who was admitted to ICU with faecal peritonitis secondary to a bowel perforation after a laparoscopic tubal ligation with resulting sepsis. She had an APACHE II score of 12, was mechanically ventilated for 9 days with an ICU LOS of 9 days.

Table 4-9 presents the data pertaining to the resting pulmonary function collected immediately prior to the ICET, and Table 4-10 presents exercise data collected during the ICET for Participant 3 with ALI. Figure 4-9 presented the physiological responses for Participant 3 with ALI during the ICET plotted as a 9-panel graphical array.

Table 4-9 Resting pulmonary function data measured in Participant 3 with ALI

Measurement	Measured	%predicted
FEV_1 (L)	2.73	97
VC (L)	3.51	108
FEV_1/VC ratio	0.84	104
IC (L)	2.36	100
TLC (L)	4.22	83
RV (L)	0.71	42
FRC (L)	1.86	68
MVV (L/min)	109	97
Hb (g/dL)	11.9	-
D_LCO (mL/min/mmHg)	22.5	82
MIP (cmH_2O)	- 80	94
MEP (cmH_2O)	101	105

ALI: acute lung injury; D_LCO: diffusion capacity of carbon monoxide; FEV_1: forced expiratory volume in one second; FRC: functional residual capacity; Hb: hemoglobin; IC: inspiratory capacity; MIP: maximal expiratory pressure; MEP: maximal expiratory pressure; MVV: maximal voluntary ventilation; RV: residual volume; TLC: total lung capacity; VC: vital capacity. %predicted values calculated using published normative reference values.[156,316,319,365,371]

Table 4-10 Exercise data collected during the ICET for Participant 3 with ALI

Measurement	Measured	%predicted
Maximum work rate (W)	120	92
Peak $\dot{V}O_2$ (L/min)	1.82	105
Peak $\dot{V}O_2$ (mL/kg/min)	24.93	-
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.7	-
AT (L/min)	0.90	91
Peak heart rate (bpm)	166	92
Peak O_2 pulse (mL/beat)	11.4	119
Peak $\dot{V}E$ (L/min)	84.9	146
Exercise breathing reserve (L/min)	24.3	-
$\dot{V}E/\dot{V}CO_2$ @ AT or lowest	32.9	120
Blood pressure (rest, peak) (mmHg)	100/60, 170/70	-
Symptoms @ test end (legs, dyspnoea) (Borg)	$8^{\dagger}$, 5	-

ALI: acute lung injury; AT: anaerobic threshold; CPET: cardiopulmonary exercise test; O_2 pulse: oxygen pulse; $\dot{V}CO_2$: rate of carbon dioxide production; $\dot{V}E$: minute ventilation; $\dot{V}O_2$: rate of oxygen uptake; WR: work rate; Δ: change; @: occurring at; †: limiting symptom to continuing CPET. %predicted values calculated using published normative reference values.[345,369,370,398]

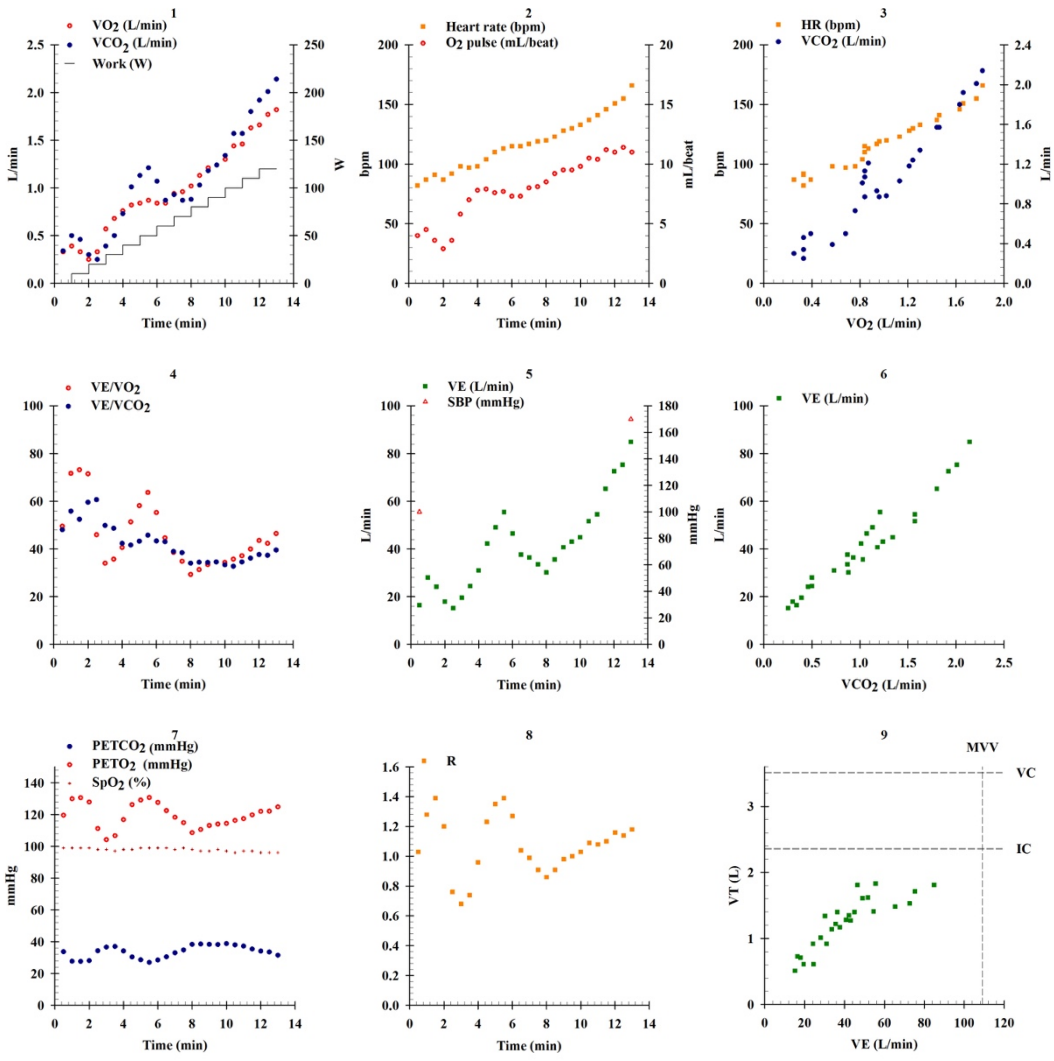

Figure 4-9 9-panel graphical array of physiological responses during the ICET for participant 3 with ALI

IC: inspiratory capacity; ICET: incremental cycle ergometry test; MVV: maximal voluntary ventilation; O_2 pulse: oxygen pulse; $PETCO_2$: end tidal carbon dioxide tension; $PETO_2$: end tidal oxygen tension; R: respiratory exchange quotient; RV: residual volume; SBP: systolic blood pressure; SpO_2: arterial oxygen saturation measured using pulse oximetry; VC: vital capacity; VCO_2: rate of carbon dioxide production; VE: minute ventilation; VO_2: rate of oxygen uptake; VT: tidal volume.

This test was a maximal exercise test as the R exceeded 1.1 and the peak HR response was maximal. The $\Delta VO_2/\Delta WR$ was normal. Exercise capacity was normal as seen by a normal maximum WR and peak VO_2. The AT was normal. Exercise was limited by leg fatigue.

At the AT, the VE/VCO_2 was elevated suggesting the ventilatory response in relation to the metabolic requirements was high. As the $\Delta VO_2/\Delta WR$ was normal and there was no evidence of arterial oxygen desaturation, the elevated VE/VCO2 at AT was unlikely to be as a result of pulmonary vascular disease related to left ventricular failure. The peak O2 pulse was within normal limits also indicating that cardiac function was normal and therefore did not contribute to the elevated ventilatory response. The cause of the elevated ventilatory response was likely due to V/Q mismatching and an increased V_D/V_T possibly associated with impaired diffusion as identified in the pulmonary function testing.

An abnormal ventilatory response was evident at approximately 5 minutes of exercise and was in response to external stimuli, specifically someone unknown to the participant entering the room, which caused temporary anxiety. There was adequate respiratory reserve at the end of exercise.

In conclusion, participant 3 with ALI showed a normal exercise capacity with a mildly elevated ventilatory response, which was likely as a result of impaired diffusion.

4.3.3.2.4 Participant 4 with ALI

This was a 68-year-old male (height 176 cm, weight 102 kg) who was admitted to ICU with aspiration pneumonia following supine positioning for a back injury and sepsis. He had an APACHE II score of 34, was mechanically ventilated for 9 days with an ICU LOS of 31 days.

Table 4-11 presents the data pertaining to the resting pulmonary function collected immediately prior to the ICET, and Table 4-12 presents exercise data collected during the ICET for Participant 4 with ALI. Figure 4-10 presented the physiological responses for Participant 4 with ALI during the ICET plotted as a 9-panel graphical array.

Table 4-11 Resting pulmonary function data measured in Participant 4 with ALI

Measurement	Measured	%predicted
FEV_1 (L)	3.34	107
VC (L)	4.01	96
FEV_1/VC ratio	0.83	111
IC (L)	2.87	86
TLC (L)	6.12	88
RV (L)	2.11	82
FRC (L)	3.25	89
MVV (L/min)	134	108
Hb (g/dL)	11.0	-
D_LCO (mL/min/mmHg)	24.1	75
MIP (cmH_2O)	- 49	41
MEP (cmH_2O)	82	55

ALI: acute lung injury; D_LCO: diffusion capacity of carbon monoxide; FEV_1: forced expiratory volume in one second; FRC: functional residual capacity; Hb: hemoglobin; IC: inspiratory capacity; MIP: maximal expiratory pressure; MEP: maximal expiratory pressure; MVV: maximal voluntary ventilation; RV: residual volume; TLC: total lung capacity; VC: vital capacity. %predicted values calculated using published normative reference values.[156,316,319,365,371]

Table 4-12 Exercise data collected during the ICET for Participant 4 with ALI

Measurement	Measured	%predicted
Maximum work rate (W)	90	49
Peak $\dot{V}O_2$ (L/min)	1.44	61
Peak $\dot{V}O_2$ (mL/kg/min)	14.1	-
$\Delta\dot{V}O_2/\Delta$WR (mL/min/W)	10.6	-
AT (L/min)	0.87	64
Peak heart rate (bpm)	107	64
Peak O_2 pulse (mL/beat)	13.5	95
Peak $\dot{V}E$ (L/min)	59.2	83
Exercise breathing reserve (L/min)	74.4	-
$\dot{V}E/\dot{V}CO_2$ @ AT or lowest	32.2	113
Blood pressure (rest, peak) (mmHg)	110/60, 130/60	-
Symptoms @ test end (legs, dyspnoea) (Borg)	5†, 2	-

ALI: acute lung injury; AT: anaerobic threshold; CPET: cardiopulmonary exercise test; O_2 pulse: oxygen pulse; $\dot{V}CO_2$: rate of carbon dioxide production; $\dot{V}E$: minute ventilation; $\dot{V}O_2$: rate of oxygen uptake; WR: work rate; Δ: change; @: occurring at; †: limiting symptom to continuing CPET. %predicted values calculated using published normative reference values.[345,369,370,398]

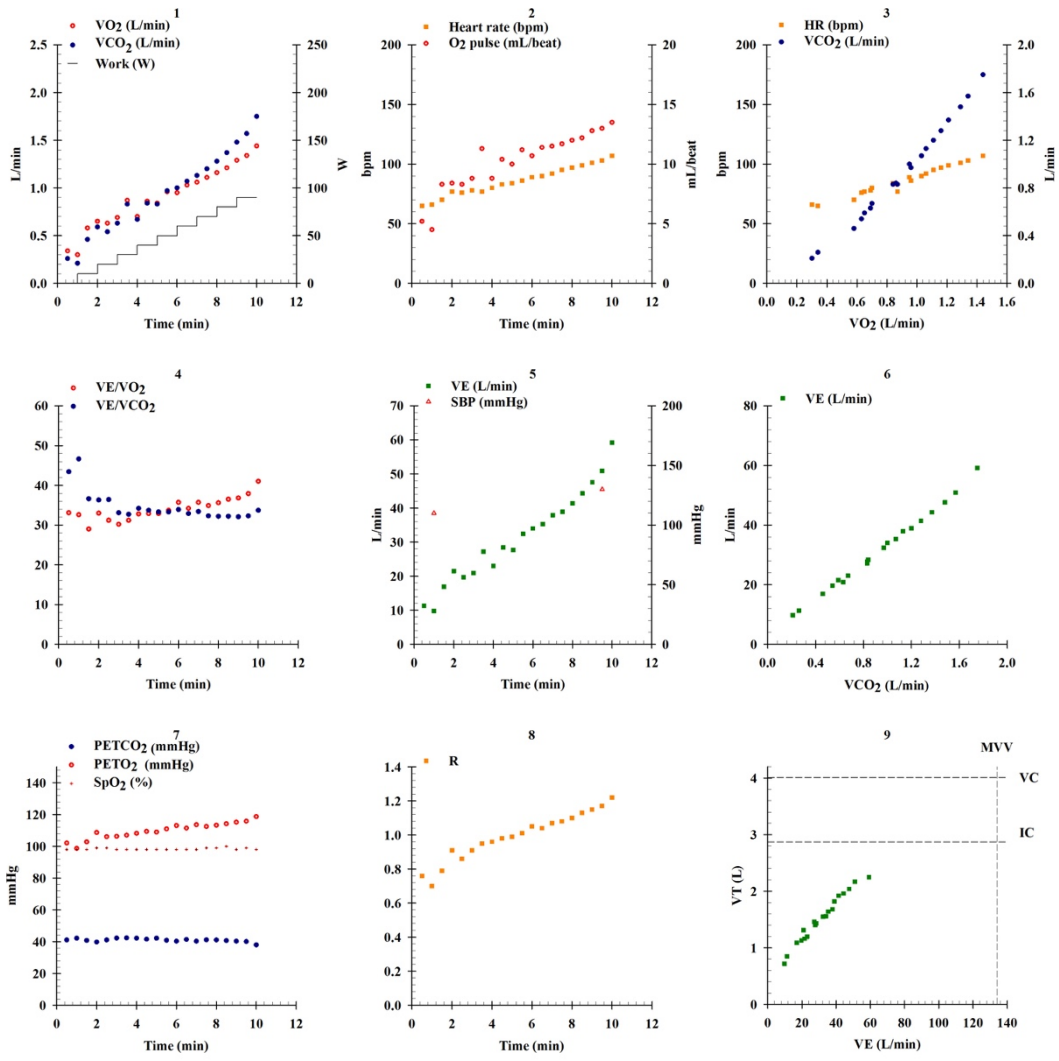

Figure 4-10 9-panel graphical array of physiological responses during the ICET for participant 4 with ALI

IC: inspiratory capacity; ICET: incremental cycle ergometry test; MVV: maximal voluntary ventilation; O_2 pulse: oxygen pulse; $PETCO_2$: end tidal carbon dioxide tension; $PETO_2$: end tidal oxygen tension; R: respiratory exchange quotient; RV: residual volume; SBP: systolic blood pressure; SpO_2: arterial oxygen saturation measured using pulse oximetry; VC: vital capacity; VCO_2: rate of carbon dioxide production; VE: minute ventilation; VO_2: rate of oxygen uptake; VT: tidal volume.

This was a submaximal exercise test as even though the R exceeded 1.2 the peak HR response was attenuated (no use of heart rate-limiting drugs was reported by the participant). The $\Delta VO_2/\Delta WR$ was normal. However, exercise capacity was impaired as seen by a reduction in both maximum WR and peak VO_2. The AT was low. Exercise capacity was limited by back pain.

At the AT, the VE/VCO_2 was normal. There was no evidence of arterial oxygen desaturation. The peak O_2 pulse was within normal limits.

The ventilatory pattern was abnormal. This was characterised by the linear relationship of the tidal volume to ventilation in Panel 9 of the graphs with an absence of plateauing of the curve that occurs toward the peak of exercise. This would suggest that the test was possibly submaximal which is supported by the attenuated peak heart rate response but in contrast to the R value. There was no ventilatory limitation to exercise as shown by the adequate breathing reserve.

In conclusion, participant 4 with ALI showed a reduced exercise capacity which was likely a result of back pain.

4.3.3.2.5 Participant 5 with ALI

This was a 42-year-old male (height 174 cm, weight 59 kg) who was admitted to ICU with community acquired pneumonia and protein losing enteropathy and sepsis. He had an APACHE II score of 22, was mechanically ventilated for 11 days with an ICU LOS of 25 days.

Table 4-13 presents the data pertaining to the resting pulmonary function collected immediately prior to the ICET, and Table 4-14 presents exercise data collected during the ICET for Participant 5 with ALI. Figure 4-11 presented the physiological responses for Participant 5 with ALI during the ICET plotted as a 9-panel graphical array.

Table 4-13 Resting pulmonary function data measured in Participant 5 with ALI

Measurement	Measured	%predicted
FEV_1 (L)	2.38	63
VC (L)	3.04	64
FEV_1/VC ratio	0.83	105
IC (L)	1.49	43
TLC (L)	4.17	61
RV (L)	1.13	57
FRC (L)	2.68	80
MVV (L/min)	95	64
Hb (g/dL)	14.6	-
D_LCO (mL/min/mmHg)	14.6	40
MIP (cmH_2O)	- 92	93
MEP (cmH_2O)	102	77

ALI: acute lung injury; D_LCO: diffusion capacity of carbon monoxide; FEV_1: forced expiratory volume in one second; FRC: functional residual capacity; Hb: hemoglobin; IC: inspiratory capacity; MIP: maximal expiratory pressure; MEP: maximal expiratory pressure; MVV: maximal voluntary ventilation; RV: residual volume; TLC: total lung capacity; VC: vital capacity. %predicted values calculated using published normative reference values.[156,316,319,365,371]

Table 4-14 Exercise data collected during the ICET for Participant 5 with ALI

Measurement	Measured	%predicted
Maximum work rate (W)	60	28
Peak $\dot{V}O_2$ (L/min)	1.04	40
Peak $\dot{V}O_2$ (mL/kg/min)	17.63	52
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	9.7	-
AT (L/min)	0.50	36
Peak heart rate (bpm)	150	82
Peak O_2 pulse (mL/beat)	6.9	48
Peak $\dot{V}E$ (L/min)	81.1	176
Exercise breathing reserve (L/min)	14.1	-
$\dot{V}E/\dot{V}CO_2$ @ AT or lowest	44.8	173
Blood pressure (rest, peak) (mmHg)	118/86, 150/90	-
Symptoms @ test end (legs, dyspnoea)	(Borg) 7†, 4	-

ALI: acute lung injury; AT: anaerobic threshold; CPET: cardiopulmonary exercise test; O_2 pulse: oxygen pulse; $\dot{V}CO_2$: rate of carbon dioxide production; $\dot{V}E$: minute ventilation; $\dot{V}O_2$: rate of oxygen uptake; WR: work rate; Δ: change; @: occurring at; †: limiting symptom to continuing CPET. %predicted values calculated using published normative reference values.[345,369,370,398]

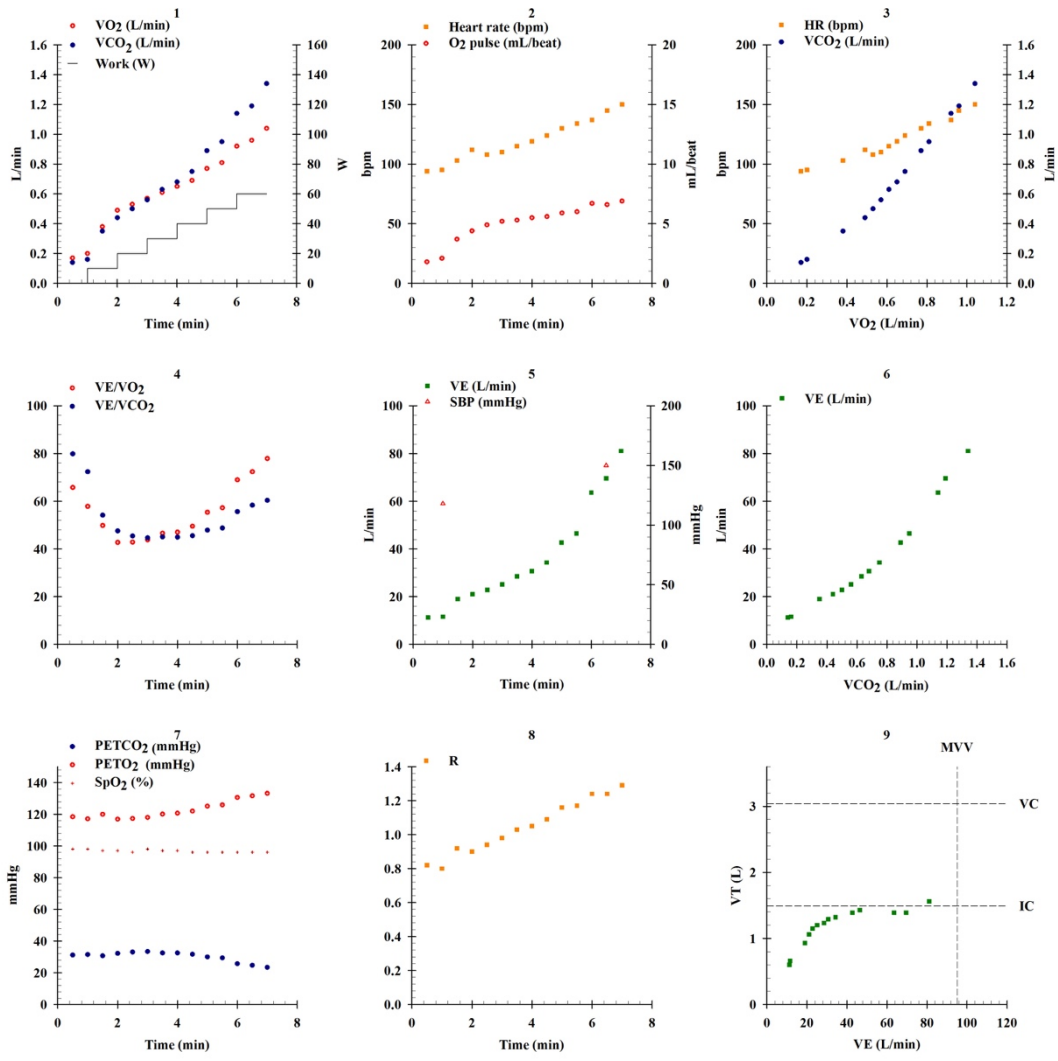

Figure 4-11 9-panel graphical array of physiological responses during the ICET for participant 5 with ALI

IC: inspiratory capacity; ICET: incremental cycle ergometry test; MVV: maximal voluntary ventilation; O_2 pulse: oxygen pulse; $PETCO_2$: end tidal carbon dioxide tension; $PETO_2$: end tidal oxygen tension; R: respiratory exchange quotient; RV: residual volume; SBP: systolic blood pressure; SpO_2: arterial oxygen saturation measured using pulse oximetry; VC: vital capacity; VCO_2: rate of carbon dioxide production; VE: minute ventilation; VO_2: rate of oxygen uptake; VT: tidal volume.

This test was a maximal exercise test as the R exceeded 1.2 although there was a slightly attenuated HR response. The $\Delta VO_2/\Delta WR$ was at the lower limits of normal. However, exercise capacity was impaired as seen by a reduction in both the maximum WR and peak VO_2. It is possible that the shortened duration of the test due to the protocols ramp increments devised for this participant may have contributed to these reductions. The AT was low. Exercise capacity was limited by leg fatigue.

The ECG revealed 1mm ST depression in leads II and III towards the end of exercise, which resolved during recovery. There was no chest pain, and no arterial oxygen desaturation evident. The O_2 pulse was low throughout the test but did not plateau. The slightly reduced $\Delta VO_2/\Delta WR$ also suggests cardiac dysfunction although the variability of data points makes it difficult to clearly identify the slope.

At the AT, the VE/VCO_2 was elevated suggesting the ventilatory response in relation to the metabolic requirements was high. As the $\Delta VO_2/\Delta WR$ was only slightly reduced and there was no evidence of arterial oxygen desaturation, the elevated VE/VCO2 at AT was unlikely to be as a result of pulmonary vascular disease related to left ventricular failure. The cause of the elevated ventilatory response was likely due to V/Q mismatching and an increased V_D/V_T possibly associated with impaired diffusion as identified in the pulmonary function testing.

The ventilatory response was appropriate characterised by the linear relationship of VT to VE which plateaued toward the peak of exercise. There was limited breathing reserve at the end of test. However, considering the peak HR achieved during the test was near maximal, the limited breathing reserve was unlikely to be a limiting factor to exercise. Tidal volume encroached upon inspiratory reserve volume as the test progressed, consistent with the restrictive pulmonary deficit noted on pulmonary function testing.

In conclusion, participant 5 with ALI showed a reduced exercise capacity likely as a result of general deconditioning, impaired pulmonary diffusion and cardiac dysfunction.

4.3.3.2.6 Participant 6 with ALI

This was a 67-year-old female (height 166cm tall, weight 108 kg) who was admitted to ICU with cryptogenic organising pneumonia/community acquired pneumonia and sepsis. She had an APACHE II score of 24, was mechanically ventilated for 8 days with an ICU LOS of 8 days.

Table 4-15 presents the data pertaining to the resting pulmonary function collected immediately prior to the ICET, and Table 4-16 presents exercise data collected during the ICET for Participant 6 with ALI. Figure 4-12 presented the physiological responses for Participant 6 with ALI during the ICET plotted as a 9-panel graphical array.

Table 4-15 Resting pulmonary function data measured in Participant 6 with ALI

Measurement	Measured	%predicted
FEV_1 (L)	2.13	94
VC (L)	2.73	102
FEV_1/VC ratio	0.79	104
IC (L)	1.81	76
TLC (L)	3.63	70
RV (L)	0.90	43
FRC (L)	1.82	65
MVV (L/min)	85	94
Hb (g/dL)	12.0	-
D_LCO (mL/min/mmHg)	12.9	53
MIP (cmH_2O)	- 43	45
MEP (cmH_2O)	76	79

ALI: acute lung injury; D_LCO: diffusion capacity of carbon monoxide; FEV_1: forced expiratory volume in one second; FRC: functional residual capacity; Hb: hemoglobin; IC: inspiratory capacity; MIP: maximal expiratory pressure; MEP: maximal expiratory pressure; MVV: maximal voluntary ventilation; RV: residual volume; TLC: total lung capacity; VC: vital capacity. %predicted values calculated using published normative reference values.[156,316,319,365,371]

Table 4-16 Exercise data collected during the ICET for Participant 6 with ALI

Measurement	Measured	%predicted
Maximum work rate (W)	64	65
Peak $\dot{V}O_2$ (L/min)	1.06	64
Peak $\dot{V}O_2$ (mL/kg/min)	9.81	-
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	11.0, 9.6†	-
AT (L/min)	0.70	69
Peak heart rate (bpm)	167	101
Peak O_2 pulse (mL/beat)	6.3	63
Peak $\dot{V}E$ (L/min)	64.3	170
Exercise breathing reserve (L/min)	20.9	
$\dot{V}E/\dot{V}CO_2$ @ AT or lowest	36.5	122
Blood pressure (rest, peak) (mmHg)	117/68, 182/82	-
Symptoms @ test end (legs, dyspnoea) (Borg)	6‡, 5	-

ALI: acute lung injury; AT: anaerobic threshold; CPET: cardiopulmonary exercise test; O_2 pulse: oxygen pulse; $\dot{V}CO_2$: rate of carbon dioxide production; $\dot{V}E$: minute ventilation; $\dot{V}O_2$: rate of oxygen uptake; WR: work rate; Δ: change; @: occurring at; †: limiting symptom to continuing CPET. %predicted values calculated using published normative reference values.[345,369,370,398]

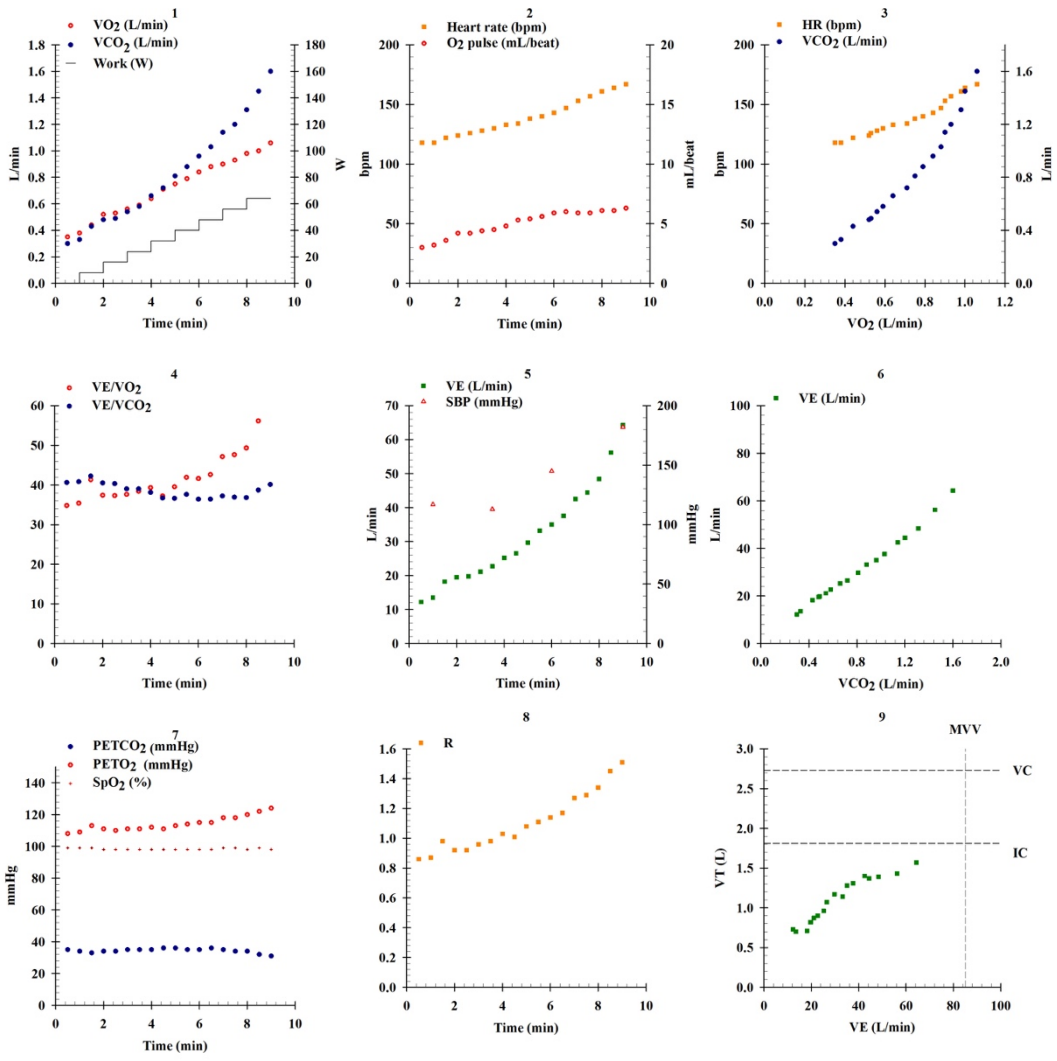

Figure 4-12 9-panel graphical array of physiological responses during the ICET for participant 6 with ALI

IC: inspiratory capacity; ICET: incremental cycle ergometry test; MVV: maximal voluntary ventilation; O_2 pulse: oxygen pulse; $PETCO_2$: end tidal carbon dioxide tension; $PETO_2$: end tidal oxygen tension; R: respiratory exchange quotient; RV: residual volume; SBP: systolic blood pressure; SpO_2: arterial oxygen saturation measured using pulse oximetry; VC: vital capacity; VCO_2: rate of carbon dioxide production; VE: minute ventilation; VO_2: rate of oxygen uptake; VT: tidal volume.

This was a maximal exercise test as the R exceeded 1.5 and the peak HR response was maximal. The $\Delta VO_2/\Delta WR$ was normal. However, exercise capacity was impaired as seen by a reduction in both the maximum WR and peak VO_2. The AT was low. Exercise was limited by leg fatigue.

The ECG revealed ST depression in ECG in leads V3-V6 at minute 5 which resolved during recovery. There was no chest pain, and no arterial oxygen desaturation evident. The O_2 pulse plateaued in the final 4 minutes of exercise corresponding with the occurrence of the ECG changes, and peak O_2 pulse was low. The $\Delta VO2/\Delta WR$ also showed a slight flattening from a previously normal slope at this time.

At the AT, the VE/VCO_2 was elevated suggesting the ventilatory response in relation to the metabolic requirements was high. As there was no evidence of arterial oxygen desaturation, the elevated VE/VCO_2 at AT was unlikely to be as a result of pulmonary vascular disease related to left ventricular failure. The cause of the elevated ventilatory response was likely due to V/Q mismatching and an increased V_D/V_T possibly associated with impaired diffusion as identified in the pulmonary function testing.

The ventilatory response was appropriate characterised by the linear relationship of VT to VE which plateaued toward the peak of exercise. There was no ventilatory limitation to exercise as shown by the adequate breathing reserve.

In conclusion, participant 6 with ALI showed a reduced exercise capacity likely as a result of deconditioning, impaired pulmonary diffusion and cardiac dysfunction.

4.3.3.2.7 Participant 7 with ALI

This was a 63-year-old male (height 175 cm, weight 99 kg) who was admitted to ICU with community acquired pneumonia and sepsis. He had an APACHE II score of 25, was mechanically ventilated for 9 days with an ICU LOS of 11 days.

Table 4-17 presents the data pertaining to the resting pulmonary function collected immediately prior to the ICET, and Table 4-18 presents exercise data collected during the ICET for Participant 7 with ALI. Figure 4-13 presented the physiological responses for Participant 7 with ALI during the ICET plotted as a 9-panel graphical array.

Table 4-17 Resting pulmonary function data measured in Participant 7 with ALI

Measurement	Measured	%predicted
FEV_1 (L)	2.38	74
VC (L)	3.77	88
FEV_1/VC ratio	0.64	84
IC (L)	2.66	80
TLC (L)	5.56	81
RV (L)	1.79	73
FRC (L)	2.90	81
MVV (L/min)	116	91
Hb (g/dL)	13.9	-
D_LCO (mL/min/mmHg)	16.0	49
MIP (cmH_2O)	- 72	61
MEP (cmH_2O)	118	79

ALI: acute lung injury; D_LCO: diffusion capacity of carbon monoxide; FEV_1: forced expiratory volume in one second; FRC: functional residual capacity; Hb: hemoglobin; IC: inspiratory capacity; MIP: maximal expiratory pressure; MEP: maximal expiratory pressure; MVV: maximal voluntary ventilation; RV: residual volume; TLC: total lung capacity; VC: vital capacity. %predicted values calculated using published normative reference values.[156,316,319,365,371]

Table 4-18 Exercise data collected during the ICET for Participant 7 with ALI

Measurement	Measured	%predicted
Maximum work rate (W)	120	64
Peak $\dot{V}O_2$ (L/min)	1.88	76
Peak $\dot{V}O_2$ (mL/kg/min)	18.99	-
$\Delta\dot{V}O_2/\Delta$WR (mL/min/W)	10.4	-
AT (L/min)	1.05	74
Peak heart rate (bpm)	158	93
Peak O_2 pulse (mL/beat)	11.9	82
Peak $\dot{V}E$ (L/min)	90.2	138
Exercise breathing reserve (L/min)	25.8	-
$\dot{V}E/\dot{V}CO_2$ @ AT or lowest	33.2	119
Blood pressure (rest, peak) (mmHg)	110/72, 207/71	-
Symptoms @ test end (legs, dyspnoea) (Borg)	9†, 5.5	-

ALI: acute lung injury; AT: anaerobic threshold; CPET: cardiopulmonary exercise test; O_2 pulse: oxygen pulse; $\dot{V}CO_2$: rate of carbon dioxide production; $\dot{V}E$: minute ventilation; $\dot{V}O_2$: rate of oxygen uptake; WR: work rate; Δ: change; @: occurring at; †: limiting symptom to continuing CPET. %predicted values calculated using published normative reference values.[345,369,370,398]

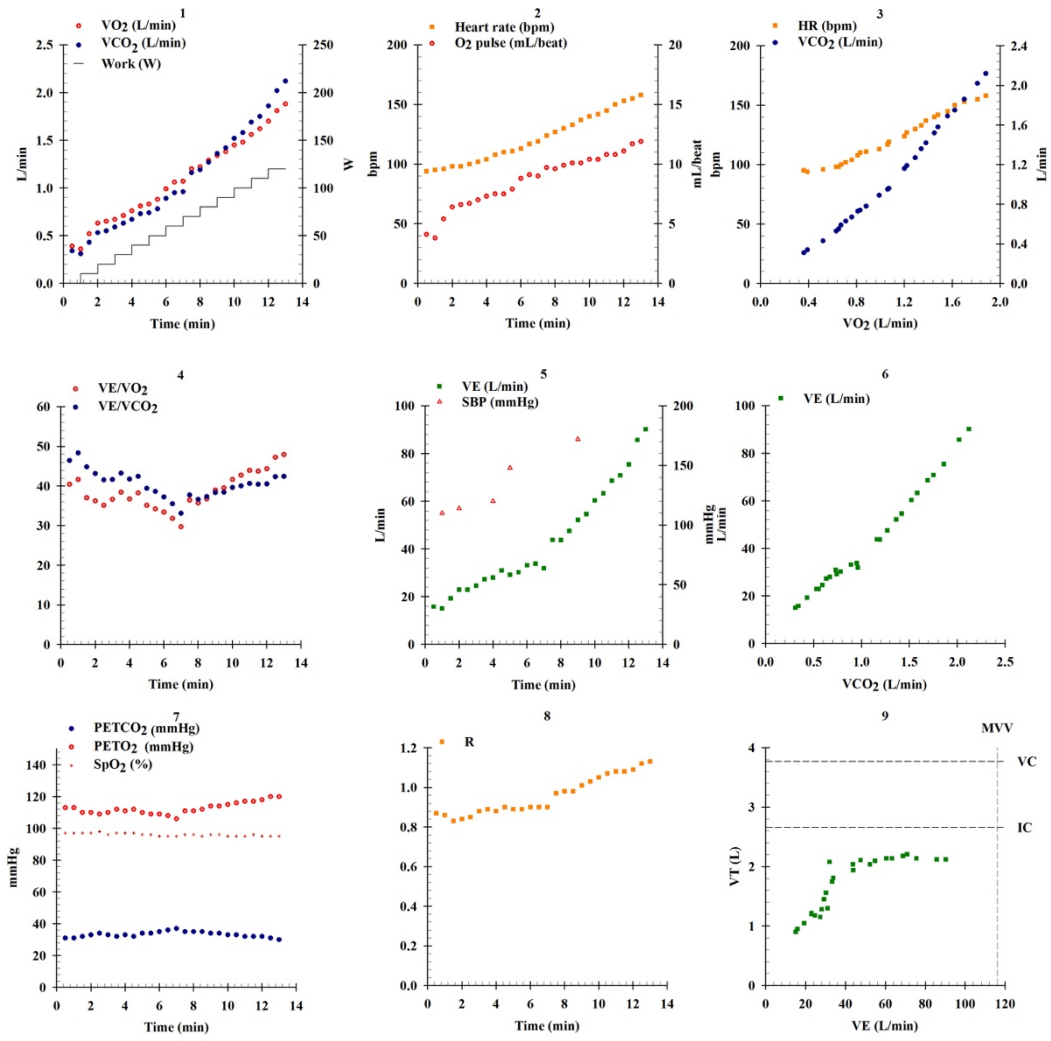

Figure 4-13 9-panel graphical array of physiological responses during the ICET for participant 7 with ALI

IC: inspiratory capacity; ICET: incremental cycle ergometry test; MVV: maximal voluntary ventilation; O_2 pulse: oxygen pulse; $PETCO_2$: end tidal carbon dioxide tension; $PETO_2$: end tidal oxygen tension; R: respiratory exchange quotient; RV: residual volume; SBP: systolic blood pressure; SpO_2: arterial oxygen saturation measured using pulse oximetry; VC: vital capacity; VCO_2: rate of carbon dioxide production; VE: minute ventilation; VO_2: rate of oxygen uptake; VT: tidal volume.

This test was a maximal exercise test as the R exceeded 1.1 and the peak HR was maximal. The $\Delta VO_2/\Delta WR$ was normal. Exercise capacity was impaired as seen by a reduction in WR and peak VO_2. The AT was low. Exercise was limited by leg fatigue.

At the AT, the VE/VCO_2 was elevated suggesting the ventilatory response in relation to the metabolic requirements was high. As the $\Delta VO_2/\Delta WR$ was normal and there was no evidence of arterial oxygen desaturation, the elevated VE/VCO2 at AT was unlikely to be as a result of pulmonary vascular disease related to left ventricular failure. The peak O_2 pulse was within normal limits also indicating that cardiac function was normal and therefore did not contribute to the elevated ventilatory response. The cause of the elevated ventilatory response was likely due to V/Q mismatching and an increased V_D/V_T possibly associated with impaired diffusion as identified in the pulmonary function testing.

The peak O_2 pulse was within normal limits with an appropriate progression throughout exercise.

The ventilatory response was appropriate, characterised by the linear relationship of VT to VE which plateaued toward the peak of exercise. There was no ventilatory limitation as shown by the adequate breathing reserve.

In conclusion, participant 7 with ALI showed reduced exercise capacity likely as a result of general deconditioning and impaired pulmonary diffusion.

4.3.3.2.8 Participant 8 with ALI

This with ALI was a 42-year-old female (height 165cm, weight 70 kg) who was admitted to ICU with biliary sepsis. She had an APACHE II score of 13, was mechanically ventilated for 6 days with an ICU LOS of 6 days.

Table 4-19 presents the data pertaining to the resting pulmonary function collected immediately prior to the ICET, and Table 4-20 presents exercise data collected during the ICET for Participant 8 with ALI. Figure 4-14 presented the physiological responses for Participant 8 with ALI during the ICET plotted as a 9-panel graphical array.

Table 4-19 Resting pulmonary function data measured in Participant 8 with ALI

Measurement	Measured	%predicted
FEV_1 (L)	2.17	76
VC (L)	2.65	80
FEV_1/VC ratio	0.82	101
IC (L)	1.86	79
TLC (L)	4.06	80
RV (L)	1.41	87
FRC (L)	2.20	81
MVV (L/min)	87	75
Hb (g/dL)	12.1	-
D_LCO (mL/min/mmHg)	13.5	48
MIP (cmH_2O)	- 129	153
MEP (cmH_2O)	102	106

ALI: acute lung injury; D_LCO: diffusion capacity of carbon monoxide; FEV_1: forced expiratory volume in one second; FRC: functional residual capacity; Hb: hemoglobin; IC: inspiratory capacity; MIP: maximal expiratory pressure; MEP: maximal expiratory pressure; MVV: maximal voluntary ventilation; RV: residual volume; TLC: total lung capacity; VC: vital capacity. %predicted values calculated using published normative reference values.[156,316,319,365,371]

Table 4-20 Exercise data collected during the ICET for Participant 8 with ALI

Measurement	Measured	%predicted
Maximum work rate (W)	100	75
Peak $\dot{V}O_2$ (L/min)	1.35	78
Peak $\dot{V}O_2$ (mL/kg/min)	19.3	-
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	10.5	-
AT (L/min)	0.75	76
Peak heart rate (bpm)	167	91
Peak O_2 pulse (mL/beat)	8.2	87
Peak $\dot{V}E$ (L/min)	60.1	168
Exercise breathing reserve (L/min)	26.5	-
$\dot{V}E/\dot{V}CO_2$ @ AT or lowest	32.4	119
Blood pressure (rest, peak)	125/75,	-
Symptoms @ test end (legs, dyspnoea) (Borg)	8†, 7	-

ALI: acute lung injury; AT: anaerobic threshold; CPET: cardiopulmonary exercise test; O_2 pulse: oxygen pulse; $\dot{V}CO_2$: rate of carbon dioxide production; $\dot{V}E$: minute ventilation; $\dot{V}O_2$: rate of oxygen uptake; WR: work rate; Δ: change; @: occurring at; †: limiting symptom to continuing CPET. %predicted values calculated using published normative reference values.[345,369,370,398]

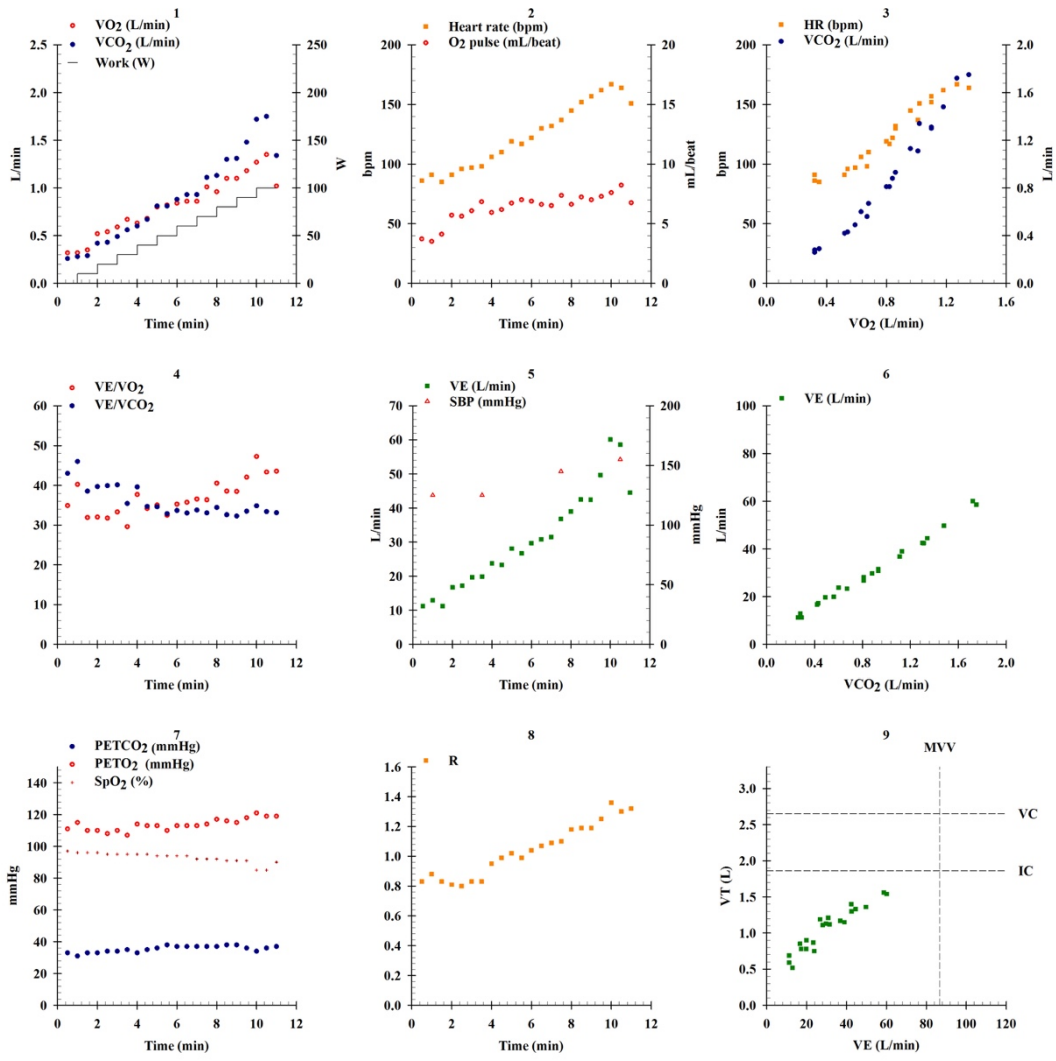

Figure 4-14 9-panel graphical array of physiological responses during the ICET for participant 8 with ALI

IC: inspiratory capacity; ICET: incremental cycle ergometry test; MVV: maximal voluntary ventilation; O_2 pulse: oxygen pulse; $PETCO_2$: end tidal carbon dioxide tension; $PETO_2$: end tidal oxygen tension; R: respiratory exchange quotient; RV: residual volume; SBP: systolic blood pressure; SpO_2: arterial oxygen saturation measured using pulse oximetry; VC: vital capacity; VCO_2: rate of carbon dioxide production; VE: minute ventilation; VO_2: rate of oxygen uptake; VT: tidal volume.

This test was a maximal exercise test as the R exceeded 1.2 and the peak HR response was maximal. The ΔVO2/ΔWR was normal. However, exercise capacity was impaired as seen by a reduction in both the maximum WR and peak VO_2. The AT was low. Exercise was limited by leg fatigue.

At the AT, the VE/VCO_2 was elevated suggesting the ventilatory response in relation to the metabolic requirements was high. While the $\Delta VO_2/\Delta WR$ was normal, progressive arterial desaturation was observed with a nadir SpO_2 of 85% at the end of exercise. The peak O_2 pulse however was within normal limits indicating that cardiac function was normal and therefore did not contribute to the elevated ventilatory response. The elevated VE/VCO_2 at AT combined with the progressive hypoxaemia may be a result of: (i) pulmonary vascular disease resulting in an increased $V_D/V_{T;}$ and/or (ii) V/Q mismatching and an increased V_D/V_T possibly associated with impaired diffusion as identified in the pulmonary function testing.

The ventilatory response was appropriate, characterised by the linear relationship of VT to VE which plateaued toward the peak of exercise. There was no ventilatory limitation as shown by the adequate breathing reserve.

In conclusion, participant 8 with ALI showed a reduced exercise capacity likely as a result of general deconditioning, pulmonary vascular disease and/or impaired diffusion.

4.3.3.2.9 Participant 9 with ALI

This was a 36-year-old male (height 177cm, weight 62 kg) who was admitted to ICU with pneumocystis carnii pneumonia and sepsis. He had an APACHE II score of 28, was mechanically ventilated for 10 days with an ICU LOS of 14 days.

Table 4-21 presents the data pertaining to the resting pulmonary function collected immediately prior to the ICET, and Table 4-22 presents exercise data collected during the ICET for Participant 9 with ALI. Figure 4-15 presented the physiological responses for Participant 9 with ALI during the ICET plotted as a 9-panel graphical array.

Table 4-21 Resting pulmonary function data measured in Participant 9 with ALI

Measurement	Measured	%predicted
FEV_1 (L)	3.27	81
VC (L)	4.40	86
FEV_1/VC ratio	0.72	89
IC (L)	3.05	83
TLC (L)	6.21	87
RV (L)	1.81	91
FRC (L)	3.16	94
MVV (L/min)	131	81
Hb (g/dL)	11.2	-
D_LCO (mL/min/mmHg)	16.1	44
MIP (cmH_2O)	- 104	100
MEP (cmH_2O)	101	75

ALI: acute lung injury; D_LCO: diffusion capacity of carbon monoxide; FEV_1: forced expiratory volume in one second; FRC: functional residual capacity; Hb: hemoglobin; IC: inspiratory capacity; MIP: maximal expiratory pressure; MEP: maximal expiratory pressure; MVV: maximal voluntary ventilation; RV: residual volume; TLC: total lung capacity; VC: vital capacity. %predicted values calculated using published normative reference values.[156,316,319,365,371]

Table 4-22 Exercise data collected during the ICET for Participant 9 with ALI

Measurement	Measured	%predicted
Maximum work rate (W)	80	35
Peak $\dot{V}O_2$ (L/min)	1.20	44
Peak $\dot{V}O_2$ (mL/kg/min)	19.5	-
$\Delta\dot{V}O_2/\Delta$WR (mL/min/W)	10.0	-
AT (L/min)	0.80	57
Peak heart rate (bpm)	129	69
Peak O_2 pulse (mL/beat)	9.5	64
Peak $\dot{V}E$ (L/min)	69.8	85
Exercise breathing reserve (L/min)	61.0	-
$\dot{V}E/\dot{V}CO_2$ @ AT or lowest	34.9	138
Blood pressure (rest, peak)	100/56,	-
Symptoms @ test end (legs, dyspnoea) (Borg)	5†, 3	-

ALI: acute lung injury; AT: anaerobic threshold; CPET: cardiopulmonary exercise test; O_2 pulse: oxygen pulse; $\dot{V}CO_2$: rate of carbon dioxide production; $\dot{V}E$: minute ventilation; $\dot{V}O_2$: rate of oxygen uptake; WR: work rate; Δ: change; @: occurring at; †: limiting symptom to continuing CPET. %predicted values calculated using published normative reference values.[345,369,370,398]

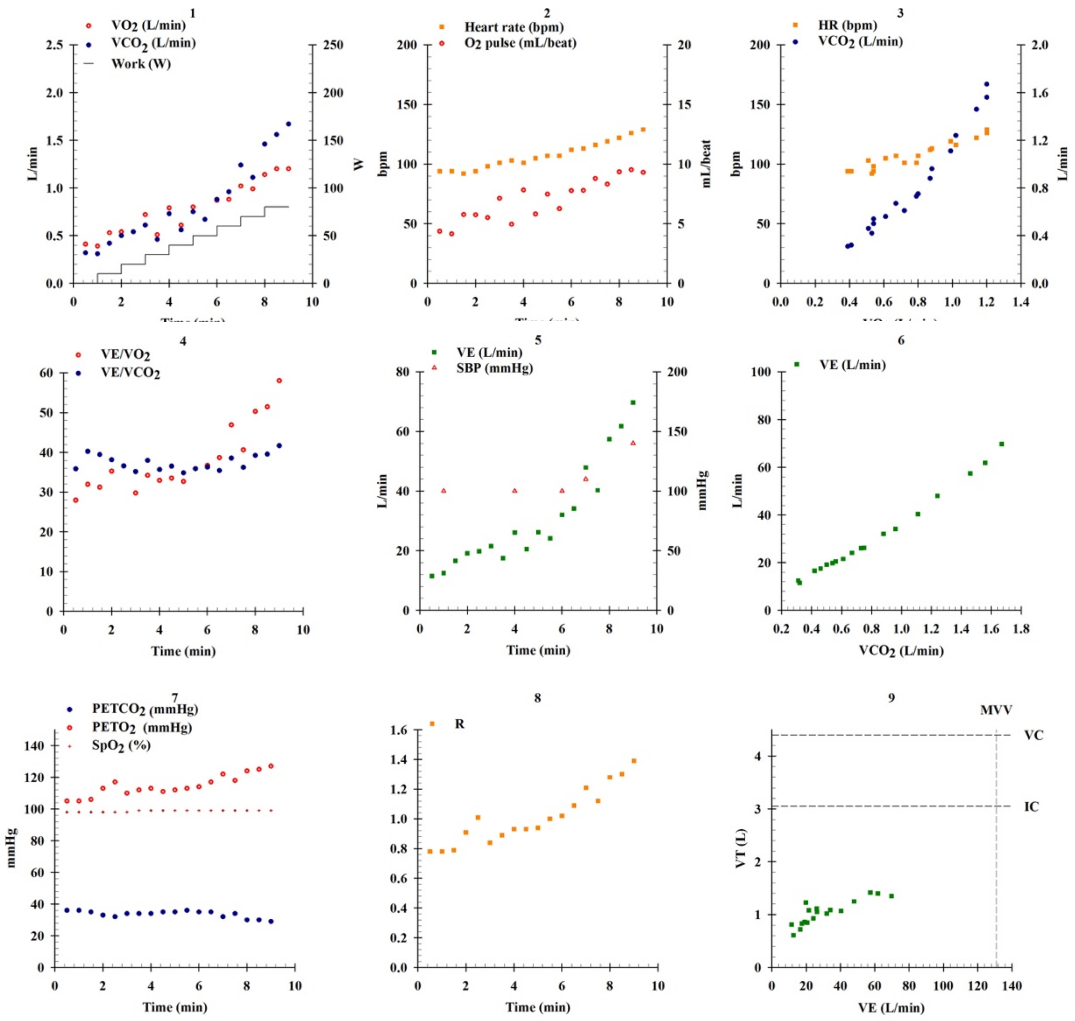

Figure 4-15 9-panel graphical array of physiological responses during the ICET for participant 9 with ALI

IC: inspiratory capacity; ICET: incremental cycle ergometry test; MVV: maximal voluntary ventilation; O_2 pulse: oxygen pulse; $PETCO_2$: end tidal carbon dioxide tension; $PETO_2$: end tidal oxygen tension; R: respiratory exchange quotient; RV: residual volume; SBP: systolic blood pressure; SpO_2: arterial oxygen saturation measured using pulse oximetry; VC: vital capacity; VCO_2: rate of carbon dioxide production; VE: minute ventilation; VO_2: rate of oxygen uptake; VT: tidal volume.

This was a submaximal exercise test as even though the R exceeded 1.3 the peak HR response was attenuated. The $\Delta VO_2/\Delta WR$ was normal. However, exercise capacity was impaired as seen by a reduction in both maximum WR and peak VO_2. The attenuated HR was likely as a result of propranolol the patient was prescribed for hand tremors. While this may have also impacted WR and peak VO_2, it is unlikely to have been a notable factor in the reduction of these factors since peak VO_2 has been shown to be minimally affected by beta agonists.[368] The AT was low. Exercise capacity was limited by leg fatigue.

At the AT, the VE/VCO_2 was elevated suggesting the ventilatory response in relation to the metabolic requirements was high. As the $\Delta VO_2/\Delta WR$ was normal and there was no evidence of arterial oxygen desaturation, the elevated VE/VCO_2 at AT was unlikely to be as a result of pulmonary vascular disease related to left ventricular failure. The cause of the elevated ventilatory response was likely due to V/Q mismatching and an increased V_D/V_T possibly associated with impaired diffusion as identified in the pulmonary function testing.

The peak O_2 pulse was reduced again potentially as a result of the prescribed beta agonist, although the reduction in left ventricular ejection fraction (LVEF) at maximal exercise as a result of beta agonist has been shown to be only approximately 10%.[368] The more likely cause of the reduction in oxygen pulse was deconditioning.

The ventilatory response was appropriate characterised by the linear relationship of VT to VE which plateaued toward the peak of exercise. There was no ventilatory limitation as shown by the adequate breathing reserve.

In conclusion, participant 9 with ALI showed a reduced exercise capacity likely as a result of deconditioning and impaired pulmonary diffusion, but also impacted upon by a medically induced attenuated peak HR response (secondary to propranolol).

4.3.3.2.10 Participant 10 with ALI

This was a 62-year-old female (height 168cm, weight 75 kg) who was admitted to ICU with Legionella pneumonia and sepsis. She had an APACHE II score of 25, was mechanically ventilated for 11 days with an ICU LOS of 12 days.

Table 4-23 presents the data pertaining to the resting pulmonary function collected immediately prior to the ICET, and Table 4-24 presents exercise data collected during the ICET for Participant 10 with ALI. Figure 4-16 presented the physiological responses for Participant 10 with ALI during the ICET plotted as a 9-panel graphical array.

Table 4-23 Resting pulmonary function data measured in Participant 10 with ALI

Measurement	Measured	%predicted
FEV_1 (L)	1.87	75
VC (L)	4.22	143
FEV_1/VC ratio	0.62	79
IC (L)	2.02	82
TLC (L)	4.56	86
RV (L)	0.34	17
FRC (L)	2.54	90
MVV (L/min)	75	75
Hb (g/dL)	13.6	-
D_LCO (mL/min/mmHg)	13.5	52
MIP (cmH_2O)	- 75	92
MEP (cmH_2O)	82	91

ALI: acute lung injury; D_LCO: diffusion capacity of carbon monoxide; FEV_1: forced expiratory volume in one second; FRC: functional residual capacity; Hb: hemoglobin; IC: inspiratory capacity; MIP: maximal expiratory pressure; MEP: maximal expiratory pressure; MVV: maximal voluntary ventilation; RV: residual volume; TLC: total lung capacity; VC: vital capacity. %predicted values calculated using published normative reference values.[156,316,319,365,371]

Table 4-24 Exercise data collected during the ICET for Participant 10 with ALI

Measurement	Measured	%predicted
Maximum work rate (W)	88	76
Peak $\dot{V}O_2$ (L/min)	1.13	71
Peak $\dot{V}O_2$ (mL/kg/min)	15.07	-
$\Delta\dot{V}O_2/\Delta$WR (mL/min/W)	10.9	-
AT (L/min)	0.75	77
Peak heart rate (bpm)	146	86
Peak O_2 pulse (mL/beat)	7.9	84
Peak $\dot{V}E$ (L/min)	62.5	81
Exercise breathing reserve (L/min)	12.3	-
$\dot{V}E/\dot{V}CO_2$ @ AT or lowest	35.5	122
Blood pressure (rest, peak) (mmHg)	132/78, 220/80	-
Symptoms @ test end (legs, dyspnoea) (Borg)	5.5†, 2	-

ALI: acute lung injury; AT: anaerobic threshold; CPET: cardiopulmonary exercise test; O_2 pulse: oxygen pulse; $\dot{V}CO_2$: rate of carbon dioxide production; $\dot{V}E$: minute ventilation; $\dot{V}O_2$: rate of oxygen uptake; WR: work rate; Δ: change; @: occurring at; †: limiting symptom to continuing CPET. %predicted values calculated using published normative reference values.[345,369,370,398]

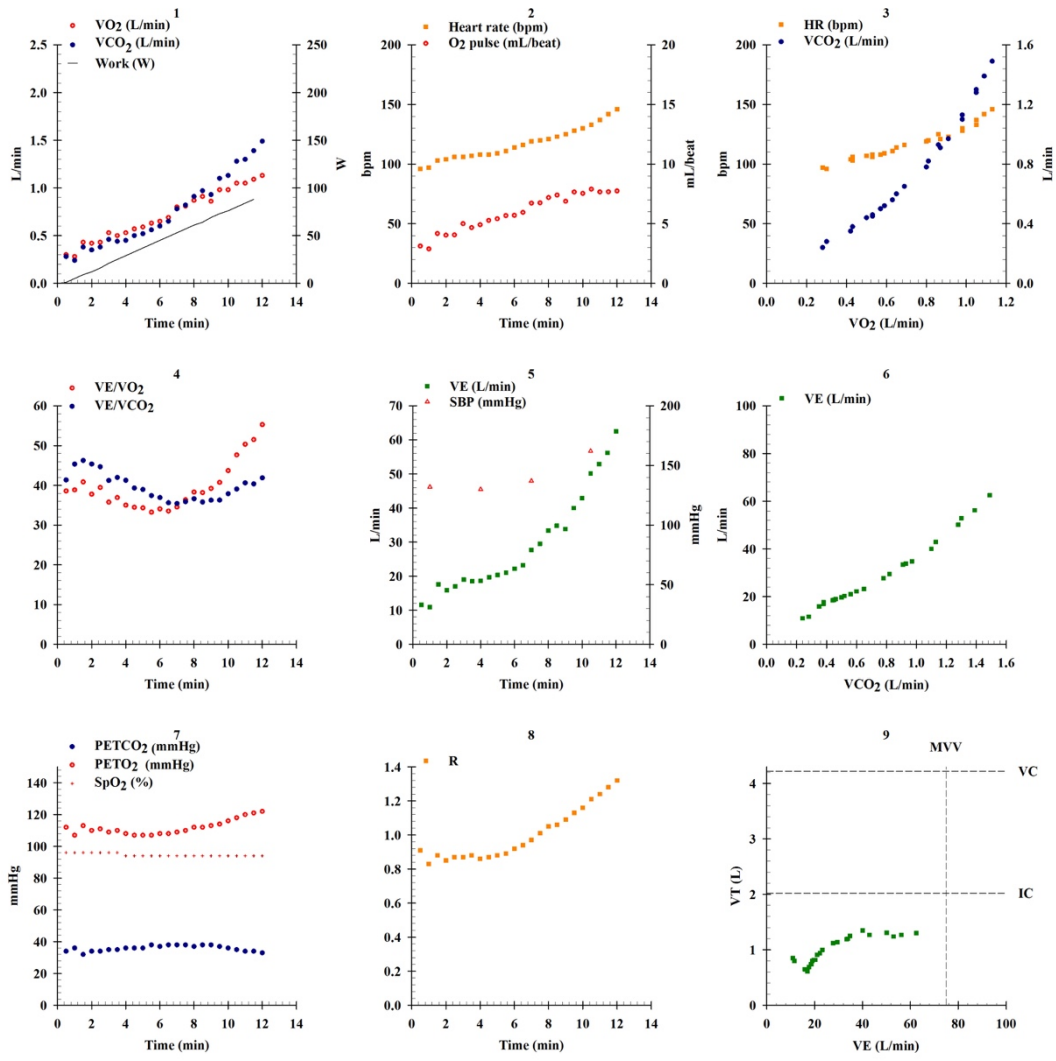

Figure 4-16 9-panel graphical array of physiological responses during the ICET for participant 10 with ALI

IC: inspiratory capacity; ICET: incremental cycle ergometry test; MVV: maximal voluntary ventilation; O_2 pulse: oxygen pulse; $PETCO_2$: end tidal carbon dioxide tension; $PETO_2$: end tidal oxygen tension; R: respiratory exchange quotient; RV: residual volume; SBP: systolic blood pressure; SpO_2: arterial oxygen saturation measured using pulse oximetry; VC: vital capacity; VCO_2: rate of carbon dioxide production; VE: minute ventilation; VO_2: rate of oxygen uptake; VT: tidal volume.

This test was a maximal exercise test as the R exceeded 1.3 and maximal peak heart rate response. The $\Delta VO_2/\Delta WR$ was normal. However, exercise capacity was impaired as seen by a reduction in both the maximum WR and peak VO_2. The AT was low. Exercise capacity was limited by leg fatigue.

At the AT, the VE/VCO_2 was elevated suggesting the ventilatory response in relation to the metabolic requirements was high. As the $\Delta VO_2/\Delta WR$ was normal and there was no evidence of arterial oxygen desaturation, the elevated VE/VCO_2 at AT was unlikely to be as a result of pulmonary vascular disease related to left ventricular failure. The peak O_2 pulse was within normal limits with an appropriate progression throughout exercise, also indicating that cardiac function was normal and therefore did not contribute to the elevated ventilatory response. The cause of the elevated ventilatory response was likely due to V/Q mismatching and an increased V_D/V_T possibly associated with impaired diffusion as identified in the pulmonary function testing.

The ventilatory response was appropriate characterised by the linear relationship of VT to VE which plateaued toward the peak of exercise. There was no ventilatory limitation as shown by the adequate breathing reserve.

In conclusion, participant 10 with ALI showed a reduced exercise capacity likely as a result of general deconditioning and impaired pulmonary diffusion.

4.3.3.2.11 Summary of mechanisms of exercise limitation observed in the participants with ALI

Table 4-25 presents a summary of the key physiological responses of the participants with ALI. Eight (80%) participants with ALI had a decreased peak VO_2. Although no participant was limited by his or her respiratory capacity, an elevated minute ventilation was present in 6 (60%) participants. One participant desaturated during the ICET, which was not associated with an elevated minute ventilation response. The cause of limitation in the participants who had a decreased peak VO_2 appeared to be impairment in pulmonary diffusion (n = 7), deconditioning (n = 7) and cardiac impairment (n = 2).

Table 4-25 Overview of the presence and direction of abnormalities in key physiological responses during the ICET for the individual participants with ALI

Participant	Peak VO_2	AT	Maximum VE	VE/VCO_2 @ AT	Nadir SpO_2	Evidence of cardiac ischaemia	Evidence of ventilatory limitation
1	↓	↓	↑	↑	→	×	×
2	→	→	→	→	→	×	×
3	→	→	↑	↑	→	×	×
4	↓	↓	→	→	→	×	×
5	↓	↓	↑	↑	→	✓	×
6	↓	↓	↑	↑	→	✓	×
7	↓	↓	↑	↑	→	×	×
8	↓	↓	↑	↑	↓	×	×
9	↓	↓	→	↑	→	×	×
10	↓	↓	→	↑	→	×	×

ALI: acute lung injury; AT: anaerobic threshold; ICET: incremental cycle ergometry test; SpO_2: arterial oxygen saturation measured via pulse oximetry; VE: minute ventilation; VO_2: rate of oxygen uptake; @: at; ↓: decreased; →: within normal limits; ↑: increased; ✓: present; ×: absent.

4.3.4 Physical activity and sedentary time

This section presents data related to PA and ST measured using the SAB. For both PA and ST, data collected in the participants with ALI have been compared with data collected in the healthy participants. These data are presented as: (i) time over which SAB data were available; (ii) time spent in PA and ST; (iii) patterns of accumulation of PA and ST; and (iv) daily step count.

4.3.4.1 Time over which SenseWear® armband data were available

All participants with ALI contributed ≥ 600 minutes of data per day over at least 7 days, which included at least one weekend day (see section 4.2.2.7.2). Among the healthy participants, 4 (19%, 2 males) participants did not meet the minimum wear time criteria for inclusion in these analyses and therefore, their data were excluded. Compared with the healthy participants whose data were included (n = 17), the healthy participants whose data were excluded (n = 4) were broadly similar in terms of age (51 [45 to 54] vs. 45 [43 to 48] yr, $p = 0.05$) and BMI (24 [22 to 29] vs. 23 [21 to 34] kg/m^2, $p = 0.46$).

Table 4-26 presents the details regarding time over which SAB data were available in both groups. For the data included in the final analyses, both the number of days and the number of hours per day that the SAB was worn were similar between the ALI and healthy participants.

Table 4-26 Time over which SenseWear® armband data were available for the ALI and healthy participants

	Participants with ALI (n = 10)	Healthy participants (n = 17)	*p*-value
Total number of days worn	5.5 [4.8 to 6.0]	6.0 [5.0 to 6.0]	0.13
No. weekdays (M-F) worn	4.0 [3.0 to 4.0]	4.0 [4.0 to 4.0]	0.006
No. weekend days (Sa-Su) worn	2.0 [1.8 to 2.0]	2.0 [1.0 to 2.0]	0.68
Time on body (hr/day)	14 ± 2	15 ± 1	0.81
Proportion of waking hours on body (%)	97 [94 to 99]	97 [94 to 98]	0.30
Determined daily start time of waking hours (24 hr time)	07:35 ± 1:17	06:52 ± 0:38	0.06

Data are mean ± standard deviation or median [interquartile range]. ALI: acute lung injury. M-F: Monday to Friday; No.: number; Sa-Su: Saturday to Sunday. All values pertain to data which met the criteria for inclusion in final analyses.

4.3.4.2 Time spent in light intensity, moderate intensity and vigorous intensity physical activity and sedentary time

Figure 4-17 presents the time spent in LPA, MPA and VPA and ST, expressed as a proportion of waking hours, in the ALI and healthy participants. Compared with the healthy participants, the participants with ALI spent less time in MPA (16 [9 to 24] vs. 5 [2 to 13] %, $p = 0.002$) and VPA (1 [0 to 2] vs. 0 [0 to 0] %, $p < 0.001$) and had greater ST (58 [48 to 70] vs. 72 [63 to 80] %, $p = 0.008$). The time spent in LPA was similar between groups being 21 [16 to 26] % in the healthy participants and 20 [11 to 28] % in the participants with ALI ($p = 0.86$). As the proportion of waking hours spent in VPA was negligible, data pertaining to MPA and VPA were combined and expressed as MVPA. Compared with the healthy participants, the participants with ALI accumulated less time in MVPA (17 [10 to 25] vs. 5 [2 to13] %, $p = 0.001$).

Table 4-27 presents the time, expressed as hr/day, spent in LPA, MVPA and ST in the ALI and healthy participants. As seen when time in MVPA and ST were expressed as a proportion of waking hours, compared with the healthy participants, the participants with ALI accumulated less time in MVPA and more ST, when time was expressed in hours and minutes.

4.3.4.3 Patterns of accumulation of light intensity, moderate and vigorous intensity physical activity and sedentary time

Table 4-28 presents the way in which time in LPA, MVPA and ST was accumulated in both groups. Compared with the healthy participants, the participants with ALI accumulated a lower proportion of the total time spent in MVPA in unbroken bouts ≥ 10 minutes and a greater proportion of ST in unbroken bouts ≥ 30 minutes. There were no differences in the proportion of total time spent in LPA in unbroken bouts ≥ 10 minutes. Compared with the healthy participants, a lower proportion of participants with ALI accumulated an average total of ≥ 30 minutes of MVPA per day (47% vs. 0%, $p = 0.009$).

4.3.4.4 Daily step count

Compared with the healthy participants, the participants with ALI accumulated fewer steps per day (9,936 ± 3,818 vs. 5,180 ± 3,099 steps per day, $p = 0.003$). Compared with the healthy participants, there was a trend for fewer participants with

ALI to accumulate an average daily step count that exceeded 10,000 steps (41% vs. 10%, $p = 0.05$).

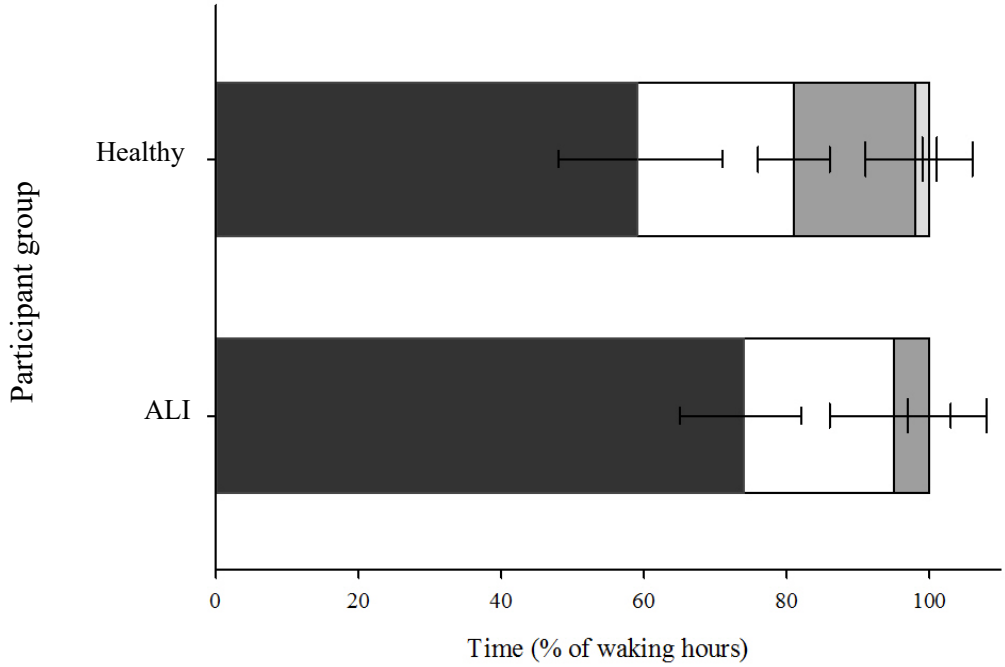

Figure 4-17 Proportion of waking hours spent in light intensity, moderate intensity and vigorous intensity physical activity and sedentary time for the ALI and healthy participants

Data are median and interquartile range. ALI: acute lung injury; : sedentary time; : light intensity physical activity; : moderate intensity physical activity; : vigorous intensity physical activity; : interquartile range for sedentary time; : interquartile range for light intensity physical activity; : interquartile range for moderate intensity physical activity; : interquartile range for vigorous intensity physical activity.

Table 4-27 Hours per day spent in light intensity, moderate and vigorous intensity physical activity and sedentary time for the ALI and healthy participants

	Participants with ALI (n = 10)	Healthy participants (n = 17)	*p*-value
Light intensity physical activity (hr/day)	2.9 ± 1.5	3.0 ± 1.1	0.74
Moderate and vigorous intensity physical activity (hr/day)	0.6 [0.3 to 1.7]	2.4 [1.4 to 3.7]	0.001
Sedentary time (hr/day)	10.3 ± 1.8	8.6 ± 1.6	0.021

All data are mean ± standard deviation or median [interquartile range]. ALI: acute lung injury.

Table 4-28 Patterns of accumulation of light intensity, moderate and vigorous intensity physical activity and sedentary time

	Participants with ALI (n = 10)	Healthy participants (n = 17)	*p*-value
Proportion of total time spent in light intensity physical activity that was accumulated in bouts ≥ 10 min (%)	19 [0 to 22]	12 [11 to 18]	0.54
Proportion of total time spent in moderate and vigorous intensity physical activity that was accumulated in bouts ≥ 10 min (%)	14 [0 to 27]	30 [20 to 44]	0.018
Proportion of total time spent in sedentary time that was accumulated in bouts ≥ 30 min (%)	51 [43 to 66]	38 [23 to 50]	0.031

All data are median [interquartile range]. ALI: acute lung injury.

4.3.5 Peripheral muscle strength

Table 4-29 presents the peripheral muscle strength for the ALI and healthy participants and the respiratory muscle strength for the ALI participants only. Compared with the healthy participants, the ALI participants recorded lower values for all measures of peripheral muscle strength. Figure 4-18 presents the muscle strength of the ALI participants as a proportion of normative reference values.

Table 4-29 Peripheral muscle strength for the ALI and healthy participants and respiratory muscle strength for the participants with ALI only

	Participants with ALI (n = 10)	**Healthy participants (n = 21)**	***p*-value**
Knee extension (N)	249 [199 to 304]	383 [310 to 564]	0.002
Grip (kg)	27 ± 7	42 ± 13	0.002
Elbow flexion (kg)	17 [15 to 22]	25 [18 to 33]	0.009
Shoulder flexion (kg)	16 ± 3	24 ± 6	0.001
MIP (cmH_20)	-82 [-66 to -110]	-	-
MEP (cmH_20)	101 [82 to 106]	-	-

Data are mean ± standard deviation or median [interquartile range]. ALI: acute lung injury; MEP: maximal expiratory pressure; MIP: maximal inspiratory pressure.

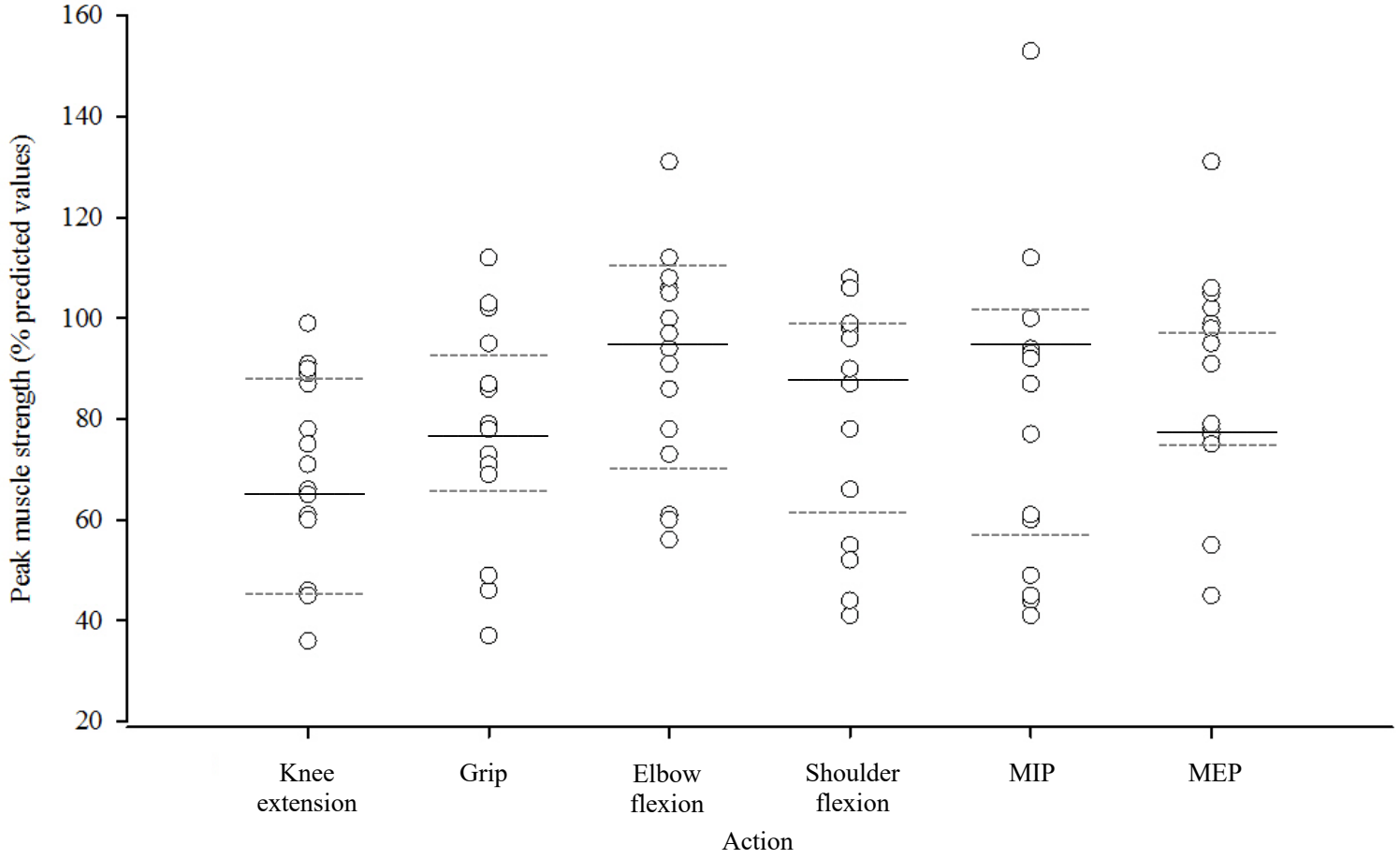

Figure 4-18 Muscle strength for all actions as a proportion of normative reference values for participants with ALI

Data are individual values, median and interquartile range. MEP: maximal expiratory pressure; MIP: maximal inspiratory pressure; —— : median; ----- : interquartile range.

4.3.6 Health-related quality of life

Figure 4-19 presents the scores for the SF36 in each domain for the ALI and healthy participants. Compared with the healthy participants, the participants with ALI scored lower on all domains. Figure 4-20 presents the values for the PCS and the MCS for the ALI and the healthy participants. Although not related to a research question, opportunistic analyses comparing SF36 scores collected via the proxy for the participants with ALI (in ICU) and the participants with ALI 6 weeks after discharge from an acute care facility, are presented in Appendix 12.

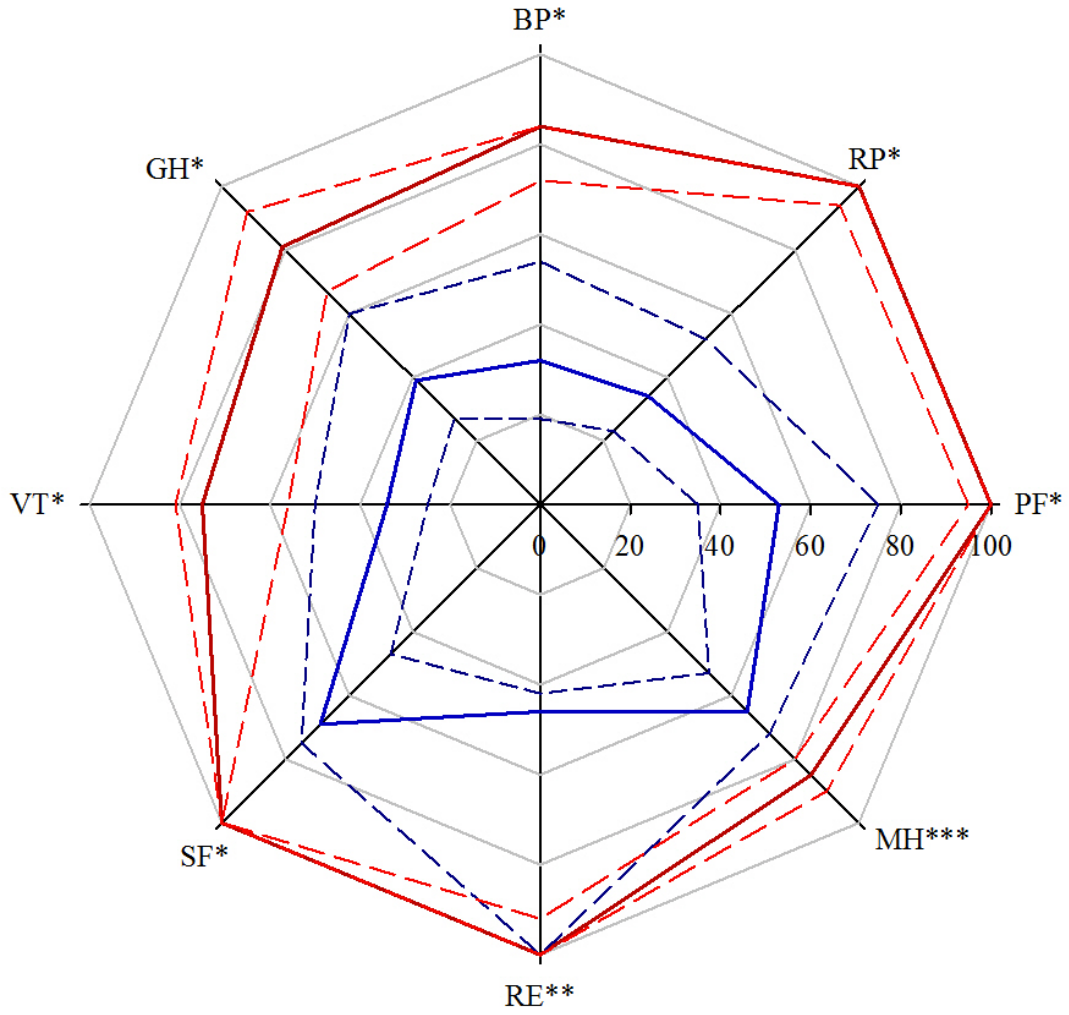

Figure 4-19 Health related quality of life domains for ALI and healthy participants

Data are median and interquartile range. ALI: acute lung injury; BP: bodily pain; GH: general health; MH: mental health; PF: physical functioning; RE: role emotional; RP: role physical; SF: social functioning; VT: vitality. ——— : ALI participants median; ---- : ALI participants interquartile range; ——— : healthy participants median. ---- : healthy participants interquartile range. * $p < 0.001$; ** $p = 0.001$; *** $p = 0.002$.

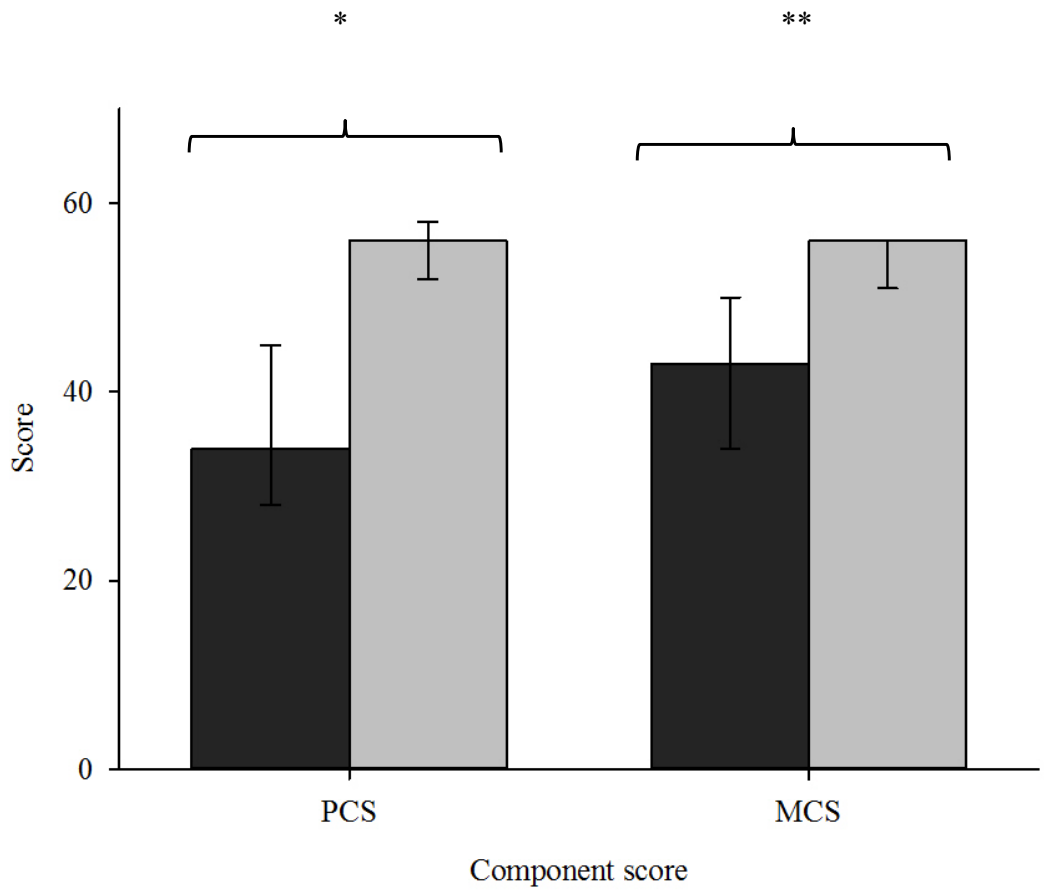

Figure 4-20 Physical component score and mental component score of the SF36 for ALI and healthy participants

Data are median and interquartile range. ALI: acute lung injury; MCS: mental component score; PCS: physical component score. ▬: ALI participants; ▭: healthy participants. * $p < 0.001$, ** $p = 0.001$.

4.3.7 Fatigue severity

Compared with the healthy participants, the participants with ALI had a higher mean FSS (2.6 ± 1.2 vs. 4.7 ± 1.6; $p < 0.001$) with a score that exceeds 4, denoting severe fatigue in other populations.[392]

4.4 Discussion

4.4.1 Overview

This study measured peak and submaximal exercise responses during an ICET as well as PA and ST, peripheral muscle strength, HRQL and fatigue in people who survived an admission to ICU with a diagnosis of ALI. All measurements in these participants were made at 6 weeks following discharge from an acute care facility. These measures were compared with a sample of healthy adults of similar age and gender proportion. The main findings of this study were, compared with a healthy control group, those people who had survived an admission to an ICU with ALI were characterised by reduced exercise capacity. The mechanism of this impairment was related to deconditioning, impaired pulmonary diffusion and cardiac dysfunction. This study also showed that when compared with a healthy control group, those who survived an admission to an ICU with ALI participated in lower levels of PA, accumulated greater ST and had reduced peripheral muscle strength, worse HRQL and higher levels of fatigue.

4.4.2 Participant recruitment

Participant recruitment in this study was challenging and was largely due to the low proportion of participants who met the criteria to be included in the ALI group. The reason for the low proportion of patients screened who met the criteria for ALI is unclear. Although strategies were implemented to optimise identification of those meeting the criteria for ALI, it is possible that patients were missed in the screening process. The under diagnosis of ARDS and ALI has been reported previously. A recent study in an international ICU cohort found that only 40% of all ARDS diagnoses were identified as part of routine care by clinicians.[87] However, it is also possible that the actual incidence of ALI in the JHH and CMN ICUs was low. A geographic variation in ARDS incidence in the previously mentioned international

cohort of ICU's which included 18 ICUs from within Australia, has been described (0.27 to 0.57 cases per ICU bed).[87]

4.4.3 Peak and submaximal exercise response

This study is the first to report peak VO_2 in a group of adults who survived an ICU admission for ALI. Compared with the healthy participants, the ALI participants had a lower peak VO_2 expressed as both L/min (p = 0.006) and mL/kg/min (p = 0.001). The peak VO_2 of these participants with ALI was similar to that reported in people with moderately severe chronic obstructive pulmonary disease (COPD)[399,400] as well as those living with heart failure.[401,402] Notwithstanding this magnitude of impairment, the peak VO_2 reported in the current study was somewhat higher than that reported in the few studies that have reported peak VO_2 in groups of critical illness survivors who had been mechanically ventilated for > 5 days, and who were assessed shortly after hospital discharge.[27,176] Specifically, in earlier studies, the peak VO_2, assessed within 6 weeks following hospital discharge was 13.8 mL/kg/min[176] and 13.4 mL/kg/min[27], respectively which is less than reported in the current study (17.80 [14.85 to 20.85] mL/kg/min).

When compared with the current study, the lower peak VO_2 in the earlier studies is likely to reflect: (i) less opportunity for natural recovery with peak VO_2 being measured approximately 3 weeks following discharge in these earlier studies compared with 6 weeks in the current study; (ii) a longer period of mechanical ventilation, which would represent a longer period of bed rest leading to mechanical unloading and deconditioning, and being closer to 3 weeks in these earlier studies compared with just over one week in the current study; (iii) a longer ICU admission which may also reflect a longer period of bed rest, and being an average of 2 to 4 weeks in these earlier studies compared with 10 days in the current study; and (iv) a higher proportion of participants who were prescribed heart rate limiting medications which may impact the ability to achieve a true physiological peak, and being 36% in one of the earlier studies,[176] compared with 10% in the current study. Paradoxically, when compared with the current study, these earlier studies[27,176] which reported a longer period of mechanical ventilation and a longer ICU LOS also reported less severe illness in their sample, when measured using the APACHE II scores. That is, the mean APACHE II scores in these earlier studies ranged from 16 to 17, which is

considerably less than the APACHE II scores in the current study of 23. The fact that our sample demonstrated less impairment in peak VO_2 despite having more severe illness at the time of admission to ICU suggests that in addition to the severity of the critical illness, the duration of mechanical ventilation and length of ICU admission may also contribute importantly to the impairment in peak VO_2. Further,

The contention that the management of critical illness plays an important role in determining magnitude of functional impairment measured following discharge from ICU, is supported by the 6MWD measured in this study. The 6MWD was greater when compared with other studies that have used this measure to assess exercise capacity in survivors of ALI and/or ARDS who had a similar severity of illness on admission, but had considerably longer periods of mechanical ventilation or duration of ICU admission.[12,15] That is, the current study and studies by Herridge et al[12] and Fan et al[15] recruited samples with APACHE II scores of 23, but in these earlier studies the 6MWD measured within 3 months following discharge from ICU was 49%[12] and 52%[15] of that predicted in a healthy population, respectively, which is less than reported in the current study, being 73% of that predicted in a healthy population.

Compared with the current study, the period of mechanical ventilation in the study by Herridge et al[12] was longer (9 ± 2 vs. 21 [12 to 40]days). Similarly, compared with the current study, the ICU LOS in the study by Fan et al[15] was longer (10 [8 to 17] vs. 14 [10 to 23] days). The influence of longer periods of mechanical ventilation and duration of ICU admission may be related to differences in sedation practices and the general management of the people with a critical illness at the time of recruitment to these earlier studies, which was at least 10 years ago. Sedation, particularly within the first 48 hours of an admission to ICU and without daily interruptions, impacts on both time to wean and LOS in ICU.[11] The study by Herridge et al[12] recruited participants between 1998 and 2002, which preceded the development and implementation of bundles of care, such as the ABCDE bundle, aiming to improve patient outcomes.[403] This influenced management within ICU, particularly related to the rationalisation of sedation.[403,404]

Although Fan et al[15] recruited participants more recently (between 2004 and 2007), this study was conducted in North America where the nursing to patient ratios are

lower than in Australia (1:2 vs. 1:1) which is likely to result in the use of larger amounts of sedation and fewer sedation interruptions.[405] Greater sedation results in longer duration of mechanical ventilation and, in turn, longer ICU LOS and is likely to worsen peripheral muscle atrophy.[40,406] This is likely due, in part, to the extended period of mechanical unloading for skeletal muscles that is associated with a prolonged ICU admission. Muscle atrophy has been suggested to be rapid during the first 10 days[40] and has been shown in a recent study to continue on a similar trajectory, as shown by the continuing decrease in rectus femoris cross-sectional area, for up to 4 weeks into an ICU admission.[406] The participants with ALI in the current study were discharged, on average by day 10, and therefore were not exposed to the ongoing mechanical unloading and subsequent atrophying of skeletal muscle that participants in the previous studies may have experienced. This may explain the better peak VO_2 and 6MWD observed in our sample. Further, differences in ICU practices which have been previously suggested to impact physical recovery, and which may include the use of neuromuscular blocking agents, glucocorticoids, and the development of hyperglycaemia, will vary between units and may therefore also have contributed to the differences observed.[71,143,144] Although there were differences in magnitude of impairment reported in this study compared with earlier work, it is clear that survivors of ALI, similar to critical illness survivors and survivors of ARDS, have impaired exercise capacity measured using both laboratory and field-based walking tests.

In addition to quantifying peak exercise capacity, undertaking the ICET with 12 lead ECG and breath by breath analysis, together with the measurement of lung function allowed information to be collected regarding the integrated physiological responses to increasing load during exercise. These data were used to provide information regarding the mechanism of limitation to exercise.[345] Integration of these data suggests that the likely mechanisms of limitation to exercise capacity can be broadly grouped into 3 factors: (i) deconditioning; (ii) impaired pulmonary diffusion; and (iii) cardiac dysfunction. General deconditioning was identified as a mechanism of limitation in 7 participants with ALI as these participants demonstrated: (i) an impaired peak VO_2 in the absence of ventilatory limitation; (ii) an impaired maximum WR in the absence of cardiac impairment; (iii) an impaired AT; and (iv) an elevated resting HR reflecting a reduced contribution by stroke volume to cardiac

output. Submaximal exercise responses in the participants with ALI, when examined as a group, also supports the argument of exercise limitation being driven, at least in part, by general deconditioning. That is, when compared with the healthy participants, those with ALI demonstrated a higher rate of change of VO_2 in relation to WR (Figure 4-3), and of HR and VE in relation to VO_2 (Figure 4-4 and Figure 4-5). These exercise responses in the participants with ALI, namely an increased HR response to activity, are likely to be a result of cardiovascular deconditioning secondary to prolonged immobility.[130,407] Indeed, studies published in healthy populations, have shown that following a period of immobility of approximately 10 to 14 days, there is evidence of remodeling of cardiac tissue,[408,409] a decrease in red blood cell mass,[407,410] and a decrease in tissue capillary density.[411]

In addition to cardiovascular deconditioning, peripheral muscle deconditioning also contributed to the limitation in exercise capacity. Support for this comes from data in the current study showing that those with ALI: (i) had a reduction in the strength of quadriceps femoris, when expressed as Newtons or as a percentage of that value predicted in a healthy population; (ii) had a reduction in median AT; and (iii) consistently reported leg fatigue as the limiting symptom at maximum WR. Similarly, previous studies have shown, that during an ICU admission, reductions in cross-sectional area of rectus femoris of approximately 18% occurs within 10-14 days of admission to ICU.[40,114,406] These changes, as measured via ultrasound, result from prolonged mechanical unloading[117,130] and also systemic factors such as increased circulating inflammatory mediators, and dysfunctional micro-circulation which contributes to muscle catabolism.[71,412-414] Furthermore, these factors which contribute to muscle catabolism during the critical illness have been shown to be present 3 to 6 months after discharge from ICU.[415] Specifically, earlier work has reported that, in a group of critical illness survivors who were mechanically ventilated for more than 48 hours, systemic inflammation as identified by the concentration of C-reactive protein, was still present in 72 (59%) of the 123 participants at 3 months after discharge from ICU.[415] These previously identified physiological changes of the skeletal muscle associated with critical illness, in conjunction with the reduction in AT and early reliance on anaerobic energy systems observed in the current study, may indicate an impaired oxidative capacity of the

skeletal muscle in this population. It is possible that the resulting increase in lactate production early in the ICET manifests as the limiting symptom of leg fatigue.

In addition to general deconditioning, impaired pulmonary diffusion was identified as a mechanism of limitation in 7 of the 10 participants with ALI. These participants had an elevated VE/VCO_2 at AT and impaired D_LCO. A raised VE/VCO_2 at AT in the presence of a reduced AT, may contribute to exercise limitation, and be indicative of pulmonary vascular disease, secondary to cardiac disease or intrinsic lung pathology.[345] However, pulmonary vascular disease that limits peak exercise capacity is usually associated with a concomitant decrease in oxygen saturation. Only one participant with ALI desaturated (decrease in $SpO_2 > 4\%$)*[416]* during the ICET. The remaining participants with an elevated VE/VCO_2 at AT also had reduced D_LCO which is most likely to be the cause of the elevation. The elevated VE/VCO_2 at AT without significant desaturation presented in the current study, is consistent with an earlier study in a cohort of 50 survivors of critical illness which described an elevated VE/VCO_2 at AT, and significant desaturation (decrease in $SpO_2 > 4\%$) in only one participant.[176] Impaired pulmonary diffusion, measured as D_LCO, has been demonstrated previously in survivors of ARDS at 3 and 12 months (63 [54 to 77] % and 72 [61 to 86] % of that predicted in a healthy population).[12,186] This impairment observed in survivors of ARDS appears to have largely resolved by 2.5 years when D_LCO was measured to be 94 ± 14 % of that predicted in a healthy population at 29.5 ± 8.7 months.[42] The impairment in pulmonary diffusion is most likely as a direct result of the pathology that defines ARDS and ALI. This pathology includes acute morphological changes seen radiologically, such as alveolar oedema, interstitial inflammation, and compression atelectasis,[417] which presents 12 months following hospital discharge as a reduction of 10 to 15% of the total lung volume and abnormalities in the lung parenchyma that are consistent with fibrosis.[418] Earlier studies have suggested that the impairment observed in lung function in those surviving ARDS and ALI is disproportionate to the severity of exercise intolerance as measured by the 6MWT and implied by the physical functioning scores of the SF36.[12,110] The current study suggests that while the impairment in pulmonary diffusion may not fully explain the impairment in exercise capacity, it may still be a contributing factor.

Cardiac dysfunction also contributed to exercise limitation in 2 participants. This finding is supported by the ischaemic changes evident on ECG during the ICET (2 participants) and the presence of a decreased $\Delta VO_2/\Delta WR$ (< 10 mL/kg/min/W) (one participant). These changes are consistent with myocardial and vascular insufficiency.[345] The incidence of cardiac dysfunction in survivors of ALI and ARDS after hospital discharge has not been investigated. Although it is possible that cardiac dysfunction was present in these 2 participants prior to their ICU admission, the dysfunction may have resulted from circulatory insufficiency during their acute illness. Circulatory failure occurring during ALI or ARDS can be attributed to sepsis related depressed intrinsic myocardial performance[187-191] and/or circulatory failure secondary to ARDS-related pulmonary hypertension and right ventricle failure (acute cor-pulmonale).[83,84] The incidence of left and right ventricular dysfunction in patients with sepsis has been reported to range between 40 and 52%.[346-348] The incidence of acute cor-pulmonale in patients following ARDS has been reported to range between 20 and 25%.[349,350] The sequelae of both of these pathologies include increased right ventricular wall shear stress, decrease in left ventricular ejection and subsequently decreased coronary blood flow,[419] all of which may lead to ongoing myocardial insufficiency and subsequent limitation in exercise capacity.

In addition to reporting the magnitude and likely mechanisms of impairment in exercise capacity, the data collected in this study also provided novel information regarding the effect of test familiarisation on the 6MWD. As presented in Table 4-2, in the current study, the participants with ALI increased their 6MWD by 40 [17 to 56] m between the first and second test (467 [440 to 580] vs. 507 [460 to 619] m, $p = 0.020$), which exceeds the minimal important difference reported in those recovering from acute respiratory failure, of 20 to 30 m.[203] This phenomenon resulting from familiarisation with a second test, while well recognised in people with chronic respiratory disease and ventilatory limitation,[329,330] has not been reported in people surviving a critical illness. Allowing participants the opportunity to improve their performance on a second test may also have contributed to the greater 6MWD, when compared with earlier work which measured the 6MWD using a single 6MWT in ICU survivors.[12,15] Future studies of ICU survivors that plan to measure exercise capacity in terms of 6MWD should consider performing 2 tests and reporting the best 6MWD as the measure.

4.4.4 Participation in physical activity and sedentary time

This study is the first to report the time spent during waking hours by survivors of critical illness in light intensity physical activity (LPA), moderate intensity physical activity (MPA), vigorous intensity physical activity (VPA) and moderate and vigorous intensity physical activity (MVPA) combined, and sedentary time (ST). With time expressed as a percentage of waking hours, compared with the healthy participants, the ALI participants spent a similar proportion of waking hours in LPA but a lower proportion of waking hours in MPA and VPA and a greater proportion of waking hours in ST. These results were similar when time was expressed in hours per day (Table 4-27).

These data, pertaining to the participants with ALI accumulating less MVPA and more ST than a similar healthy cohort, are consistent with earlier studies that report time spent walking and step count in survivors of a critical illness.[70,240] These studies which recruited adults who had survived a prolonged intensive care admission, measured daily physical activity following hospital discharge using accelerometers (AMP 331 accelerometer [Activity Monitoring Pod, Dynastream Innovations Inc, Cochrane, Alberta, Canada] and Dynaport Minimod [McRoberts, Netherlands]).[70,240] Specifically, Denehy and colleagues[240] demonstrated that, at 2 months after ICU discharge their sample participated in low levels of locomotion (> 20 steps in a row or 3% of waking hours) and accumulated a daily step count that was similar to that reported in the current study (4,894 ± 3,070[240] vs. 5,180 ± 3,099 steps). Likewise, the proportion of participants who achieved the recommended 10 000 steps per day was similar in the current study and the study by Denehy and colleagues[240] (10% vs. 6%[240]). Borges and colleagues[70] demonstrated that, at 3 months following discharge from ICU, when compared with a healthy group, their sample spent a lower proportion of their waking hours walking (6.3 ± 3.0 vs. 10.1 ± 4.4 %, $p < 0.05$).

The data in the current study extends these findings by exploring differences in both the total time in each category, as well as the way in which time in each of these categories was accumulated. Specifically, compared to the healthy participants, the ALI participants accumulated less of their total time in MVPA in bouts of more than 10 minutes ($p = 0.018$) and accumulated more of their total ST in prolonged bouts of

more than 30 minutes ($p = 0.031$). This suggests that both the total time spent in these categories, as well as the way in which time is accumulated may be targets for therapy. In previous epidemiological studies, the overall volume of PA was most consistently related to mortality risk,[420-422] through cardiovascular remodeling, and regulation of inflammatory processes, lipid levels and glucose levels.[227,423,424] Although, recent research has identified that reduction in mortality risk associated with PA was independent of patterns of accumulation,[231,232] accumulation of MVPA in bouts ≥ 10 minutes is likely to provide additional health benefits.[230] These health benefits associated with sustained bouts of MVPA are thought to arise from exercise-induced shear stress of blood vessel endothelium, subsequent production and release of nitric oxide and enhanced endothelial function leading to decreased cardiovascular risk.[425,426]

There are several possible reasons that survivors of critical illness may participate in reduced MVPA. In addition to those factors which have been associated with lower participation in daily PA in the general population, such as advancing age, low self-efficacy for changing lifestyle and worse socioeconomic status,[71,72] survivors of a critical illness are likely to have added barriers to participating in PA, which include cognitive factors such as impaired executive functioning including concentration, post-traumatic stress disorder, and depression.[427,428] Furthermore, similar to that described in those living with COPD,[429] the lower levels of MVPA in the participants with ALI in the current study, may result from their low peak exercise capacity. That is, the peak VO_2 measured in the participants with ALI (17.80 [14.85 to 20.85] mL/kg/min), is equivalent to 5.1 [4.2 to 6.0] MET. This means, that in order for survivors of ALI to participate in MVPA (> 3.0 MET), they need to work at more than 60% of their peak VO_2, which is likely to evoke considerable symptoms. In contrast, people with a normal exercise capacity (e.g. 35 mL/kg/min or 10 MET) are required to work at only 30% of their peak exercise capacity to participate in MVPA.[75] As increased participation in MVPA has been associated with several health benefits, such as decreased risk of cardiovascular disease, obesity, some cancers and mental health issues such as depression, [227-230,238,430] achieving greater participation in MVPA by ICU survivors is likely to be a goal of therapy. In order to achieve this goal, it would seem sensible in this population to first attempt to

increase peak VO_2, thereby increasing functional reserve, prior to increasing participation in MVPA.

In addition to reduced participation in MVPA, the data in the current study showed that compared with healthy controls, survivors of ALI accumulated more of their waking hours in ST, and also accumulated more ST in prolonged bouts ≥ 30 minutes Of note, the amount of ST accumulated by the ALI participants in this study was similar to that reported in office workers and community dwelling stroke survivors.[431-435] This is important given the growing awareness of the health consequences of accumulating long periods of ST. Specifically, several large epidemiological studies have demonstrated that increased ST is associated with abdominal obesity, systemic hypertension, abnormal glucose uptake, hypercholesterolaemia and worse survival.[233-238] For example, the AusDiab study conducted in Australia between 1999 and 2012, demonstrated that compared with sitting for less than 4 hours per day, sitting for between 8 and 10 hours significantly increased the risk of all-cause mortality (hazard ratio [95% CI], 1.15 [1.06 to 1.25]). This risk was greater amongst those who sit for 11 or more hours per day (hazard ratio [95% CI], 1.40 [1.27 to 1.55]).[436] This seems to be related to changes in skeletal muscle metabolism associated with prolonged skeletal muscle unloading. Specifically, the loss of muscle contraction results in a dramatic loss of skeletal muscle lipoprotein lipase activity, which reduces the capacity of skeletal muscle to siphon off and use triglycerides for energy and impairs glucose uptake. Studies in humans and animal models suggest that participation in small amounts of LPA, to break up ST, is sufficient to ameliorate these changes in skeletal muscle and the corresponding cardio-metabolic risk.[237,437,438] This is likely to be important as it suggests that increasing participation in LPA, which requires a lower proportion of aerobic reserve, may assist in ameliorating the risk of prolonged ST and it likely to be a more achievable goal for people following ALI who are characterised by low exercise capacity.

4.4.5 Peripheral muscle strength and respiratory pressures

The current study is the first to report the muscle strength of knee extension, elbow flexion and shoulder flexion within 6 weeks following hospital discharge using dynamometry. The current study also confirms these impairments by collecting data

in healthy control participants of similar age and gender proportion, using identical equipment and methodology, rather than relying on regression equations to estimate normative values. Although several previous studies have reported a reduction in muscle strength in survivors of critical illness, to date, these studies have assessed strength via manual muscle testing[16,115,141] which is limited by its sensitivity at the higher grades.[152] Compared with the healthy participants, the ALI participants in this study generated less peripheral muscle force during knee extension, shoulder flexion, elbow flexion, and hand grip. The participants with ALI also generated lower MEP when described as a proportion of normative reference values. Regarding grip strength, the participants with ALI in the current study generated less strength than that measured in the healthy population. The magnitude of impairment present in the participants with ALI (median 78% of normative values) was comparable to that reported in earlier work undertaken in ALI survivors at 3 and 6 months using hand dynamometry, being 64%[15] and 76%[16] of normative reference values, respectively.

The current study also reported MIP and is the first to report MEP in participants with ALI within 6 weeks following hospital discharge. In relation to MIP, a single study by Needham and colleagues,[16] showed similar values collected at 6 months after discharge to that collected in the participants with ALI in the current study, that is, 88 ± 31 vs. 93 [57 to 103] % of that predicted in a healthy population. It appears that, on average, MIP was not substantially impaired in survivors of critical illness 6 weeks after discharge from hospital. Nevertheless, the considerable variability in the magnitude of impairment suggests that in some people, MIP may be impaired. It is possible that these people may benefit from inspiratory strength training.

Examination of the distribution of weakness suggests that knee extension strength is the most affected when compared with upper limb and respiratory muscle strength. This is supported by an earlier report, showing a greater decrease in muscle thickness in the knee extensors in a cohort of critically ill patients, when compared with upper limb muscles, as determined by ultrasound.[69,439] The preferential atrophy of the knee extensor musculature, and generally those muscles termed as antigravity or postural muscles, have also been reported in the healthy population when mechanically unloaded with prolonged bed rest.[440] In survivors of ALI at 6 months after hospital discharge, a single study by Needham et al,[16] provides measures of 2

muscle groups that were comparable with the current study, that of grip and MIP. The distribution of weakness appears to be similar in both studies, whereby, in both the earlier and the current study the grip strength was notably lower than the MIP presented as a proportion of normative values (67% and 88% vs. 76% and 93%, respectively).

The reasons underpinning differences in the distribution of weakness suggested in the current study are potentially multifactorial. The preservation of MIP and elbow flexion strength relative to measures of lower limb and grip strength, may be a result of the early use of the muscles involved in inspiration and elbow flexion during recovery from a critical illness. That is, as patients are liberated from mechanical ventilation, they are required to utilise inspiratory muscles. This may occur early in the admission to ICU and prior to the patient being conscious and cooperative. Similarly, as soon as patients in the ICU are conscious and cooperative, they are encouraged to use their upper limbs for activities of daily living which required little assistance. However, it would be expected that these activities would also act to preserve grip strength and shoulder flexion strength. As such, it is possible that the variation in upper limb strength is an anomalous finding. Irrespective of this, knee flexion demonstrated notably lower strength values when compared with upper limb strength values. In comparison to the upper limb, lower limb muscles are used functionally only once the patient is standing. This involves mobilising the patient out of bed, which, in an ICU environment, is considerably more challenging and resource intensive than promoting the use of the arms whilst resting in bed. Furthermore, upon discharge from hospital, low participation in PA and high ST as measured in the participants with ALI in the current study, suggests that the mechanical loading required for the regrowth of atrophied muscle continues to be limited.

4.4.6 Health-related quality of life and fatigue

Compared with the healthy participants, participants with ALI in the current study were impaired for all domains of HRQL in the SF36. Those with ALI demonstrated the greatest deficit in the physical domains of pain, physical role and vitality (Figure 4-19). A similar pattern of impairment in HRQL, that is, greater deficits in physical domains rather than the mental health domains, has been demonstrated in both

survivors of ARDS and heterogeneous groups of survivors of critical illness.[12,23,110,257-259] Comparison of HRQL between these 2 groups however have been reported in few studies. Davidson and colleagues[32] compared HRQL of 73 survivors of ARDS with a matched group of survivors of non-ARDS. The survivors of ARDS reported greater impairments than the non-ARDS survivors in the physical and respiratory domains of the SF36 and St George's Respiratory Disease Questionnaire, respectively.[32] However, the absence of comparative preadmission data was a limitation. Preadmission comorbidity and resource use has been identified as an important determinant of morbidity after ICU discharge.[261,262] A more recent study accounting for preadmission functioning, demonstrated no difference between ARDS (n=26) and non-ARDS (n=41) survivors in both the decline of physical function and HRQL from preadmission to 6 months after ICU admission.[441]

The impairments noted in HRQL in survivors of critical illness and in ARDS survivors specifically is multifactorial. Pulmonary impairments observed in those recovering from ARDS approaches normal values within 12 months after ICU admission and is unlikely to contribute greatly to the ongoing reduction in HRQL experienced by survivors.[12] Physical function as measured by the 6MWD does contribute to the PCS of the SF36 albeit only accounting for 30% of the variance noted in the PCS (Section 2.4.5). Study 1 (Section 3.3) reported greater impairments in exercise capacity, walk speed and peripheral muscle strength in the ALI participants when compared with a group of critical illness participants with similar preadmission HRQL and FCI. This finding suggests that the pathological processes inherent in ALI, that of, excessive inflammatory responses, endothelial and epithelial damage and disruption to the alveolar–capillary membrane,[112] appear to lead to greater impairments in peripheral muscle strength. Although these acute responses appear to diminish over time with normalisation of autophagy and mitochondrial content, in the absence of markers of muscle proteolysis and inflammation,[41] muscle atrophy appears to remain present. It is reasonable to posit that survivors of ALI may experience more profound ongoing physical impairments when compared with survivors of critical illness. This may in turn translate into greater impairments experienced in HRQL.

Regarding fatigue, the current study demonstrated that compared with the healthy participants, the participants with ALI reported higher levels of fatigue (section 4.3.7). Of note, scores of 4.6 ± 1.4, as reported by the ALI group represent severe fatigue, and are of similar severity to that reported in patients with multiple sclerosis and systemic lupus erthymatosus.[392] Similarly, extreme fatigue has been described in other survivors of critical illness, with an ICU stay > 4 days and who attended a follow-up clinic after discharge from hospital.[268] Survivors of ARDS have also reported that fatigue contributed significantly to the impaired physical function and HRQL that the survivors experienced at 3 and 12 months,[12] as well as the severe physical and cognitive dysfunction which they experienced.[269] Given that fatigue has been reported as being a barrier for patients to exercise and participate in PA within the ICU,[127,442] and remains high in this population following discharge from acute care, fatigue is also likely to continue to be a barrier to therapies which aim to optimise exercise capacity. Identification, monitoring and education regarding fatigue, for survivors of critical illness, may aid in optimising the delivery of physical rehabilitation programs.

4.4.7 Limitations

As previously noted, the incidence of ALI in the participating ICUs was markedly lower than anticipated and recruitment was challenging. As a result, the required sample size was not attained. This was in spite of implementing numerous strategies to optimize both screening processes and recruitment. The small number of participants with ALI subsequently limits the generalisability of the group results.

4.4.8 Clinical implications and conclusions

The data presented in this study has shown that 6 weeks after hospital discharge, following an ICU admission for ALI, people present with considerable impairments in exercise capacity (measured via a laboratory-based test and a field-based walking test), participate in low levels of PA and accumulate high ST, have reduced peripheral and expiratory muscle strength, poor HRQL and profound fatigue. These impairments are likely to be interrelated.

Data showing that following an ICU admission for ALI, reductions in exercise capacity 6 weeks following hospital discharge are most often mediated by

cardiovascular and skeletal muscle deconditioning, provides insight to a possible role exercise training may have in ameliorating this impairment; both early in the ICU admission and after discharge. Specifically, to date, studies of exercise carried out during an ICU stay have focused on increasing strength and functional ability via early rehabilitation. Interventions that have been employed have included strengthening and functional exercises,[60,174,218,286,442,443] the use of cycle ergometers for the upper or lower limb,[171,444] and neuromuscular electrical stimulation.[445,446] Given the strength impairments noted in the participants with ALI in the current study, the use of equipment such as cycle ergometery may improve strength and also aid in minimising prolonged periods of mechanical unloading that is likely to contribute to the development of weakness in these patients. However, in order to ameliorate the cardiovascular impairment noted in these participants with ALI, duration, frequency and type of exercise should be considered carefully in the development of early rehabilitation protocols within ICU, in order to ensure both efficacy and safety. The greater strength noted in the inspiratory muscles and elbow flexors compared with the knee extensors also suggest that regular initiation by staff of weight bearing exercise or an appropriate substitute may lead to a less notable decline in lower limb strength.

Exercise-based rehabilitation programs (EBRP) initiated after discharge from hospital in survivors of critical illness have shown no consistent effect on 6MWD or AT.[26-28,38] A number of factors have been postulated to explain the findings including inappropriate patient selection, changes in the muscle structure in some survivors as a result of the critical illness that are not responsive to the implemented interventions, and the effect of pre-existing comorbidities on physical outcome.[41,43,109] It is probable however, that the training stimulus applied to the cardiovascular and skeletal muscles in the studies investigating EBRP after critical illness was not sufficient to achieve additional adaptation over and above the process of natural recovery. High intensity training in other populations such as those with COPD, has been shown to be both safe and essential in order to observe physiological evidence of adaptations.[447] It is possible that given the unique cellular changes in the skeletal muscle that have been identified in the small cohorts of survivors of critical illness,[40,41] high intensity exercise is required to elicit adaptations over and above those that result during natural recovery. Furthermore, in

order to optimise the prescription of intensity during exercise, accurate measures of exercise capacity are required. As such, consideration should be given to performing at least 2 6MWTs, and recording the best 6MWD as the result.

This study demonstrated that, on average, survivors of ALI increased their 6MWD with a second attempt at the 6MWT, exceeding the minimally important difference of 20 to 30 m reported for survivors of respiratory failure.[203] Using a single test may underestimate the baseline 6MWD and over-estimate the effect of an intervention given the individual patient may achieve a higher 6MWD on the post-intervention test as a result of increased familiarization with the test. Impaired diffusion capacity of the lung was shown in this study to still be apparent in the participants and contributed to the impairment in exercise capacity. Due to this, these patients are more likely to demonstrate oxygen desaturation during exercise. Although not observed in the majority of participants with ALI (n = 9), other clinical populations with impaired pulmonary diffusion, have demonstrated a greater magnitude of desaturation with walking than cycle based exercise.[448] The cardiac insufficiency evident in 2 of the participants suggests that some participants may be precluded from exercising at high intensities, and for those not performing ICET prior to exercise, a high level of suspicion for cardiac dysfunction should be present when providing rehabilitation. Given the high level of fatigue present in these participants, consideration should be given to the delivery of the exercise-based rehabilitation. Starting a program with short duration, high intensity interval-training, may limit exacerbation of both leg fatigue and general fatigue, while optimising training intensity and enhancing adherence.

Regarding PA and ST, low levels of MVPA and high ST may be addressed in a number of ways. Of note, the low levels of MVPA co-exist with a low peak VO_2. These low levels of MVPA may be ameliorated once the peak VO_2 has increased via exercise-based training. With a higher peak VO_2, accumulating time in MVPA would be more achievable. In regard to accumulation of MVPA in timed bouts, physical activity guidelines have specified that in order to confer optimal health benefits MVPA should be accumulated in bouts ≥ 10 minutes.[230] However, recent literature suggests that the accumulation of MVPA in bouts < 10 minutes may still yield health.[231,232,449,450] Moderate and vigorous physical activity accumulated in

bouts < 10 minutes or what has been termed 'lifestyle physical activity',[451] and MVPA accumulated in bouts ≥ 10 minutes have been shown to have similar associations with reduced cardiovascular disease risk factor profile and reduced incidence of metabolic syndrome.[449,450] A recent systematic review demonstrated that PA accumulated in any bout duration was associated with improved health outcomes.[452] Activities such as pacing or walking while on the phone instead of sitting or taking the stairs instead of using an escalator or elevator, may be encouraged and provide additional benefit to the planned MVPA that may be challenging in this population initially due to impairments in strength and high levels of fatigue. Furthermore, due to these impairments in strength and high levels of fatigue, in the short term it may be useful and more realistic to encourage displacement of ST with LPA. While this may not achieve the same physiological effects as an increase in MVPA, regular breaks in ST using LPA such as standing and slow walking, may be sufficient to ameliorate the changes in skeletal muscle and the corresponding cardio-metabolic risk that is associated with prolonged periods of ST, as has been shown in other healthy sedentary populations.[237,437,438]

CHAPTER 5 Study 3

5.1 Overview

This chapter presents Study 3. The purpose of this study was:

(i) In adults who have survived an admission to an intensive care unit (ICU) for acute lung injury (ALI), to examine the adherence to as well as tolerance and progression of a high intensity exercise-based rehabilitation program (EBRP) initiated 8 weeks after discharge from an acute care facility.

(ii) In adults who have survived an admission to an ICU for ALI, to examine within participant changes in resting lung function and submaximal and peak physiological responses during an incremental cycle ergometry test (ICET) and 6-minute walk test (6MWT) as well as physical activity (PA) and sedentary time (ST), peripheral muscle strength, health-related quality of life (HRQL) and fatigue following a program of high intensity EBRP initiated 6 weeks after discharge from an acute care facility.

5.2 Methodology

Section 5.2 presents information pertaining to the methodology used in Study 3 Specifically, section 5.2 presents information related to approval from the relevant Human Research Ethics Committees, recruitment of participants, outcome measures, and statistical analyses.

5.2.1 Study design and participants

This study is presented as 2 single case reports.

5.2.1.1 Comment regarding Study 3

The original aim of Study 3 was to investigate the effect of a high intensity EBRP program in survivors of ALI on the exercise capacity and physical function using a randomised controlled trial (RCT) (registered with the Australia New Zealand Clinical Trial Registry Registration No. ACTRN12611000298910). Randomisation

was performed using a computer-generated random number sequence, stratified according to baseline 6-minute walk distance (6MWD) (i.e. ≤ 200 m vs. > 200 m). Concealment was maintained using opaque envelopes. Each strata was blocked for equal allocation to the intervention and control group in order to ensure similarity between the groups for severity of impairment in baseline exercise capacity. The assessor (PhD candidate) was blinded to group allocation in order to minimise assessor bias. Training was performed by a physiotherapist at Calvary Mater Newcastle hospital Physiotherapy Department. The PhD candidate responsible for performing all assessments was not involved with the randomisation process or the training of participants. The physiotherapist supervising the EBRP and performing weekly phone calls to the control group, was not involved in any of the assessments. The participants were instructed, by both the assessor at the pre-EBRP assessments and the physiotherapist conducting the EBRP or the weekly telephone calls, not to discuss their activities during the intervention or control period, with the assessor. Statistical analyses were conducted by the assessor without knowledge of specific group allocation.

Recruitment to this study commenced in 2011 and halted in 2014, due to profound difficulty in recruiting participants. During this time, 2 participants completed measures before and after the EBRP and 3 participants completed measures before and after a control period. The CONSORT diagram for the RCT is presented in Appendix 13. The protocol used to minimise bias and described previously was successfully adhered to throughout data collection.

As it would be inappropriate to undertake between-group comparisons on this small sample, this chapter takes the pragmatic approach of reporting the data on the 2 participants who completed measures before and after the EBRP. For the sake of completeness, data pertaining to the primary outcome of peak oxygen uptake (VO_2) and the associated physiological responses measured during the ICET, for the 3 participants who completed the assessment before and after the control period have been summarised in Appendix 14.

5.2.1.2 Approval from Human Research Ethics Committees

The study was approved by the Human Research Ethics Committees of Hunter New England Area Health (HNEHREC) (HREC 10/11/17/4.06), Curtin University (HR

27/2011) and The University of Newcastle (H-2011-0029) (Appendix 1 and Appendix 2).

5.2.1.3 Recruitment and study criteria

Patients admitted to the ICU at John Hunter Hospital (JHH) or Calvary Mater Newcastle hospital (CMN) were screened on a daily basis to determine their eligibility to participate in this study.

Inclusion criteria for participants with ALI comprised: (i) aged over 18 years; (ii) had an ICU admission during which they met the criteria for ALI (section 3.2.1.2)[1]; and (iii) resided within one-hour travel of the JHH (so that travel time to attend the assessments required for this study was reasonable). Exclusion criteria comprised: (i) the presence of any neurological or musculoskeletal condition likely to adversely affect the ability to mobilise safely, including documented neurological disease and orthopaedic injuries with mobility restrictions: (ii) non-ambulant prior to admission; (iii) treatment or diagnosis of malignant cancer within preceding 12 months; (iv) history of recent major pulmonary resection; (v) poorly managed psychiatric disorders; (vi) an inability to follow commands; and (vii) inability to understand English.

5.2.1.4 Study protocol

Participants with ALI who were eligible and consented to participate in Study 2 were invited to participate in Study 3, as Study 2 assessments formed the baseline assessments for Study 3. Participants could choose to enter only Study 3 without consenting to participate in Study 2, however, the baseline measures performed pre-EBRP were identical to that performed in Study 2.

Consent to be included in the current study was obtained via the participant's next of kin during their ICU admission, and thereafter, by the participant's themselves once they were deemed capable of doing so by a senior treating medical officer. In the event that the patient was to be discharged from hospital and a decision had not been made regarding participation, consent for the candidate to contact the patient at home via the proxy or patient to discuss participation further. Information pertaining to the participant's ICU and ward admission were extracted from the patient's notes by the candidate. Intensive care length of stay (LOS) was recorded upon ICU discharge.

Participants were invited to participate in a study to evaluate the effect of an EBRP that commenced 8 weeks after discharge from an acute care facility. Four weeks after hospital discharge, contact was made with the participants via phone or email.to arrange 2 assessment sessions with the finalised details mailed to the participants. Six weeks after discharge from an acute care facility (acute care hospital or acute rehabilitation facility), participants with ALI were invited to attend 2 assessment sessions, separated by 7 days. These assessments were performed both before and after the 8-week intervention period. During the assessment sessions completed before the intervention period (i.e. baseline assessment), demographic and anthropometric data were recorded. Thereafter, measures were made of resting pulmonary function, peak and submaximal exercise responses during a symptom-limited ICET and 6MWD (2 tests performed with 30 minute rest between each test), as well as measures of peripheral muscle strength via a custom-designed fixed force gauge, hand-held dynamometry (HHD) or a hand dynamometer, HRQL via the Medical Outcomes Study Short Form 36 General Health Survey Version 2 (SF36), and fatigue via the fatigue severity score (FSS) questionnaire. In the days between the 2 assessment sessions, participants wore a portable metabolic monitor (SenseWear® armband [SAB], BodyMedia Inc., Pittsburgh, Pennsylvania, USA) to measure PA and ST. Regarding the order in which these measures were made, demographic and anthropometric data were always collected during the first assessment and the SAB was always used in the period between the 2 assessment days. The first assessment day involved measurement of peripheral muscle strength, completion of the SF36 and the FSS questionnaires, and the 6MWT. The second assessment day involved the completion of pulmonary function testing and the ICET. During the post intervention assessment sessions the same measures were repeated.

Figure 5-1 shows the measurements collected in the ALI participants, the order in which the assessment sessions were conducted, timing of the assessments, intervention/control, and the individuals responsible for each of the components. For completeness of data, Figure 5-1 includes the randomisation point and therefore the control arm.

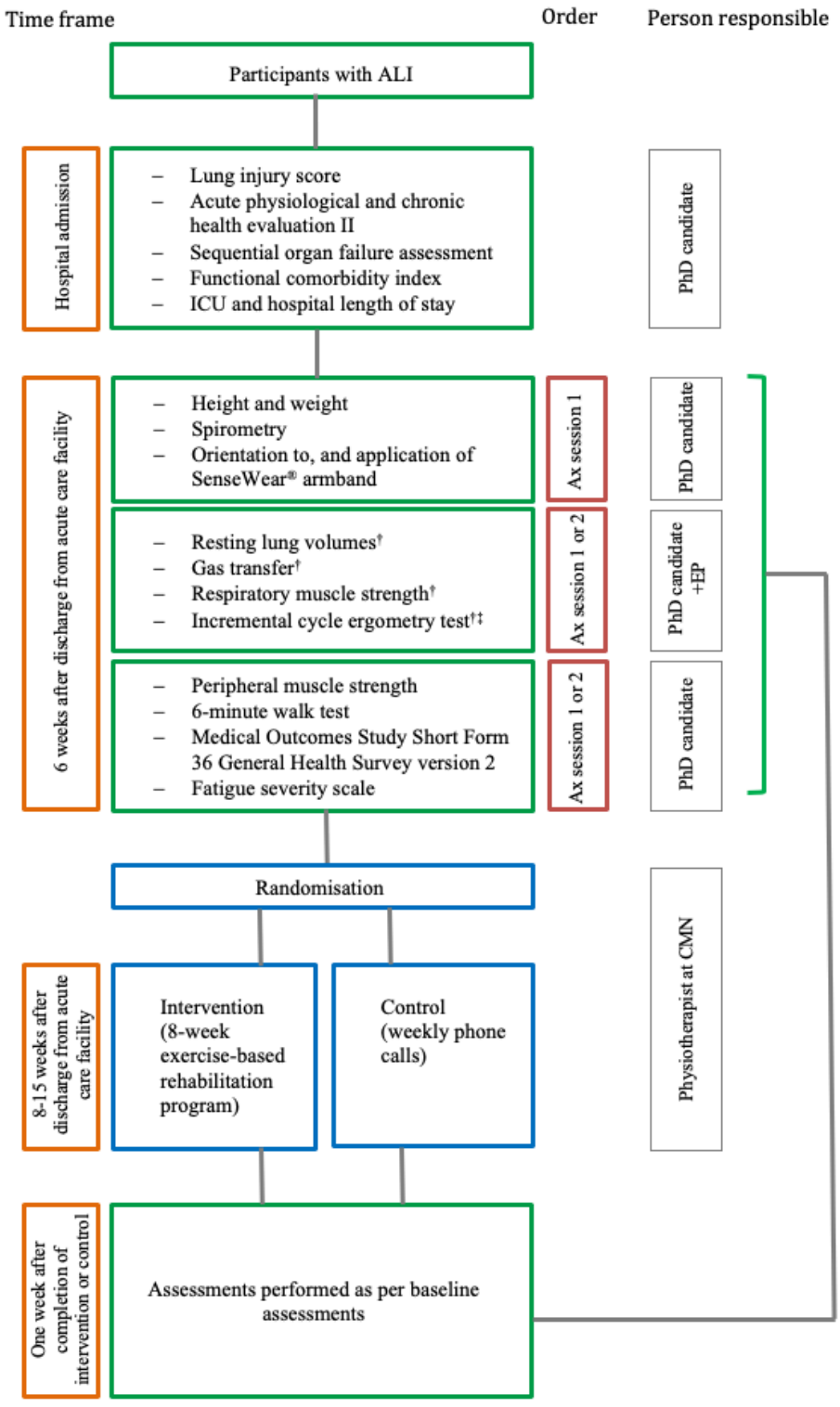

Figure 5-1 Timeframe and order of assessments and intervention/control, and the person responsible for each component for the participants with ALI

ALI: acute lung injury; Ax: assessment; ICU: intensive care unit; EP: exercise physiologist; PhD: Doctor of Philosophy; †: conducted by exercise physiologist (JP); ‡: conducted by PhD candidate.

5.2.2 Measurements pertaining to the first research question

5.2.2.1 Adherence to and tolerance of the supervised and unsupervised exercise-based rehabilitation program

For the supervised exercise intervention, attendance at scheduled sessions was recorded for each individual. The number of sessions attended was expressed as a proportion of the total number of sessions that were scheduled. High adherence to the EBRP was defined as attendance at > 90% of the supervised sessions.[453] Breaks in the continuity of the program were also reported. The intensity of exercise training was recorded for each individual for each mode of exercise at each session. Based on the domains of intensity of exercise and physical activity defined by the American College of Sport Medicine's (ACSM) consensus guidelines, moderate intensity exercise was defined as 64 to 73% of peak heart rate (HR) as determined from the ICET and high intensity, categorised as vigorous and 'near maximal intensity' in the consensus guidelines, was defined as ≥ 74% of peak HR determined from the ICET.[230] These definitions were applied to both the cycle-based and walking-based training to enable comparison between the modes. Tolerance of the EBRP was expressed as the number of sessions where high intensity exercise was achieved, as a proportion of the total number of sessions.

For the unsupervised walking program, details of the physical activity performed and recorded in the exercise diary were reported.

5.2.2.2 Progression of exercise intensity

For the cycle ergometer component of the EBRP, progression of the training load was assessed using the product of work rate (WR) and time (W·min). Progression in cycle ergometer training was evaluated by comparing the W·min achieved during the initial and final supervised training session.

For the walking component of the EBRP, progression of the training load was assessed using the following equation developed from first principles: (distance walked [m] x body weight [kg] x 9.8 x sin90°) + (distance walked [m] x body weight [kg] x 9.8 x sinθ°), where θ is the angle of incline of the treadmill (Appendix 15). Progression in walking training was evaluated by comparing the km·kg achieved during the initial and final supervised training session.

For the resistance training component of the EBRP, the product of weight, sets and repetitions (kg·sets·reps) were used to progress the upper and lower limb training component. Progression in upper and lower limb training was evaluated by comparing the kg·sets·reps achieved during the initial and final supervised training session.

5.2.3 Measurements pertaining to the second research question

This section briefly describes the measurements made in this study. These measurements have been described fully in section 4.2.2.

5.2.3.1 Severity of illness, prognostic indicators and length of stay (in participants with ALI only)

At the time of the ICU admission, details were collected regarding severity of illness and prognostic indicators. These measures comprised the lung injury score,[301] the acute physiologic and chronic health evaluation II (APACHE II)[300] calculated on admission, and the sequential organ failure assessment (SOFA)[302] calculated daily from the patients' notes. The pre-admission functional comorbidity index (FCI)[293] was calculated from information obtained from the participants next of kin. Both ICU LOS and hospital LOS were recorded. Details of these measures and how they were collected have been previously described in Chapter 4 (4.2.2.1).

5.2.3.2 Demographic and anthropometric information

Age and sex were recorded. Body weight and height were collected via digital scales (DS-530 MkII, Teraoka Seiko, Tokyo, Japan) and a wall mounted stadiometer (seca 206, seca gmbh & co. kg, Hamburg, Germany), respectively.

5.2.3.3 Spirometry, resting lung volumes, gas transfer and maximal respiratory pressures

Measures were collected of forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) (EasyOne™ spirometer, NDD Medical Technologies, Zurich, Switzerland, or Vmax® Encore plethysmograph system, SensorMedics, Yorba Linda, California, USA) both pre- and post-administration of a bronchodilator (Salbutamol 100 micrograms, 4 metered actuations). Measures were collected of resting lung volumes (functional residual capacity [FRC], residual volume [RV],

total lung capacity [TLC]), gas transfer (diffusing capacity of the lung of carbon monoxide [D_LCO] [Vmax® Encore plethysmography system, Carefusion, Hoechberg, Germany]). Haemoglobin levels were measured in a drop of venous blood obtained via a finger prick. This was then used to correct the D_LCO value in the presence of anaemia. Measures were collected of maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) from RV and TLC, respectively (MicroRPM respiratory pressure metre, Vyaire Medical GmbH, Illinois, USA). Data were expressed as absolute values and as a percentage of predicted normative values (Appendix 9) estimated using regression equations. [316,362-365] Details of these measures and how they were collected have been previously described in Chapter 4 (sections 4.2.2.2 and 4.2.2.5).

5.2.3.4 Peak and submaximal exercise responses during an incremental cycle ergometry test

Peak and submaximal exercise responses were measured during an ICET performed on an electrically braked cycle ergometer (Ergoselect 200K; Ergoline GmbH, Bitz, Germany). Tests were conducted by an exercise physiologist or the PhD candidate in the Diagnostic Suite of the John Hunter Hospital and were supervised by a senior member of the medical staff as per American Thoracic Society/ American College of Chest Physicians (ATS/ACCP) guidelines.[205] Data were expressed as absolute values and as a proportion of predicted normative values (Appendix 10).[345,368-371] For each participant with ALI, to explore the mechanisms of exercise limitation, measures of rate of oxygen uptake (VO_2), the rate of carbon dioxide production (VCO_2), end-tidal oxygen tension ($PETO_2$), end-tidal carbon dioxide tension ($PETCO_2$), minute ventilation (VE), respiratory exchange quotient (R), and respiratory rate (RR), tidal volume (VT), arterial oxygen saturation (SpO_2), oxygen pulse (O_2 pulse) and HR were averaged over 30-second intervals and plotted on a 9-panel graphical array previously described by Wasserman et al.[205,345] Details of these measures and how they were collected have been previously described in Chapter 4 (section 4.2.2.6).

5.2.3.5 Functional exercise capacity

Functional exercise capacity was measured using the 6MWT. To account for any increases resulting from test familiarisation, 2 6MWTs were completed. The 2 tests were separated by 30 minutes and the highest distance of the 2 tests was recorded as

the test result. The 6MWD was expressed in absolute values (m) and as a percentage of predicted normative values.[333] The details of the assessment have been previously described in Chapter 4 (section 4.2.2.3).[366]

5.2.3.6 Physical activity and sedentary time

Participants were instructed to wear the SenseWear® armband (SAB) (BodyMedia Inc., Pittsburgh, Pennsylvania, USA) over the triceps brachii muscle bulk of the left arm for 7 consecutive days, removing it only for water-based activities such as bathing or swimming. Details of these measures, how they were collected and management of the data have been previously described in Chapter 4 (section 4.2.2.7). Briefly, data were grouped and grouped into 3 categories: (i) ST (defined as any time with an energy expenditure ≤ 1.5 MET; (ii) light intensity PA (LPA) (defined as any time with an energy expenditure > 1.5 and ≤ 3 MET); (iii) moderate and vigorous intensity PA (MVPA) (defined as any time with an energy expenditure > 3 MET.[230] Time spent in each category was averaged across days. The accumulation of ST in uninterrupted bouts ≥ 30 minutes as a percentage of total ST, and of MVPA in bouts of ≥ 10 minutes as a percentage of total time spent in MVPA, was calculated for each participant. Measures of daily step count were also averaged across days.

5.2.3.7 Peripheral muscle strength

Peripheral muscle strength was assessed as peak isometric force as measured on the dominant limb during knee extension, shoulder flexion, elbow flexion, and handgrip. Data were expressed as absolute values and as a percentage of predicted normative values estimated using regression equations (Appendix 3).[155,156,319] The details of the measurement of muscle force has been previously described in Chapter 3 (section 3.2.2.5).

5.2.3.8 Health-related quality of life

The HRQL was assessed via self-completion of the SF36 questionnaire.[295] The questionnaire was completed with the PhD candidate in attendance to clarify any questions and to ensure all questions were answered. The properties of the SF36 and analysis of the data obtained from the SF36 have been previously described in Chapter 4 (section 4.2.2.9). Data pertaining to the individual domains of the SF36

were presented as transformed scores using a 0 to 100 scale with a higher score indicating a better HRQL. The 2 component summary scores, physical component score (PCS) and mental component score (MCS), were calculated using a scoring algorithm and were normative based values.[298,299]

5.2.3.9 Fatigue severity

Fatigue severity was assessed via completion of the FSS. The questionnaire was self-completed by the participants with the PhD candidate in attendance to clarify any questions and to ensure all questions were answered. Data pertaining to the FSS were presented as a mean of the 7 items with a mean score of greater than 4.0 representing severe fatigue.[392] Details of this measure and how it was collected has been previously described in Chapter 4 (section 4.2.2.10).

5.2.4 Intervention

Participants completed an 8-week EBRP, during which time, they attended 2 supervised training sessions of 60 minutes in duration each week in conjunction with an unsupervised home-based walking program on the remaining days of the week. In the event of illness or inability to attend a supervised training session, the duration of the program was extended to enable attendance at 16 sessions. This program was embedded in a small existing group program conducted for people who were deconditioned at CMN Hospital Physiotherapy outpatient gymnasium.

At the commencement of this program of research, there were few reports of supervised exercise training in survivors of an ICU admission. For this reason, the approach used in this study was informed largely by the pulmonary rehabilitation literature and foundational exercise training principles.[46,454] Briefly, the aim was for all participants to complete a minimum of 30 minutes of aerobic exercise during each supervised training session.[46]

Cycle-based and walking-based training were prescribed. During the supervised sessions, the largest component of aerobic exercise training was spent as cycle-based exercise. This was because, the primary outcome for this study was peak VO_2 measured during an ICET and therefore, in keeping with the principles of task specificity, the goal was to maximise time exercising using this modality. Both

interval and continuous cycling training protocols were used with the goal of optimising performance during the ICET. That is, interval training was prescribed during which high intensity training (i.e. ≥ 60% maximum WR achieved during the ICET for 2 minutes) was regularly interspersed with rest intervals (i.e. 0 W for 1 minute). This training approach has been shown to optimise the training load that can be achieved during the work intervals as the introduction of regular rest intervals minimises the experience of intolerable symptoms.[48] The continuous cycling was prescribed at a lower workload (i.e. 40% maximum WR) and was designed to optimise the tolerance of continuous cycling which is similar to that performed during the ICET which ideally lasts for between 8 and 12 minutes.[205,455] Walking-based training was undertaken as this type of exercise can be readily transferred into the home environment and would comprise the mainstay of aerobic exercise in the home exercise program. The resistance training was also prescribed in order to improve the force generating capacity of the peripheral muscles.[456] Earlier work has shown that peripheral muscle strength is an important determinant in determining the peak work rate achieved during an ICET.[457]

5.2.4.1 Supervised exercise

Each supervised exercise session comprised aerobic training (walking and cycling) and resistance training (upper and lower limbs). The program was supervised by a physiotherapist with 16 years of experience in cardiac and pulmonary rehabilitation and intensive care. Heart rate using telemetry (Polar A1, Polar Electro Oy, Kempele, Finland) and SpO_2 via pulse oximetry (Masimo® Rad-5V, Irvine, California, USA) were monitored continuously for safety. Both SpO_2 and HR were recorded in the last 2 minutes of each component. Participants were familiarised with the Borg scale for dyspnoea (0 to 10) and the rating of perceived exertion (RPE) scale (6 to 20).[332] These scales have been used in populations characterised by deconditioning and were used to monitor and progress the exercise intensity.[46] Both the score for dyspnoea and RPE were recorded at the end of each mode of exercise.

5.2.4.1.1 Cycle ergometry: prescription

All cycle-based training was undertaken on a Tunturi E40 Upright bike (Almere, Netherlands). For the interval cycling portion, participants were asked to complete 15 minutes of high intensity training. This was prescribed as 2 minutes of work (i.e.

at 60% of maximum WR), separated by 1 minute of rest (i.e. unloaded cycling), with this 3-minute cycle repeated 5 times for a total duration of interval cycling of 15 minutes.[47,458]

For the continuous cycling portion, participants were asked to complete 5 minutes of continuous cycling training. This was prescribed at 40% of the maximum WR achieved during the ICET.[46] The goal for this component was to cycle continuously for 5 minutes. Participants with a low maximum WR achieved during the ICET (i.e. ≤ 60 Watts) were prescribed interval training with an initial prescription of 2 intervals of 2-minute exercise interspersed with one minute of rest.[458] The intervals were prescribed as it was unlikely that these participants would tolerate continuous cycling initially.[459] The goal then was to achieve a total of 5 minutes of continuous cycling as soon as symptoms permitted.

5.2.4.1.2 Cycle ergometry: monitoring and progression

Participants were encouraged to take rests in the case of desaturation (SpO_2 < 85%) or intolerable dyspnoea or leg fatigue. Participants were encouraged to continue cycling when SpO_2 ≥ 85 % or when the symptoms were again tolerable. Training intensity was titrated with the goal of evoking symptoms that were perceived to be between 4 and 5 on the modified Borg score for dyspnoea or 12 to 16 on the RPE. Progression of the interval and continuous cycling components was achieved by increasing the work rate by increments of 5W as symptoms permitted; that is, Borg < 4 and/or RPE < 12.

5.2.4.1.3 Walking: prescription

Participants performed a walking program on a treadmill. They were asked to walk for 10 min at 80% of the average speed achieved during their baseline 6MWT. For example, if a participant achieved 450 metres on their 6MWT, the participant would be asked to walk 600 metres in 10 minutes. This is consistent with the method used to prescribe the intensity of walking training described in pulmonary rehabilitation exercise guidelines.[46,361]

The decision to use the treadmill rather than a corridor for the walking program was made for practical reasons. Specifically, by completing the walking training on a treadmill, close supervision of the participant was possible. In contrast, the corridor

used for walking training was located approximately 40 metres from the gym and precluded a single therapist from offering sufficient supervision of adults exercising in the gym at the same time study participants would be walking in the corridor.

5.2.4.1.4 Walking: monitoring and progression

Participants were encouraged to take rests in the case of desaturation ($SpO_2 < 85\%$) or intolerable dyspnoea or leg fatigue. They were encouraged to recommence walking when $SpO_2 \geq 85\%$ or when the symptoms were again tolerable. The number and duration of rests were recorded. Training intensity was titrated with the goal of evoking symptoms that were perceived to be between 4 and 5 on the modified Borg score for dyspnoea or 12 to 16 on the RPE. This was achieved in 3 ways. First, in those who required a rest, the number, and duration of rests was decreased. Second, in those who could complete the 10 min walk without the need to rest, walking speed was increased by increments of 0.1 km/hr. Third, in those who were walking at their maximal comfortable speed, intensity was increased using an incline, which incremented by 5°.

5.2.4.1.5 Resistance training: prescription

Participants performed unsupported upper limb training comprising elbow flexion and shoulder forward flexion. Each exercise was performed in 2 sets of 5 repetitions with hand weights. The initial weight was set at 1.5 kg for women and 2 kg for men.[46] Participants also performed functional lower limb resistance exercise comprising step ups and half squats. Each exercise was performed in 2 sets of 5 repetitions. For the step-ups, the step height used was 21cm in height. The cadence of the step-ups was paced by a metronome set at 30 steps per minute. The half squats were conducted beside the parallel bars for support.

5.2.4.1.6 Resistance training: monitoring and progression

Participants were encouraged to take rests in the case of intolerable dyspnoea or limb fatigue. They were encouraged to recommence when the symptoms were again tolerable. Progression of the upper limb resistance training was achieved by increasing the weight by 0.5 to 1 kg once the participant was able to perform 10 continuous repetitions and symptoms were tolerable (RPE < 12). Progression of the lower limb resistance training was achieved by increasing both the sets and

repetitions in order to achieve 3 sets of 10 repetitions and symptoms were tolerable (RPE < 12).

5.2.4.2 Unsupervised exercise (home exercise program)

On 2 of the days that the participants did not attend supervised exercise training, they were encouraged to walk for 20 min. The participants were provided with a home exercise diary card with the prescription of exercise and were instructed to diarise their exercise activity on this card. The unsupervised walking program was prescribed at a pace that elicited a Borg score for dyspnoea of 4 to 5 or RPE of 12 to 16. Progression involved increasing the frequency of unsupervised walking from 2 to 3 days each week. On 2 of the days, participants did not attend supervised exercise training, they were also encouraged to perform squats and step-up exercise. The squats and step-ups were progressed in tandem with the supervised exercise, but the frequency remained at twice a week.

5.2.5 Usual care

Participants allocated to the control group participated in 8 weeks of usual care which comprised: (i) usual medications; and (ii) interacting with medical staff as required. The control group also interacted with the investigators once a week via a telephone call, using scripted questions regarding their activity during the week, to allow for the effect of attention. The control group were provided with a home exercise diary card and were instructed to diarise their exercise activity on this card.

5.2.6 Data reporting

Data were presented as; (i) absolute values and proportion of the total number of sessions as collected during the EBRP for adherence and progression, and (ii) absolute values and the proportion of predicted values collected before and after the EBRP, for each individual participant.

5.3 Results

5.3.1 Overview

Section 5.3 presents data to address the research questions posed for Study 3. Specifically, sections 5.3.3.1 and 5.3.4.1 addresses the first question by presenting the details of adherence to, and tolerance and progression of the EBRP of 2 participants. Sections 5.3.3.2 and 5.3.4.2 addresses the second question by presenting measures collected before and after the intervention.

5.3.2 Participant recruitment and characteristics

Participant recruitment commenced in February 2011 and was ceased in December 2014. Ten people who met the inclusion criterion and participated in Study 2 were invited to participate in Study 3. Of these, 7 participants agreed to participate in the RCT. Four were allocated to the intervention group and 3 were allocated to the control group.

The 3 participants who participated in Study 2 but chose not to participate in Study 3 made this decision based on: (i) a planned extended holiday; (ii) return to full time work which precluded attendance at the supervised training sessions during the day; (iii) medical follow up regarding the cardiac dysfunction noted on ICET; (iv) presentation of new illness (i.e. shingles), which prevented them from participating; and (v) did not want to be involved in an exercise program due to the perceived lack of benefit.

Of the 4 participants in the intervention group, this chapter presents data collected on the 2 participants who completed the study (participants 3 and 7). The other 2 participants who were allocated to the intervention group (participants 9 and 10), did not respond to any communication with the study team following randomisation (5 telephone calls/messages left per participant). Their baseline data were presented in Chapter 4, but as they neither attended training or completed post-training measures, their data are not presented in this chapter.

Of the 3 participants in the control group, 3 completed the study (participants 1, 4 and 8). Data pertaining to the primary outcomes as measured during the ICET on the

3 participants who completed measures before and after a control period have been summarised in Appendix 14.

5.3.3 Participant 3

Participant 3, Annie (fictitious alias), was a 43-year-old female who was 165 cm tall and weighed 73 kg. Prior to her ICU admission, she was active and worked full-time as a social worker for a government organisation that addressed family and community services for children who are at risk of harm or neglect. Annie was admitted to ICU with faecal peritonitis secondary to a bowel perforation after a laparoscopic tubal ligation with resulting sepsis. On admission to the ICU, she had an APACHE II score of 12 and a SOFA score of 10. Her preadmission FCI was 1. She was mechanically ventilated for 9 days with an ICU LOS of 9 days and total hospital LOS of 16 days. After discharge from hospital, Annie initiated access to both medical and psychological services to address the physical and cognitive deficits that she noted.

5.3.3.1 Adherence to as well as tolerance and progression of the supervised and unsupervised exercise training

Regarding attendance, Annie attended and completed all 16 sessions of the supervised EBRP over 8 weeks. She completed 2 sessions per week for 7 weeks and 1 session per week for 2 weeks. The home exercise diary was not completed therefore no results were available regarding the participant's adherence with the unsupervised training program. The reason provided by the participant for not completing the diary was that she had forgotten.

Regarding tolerance of the cycle-based training, 5 interval cycling, 3 continuous cycling and 8 walking training sessions were of a high intensity (≥ 123bpm)[230] and 8, 11 and 8 were of a moderate intensity (106 to 122 bpm),[230] respectively. Figure 5-2, Figure 5-3 and Figure 5-4 present data collected during each supervised training session for the interval cycling, continuous cycling and walking training. Variables include the work rate, physiological responses, dyspnoea and RPE. Table 5-1 presents the data pertaining to the progression of the supervised EBRP, from the first session (session 1) to the final session (session 16).

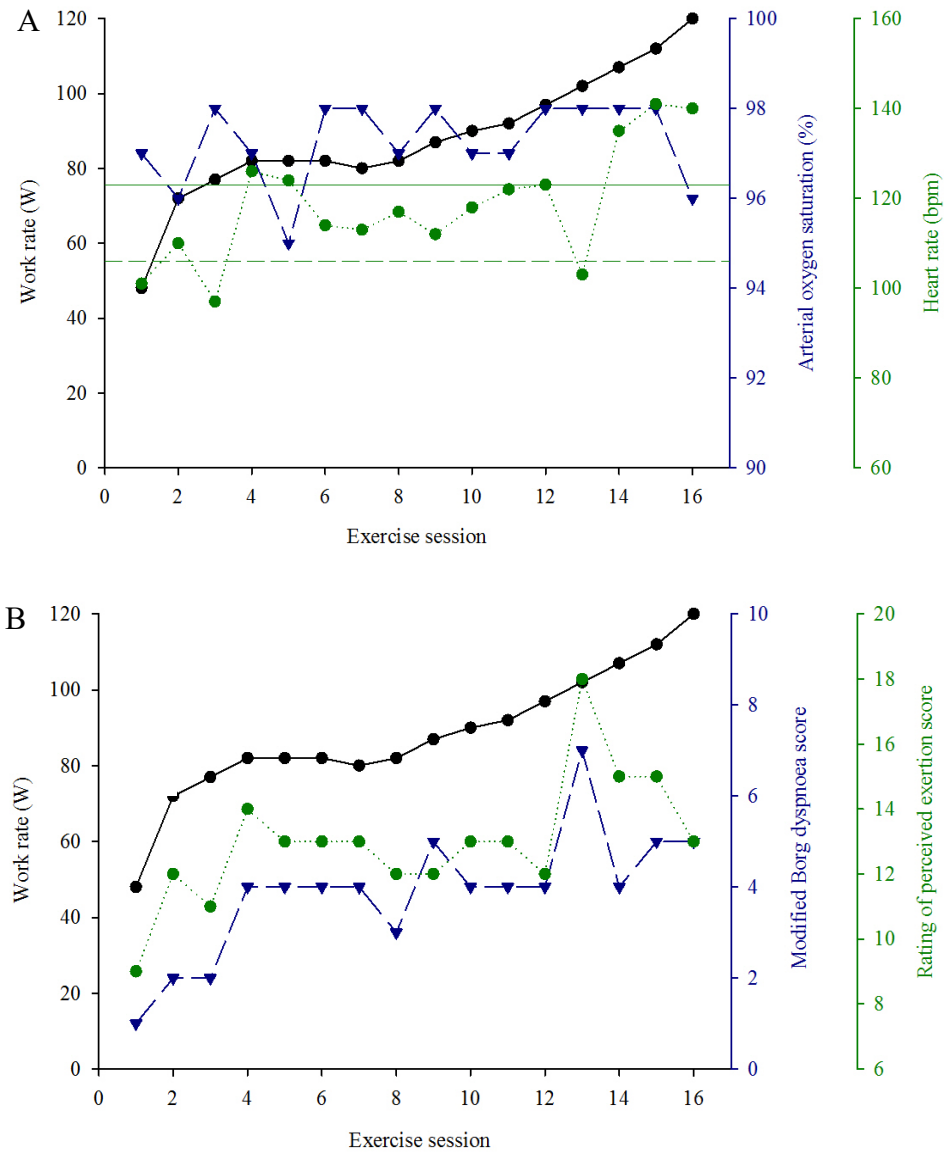

Figure 5-2 Measurements collected during interval cycling training for each session for Annie, of A) work rate, peak heart rate and nadir arterial oxygen saturation and B) work rate, peak score reported on the modified Borg dyspnoea and peak rating of perceived exertion.

—●— : work rate; - -▼- - : arterial oxygen saturation or modified Borg dyspnoea score; ····●···· : heart rate or rating of perceived exertion; ——— : 77% of peak heart rate determined from the incremental cycle ergometry test denoting the lower limit of high intensity exercise[230]; - - - - : 64% of peak heart rate determined from the incremental cycle ergometry test denoting the lower limit of moderate intensity exercise.[230]

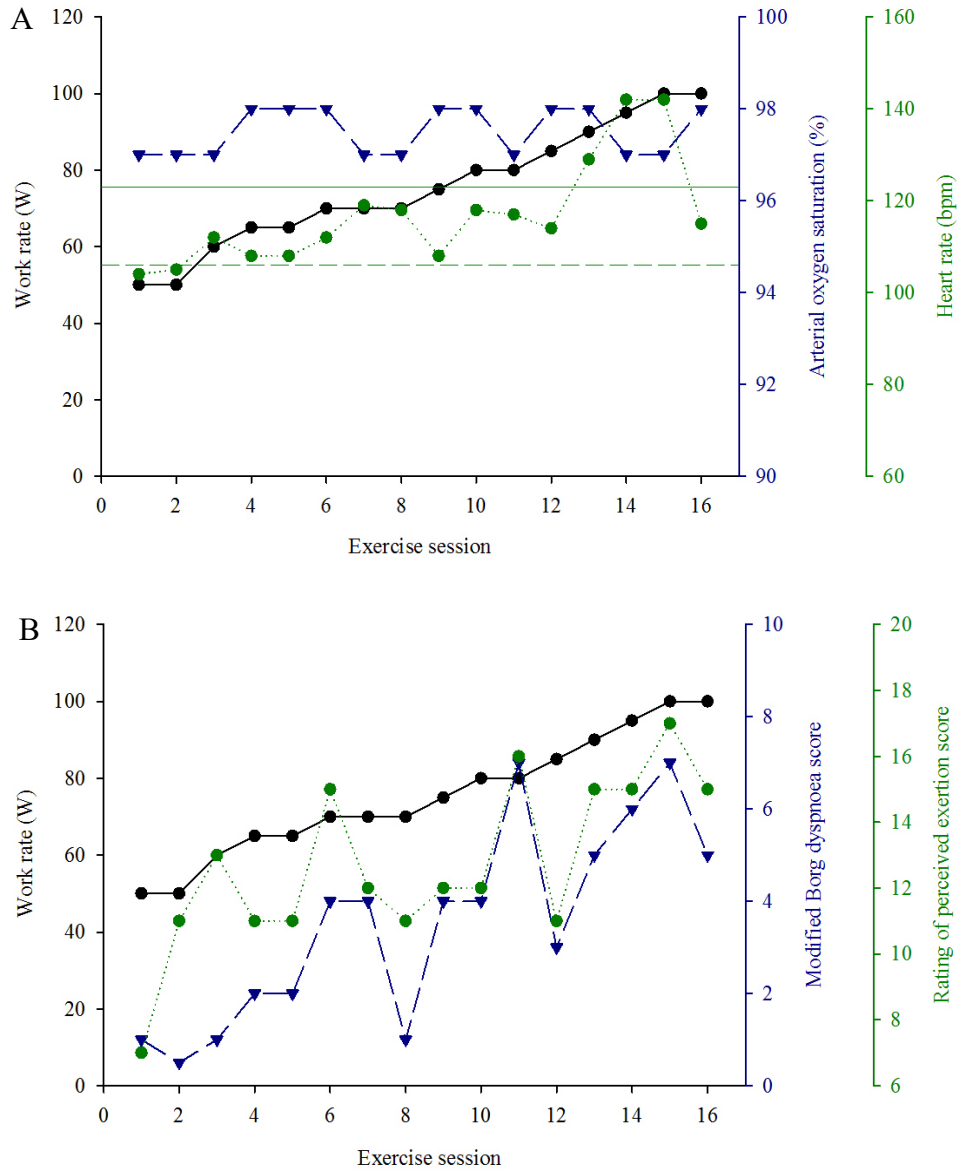

Figure 5-3 Measurements collected during each continuous cycling training session for Annie, of A) work rate, peak heart rate and nadir arterial oxygen saturation and B) work rate, modified Borg dyspnoea score and rating of perceived exertion score.

—●— : work rate; - -▼- -: arterial oxygen saturation or modified Borg dyspnoea score; ···●··· : heart rate or rating of perceived exertion; ——: 77% of peak heart rate determined from the incremental cycle ergometry test denoting the lower limit of high intensity exercise[230]; - - - - : 64% of peak heart rate determined from the incremental cycle ergometry test denoting the lower limit of moderate intensity exercise.[230]

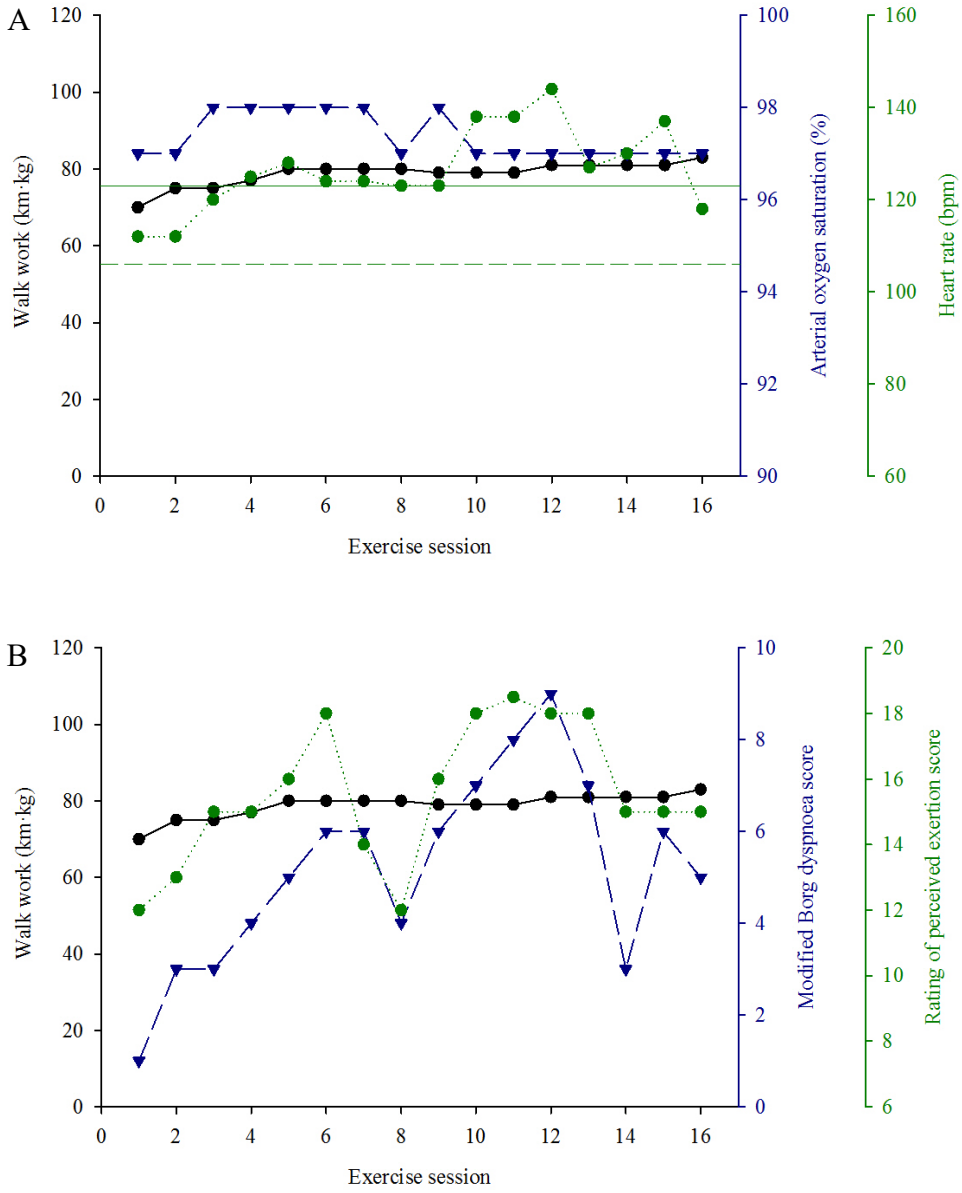

Figure 5-4 Measurements collected during each walking training session for Annie, of A) walk work, peak heart rate and nadir arterial oxygen saturation and B) walk work, modified Borg dyspnoea score and rating of perceived exertion score.

—●— : work rate; - -▼- -: arterial oxygen saturation or modified Borg dyspnoea score; ····●···· : heart rate or rating of perceived exertion; ——: 77% of peak heart rate determined from the incremental cycle ergometry test denoting the lower limit of high intensity exercise[230]; - - - - : 64% of peak heart rate determined from the incremental cycle ergometry test denoting the lower limit of moderate intensity exercise.[230]

Table 5-1 Progression of the exercise-based rehabilitation program from Session 1 to Session 16 for Annie

	Session 1 of EBRP	Session 16 of EBRP	% difference
Aerobic training			
Cycle ergometry			
Interval cycling (W·min)	480	1200	+ 150
Continuous cycling (W·min)	250	1050	+ 320
Walking			
Distance (m)	960	1,030 at elevation 5.7°	-
Walk work (km·kg)	70	83	+ 19
Speed (km/hr)	5.8	6.3 at elevation 5.7°	-
Resistance training			
Elbow flexion (kg·sets·reps)	20	75	+ 275
Shoulder forward flexion (kg·sets·reps)	20	60	+ 200
Step ups (kg·sets·reps)	15	150 (5kg·1set·30reps)	+ 900
Half squats (kg·sets·reps)	15	30	+ 100

EBRP: exercise-based rehabilitation program. The duration of the aerobic training was held constant throughout the EBRP, that is, the duration of the interval cycling was consistently15 minutes, continuous cycling 5 minutes and walking 10 minutes. % difference = (Session 16 of EBRP value - Session 1 of EBRP value) x 100 / Session 1 of EBRP value.

5.3.3.2 Outcomes collected before and after the exercise-based rehabilitation program

For Annie, the period of time between the assessments completed before and after the EBRP was 75 days.

5.3.3.2.1 Resting pulmonary function data and exercise data collected during the ICET

Table 5-2 presents measures of resting lung function collected before and after the EBRP. Measures were similar at both time points, with reductions noted in RV, FRC and D_LCO. Both FEV_1 and FVC were similar at both time points and were within normal limits.

Table 5-3 presents measures collected during the ICET performed before and after the EBRP. Compared with measures collected before the EBRP, the measures collected after the EBRP were all greater, with the exception of peak HR which was similar, and breathing reserve and VE/VCO_2 which were lower. Physiological responses collected during the ICET conducted before the EBRP were presented in Chapter 4 (see 4.3.3.2.3). These data were also interpreted in Chapter 4 (see 4.3.3.2.3). Figure 5-5 presents these data collected during the ICET conducted after the EBRP. These data are followed by a narrative interpretation of the data collected during the ICET conducted after the EBRP as well as a brief description of differences in responses noted between these tests.

Table 5-2 Resting pulmonary function data measured before and after the exercise-based rehabilitation program for Annie

Measurement	Measured		Change	%predicted		Change
	Before EBRP	After EBRP		Before EBRP	After EBRP	
FEV_1 (L)	2.73	2.55	- 0.18	97	90	- 9
VC (L)	3.51	3.28	- 0.23	108	100	- 8
FEV_1/VC ratio	0.84	0.78	- 0.06	104	96	- 8
IC (L)	2.36	2.09	- 0.27	100	89	- 11
TLC (L)	4.22	4.14	- 0.08	83	81	- 2
RV (L)	0.71	0.77	+ 0.06	42	46	+ 4
FRC (L)	1.86	2.05	+ 0.19	68	75	+ 7
MVV (L/min)	109	102	- 7	97	94	- 3
Hb (g/dL)	11.9	12.8	+ 0.9	-	-	-
D_LCO (mL/min/mmHg)	22.5	20.3	- 2.2	82	74	- 8

D_LCO: diffusion capacity of carbon monoxide; EBRP: exercise-based rehabilitation program; FEV_1: forced expiratory volume in one second; FRC: functional residual capacity; Hb: haemoglobin; IC: inspiratory capacity; ICET: incremental cycle ergometry test; MVV: maximal voluntary ventilation; RV: residual volume; TLC: total lung capacity; VC: vital capacity.

Table 5-3 Exercise data collected during the ICET before and after the exercise-based rehabilitation program for Annie

Measurement	**Measured**		**Change**	**%predicted**		**Change**
	Before EBRP	After EBRP		Before EBRP	After EBRP	
Maximum work rate (W)	120	150	+ 30	92	115	+ 23
Exercise time (min)	14	17	+ 3	-	-	-
Incremental Δ in work rate (W)	10	10	-	-	-	-
Peak VO_2 (L/min)	1.82	2.20	+ 0.38	105	126	+ 21
Peak VO_2 (mL/kg/min)	24.93	30.1	+ 5.17	-	-	-
$\Delta VO_2/\Delta WR$ (mL/min/W)	10.7	11.3	+ 0.6	-	-	-
AT (L/min)	0.90	1.3	+ 0.4	-	-	-
AT (ml/kg/min)	12.3	17.9	+ 5.6	-	-	-
Peak heart rate (bpm)	166	167	- 1	92	92	0
Peak O_2 pulse (mL/beat)	11.4	13.2	+ 1.8	119	138	+ 19
Peak VE (L/min)	84.9	104.7	+ 20.1	146	180	+ 34
Exercise breathing reserve (L/min)	24.3	- 2.7	- 27.0	-	-	-
VE/VCO_2 @ AT or lowest	32.9	30.3	- 1.6	120	111	- 9
Blood pressure (rest, peak) (mmHg)	100/60, 170/70	100/60, 160/70	-	-	-	-
Symptoms at test end	$8^{\dagger}$, 5	7, $9^{\dagger}$	-	-	-	-

ALI: acute lung injury; AT: anaerobic threshold; EBRP: exercise-based rehabilitation program; ICET: incremental cycle ergometry test; O_2 pulse: oxygen pulse; VCO_2: rate of carbon dioxide production; VE: minute ventilation; VO_2: rate of oxygen uptake; WR: work rate; Δ: change; @: occurring at; †: limiting symptom to continuing ICET.

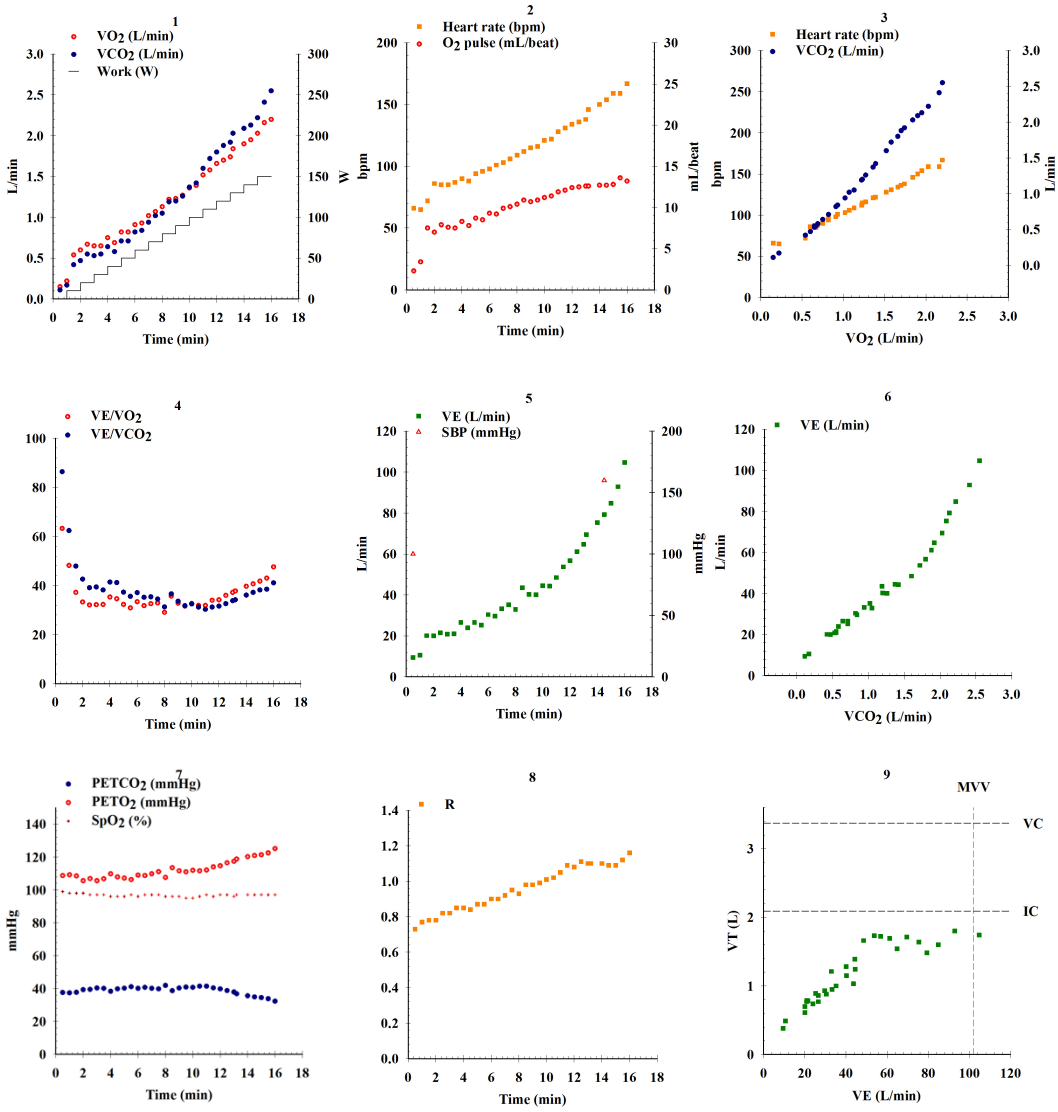

Figure 5-5 9-panel graphical array of physiological responses during ICET completed after the exercise-based rehabilitation program for Annie

IC: inspiratory capacity; ICET: incremental cycle ergometry test; MVV: maximal voluntary ventilation; O_2 pulse: oxygen pulse; $PETCO_2$: end tidal carbon dioxide tension; $PETO_2$: end tidal oxygen tension; R: respiratory exchange quotient; RV: residual volume; SBP: systolic blood pressure; SpO_2: arterial oxygen saturation; VC: vital capacity; VCO_2: rate of carbon dioxide production; VE: minute ventilation; VO_2: rate of oxygen uptake; VT: tidal volume.

5.3.3.2.2 Interpretation of the physiological responses collected during the ICET

The results and interpretation of Annie's ICET performed before training was presented in chapter 4 (section 4.3.3.2.3). Her ICET performed on completion of training was a maximal exercise test as the R exceeded 1.1 and the peak HR response was maximal. The $\Delta VO_2/\Delta WR$ was normal. Exercise capacity was above normal as seen by a high maximum WR and peak VO_2. The AT was above normal. Exercise was limited by dyspnoea.

At the AT, the VE/VCO_2 was slightly elevated suggesting the ventilatory response in relation to the metabolic requirements was high. As the $\Delta VO_2/\Delta WR$ was normal and there was no evidence of arterial oxygen desaturation, the elevated VE/VCO_2 at AT was unlikely to be as a result of pulmonary vascular disease related to left ventricular failure. The peak O_2 pulse was above normal limits also indicating that cardiac function was normal and therefore did not contribute to the elevated ventilatory response. The cause of the elevated ventilatory response was likely due to V/Q mismatching and an increased dead space (V_D/V_T) possibly associated with impaired diffusion as identified in the pulmonary function testing.

The ventilatory response was appropriate characterised by the linear relationship of V_T to VE which plateaued toward the peak of exercise. While exercise breathing reserve was low, in light of the maximal nature of the test, the limitation was unlikely to be ventilatory. A breathing reserve that approaches zero is a common finding in highly trained individuals.[345]

In conclusion, Annie showed an above normal exercise capacity with a mildly elevated ventilatory response, which was likely as a result of impaired diffusion.

5.3.3.2.3 Comparison of the physiological responses collected during the ICET before and after the EBRP

Both ICETs conducted before and after the EBRP were maximal tests. Compared with the ICET conducted before the EBRP, a similar magnitude of increase in both peak VO_2 and AT were noted in the ICET after the EBRP. An elevated VE/VCO_2 at AT was noted in the tests at both time points and is most likely related to abnormalities in pulmonary function and impaired diffusion which was similar

between before and after the EBRP. Breathing reserve diminished to negative values in the ICET conducted after the EBRP, most likely as a result of training.

5.3.3.2.4 Functional exercise capacity

After training, the 6MWT was performed twice and this distance achieved on the first and second test increased by +55 m (656 vs.712 m). Compared with the best 6MWD achieved before the EBRP, the best 6MWD achieved after the EBRP was 6 m less (718 vs.712 m).

5.3.3.2.5 Physical activity and sedentary time

After training, Annie wore the SAB for a total of 6 days, which comprised 4 weekdays and 2 weekend day. The average time that the SAB was worn was each day was 15 ± 2 hr and during this time, the SAB was collecting data for an average of 98 ± 3% of total wear time. The average daily start time was 0822 ± 1 hr (24-hour time).

Table 5-4 presents the average time spent in LPA, MVPA and ST, expressed as a proportion of waking hours and as hr/day, both before and after the EBRP. As the time spent in VPA was < 1 minute before and after the EBRP, data pertaining to MPA and VPA were combined and expressed as MVPA. Compared with the measures collected before the EBRP, after the EBRP, more time was spent in LPA, and less ST was accumulated.

Table 5-4 also presents the way in which time in LPA, MVPA and ST was accumulated. Compared with the measures collected before the EBRP, after the EBRP, a lower proportion of LPA was accumulated in bouts ≥ 10 minutes and a greater proportion of ST was accumulated in bouts ≥ 30 minutes.

Regarding daily step count, measures before and after the EBRP were similar (6,150 vs. 6,967 steps/day, respectively).

5.3.3.2.6 Peripheral muscle strength

Table 5-5 presents the peripheral muscle force and respiratory pressures generated by Annie before and after the EBRP. Compared with the measures collected before

the EBRP, after the EBRP, greater forces were generated for all actions, except knee extension, and greater inspiratory pressures were generated.

5.3.3.2.7 Health-related quality of life

Figure 5-6 presents the scores for the SF36 in each domain before and after the EBRP for Annie. General health and vitality were similar before and after the EBRP. Compared with the values measured before the EBRP, all remaining domains, apart from role physical which decreased by 6 (19 vs. 13), increased after the EBRP. Figure 5-7 presents the values for the PCS and the MCS before and after the EBRP.

5.3.3.2.8 Fatigue

Compared with the FSS measured before the EBRP, the FSS measured after the EBRP was lower (improved) (4.44 vs. 3.22).

Table 5-4 Proportion of waking hours and hours per day spent in light intensity, moderate and vigorous intensity physical activity and sedentary time, and patterns of accumulation of light intensity, moderate and vigorous intensity physical activity, and sedentary time before and after the exercise-based rehabilitation program for Annie

	Before EBRP	After EBRP	Change
Light intensity physical activity			
% of waking hours	28	35	+ 7
hours/day	4.0	5.3	+ 1.3
Moderate and vigorous intensity physical activity			
% of waking hours	12	11	- 1
hours/day	1.7	1.7	0
Sedentary time			
% of waking hours	60	54	- 6
hours/day	8.5	8.1	- 0.4
Proportion of total time spent in light intensity physical activity that was accumulated in bouts ≥ 10 min (%)	26	19	- 7
Proportion of total time spent in moderate and vigorous intensity physical activity that was accumulated in bouts ≥ 10 min (%)	24	23	- 1
Proportion of total time spent in sedentary time that was accumulated in bouts ≥ 30 min (%)	49	67	+ 18

EBRP: exercise-based rehabilitation program.

Table 5-5 Peripheral and respiratory muscle strength measured before and after the exercise-based rehabilitation program for Annie

	Before EBRP	After EBRP	Difference
Knee extension (N)	370.8	335.8	- 35.0
Shoulder flexion (kg)	17.4	19.4	+ 2.0
Elbow flexion (kg)	15.5	17.6	+ 2.2
Grip (kg)	27.5	30.0	+ 2.5
MIP (cmH_2O)	- 80	-87	- 7
MEP (cmH_2O)	101	75	- 26

EBRP: exercise-based rehabilitation program; MEP: maximal expiratory pressure; MIP: maximal inspiratory pressure.

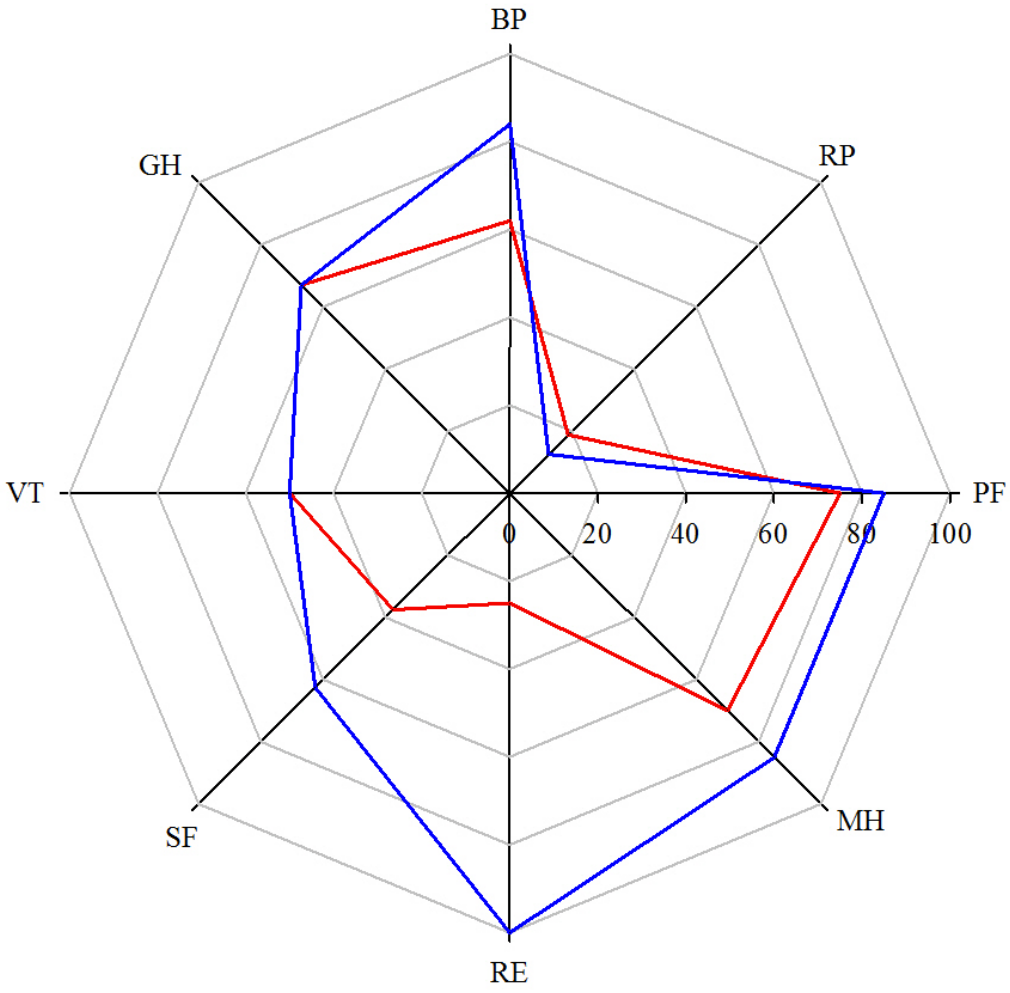

Figure 5-6 Health related quality of life domains collected before and after the exercise-based rehabilitation program for Annie

BP: bodily pain; GH: general health; MH: mental health; PF: physical functioning; RE: role emotional; RP: role physical; SF: social functioning; VT: vitality; —— : before the EBRP; —— : after the EBRP.

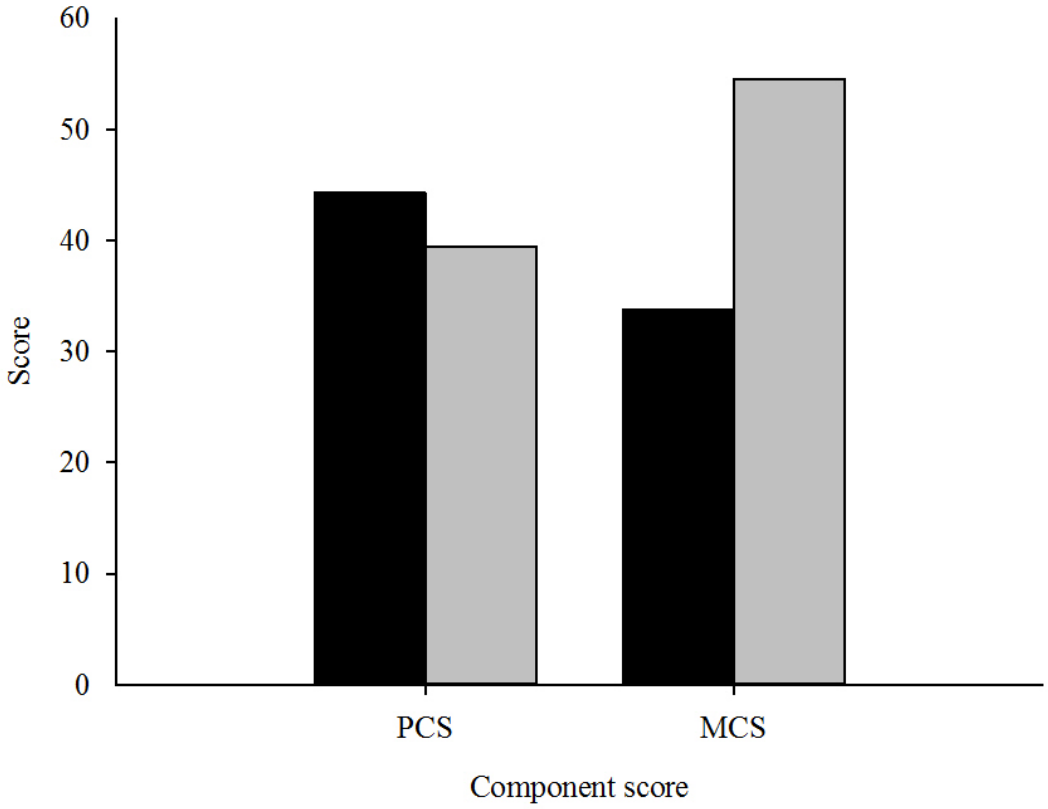

Figure 5-7 Physical component score and mental component score of the SF36 collected before and after the exercise-based rehabilitation program for Annie

EBRP: exercise-based rehabilitation program; MCS: mental component score; PCS: physical component score; ▬: before the EBRP; ▭: after the EBRP.

5.3.4 Participant 7

Participant 7, James (fictitious alias), was a retired 63-year-old male who was 175 cm tall and weighed 99 kg. Prior to his ICU admission, he was unwell for a period of 12 months with an unspecified respiratory illness which had been managed by his local medical officer. James was admitted to ICU with community acquired pneumonia with resulting sepsis. On admission to the ICU, he had an APACHE II score of 25 and a SOFA score of 10. His preadmission FCI was 6. He was mechanically ventilated for 9 days with an ICU LOS of 11 days and a total hospital LOS of 20 days. After discharge from hospital, James was admitted to a rehabilitation facility for a period of approximately 2 weeks before he was discharged home.

5.3.4.1 Adherence to as well as tolerance and progression of the supervised and unsupervised exercise training

Regarding attendance, James attended and completed all 16 sessions as scheduled. James' exercise schedule however, extended across the Christmas holiday period which meant that the program was interrupted for a single block of time. As James had previously arranged to visit family over this period, there was a planned period of 4 weeks in which James did not attend the supervised exercise program. That is, he completed 9 sessions over 4 weeks prior to Christmas, and a further 7 sessions occurred over a period of 3 weeks after Christmas. The home exercise diary was not completed therefore no results are available regarding the participant's adherence with the unsupervised training program. No reason was given for not completing the home exercise diary.

Regarding tolerance of the cycle-based training, 4 interval cycling, zero continuous cycling and zero walking training sessions were of a high intensity (≥ 117bpm)[230]and 9, 12 and 13 were of a moderate intensity (99 to 116 bpm),[230] respectively. Figure 5-8, Figure 5-9 and Figure 5-10 present data collected during each supervised training session for the interval cycling, continuous cycling and walking training. Variables include the work rate, physiological responses, dyspnoea and RPE. Table 5-6 presents the data pertaining to the progression of the supervised EBRP, from the first session (session 1) to the final session (session 16).

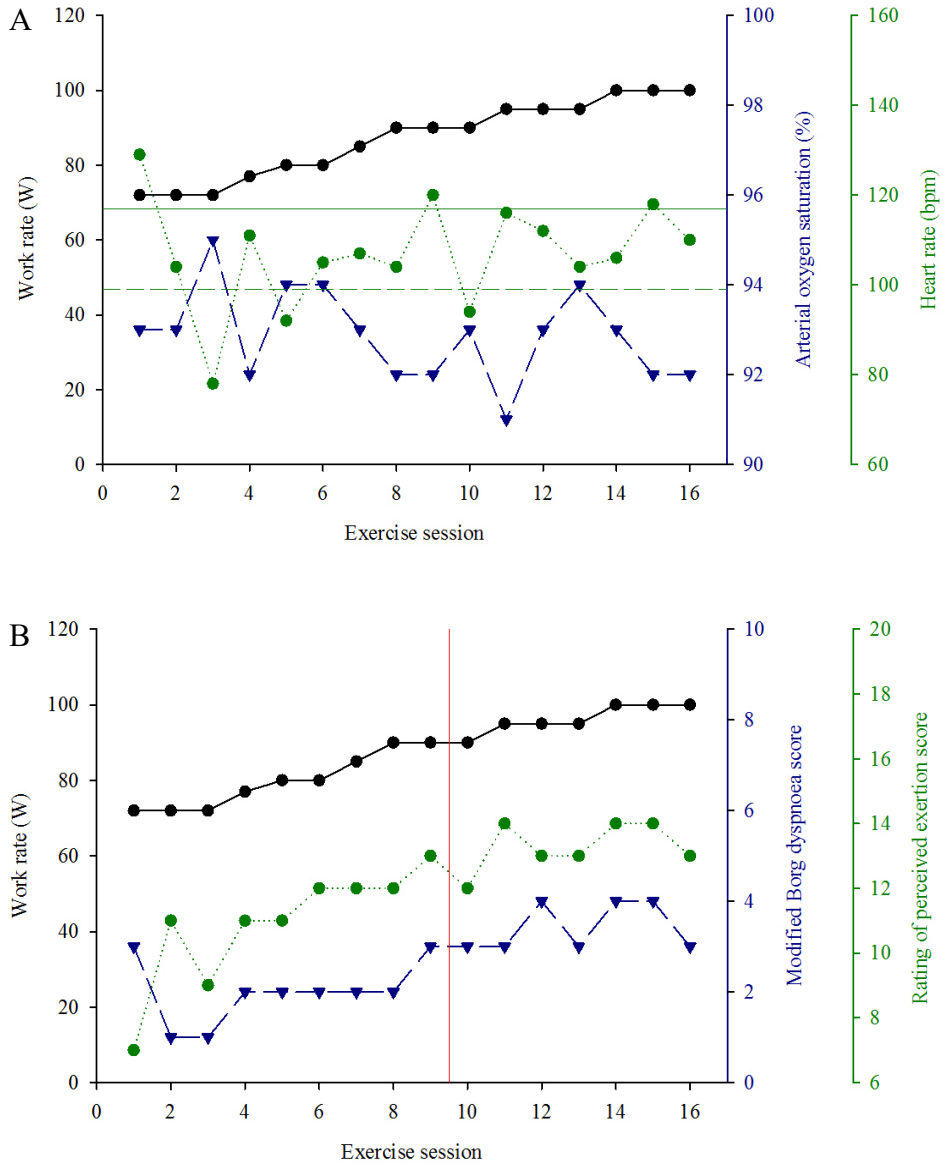

Figure 5-8 Measurements collected during interval cycling training for each session for James, of A) work rate, peak heart rate and nadir arterial oxygen saturation and B) work rate, peak score reported on the modified Borg dyspnoea and peak rating of perceived exertion.

—●— : work rate; - -▼- -: arterial oxygen saturation or modified Borg dyspnoea score; ····●···· : heart rate or rating of perceived exertion; ——: 77% of peak heart rate determined from the incremental cycle ergometry test denoting the lower limit of high intensity exercise[230]; - - - - : 64% of peak heart rate determined from the incremental cycle ergometry test denoting the lower limit of moderate intensity exercise[230]; —— : period of 4 weeks in which James did not attend the supervised exercise program.

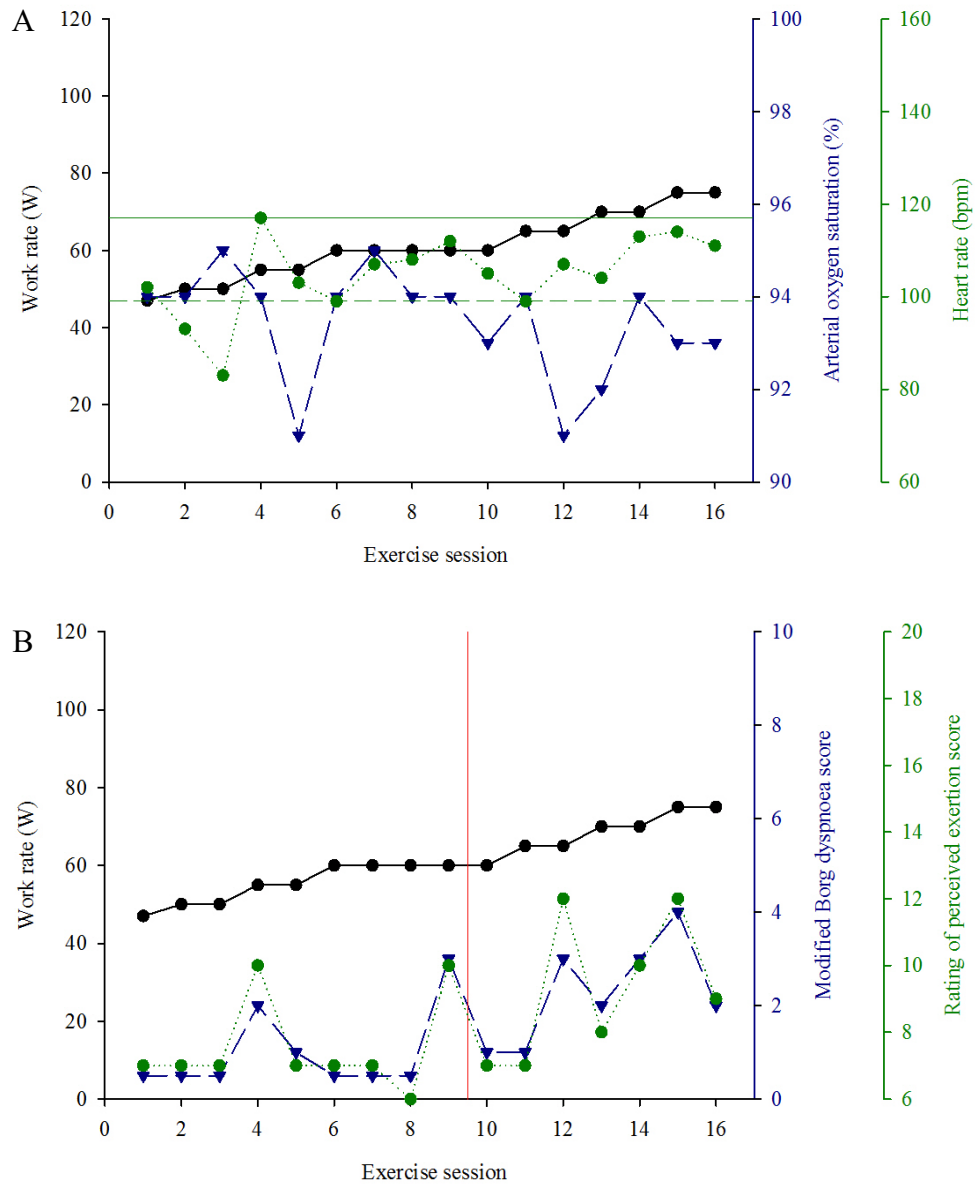

Figure 5-9 Measurements collected during each continuous cycling training session for James, of A) work rate, peak heart rate and nadir arterial oxygen saturation and B) work rate, modified Borg dyspnoea score and rating of perceived exertion score.

—●— : work rate; - -▼- -: arterial oxygen saturation or modified Borg dyspnoea score; ···●··· : heart rate or rating of perceived exertion; ——: 77% of peak heart rate determined from the incremental cycle ergometry test denoting the lower limit of high intensity exercise[230]; - - - - : 64% of peak heart rate determined from the incremental cycle ergometry test denoting the lower limit of moderate intensity exercise[230]; —— : period of 4 weeks in which James did not attend the supervised exercise program.

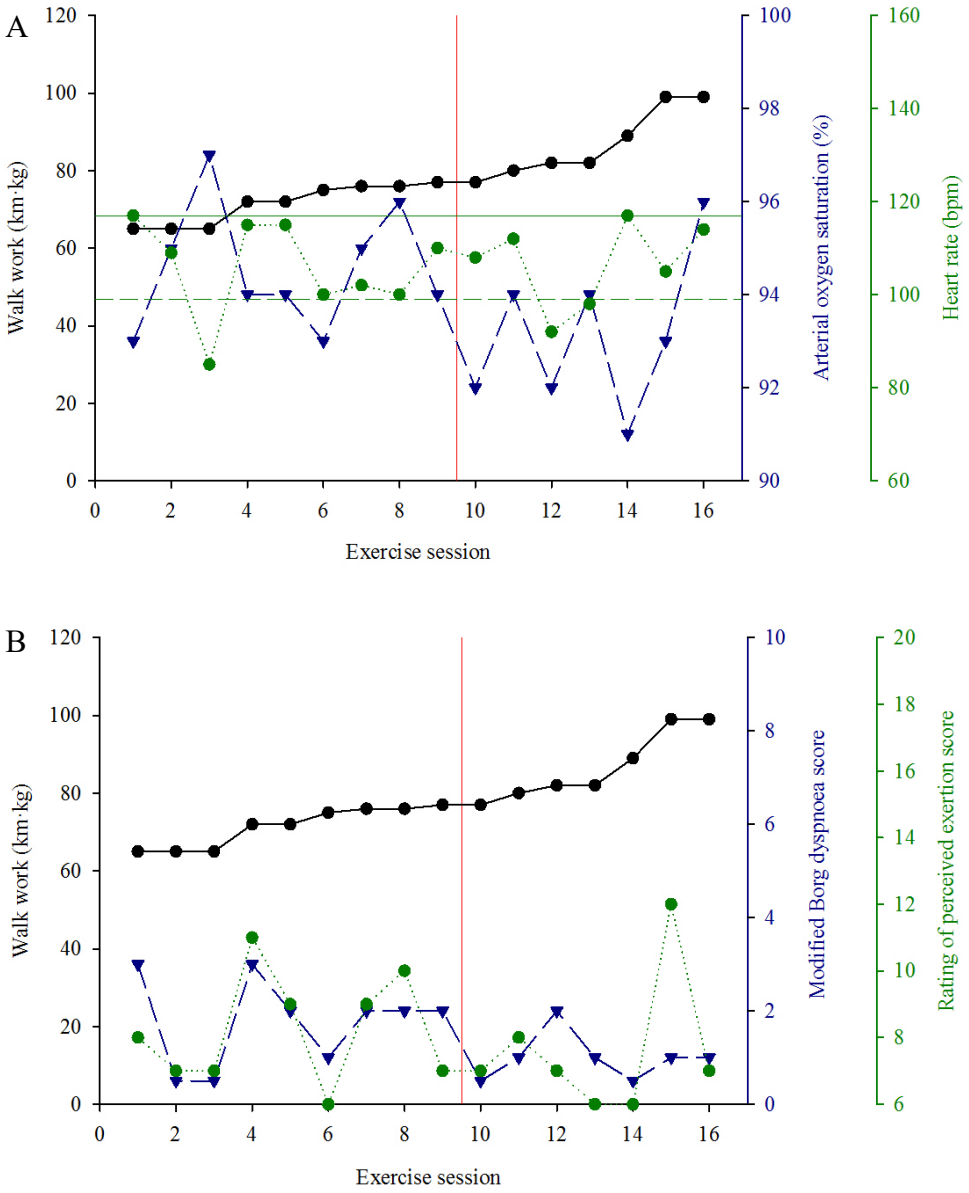

Figure 5-10 Measurements collected during each walking training session for James, of A) walk work, peak heart rate and nadir arterial oxygen saturation and B) walk work, modified Borg dyspnoea score and rating of perceived exertion score.

—●— : work rate; - -▼- -: arterial oxygen saturation or modified Borg dyspnoea score; ····●···· : heart rate or rating of perceived exertion; ——: 77% of peak heart rate determined from the incremental cycle ergometry test denoting the lower limit of high intensity exercise[230]; - - - - : 64% of peak heart rate determined from the incremental cycle ergometry test denoting the lower limit of moderate intensity exercise[230]; —— : period of 4 weeks in which James did not attend the supervised exercise program.

Table 5-6 Progression of the exercise-based rehabilitation program from Session 1 to Session 16 for James

	Session 1 of EBRP	Session 16 of EBRP	% difference
Aerobic training			
Cycle ergometry			
Interval cycling (W·min)	720	1000	+ 39
Continuous cycling (W·min)	235	375	+ 60
Walking			
Distance (m)	660	999	+ 51
Walk work (km·kg)	65	102	+ 57
Speed (km/hr)	4.0	6.0	+50
Resistance training			
Elbow flexion (kg·sets·reps)	20	105	+ 425
Shoulder forward flexion (kg·sets·reps)	20	105	+ 425
Step ups (kg·sets·reps)	10	75 (30+2·5kg)	+ 650
Half squats (kg·sets·reps)	10	105 (30+3.5kg)	+ 950

EBRP: exercise-based rehabilitation program. The duration of the aerobic training was held constant throughout the EBRP, that is, the duration of the interval cycling was consistently 5 minutes, continuous cycling 10 minutes and walking 20 minutes. % difference = (Session 16 of EBRP value - Session 1 of EBRP value) x 100 / Session 1 of EBRP value.

5.3.4.2 Outcomes collected before and after the exercise-based rehabilitation program

For James, the period of time between the assessments before and after the EBRP was 119 days.

5.3.4.2.1 Resting pulmonary function data and exercise data collected during the ICET

Table 5-7 presents measures of resting lung function collected before and after the EBRP. Measures were similar at both time points, with slight improvements observed in all measures except for FRC. Both FEV_1 and FVC also demonstrated slight improvements after the EBRP.

Table 5-8 presents measures collected during the ICET performed before and after the EBRP. Compared with measures collected before the EBRP, the measures collected after the EBRP were all greater, with the exception of peak HR which was similar and breathing reserve which was lower. Physiological responses collected during the ICET conducted before the EBRP were presented in Chapter 4 (section 4.3.3.2.7). These data were also interpreted in Chapter 4 (section 4.3.3.2.7). Figure 5-11 presents these data collected during the ICET conducted after the EBRP. These data are followed by a narrative interpretation of the data collected during the ICET conducted after the EBRP as well as a brief description of differences in responses noted between these tests.

Table 5-7 Resting pulmonary function data measured before and after the exercise-based rehabilitation program for James

Measurement	Measured		Change	%predicted		Change
	Before EBRP	After EBRP		Before EBRP	After EBRP	
FEV_1 (L)	2.38	2.67	+ 0.29	74	83	+ 9
VC (L)	3.77	4.08	+ 0.31	88	96	+ 8
FEV_1/VC ratio	0.64	0.65	+ 0.01	84	86	+ 2
IC (L)	2.66	3.12	+ 0.46	80	94	+ 14
TLC (L)	5.56	5.99	+ 0.43	81	87	+ 6
RV (L)	1.79	1.91	+ 0.12	73	78	+ 5
FRC (L)	2.90	2.87	- 0.03	81	80	- 1
MVV (L/min)	95	107	+ 12	75	84	+ 9
Hb (g/dL)	13.9	15.4	+ 1.5	-	-	
D_LCO (mL/min/mmHg)	16.0	17.1	+ 1.1	49	52	+ 3

D_LCO: diffusion capacity of carbon monoxide; EBRP: exercise-based rehabilitation program; FEV_1: forced expiratory volume in one second; FRC: functional residual capacity; Hb: haemoglobin; IC: inspiratory capacity; ICET: incremental cycle ergometry test; MVV: maximal voluntary ventilation; RV: residual volume; TLC: total lung capacity; VC: vital capacity.

Table 5-8 Exercise data collected during the ICET before and after the exercise-based rehabilitation program for James

Measurement	Measured		Change	%predicted		Change
	Before EBRP	After EBRP		Before EBRP	After EBRP	
Maximum work rate (W)	120	150	+ 30	64	81	+ 17
Exercise time (min)	13	16	+ 3	-	-	
Incremental Δ in work rate (W)	10	10	0	-	-	
Peak VO_2 (L/min)	1.88	2.43	+ 0.55	76	99	+ 23
Peak VO_2 (mL/kg/min)	18.99	24.0	+ 5.01	-	-	
$\Delta VO_2/\Delta WR$ (mL/min/W)	10.4	10.7	+ 0.3	-	-	
AT (L/min)	1.05	1.2	+ 0.15	-	-	
AT (mL/kg/min)	10.61	11.76	1.15	-	-	
Peak heart rate (bpm)	158	154	- 4	93	91	- 2
Peak O_2 pulse (mL/beat)	11.9	15.8	+ 3.9	82	109	+ 27
Peak VE (L/min)	90.2	97.3	+ 7.1	138	150	+ 12
Exercise breathing reserve (L/min)	25.8	9.7	- 16.1	-	-	
VE/VCO_2 @ AT or lowest	33.2	34.5	+ 1.03	119	123	+ 4
Blood pressure (rest, peak) (mmHg)	110/72, 207/71	120/75, 190/90	-	-	-	
Symptoms at test end	9†, 5.5	9†, 7	-	-	-	

ALI: acute lung injury; AT: anaerobic threshold; EBRP: exercise-based rehabilitation program; ICET: incremental cycle ergometry test; O_2 pulse: oxygen pulse; VCO_2: rate of carbon dioxide production; VE: minute ventilation; VO_2: rate of oxygen uptake; WR: work rate; Δ: change; @: occurring at; †: limiting symptom to continuing ICET.

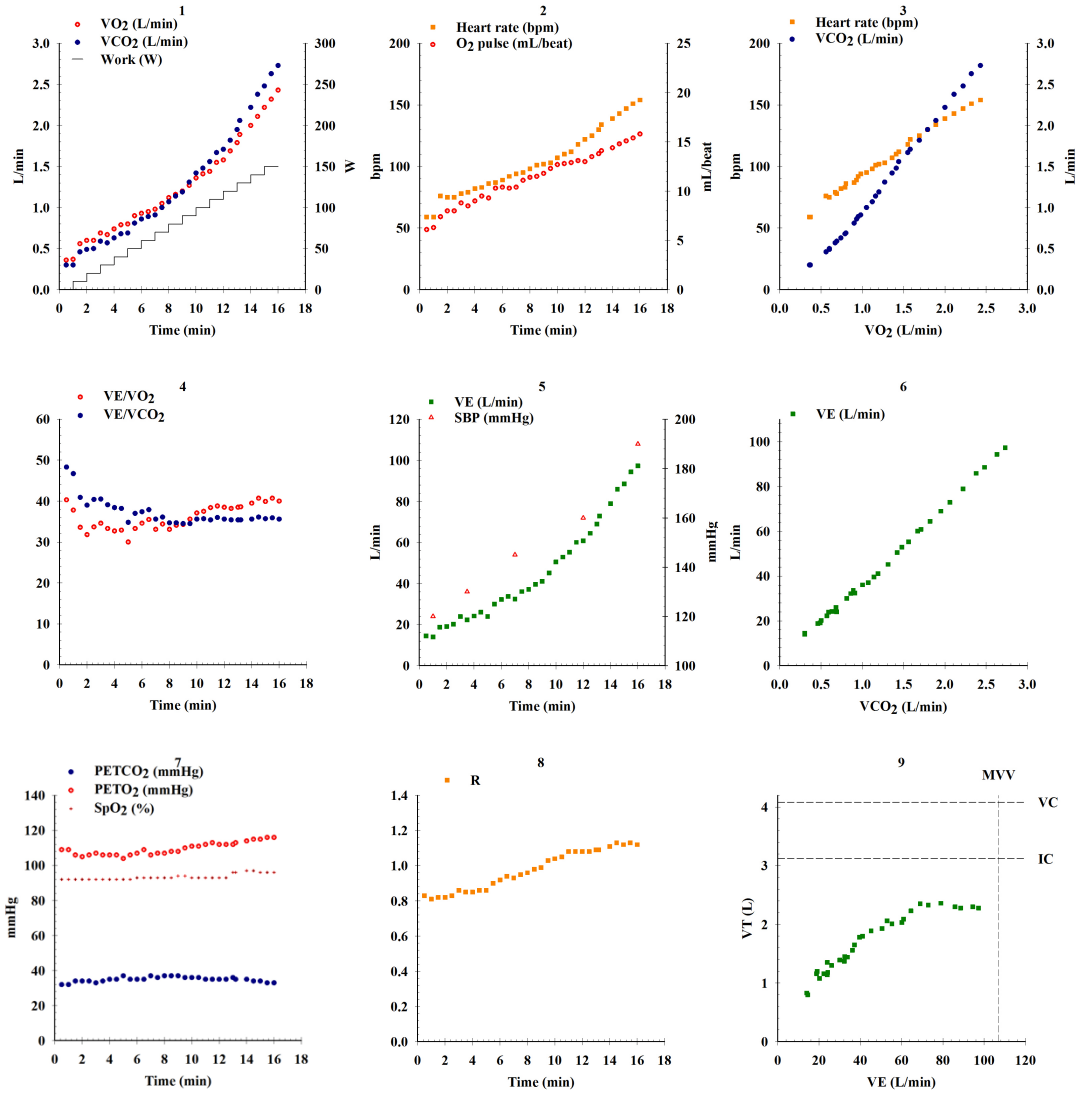

Figure 5-11 9-panel graphical array of physiological responses during ICET completed after the exercise-based rehabilitation program for James

IC: inspiratory capacity; ICET: incremental cycle ergometry test; MVV: maximal voluntary ventilation; O_2 pulse: oxygen pulse; $PETCO_2$: end tidal carbon dioxide tension; $PETO_2$: end tidal oxygen tension; R: respiratory exchange quotient; RV: residual volume; SBP: systolic blood pressure; SpO_2: arterial oxygen saturation; VC: vital capacity; VCO_2: rate of carbon dioxide production; VE: minute ventilation; VO_2: rate of oxygen uptake; VT: tidal volume.

5.3.4.2.2 Interpretation of the physiological responses collected during the ICET

The results and interpretation of James' ICET performed before training was presented in Chapter 4 (section 4.3.3.2.7). His ICET performed on completion of training was a maximal exercise test as the R exceeded 1.1 and the peak HR was maximal. The $\Delta VO_2/\Delta WR$ was normal. Exercise capacity was normal as seen by normal WR and peak VO_2. The AT was normal. Exercise was limited by leg fatigue.

At the AT, the VE/VCO_2 was elevated suggesting the ventilatory response in relation to the metabolic requirements was high. As the $\Delta VO_2/\Delta WR$ was normal and there was no evidence of arterial oxygen desaturation, the elevated VE/VCO_2 at AT was unlikely to be as a result of pulmonary vascular disease related to left ventricular failure. The peak O_2 pulse was within normal limits also indicating that cardiac function was normal and therefore did not contribute to the elevated ventilatory response. The cause of the elevated ventilatory response was likely due to V/Q mismatching and an increased V_D/V_T possibly associated with impaired diffusion as identified in the pulmonary function testing.

The peak O_2 pulse was within normal limits with an appropriate progression throughout exercise.

The ventilatory response was appropriate characterised by the linear relationship of V_T to VE which plateaued toward the peak of exercise. While exercise breathing reserve was low, in light of the maximal nature of the test, the limitation was unlikely to be ventilatory. Ventilatory limitation is a common finding in highly trained individuals.

In conclusion, participant 7 showed normal exercise capacity with the limiting factor likely to be a result of general deconditioning and impaired pulmonary diffusion.

5.3.4.2.3 Comparison of the physiological responses collected during the ICET before and after the exercise-based rehabilitation program

Both ICETs conducted before and after the EBRP were maximal tests. Compared with the ICET conducted before the EBRP, an increase in the magnitude of both peak VO_2 and AT were noted in the ICET conducted after the EBRP, although when compared with the change in the AT, the change in peak VO_2 was greater. An

elevated VE/VCO_2 at AT was noted in both tests and is most likely related to abnormalities in pulmonary function and impaired diffusion which was similar between before and after the EBRP. Breathing reserve diminished to less than predicted values in the ICET conducted after the EBRP, most likely as a result of training.

5.3.4.2.4 Functional exercise capacity

After training, the 6MWT was performed twice and this distance achieved on the first and second test increased by +106 m (495 vs.601 m). Compared with the best 6MWD achieved before the EBRP, the 6MWD achieved after the EBRP was 58 m greater (543 vs. 601 m).

5.3.4.2.5 Physical activity and sedentary time

After training, James wore the SAB for a total of 6 days, consisting of 4 weekdays and 2 weekend days. The average time that the SAB was worn was each day was 14 ± 1 hr. The proportion of waking hours that the SAB was on the participants body was 98 ± 2% and the daily start time was 0801 ± 1 hr (24-hour time).

Table 5-9 presents the time spent in LPA, MVPA and ST, expressed as a proportion of waking hours and as hr/day, both before and after the EBRP. Compared with the measures collected before the EBRP, after the EBRP, more time was spent in LPA and MVPA, and less ST was accumulated. Table 5-9 also presents the way in which time in LPA, MVPA and ST was accumulated. Compared with the measures collected before the EBRP, after the EBRP, a greater proportion of LPA was accumulated in bouts ≥ 10 minutes, and MVPA accumulated in bouts ≥ 10 minutes, and a lower proportion of ST was accumulated in bouts ≥ 30 minutes.

Regarding average daily step count, compared with the measures collected before the EBRP, after the EBRP, James accumulated more steps per day (2,987 vs. 5,243 steps per day, respectively).

5.3.4.2.6 Peripheral muscle strength

Table 5-10 presents the peripheral and respiratory muscle force generated by James at baseline and after the EBRP. Compared with the measures collected before the

EBRP, after the EBRP, greater forces were generated for all actions, and greater pressures were generated on inspiration.

5.3.4.2.7 Health-related quality of life

Figure 5-12 presents the scores for the SF36 in each domain before and after the EBRP for James. Compared with the values collected before the EBRP, after the EBRP, values in all domains were greater, apart from bodily pain which was 12 points less (22 vs. 10). Figure 5-13 presents the values for the PCS and the MCS before and after the EBRP.

5.3.4.2.8 Fatigue

Compared with the FSS measured before the EBRP, after the EBRP, the FSS was marginally lower (improved) (5.5 vs. 5.4).

Table 5-9 Proportion of waking hours and hours per day spent in light intensity, moderate and vigorous intensity physical activity and sedentary time, and patterns of accumulation of light intensity, moderate and vigorous intensity physical activity, and sedentary time before and after the exercise-based rehabilitation program for James

	Before EBRP	After EBRP	Change
Light intensity physical activity			
% of waking hours	15	28	+ 13
hours/day	2.0	3.6	+ 1.6
Moderate and vigorous intensity physical activity			
% of waking hours	4	9	+ 5
hours/day	0.5	1.3	+ 0.8
Sedentary time			
% of waking hours	81	78	- 3
hours/day	10.5	9.2	- 1.3
Proportion of total time spent in light intensity physical activity that was accumulated in bouts ≥ 10 min (%)	21	31	+ 10
Proportion of total time spent in moderate and vigorous intensity physical activity that was accumulated in bouts ≥ 10 min (%)	17	30	+ 13
Proportion of total time spent in sedentary time that was accumulated in bouts ≥ 30 min (%)	65	49	- 16

EBRP: exercise-based rehabilitation program.

Table 5-10 Peripheral and respiratory muscle strength measured before and after the exercise-based rehabilitation program for James

	Before EBRP	After EBRP	Difference
Knee extension (N)	289.4	335.2	+ 45.8
Shoulder flexion (kg)	22.7	24.0	+ 1.3
Elbow flexion (kg)	20.7	24.2	+ 3.5
Grip (kg)	32	39.0	+ 7
MIP (cmH_2O)	- 72	- 79	- 7
MEP (cmH_2O)	118	111	- 7

EBRP: exercise-based rehabilitation program; MEP: maximal expiratory pressure; MIP: maximal inspiratory pressure.

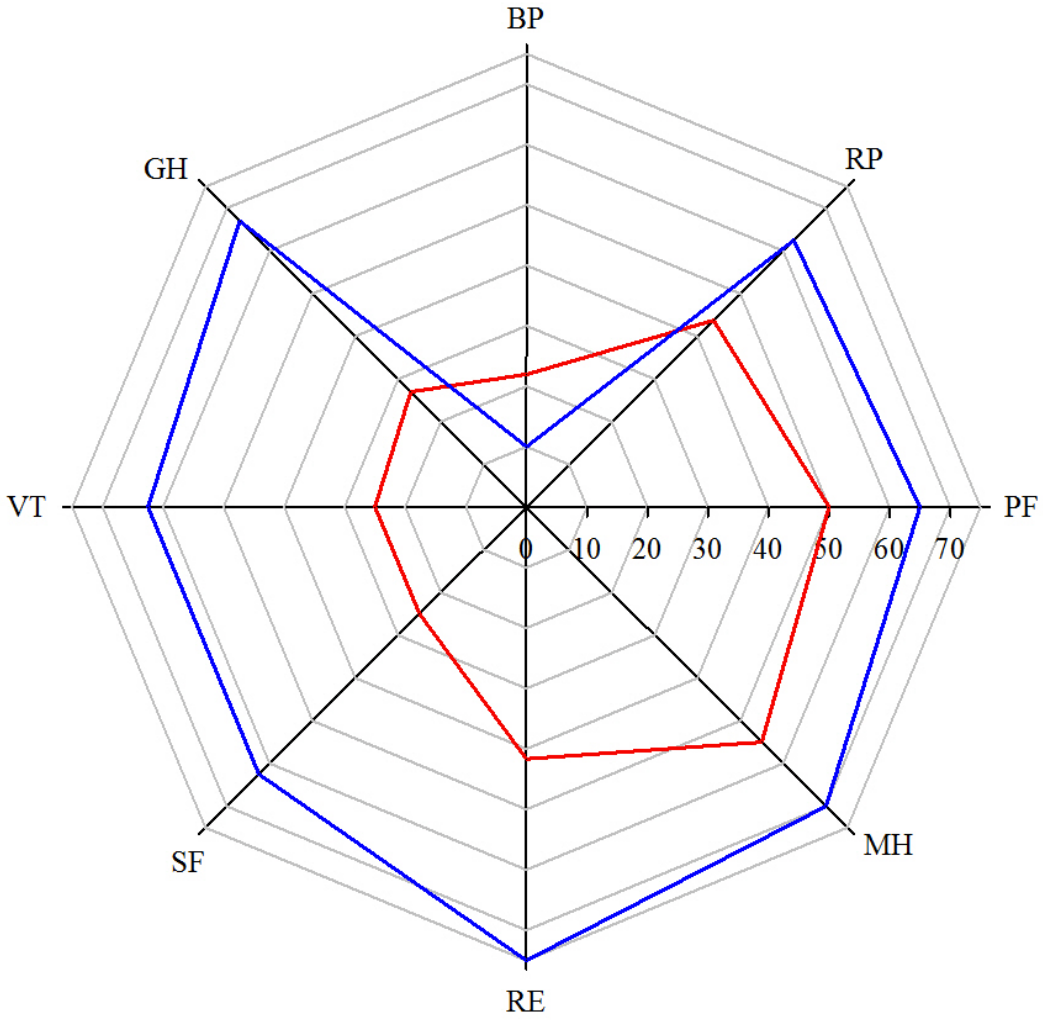

Figure 5-12 Health related quality of life domains collected before and after the exercise-based rehabilitation program for James

BP: bodily pain; EBRP: exercise-based rehabilitation program; GH: general health; MH: mental health; PF: physical functioning; RE: role emotional; RP: role physical; SF: social functioning; VT: vitality; —— : before the EBRP; —— : after the EBRP.

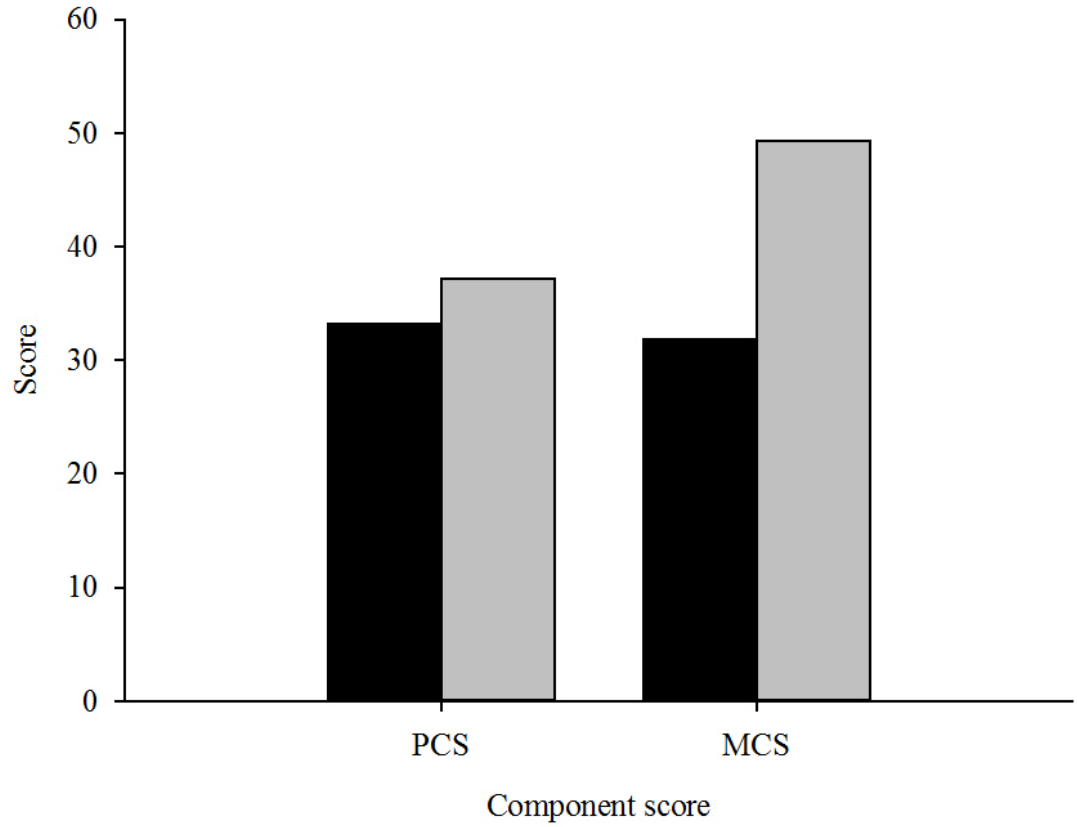

Figure 5-13 Physical component score and mental component score of the SF36 collected before and after the exercise-based rehabilitation program for James

EBRP: exercise-based rehabilitation program; MCS: mental component score; PCS; physical component score; ▬: before the EBRP; ▭: after the EBRP.

5.4 Discussion

5.4.1 Overview

This study examined the adherence to, as well as tolerance and progression of an EBRP initiated 8 weeks after discharge from an acute care facility, in 2 survivors of ALI. The change within participants following completion of the EBRP on the submaximal and peak physiological responses during an ICET and 6MWT, the accumulation of PA and ST, peripheral muscle strength, HRQL and fatigue were also examined. The main findings of this study were that a structured EBRP, initiated after hospital discharge was feasible, and in both cases, compared with pre-training measures, on completion of the EBRP, increases in exercise capacity and participation in PA, and reductions in the accumulation of ST during waking hours, was observed. The effect of the EBRP on peripheral muscle strength, way in which ST was accumulated and the perception of physical function differed between participants.

5.4.2 Participant recruitment

Recruitment to this study was challenging. The reasons people provided for choosing not to participate related to pre-existing and new illness, work and family commitments, and the perception that exercise would be of little benefit in their recovery. Two participants consented but did not respond to repeated attempts at contact following randomisation to the intervention group. Both of these participants had social and psychiatric disability and were of a low socioeconomic status. In reports detailing attrition in other study populations such as patients presenting to the emergency department and those with burn injuries, psychiatric comorbidity, sex (male), non-Caucasian race and low socioeconomic status have all been associated with greater loss to follow-up.[460-462] Studies investigating PA and exercise interventions have shown that those least likely to participate have low levels of education.[463] In a mixed methods study investigating factors that affect participation in organised PA by low-income groups, barriers which were identified included low recognition of the benefits of PA for themselves, lack of time and poor access to the services.[464] In a group of adults with newly diagnosed Type II diabetes mellitus, themes describing the barriers to engaging in exercise included the impact of the new

diagnosis on the ability to exercise and fear of adverse events during exercise such as hypoglycaemia; exacerbation of fatigue; potential for injury; and advice from other healthcare practitioners who had advised them not to exercise.[465] All of these factors that have served as barriers to recruitment in previous work may also be pertinent in the population surviving a critical illness, including fear and misinformation around a new diagnosis or disability that may be associated with surviving a critical illness.[60,171,463,465] Recruitment to longitudinal studies of survivors of critical illness is an acknowledged challenge.[60]

A systematic review of studies, and interviews with research teams, who have achieved exceptionally high recruitment and retention rates in longitudinal studies have identified a number of strategies that appear to be consistently used.[454,466] Those studies with higher retention used a variety of retention strategies.[466] These strategies include (i) the use of research staff members who are specialised, persistent and collaborative with a shared goal to accomplish high retention, (ii) individualised and tailored retention strategies, as identified by the study staff, and according to the social, cultural and environnmental considerations of the population,[454] and (iii) the use of financial incentives to both recruit and retain participants. Examination of this final strategy demonstrated a positive correlation between the magnitude of incentive and retention rates.[466] Strategies to optimise recruitment and retention were employed in the current study, including a consistent contact person from ICU admission to the end of the studies and reminders for appointments. However, the use of a dedicated team to recruit and retain participants may have enhanced the sample size. Similarly, while reimbursement was offered for travel to and from the hospital, both for assessments and during participation in the EBRP, the use of additional financial incentives to participate may have improved recruitment. However, given the nature of this study being largely performed by a single person (PhD candidate), and the small amount of funding available to this program, neither a dedicated team nor additional financial incentives were feasible. In order to enhance recruitment and retention in longitudinal studies, multiple strategies should be considered as part of the protocol a priori. Utilisation of these strategies are likely to require additional funding.

5.4.3 Adherence to as well as tolerance and progression of the exercise-based rehabilitation program

Although a limited number of participants completed the EBRP, the frequent and detailed measures taken during each training session provides a unique insight into the adherence, tolerance and progression of these programs in those who choose to attend. Regarding adherence to the EBRP in the current study, both participants completed all sessions although for James, a previous planned holiday resulted in a 4-week hiatus in the middle of the program. Neither Annie or James completed the home exercise diary; Annie, because she found it difficult to remember, and no reason was given for James. Annie and James' adherence with the unsupervised training program is therefore unclear but likely to be poor.

Currently, there is no gold standard for the measurement of adherence to unsupervised home-based exercise. The majority of outcome measures used in the literature rely on patient self-report and are therefore susceptible to acquiescence and recall bias.[467,468] The reasons for the poor completion of the exercise diaries in the current study were not explored. The PhD candidate was blinded to group allocation for the planned RCT, and therefore was not in contact with the participants during the intervention or control period. However, barriers to adherence with the reporting of the unsupervised program may include the high incidence of cognitive dysfunction and mental fatigue that survivors of critical illness experience. Strategies to enhance adherence with performance and recording of any unsupervised components of an EBRP should be considered. These strategies may include prompts and engaging family members.[16,270] Novel approaches involving monitoring, coaching, education, and goal setting can also be accessed using a variety of technologies. These technologies include digital, mobile health and telehealth platforms,[469,470] and ensure all stakeholders are connected with the data in an accurate and timely manner. This is turn enables monitoring of the unsupervised elements of a program and subsequent remediation.

Regarding tolerance and progression, for Annie, the RPE and HR documented during exercise suggested both the interval and continuous cycling regimes were of moderate to high intensity. Specifically, the RPE ranged from 13 to 18 for the interval cycling and from 11 to 17 for the continuous cycling. The peak HR recorded

during the interval and continuous cycling sessions, when expressed as a proportion of the peak HR achieved by Annie during the ICET (166 bpm), ranged from 63 to 85% (HR 105 to 140 bpm) and 60 to 85% (HR 100 to 140 bpm), respectively.[471] Similarly, the peak HR recorded during the walking training, when expressed as a proportion of the peak HR achieved by Annie during the ICET (166 bpm), ranged from 67 to 86% (HR 112 to 142 bpm), with a gradual increase in the RPE (from 12 to 18) during the walking training, which constrained the rate of increase in walk·work. Based on the domains of intensity of exercise and physical activity defined by the ACSM's consensus guidelines, high intensity exercise was defined as achieving a peak HR, expressed as a percentage of that achieved during the ICET, of ≥ 77%.[230] Using this cut point for HR to define high intensity exercise, over 16 training sessions completed, Annie achieved high intensity exercise in 6, 3 and 12 of her interval, continuous and walking-based training sessions respectively. Annie achieved moderate intensity exercise, defined as 64 to 76% of the peak HR,[230] in 7, 11 and 4 of her respective training sessions. Regarding progression, the WR set for the cycle-based exercise increased more dramatically than the walk·work for the walking-based exercise. One possible reason for this was that during each training session, cycle exercise preceded walking exercise. Therefore, it is also possible that the limited increase in the intensity of walking-based exercise, reflected a fatigue response that followed the high intensity cycling training.

For James, the RPE and HR documented during exercise suggested both the interval and continuous cycling regimes were of a lower intensity than that achieved by Annie. The RPE ranged from 7 to 14 for the interval cycling and from 6 to 12 for the continuous cycling. The peak HR recorded during the interval and continuous cycling sessions, when expressed as a proportion of the peak HR achieved by James during the ICET (158 bpm), ranged from 49 to 82% (HR 78 to 130 bpm) and 51 to 75% (HR 81 to 118 bpm), respectively.[471] The peak HR recorded during the walking training, when expressed as a proportion of the peak HR achieved by James during the ICET (158 bpm), ranged from 54 to 75% (HR 85 to 118 bpm). In contrast to Annie, the walk·work was progressed as James' RPE remained quite low (6 to 12). When the same criteria for high and moderate intensity exercise were applied to James' training data,[230] he achieved high intensity exercise in 3 of the interval cycling training sessions, one of the continuous cycling training sessions and 2 of the

walking training sessions. James achieved moderate intensity in 10, 13 and 12 of the respective training sessions. It is notable that James reported lower symptoms and achieved a lower heart rate response during exercise. Although it is possible that this was due to differences in the therapist's approach to training, this seems unlikely as the same therapist trained both Annie and James and used the same criteria for progression across both participants. The low symptoms scores may reflect that James was a 'poor perceiver' and was unable to consistently grade sensations using numerical scales or had decreased sensitivity to internal sensations (limited interoceptive accuracy).[472-474] However, this seems unlikely as the lower symptom scores were accompanied by a lower heart rate response during exercise. Perhaps the most likely reason was that James was less willing to attempt high intensity exercise, despite encouragement to do so.

The importance of intensity exercise on optimising the training response in ICU survivors is unknown. Nevertheless, earlier studies that have explored the effect of providing EBRPs after hospital discharge in survivors of critical illness that have prescribed moderate intensity exercise have shown no effect on physical functioning outcomes.[25-30] Although these results might be due to a number of factors, such as the inclusion of participants with minimal impairment, lack of supervision and poor adherence with the program, it does raise the possibility that the moderate training intensity is inadequate to induce meaningful training related responses. Notably, high intensity exercise has resulted in additional benefits when compared with moderate intensity exercise in other populations.[48,475,476]

The data presented in the current study show that despite the close supervision of training load, symptoms and cardiorespiratory responses, high intensity exercise was not consistently achieved across all types of aerobic exercise in each training session. This suggests that achieving high intensity aerobic exercise will be challenging in clinical practice, when the therapist:patient ratio is less favourable than it was in this study. It also suggests that future studies in the area of high intensity exercise training in this patient population will need to consider applying for funding to support a high therapist:patient ratio. Notwithstanding these challenges, the data in the current study showed that moderate to high intensity training, when achieved by these participants, was not associated with any evidence of adverse events and

induced minimal arterial oxygen desaturation. Larger numbers are needed to confirm if moderate to high intensity training is safe.

5.4.4 Changes in outcome measures collected before and after the exercise-based rehabilitation program

Both Annie and James demonstrated increases in peak VO_2 (+5.17 and +5.01 mL/kg/min, respectively). In both participants, the exercise training conveyed positive benefits in cardiovascular fitness irrespective of their baseline fitness, acuity of illness or comorbidities. These increases in peak VO_2 exceeded those previously reported during natural recovery over 8 weeks following discharge from ICU of 2.1 mL/kg/min.[27] Similarly, the increase in peak VO_2 demonstrated by both Annie and James greatly exceeded the change seen in the control participants, for whom the change peak VO_2 ranged from -0.1 to 2.5 mL/kg/min (Appendix 14). Although the threshold for a minimal clinically importance difference in peak VO_2 in ICU survivors has not been reported, earlier work has demonstrated that in a cohort of 6,213 men, an increase in peak VO_2 of 3.5mL/kg/min corresponded with a 12% improvement in survival at 6.2 ± 3.7 years following performance of the test.[477] If this criterion is applied to the change seen in the current study, then both Annie and James appeared to have achieved an improvement in peak VO_2 that is likely to be clinically meaningful. Further, a peak VO_2 of less than 20mL/kg/min[181] has been suggested to indicate the threshold at which physical function becomes suboptimal and where assistance with activities of daily living may be required.[179-181] On completion of EBRP, the peak VO_2 of both Annie and James exceeded this value.

Regarding the change in AT, consistent with the large increase in peak VO_2, Annie also demonstrated a large increase in AT (+5.60 mL/kg/min). The magnitude of this change exceeded that previously reported during an 8-week period of natural recovery following discharge from ICU of 1.20 mL/kg/min.[27] It was also greater than the range in changes observed in the control participants over the same time period (0.18 to 0.25 mL/kg/min). Nevertheless, the increase in AT observed for James (+1.15 mL/kg/min) was small and within the scope of what might be expected as a result of natural recovery. This result may be related to a multitude of factors which cannot be elucidated as part of a case report. However, they include the lower intensity of exercise with which James engaged during the EBRP, the structure of

skeletal musculature specifically related to progenitor cells, older age and greater APACHE II score reflecting both a greater number of comorbidities and higher acuity of illness on admission.[48,114,287,478] The degree to which survivors of critical illness respond to exercise training, and why some respond and some do not, is a relevant and topical question which requires further research.[287] Notwithstanding the difference in both exercise intensity, progression and the difference in physiological response to the prescription, both Annie and James, during the ICET performed on completion of the EBRP, demonstrated no ventilatory reserve defined as < 15L/min, which is consistent with a trained response (-2.7 and 9.7 L/min respectively).

The majority of studies previously published investigating the effect of exercise training implemented after discharge from hospital in survivors of critical illness have reported no effect on various physical outcomes.[25-30] Two studies have reported the AT and VO_2.[27,38] McWilliams et al[27] reported no effect on AT and peak VO_2 of an EBRP consisting of 3 20 minutes sessions (one supervised) each week over 7 weeks. Another study by Batterham et al,[38] showed that compared with a usual care group, those that received a training program consisting of 2 supervised sessions per week of moderate intensity exercise demonstrated a small advantage in AT on the completion of the exercise program (exercise vs. control, 10.7 ± 17 vs. 12.5 ± 13 mL/kg/min, respectively). This advantage, however, was no longer evident when AT was measured in both groups again 4 months later (exercise vs. control 12.1 ± 20 vs. 12.7 ± 18 mL/kg/min, respectively). Further, in this earlier study, there was no between-group difference in peak VO_2 at either time point following completion of training.[38] This earlier study suggests that an EBRP implemented after hospital discharge has little benefit on physical fitness over and above natural recovery. Interestingly, compared these earlier studies that demonstrated no improvement in peak VO_2 on completion of an EBRP,[27,38] the change observed in peak VO_2 for both Annie and James was substantial (+5.17 and +5.01 mL/kg/min). As mentioned earlier, this may be related to the higher intensity of exercise prescribed to the participants in the current study. However, other factors that may have served to optimise the training response observed in the current study include both: (i) individualised prescription of intensity based on objective measures of exercise capacity; and (ii) the preponderance of supervised versus unsupervised exercise training sessions. That is, both previous studies have based prescription of exercise

intensity on symptoms only[27,38] and have offered less supervision of the exercise training sessions. The cognitive deficits reported in this population and evidenced by Annie forgetting to complete the home exercise diary, means that unsupervised exercise training may be ineffective.[29]

Although on completion of the EBRP, there was a notable increase in the AT for Annie and the peak VO_2 for both Annie and James, the change in the other outcomes was less consistent. Specifically, James demonstrated improvements in all functional outcomes, which is consistent with the proposed benefits of exercise training such as improved cardiovascular fitness, greater strength, greater participation in physical activity, and improvement in perception of physical function with less fatigue.[48,475,476,479] However, the pattern of response for Annie was not the same. While Annie's participation in the EBRP increased time spent in LPA and decreased ST, lower limb strength decreased, her perception of her physical function declined, and the proportion of time spent in ST that was accumulated in prolonged bouts increased. One interpretation of Annie's response is that is consistent with over-training and that intensity of exercise that Annie engaged in led to exercise-induced oxidative stress and impaired skeletal muscle contractility and excessive physical fatigue.[480,481] However, Annie's levels of fatigue, measured using the FSS improved at the end of training and over-training to an extent that it causes detrimental effects is also associated with worsened mental health/mood which was not the case for Annie.[482] It is possible that a difference in pre-ICU levels of functioning between by James and Annie may also explain the difference in functional outcomes. While pre-admission comorbidities may impair the response to an EBRP in survivors of critical illness,[287] in James' case, the respiratory comorbidity which went undiagnosed and unmanaged in the 12 months prior to his ICU admission, and which eventually led to the ICU admission, may have been improved by the treatment received during the critical illness. Further, prior to commencing the EBRP, when compared with Annie, James demonstrated greater impairment in peak VO_2, lower participation in LPA and MVPA, and high levels of ST both in absolute terms and as accumulated in prolonged bouts ≥ 30 minutes. The more profound limitation demonstrated by James may have reflected a greater capacity to improve. That is, for Annie, the high level of pre-morbid function coupled with the modest level of impairment following discharge from the ICU curtailed the capacity for improvement in some outcomes

(i.e. a ceiling effect). Further research is needed to identify the characteristics that are associated with a positive response to exercise training across all outcomes in the population.

5.4.5 Conclusion and clinical implications

This study aimed to implement a high intensity exercise program in people surviving an admission to ICU with a diagnosis of ALI. The recruitment of participants into the current study was suboptimal. However, the retention of participants in the intervention group once they commenced the program was high. Recruitment and retention of people surviving a critical illness to studies addressing outcomes after hospital discharge is a recognised challenge.[60,288,483] The high retention in the participants in the current study is likely due in part to the specific prescription based on objective measures of performance and the close supervision provided by the same physiotherapist. However, the need to attend a healthcare centre for measurement of outcome or delivery of intervention has been identified as a barrier to participation for some survivors of ICU.[483] Unsupervised exercise training which can be performed within the home has subsequently been used to overcome this barrier, but appears to compromise effectiveness.[30,31,483]

The current study has demonstrated that in 2 participants an EBRP consisting of moderate to high intensity training was safe and likely to convey optimal physiological gains in exercise capacity.[48,475,476] However, supervision during a high intensity exercise based intervention is strongly advocated to optimise adherence. Further, the inconsistent achievement of high intensity exercise across all types of aerobic exercise in each training session suggests that high therapist:patient ratios may be required. Novel patterns of supervised delivery of a high intensity EBRP may include: (i) allowing for participant nomination of exercise mode preference while still maintaining the intensity load throughout the sessions; (ii) provision of a rest period mid program which may minimise the risk of fatigue; and (iii) the use of telehealth to provide supervision. Irrespective of the pattern of program delivery, monitoring for fatigue should be included. When prescribing unsupervised exercise, given the cognitive deficits reported in previous literature and the participants in the current study not completing the unsupervised exercise diaries, prompts and family member engagement should be considered to enhance adherence.

In the 2 participants, the program elicited an increase in peak VO_2 which exceeded that expected as part of natural recovery, was clinically meaningful, and which has not been demonstrated previously in large intervention studies examining the effect of exercise in survivors of critical illness after hospital discharge.[25-30] The effect of the EBRP on the remaining outcomes reported were inconsistent. However, the baseline functioning measured prior to the EBRP is also likely to have contributed to the response to the EBRP.[287] Further study is required to identify the factors that contributed to the varied response observed in the 2 participants reported in this study, and what is likely a reflection of the variance in response in the larger population of survivors of critical illness.

Finally, although low levels of PA and high ST may be improved using supervised exercise training in healthy adults, specific behavioural strategies have demonstrated benefit and should be considered where the specific aim is to increase time spent in PA and decrease ST.[484]

CHAPTER 6 Summary and conclusions

6.1 Overview

The aim of this research was to examine the physical function of survivors of acute lung injury (ALI) shortly after discharge from an intensive care unit (ICU) and also after discharge from acute care, and to examine the adherence to and effect of a high intensity exercise-based rehabilitation program (EBRP) performed 8 weeks after hospital discharge, on physical function.

This chapter summarises the novel findings of this research. The implications of these findings for clinical practice and future research are discussed.

6.2 Study 1

Both survivors of ALI and a general population of critical illness survivors exhibited profound impairments in peripheral muscle strength, balance, walking speed, and functional exercise capacity when assessed within 7 days of discharge from ICU to the ward. When comparing these 2 participant groups, the survivors of ALI exhibited greater impairments in shoulder flexion and grip strength, maximal walk speed and 6-minute walk distance (6MWD). However, the hypothesis that all of the measures would be more profoundly impaired in the ALI survivors was not proven, with knee and elbow flexion and balance being similar between the groups. Nevertheless, these data highlight the need for rehabilitation in critical illness survivors. They also suggest that ward-based physiotherapists who may choose to manage a busy caseload by triaging according to the magnitude of deficits, should prioritise those who have survived an ICU admission for ALI.

Undertaking a 6-minute walk test (6MWT) shortly after discharge from ICU, using specific criterion for enforced rests, was both feasible and safe. All participants who remained in hospital for 7 days following ICU discharge completed the 6MWT. Four participants with ALI and 2 participants with critical illness were unable to stand and/or ambulate. Three participants with ALI and 3 participants with critical illness were subject to an enforced rest due to arterial oxygen desaturation below 85% as

identified a priori. There were no other adverse events observed. Further, the data confirmed the hypothesis that the 6MWD measured on the hospital ward would provide information regarding both hospital length of stay (LOS) and discharge destination. Specifically, a 6MWD < 100m was suggestive of a ward LOS > 2weeks and discharge to another care facility. These findings have the potential to enhance discharge planning and guide expectations of recovery for both the patients and their carers. Notwithstanding these findings, it is notable that undertaking the 6MWT shortly after discharge from ICU on the ward can be challenging for the clinician. Of the participants with ALI and critical illness 9% and 17% used walking aids, 5% and 5% ambulated with supplemental oxygen, and 8% and 11% required a rest, respectively. For this reason, this study also explored the relationship between the less burdensome assessment of maximal walk speed, determined using the 10-meter walk speed (10MWS), and 6MWD. Although these measures were associated, the hypothesis that the 10MWS would explain more than 50% of the variance in 6MWD was not proven as demonstrated as the coefficient of determination was only 4.9%.

6.3 Study 2

People surviving an admission to an ICU with ALI who completed measures 6 weeks after hospital discharge, when compared with a similar healthy group, demonstrated a marked reduction in submaximal exercise responses and peak exercise capacity as determined using an incremental cycle ergometry test. These findings confirm the first hypothesis related to submaximal and peak exercise responses when compared with healthy individuals. The mechanism of this impairment was related to deconditioning, and impaired pulmonary diffusion which were hypothesised to be the only contributors to the impairment. However, a further mechanism of impairment was also identified, that of cardiac dysfunction. Deconditioning was an expected contributor to the impaired exercise capacity in the participants with ALI and likely related to mechanical unloading and factors related to the critical illness.[71,130,407-415] Impaired pulmonary diffusion, while evident was unlikely to have contributed greatly to the impairment. Clinicians should have a high level of suspicion of cardiac dysfunction in those who survive an admission to ICU with ALI and demonstrated impairment in exercise capacity. Future research is required to identify the optimal prescription of whole-body rehabilitation to

ameliorate these physical impairments, both during the ICU admission and after discharge to the ward and home.

Survivors of ALI also participated in lower levels of physical activity (PA), accumulated greater sedentary time (ST) and had reduced peripheral muscle strength, worse health related quality of life and higher levels of fatigue. These findings confirm the second of the hypotheses. While improvements in exercise capacity may affect the accumulation of PA and ST, investigation of specific interventions with the aim to change these outcomes is required. Finally, when assessed 6 weeks following discharge, this study demonstrated an improvement in the 6MWD with test repetition. The magnitude of the difference between the 2 6MWDs exceeded the minimally important difference for this outcome (20 to 30m).[203] Therefore, these data support the need for 2 6MWTs to be performed in survivors of a critical illness when assessed following hospital discharge.

6.4 Study 3

Recruitment of participants into a high intensity EBRP implemented after discharge from hospital was suboptimal but is an acknowledged difficulty in the literature.[60,171,463,465] Retention of the participants within the study however was excellent. Close supervision and specific exercise prescription based on objective measures of performance are likely to have contributed to this and should be employed to optimise retention. Adherence with unsupervised exercise may be low, due in part to the high incidence of cognitive impairment following a critical illness.[16,270] This highlights the importance of clinicians using strategies to optimise adherence such as frequent reminders and asking family members to prompt.

Achieving high intensity exercise during an EBRP was challenging. A high therapist:patient ratio may be required to enhance the adherence to a high intensity EBRP in survivors of critical illness. Notwithstanding this, the data in this study showed that moderate to high intensity training was not associated with any evidence of adverse events suggesting that high intensity training is likely to be safe.

Furthermore, in both participants examined, the EBRP increased peak exercise capacity to an extent that exceeded that expected as part of natural recovery. The magnitude of this increase was also likely to be clinically meaningful and such

improvements have not been demonstrated previously in large intervention studies examining the effect of exercise in survivors of critical illness after hospital discharge.[25-28,30,38,39] The effect of the EBRP on the remaining outcomes reported however were inconsistent. Future research is required to examine the effect of a supervised high intensity EBRP in survivors of critical illness via large multicentre trials.

6.5 Translation to current practice and future research

At the commencement of this program of research, the accepted definition for ALI was that published by the American and European Consensus Conference (AECC) in 1994.[1] This definition was used for participant inclusion into the ALI group and was maintained throughout recruitment to ensure consistency. It is acknowledged that the term ALI is no longer used in current practice, with the Berlin definition being introduced into clinical practice in 2012.[3] Notably, the Berlin definition eliminated the term ALI. The criterion for ARDS according to the AECC and the Berlin definitions however are broadly the same.[1,3] Both ALI (AECC) and ARDS (Berlin) are defined by acute onset, profound hypoxaemia ($PaO_2/FiO_2 < 300$ mmHg), bilateral opacities on chest x-ray and no evidence of left atrial hypertension. The changes in the Berlin definition included categorisation of ARDS according to severity of hypoxaemia and eliminating the term ALI and clarified elements of the original Berlin criterion, for example, the time frame used for 'acute onset' was specified as 7 days. In order to explore whether or not this change in diagnostic criteria would have affected the potential eligibility of participants in these studies, participant data used for inclusion into the ALI group was reviewed and used to identify those who met the criterion for ARDS, including the severity types, as per the Berlin definition.[3] This analysis is presented in Appendix 16 and confirms that all participants met the criteria for ARDS as per the Berlin definition and demonstrates that a large proportion of participants met the criteria for moderate or severe ARDS in Study 1 (n [%]) 19 [86%]) and Study 2 (9 [90%]). In a recent international prospective study carried out in 459 ICUs across 50 countries, the proportion of patients diagnosed with moderate or severe ARDS in a 4 weeks period was 70% (moderate ARDS 47% and severe ARDS 23%) suggesting that the sample in the current study presented with a higher severity of illness than what might be expected.[87]

This body of research demonstrates that physical function as measured by strength, exercise capacity, walk speed and balance are impaired in both survivors of ALI and survivors of other critical illnesses. Importantly however, the extent of the impairments, specifically impairments in exercise capacity, walk speed and some measures of peripheral muscle strength were greater in survivors of ALI than that observed in survivors of other critical illnesses. This suggests, that while individual assessment of function is advocated, provision of rehabilitation for those surviving ALI should be a priority within an ICU rehabilitation caseload.

The physiological cause of the differences in physical function between the 2 groups, however, is unclear and requires further investigation. Given the similarities in the ALI and critical illness groups related to age, sex, preadmission comorbidities, acuity of illness and lung function, it is possible that the differences exist at the level of peripheral muscle morphology and biochemistry which may be related to the cascade of dysregulated inflammation[75,78] and release of harmful mediators[79] inherent in ARDS/ALI. Peripheral muscle dysfunction leading to deconditioning was further evident in the ICET results in Study 2. Future directions in research should explore the physiological differences in peripheral muscle structure using muscle biopsies and scanning techniques although ethical considerations regarding invasive investigations employed in a vulnerable patient population is acknowledged.[485] Greater understanding of the physiological effects of critical illness and ALI on muscle structure and function may inform management within the ICU and exercise-based interventions after ICU and hospital discharge.

There is a paucity of literature examining the optimal management of impaired exercise capacity and strength in survivors of critical illness as experienced after ICU discharge and prior to hospital discharge. Further, the effective prescription of exercise with the aim to elicit physiological change after hospital discharge is unknown. In people living with COPD, the 6MWT is used to prescribe walking programs.[361] The 6MWT is an objective measure of functional exercise capacity,[331] and in survivors of ICU has been demonstrated to be safe and feasible when performed immediately after ICU discharge and following hospital discharge. The 6MWD in the current study has been demonstrated to provide information regarding discharge destination. The use of the 6MWD to optimise exercise prescription in this

group should also be explored. Further, exploration of methods to increase time spent in PA and reduce ST in survivors of critical illness should be undertaken, specifically related to how increasing exercise capacity and strength may impact participation in PA and ST.

Greater understanding of the impairment survivors experience after an admission to ICU is needed. Knowledge related to the physiological factors contributing to these impairments, specifically related to the differences between survivors of ALI and critical illness, should be explored further.

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Appendix

Appendix 1 Approval to conduct the research from the Hunter New England Local Health Network

- with reciprocal approval from The University of Newcastle Human Research Ethics Committee

NSW GOVERNMENT Health
Hunter New England
Local Health Network

27 January 2011

Ms Jenny Mackney
Lecturer in Physiotherapy
School of Health Sciences
University of Newcastle

Dear Ms Mackney,

Re: Acute Lung Injury: Evaluating and improving functional outcomes in survivors (10/11/17/4.06)

HNEHREC Reference No: 10/11/17/4.06
NSW HREC Reference No: HREC/10/HNE/333

Thank you for submitting the above protocol for single ethical review. This project was first considered by the Hunter New England Human Research Ethics Committee at its meeting held on **27 January 2011.** This Human Research Ethics Committee is constituted and operates in accordance with the National Health and Medical Research Council's *National Statement on Ethical Conduct in Human Research (2007)* (National Statement) and the *CPMP/ICH Note for Guidance on Good Clinical Practice*. Further, this Committee has been accredited by the NSW Department of Health as a lead HREC under the model for single ethical and scientific review. The Committee's Terms of Reference are available from the Hunter New England Area Health Service website: http://www.hnehealth.nsw.gov.au/Human_Research_Ethics.

I am pleased to advise that following acceptance under delegated authourity of the requested clarifications and revised Information Statements by Dr Nicole Gerrand Manager, Research Ethics & Governance, the Hunter New England Human Research Ethics Committee has granted ethical approval of the above project.

The following documentation has been reviewed and approved by the Hunter New England Human Research Ethics Committee:

- For the ALI Participant Information Statement (Version 2 dated 9 December 2010);
- For the ALI Participant Next of Kin Information Statement (Version 2 dated 9 December 2010);
- For the Critical Illness Participant Information Statement (Version 2 dated 9 December 2010);
- For the Participant Next of Kin (Critical Illness) Information Statement (Version 2 dated 9 December 2010);

Hunter New England Research Ethics & Governance Unit

(Locked Bag No 1)
(New Lambton NSW 2305)
Telephone (02) 49214 950 Facsimile (02) 49214 818
Email: hnehrec@hnehealth.nsw.gov.au
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- For the Participant Healthy Control Information Statement (Version 2 dated 9 December 2010);
- For the ALI Participant Consent Form (Version 1 dated 25 October 2010);
- For the Participant Next of Kin Consent Form (Version 1 dated 25 October 2010);
- For the Participant Next of Kin (Critical Illness) Consent Form (Version 1 dated 25 October 2010);
- For the Critical Illness Participant Consent Form (Version 1 dated 25 October 2010); and
- For the Healthy Control Consent Form (Version 1 dated 25 October 2010);
- For the Data Collection Form (Version 1 dated 25 October 2010);
- For the Berg Balance Scale;
- For the Subject Number: R 6MWT Data Form;
- For the Subject Number: Peripheral Muscle Strength Form; and
- For the Fatigue Severity Scale

For the protocol: **Acute Lung Injury: Evaluating and improving functional outcomes in survivors**

Approval has been granted for this study to take place at the following sites:

- **John Hunter Hospital**
- **Calvary Mater Newcastle**

Approval from the Hunter New England Human Research Ethics Committee for the above protocol is given for a maximum of **3** years from the date of this letter, after which a renewal application will be required if the protocol has not been completed.

The *National Statement on Ethical Conduct in Human Research (2007)*, which the Committee is obliged to adhere to, include the requirement that the committee monitors the research protocols it has approved. In order for the Committee to fulfil this function, it requires:

- a report of the progress of the above protocol be submitted at 12 monthly intervals. Your review date is **January 2012.** A proforma for the annual report will be sent two weeks prior to the due date.

- A final report be submitted at the completion of the above protocol, that is, after data analysis has been completed and a final report compiled. A proforma for the final report will be sent two weeks prior to the due date.

- All variations or amendments to this protocol, including amendments to the Information Sheet and Consent Form, must be forwarded to and approved by the Hunter New England Human Research Ethics Committee prior to their implementation.

- The Principal Investigator will immediately report anything which might warrant review of ethical approval of the project in the specified format, including:

    - any serious or unexpected adverse events
        - Adverse events, however minor, must be recorded as observed by the Investigator or as volunteered by a participant in this protocol. Full details will be documented, whether or not the Investigator or his deputies considers the event to be related to the trial substance or procedure. These do not need to be reported to the Hunter New England Human Research Ethics Committee

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- Serious adverse events that occur during the study or within six months of completion of the trial at your site should be reported to the Manager, Research Ethics & Governance, of the Hunter New England Human Research Ethics Committee as soon as possible and at the latest within 72 hours.

- All other safety reporting should be in accordance with the NHMRC's Safety Monitoring Position Statement – May 2009 available at http://www.nhmrc.gov.au/health_ethics/hrecs/reference/_files/090609_nhmrc_position_statement.pdf

- Serious adverse events are defined as:

  - Causing death, life threatening or serious disability.
  - Cause or prolong hospitalisation.
  - Overdoses, cancers, congenital abnormalities whether judged to be caused by the investigational agent or new procedure or not.

- unforeseen events that might affect continued ethical acceptability of the project.

- If for some reason the above protocol does not commence (for example it does not receive funding), is suspended or discontinued, please inform Dr Nicole Gerrand, as soon as possible.

You are reminded that this letter constitutes ethical approval only. You must not commence this research project at a site until separate authorisation from the Chief Executive or delegate of that site has been obtained.

A copy of this letter must be forwarded to all site investigators for submission to the relevant Research Governance Officer.

Should you have any concerns or questions about your research, please contact Dr Gerrand as per her details at the bottom of the page. The Hunter New England Human Research Ethics Committee wishes you every success in your research.

Please quote **10/11/17/4.06** in all correspondence.

The Hunter New England Human Research Ethics Committee wishes you every success in your research.

Yours faithfully

[redacted]

For: Dr M Parsons
Chair
Hunter New England Human Research Ethics Committee

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Appendix 2 Approval to conduct the research from Curtin University

Curtin University

Memorandum

To	Dr Kylie Hill, School of Physiotherapy
From	A/Professor Stephan Millett, Chair, Human Research Ethics Committee
Subject	Protocol Approval **HR 27/2011**
Date	18 February 2011
Copy	Ms Jenny Mackney, School of Physiotherapy Dr Sue Jenkins, School of Physiotherapy Dr Ken Havill, Director, Intensive Care, John Hunter Hospital, Graduate Studies Officer, Faculty of Health Sciences

Office of Research and Development

Human Research Ethics Committee

TELEPHONE 9266 2784
FACSIMILE 9266 3793
EMAIL hrec@curtin.edu.au

Thank you for your application submitted to the Human Research Ethics Committee (HREC) for the project titled "***Acute Lung Injury (ALI): Evaluating and improving functional outcomes in survivors***". The Committee notes the prior approval by Hunter New England Human Research Ethics Committee (HNEHREC Ref No: 10/11/17/4.06, HREC Ref: HREC/10/HNE/333, SSA Ref: SSA/10/HNE/382.) and has reviewed your application consistent with Chapter 5.3 of the *National Statement on Ethical Conduct in Human Research*.

- You have ethics clearance to undertake the research as stated in your proposal.
- The approval number for your project is **HR 27/2011.** *Please quote this number in any future correspondence.*
- Approval of this project is for a period of twelve months **18-02-2011** to **18-02-2012**. To renew this approval a completed Form B (attached) must be submitted before the expiry date **18-02-2012**.
- If you are a Higher Degree by Research student, data collection must not begin before your Application for Candidacy is approved by your Faculty Graduate Studies Committee.
- The following standard statement **must be** included in the information sheet to participants:
  This study has been approved by the Curtin University Human Research Ethics Committee (Approval Number HR 27/2011). The Committee is comprised of members of the public, academics, lawyers, doctors and pastoral carers. Its main role is to protect participants. If needed, verification of approval can be obtained either by writing to the Curtin University Human Research Ethics Committee, c/- Office of Research and Development, Curtin University, GPO Box U1987, Perth, 6845 or by telephoning 9266 2784 or by emailing hrec@curtin.edu.au.

Applicants should note the following:

It is the policy of the HREC to conduct random audits on a percentage of approved projects. These audits may be conducted at any time after the project starts. In cases where the HREC considers that there may be a risk of adverse events, or where participants may be especially vulnerable, the HREC may request the chief investigator to provide an outcomes report, including information on follow-up of participants.

The attached **FORM B** should be completed and returned to the Secretary, HREC, C/- Office of Research & Development:
When the project has finished, or

- If at any time during the twelve months changes/amendments occur, or
- If a serious or unexpected adverse event occurs, or
- 14 days prior to the expiry date if renewal is required.
- An application for renewal may be made with a Form B three years running, after which a new application form (Form A), providing comprehensive details, must be submitted.

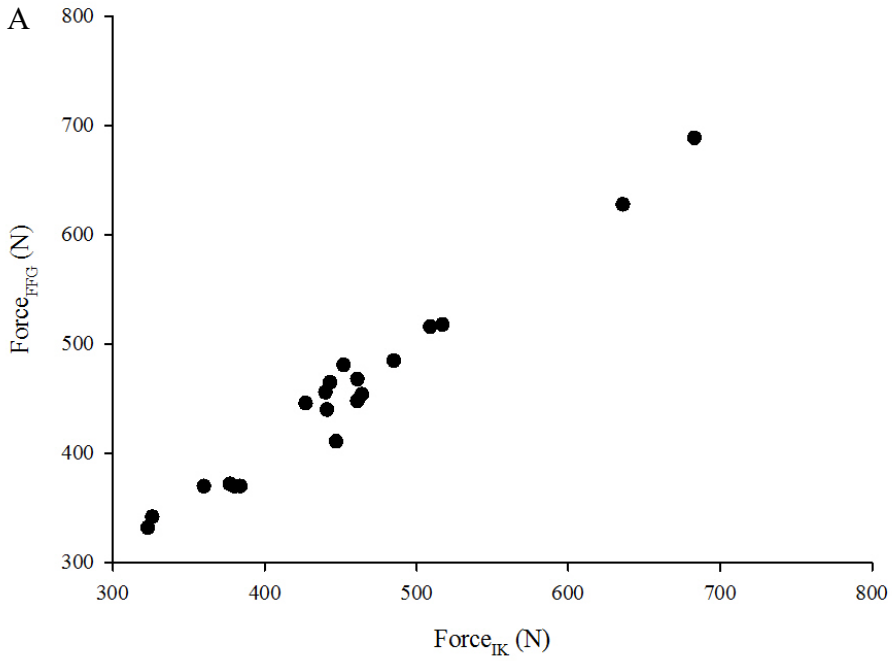
A/Professor Stephan Millett
Chair Human Research Ethics Committee

Appendix 3 Reference equations and normative values used to identify the predicted values for each participants knee extension, shoulder flexion and elbow flexion muscle strength (Study 1 and 2)

Muscle action	Equation	
	Female	***Male***
Knee extension (N)[156]	465.22 - 84.7 - (4.803 x age) + (0.325 x weight x 9.8)	465.22- (4.803 x age) + (0.325 x weight x 98)
Shoulder flexion (N)[155]	234.947 – 74.442 + (0.146 x weight x 9.8) – (1.718 x age)	234.947 + (0.146 x weight x 9.8) – (1.718 x age)
Elbow flexion (N)[156]	188.36 – 96.5 - (0.61 x age) + (0.14 x weight x 9.8)	188.36 – (0.61 x age) + (0.14 x weight x 9.8)
Grip[319]	Mean normative values for grip strength for sex and 5-year age ranges	

Age measured in years; weight measured in kg.

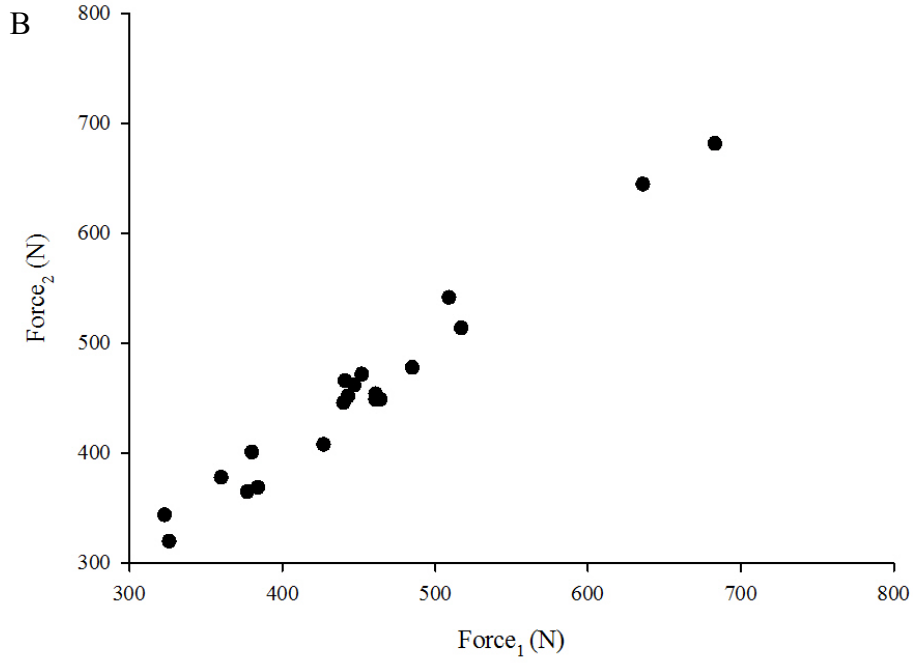
Appendix 4 Validity and intra-rater reliability of the custom-designed fixed force gauge used to measure knee extension strength (Study 1, 2 and 3)



(A) Force generated using the custom-designed fixed force gauge and the isokinetic machine for each participant (validity).

Force$_{FFG}$: force measured using the custom-designed fixed force gauge;
Force$_{IK}$: force measured using the isokinetic dynamometer.

A group of 20 healthy participants (8 male, age [mean ± SD] 22 ± 2 years) completed 3 isometric contractions for knee extension using their dominant leg, using the custom-designed fixed force gauge (FFG) (Mecmesin® BFG 1000, Mecmesin, West Sussex, UK) and an isokinetic dynamometer (IK) (Kinetic Communicator 500H, Chattecx Corp., Inc, Hixson, TN). Assessments were performed at the same assessment session allowing one-minute recovery between each of the 3 attempts on respective devices and 5 minutes recovery between the measurements using the FFG and the IK devices. The association between the measurements represented excellent validity with Spearmans rho (r_s) = 0.93, $p < 0.001$.



(B) Force generated using the custom-designed fixed force gauge as measured on 2 separate days by the same assessor for each participant (intra-rater reliability).

Force$_1$: force measured using the custom-designed fixed force gauge at the first assessment session; Force$_2$: force measured using the custom designed fixed force gauge at the second assessment session.

A group of 20 healthy participants (8 male, aged [mean ± SD] 22 ± 2 years) completed 3 isometric contractions for knee extension using their dominant leg, on the custom-designed FFG on 2 separate days with the same assessor. One-minute recovery was allowed between each of the 3 attempts. The association between the measures collected on the first and second day as measured by the same assessor represented excellent intra-rater reliability with $r_s = 0.93$, $p < 0.001$.

Appendix 5 Characteristics of participants with ALI and critical illness who did contribute vs. those who did not contribute data to the analyses (Study 1)

Outcome	Participant group (n included in analyses)	Age (yr) Male (n [%]) APACHE II	Participant group (n not included in analyses)	Age (yr) Male (n [%]) APACHE II	*p*-value
Overall recruitment	ALI (22)	50 [42 to 66] 10 [45] 10 [9 to 13]†	ALI (6)	39 [30 to 47] 5 [71] 8 [8 to 14]†	0.018 0.23 0.45
	Critical illness (33)	57 [52 to 63] 19 [58] 10 [8 to 12]	Critical illness (11)	60 [53 to 64] 6 [55] 11 [9 to 12]	0.82 1.00 0.27
Peripheral muscle strength	ALI (19)	52 [42 to 67] 8 [42] 22 [17 to 28]	ALI (3)	40 [42 to 42] 2 [67] 29 [18 to 29]	0.46 0.43 0.31
	Critical illness (27)	58 [52 to 66] 16 [59] 24 [17 to 34]	Critical illness (6)	55 [44 to 59] 3 [50] 15 [14 to 30]	0.19 0.68 0.26
Time to stand from supine	ALI (19)	48 [42 to 67] 9 [47] 22 [17 to 28]	ALI (3)	56 [40 to 56] 1 [33] 29 [21 to 29]	1.00 0.65 0.19
	Critical illness (22)	57 [51 to 63] 13 [59] 21 [15 to 32]	Critical illness (11)	58 [53 to 66] 6 [55] 25 [15 to 35]	0.36 0.80 0.48
6-minute walk test	ALI (21)	52 [42 to 67] 10 [48] 22 [17 to 28] vs.	ALI (1)	40 [40 to 40] 0 [0] 34 [34 to 34]	0.32 0.35 0.29
	Critical illness (28)	57 [52 to 64] 17 [59] 21 [15 to 33]	Critical illness (5)	58 [55 to 66] 2 [20] 27 [19 to 34]	0.50 0.39 0.50
10-metre walk test	ALI (16)	47 [42 to 64] 7 [44] 22 [17 to 28]	ALI (6)	61 [46 to 68] 3 [50] 24 [19 to 32]	0.22 1.00 0.48
	Critical illness (19)	58 [50 to 63] 10 [53] 19 [15 to 32]	Critical illness (14)	57 [53 to 66] 9 [64] 25 [15 to 34]	0.39 1.00 0.46

APACHE II: acute physiology and chronic health evaluation II; †: represents sequential organ failure (SOFA) assessment score. All data are median [IQR] unless specified.

Appendix 6 Data recorded in the participants who rested during the 6-minute walk test (Study 1)

Participant number	Number of rests	Time of onset of rest (*min:sec)*	Duration of rest *(min:sec)*	HR *(bpm) at onset of rest*	SpO_2 *(%) at onset of rest*	Dyspnoea *at onset of rest*	6MWD *(m)*
CIS3	1*	5:10	0:50	123	84	7	49
6	1	3:40	0:58	137	95	4	105
16	1	3:00	2:10	97	91	5	51
17	1	4:15	0:30	130	93	1	278
18	2	2:34	0:55	100	97	4	188
		5:04	0:41	103	95	4	
21	3	0:40	0:10	133	98	3	50
		1:45	2:16	133	97	5	
		4:50	1:10	135	96	7	
24	1*	4:38	0:22	120	77	3	372
29	1*	4:40	1:20	72	77	4	180
34	2	2:00	1:00	103	94	4	60
		4:40	1:20	111	96	3	
38	2	1:38	0:33	80	91	3	30
		5:40	0:20	79	93	3	
48	2	2:30	0:35	106	97	7	218
		4:42	0:50	98	98	8	
ALI 4	1	3:14	2:01	145	97	2	60
8	3	1:29	0:36	145	99	4	120
		4:00	1:00	142	95	7	
		5:30	0:30	142	99	7	
11	1*	1:50	4:10	125	80	0	60
12	1*	3:06	1:02	132	79	3	165
13	3	1:40	0:10	142	91	3	120
		3:08	0:17	144	91	3	
		5:10	0:50	145	90	3	
17	2*	1:35	2:25	103	83	5	47
		5:07	0:53	87	81	5	
24	2	2:115	1:17	132	91	7	120
		5:40	0:20	128	92	7	
33	2	1:10	1:25	106	89	3	180
		3:36	0:36	107	90	3	

HR = heart rate; SpO_2 = arterial oxygen saturation; *: enforced rest. Dyspnoea measured using the modified Borg scale.[24]

Appendix 7 Observations recorded before, during and after the 6-minute walk test in individual participants (Study 1)

Participant number	BP (systolic/diastolic mmHg)		HR (bpm)			SpO_2 (%)			Dyspnoea	
	Pre-test	End-test	Pre-test	Peak	Post-test	Pre-test	Nadir	Post-test	Pre-test	Post-Test
CIS 3	159/98	155/94	109	131	119	97	84	95	3	5
4	98/75	117/83	110	126	105	96	87	100	2	1
6	121/85	162/92	107	137	116	97	95	95	0	3
16	142/71	132/72	85	101	75	95	90	96	4	3
17	120/71	133/84	95	130	103	97	93	97	0	0
18	136/74	160/79	77	103	89	95	92	96	3	3
21	155/71	142/77	112	135	115	96	95	64	3	0.5
23	115/78	106/71	64	102	103	99	97	98	1	3
24	146/99	148/97	99	123	113	99	77	98	0	0.5
29	110/63	131/62	73	83	76	97	77	100	0.5	1
30	107/61	134/60	96	113	100	98	96	98	4	4
31	133/80	144/88	110	135	121	98	90	98	3	0
32	107/64	113/66	105	123	111	91	87	94	2	1
34	171/78	174/80	91	112	97	99	93	98	2	0.5
35	112/77	107/74	89	112	102	97	93	96	3	3
38	105/70	99/66	78	96	78	94	90	89	4	3
40	154/76	150/89	87	112	87	98	97	100	0.5	3
41	131/84	144/7	96	155	105	99	98	100	0	3
43	120/86	118/75	80	111	80	98	89	98	0.5	1
45	124/81	122/83	85	125	92	100	922	100	0	3
46	124/78	125/83	66	105	71	98	96	97	0	2
47	104/41	136/68	67	87	71	94	91	99	0	2
48	136/78	126/82	96	107	98	96	96	95	3	8
51	147/83	161/84	100	129	101	99	94	96	1	4
52	106/68	117/72	94	116	99	93	90	95	0.5	3

54	122/80	140/73	64	96	64	99	90	99	0	1
ALI 2	110/74	119/74	87	106	90	95	90	95	0.5	1
4	134/90	135/88	123	159	131	97	92	98	0.5	1
5	113/76	116/68	91	110	89	95	85	92	0.5	0.5
7	136/77	128/79	86	102	87	99	95	98	0.5	1
8	144/92	148/87	83	145	91	98	95	98	0.5	2
9	109/65	100/60	75	93	75	97	96	100	0	0
11	117/76	104/73	113	125	114	91	80	90	0	0
12	121/84	121/84	113	137	121	95	79	96	0.5	1
13	115/74	126/64	113	145	131	91	90	93	0.5	1
17	117/55	127/59	83	108	87	82	70	91	5	5
21	118/83	132/87	122	146	127	99	87	127	1	2
23	117/62	130/81	88	133	91	97	90	91	0	1
24	121/84	115/79	105	132	115	95	90	115	3	7
26	112/73	119/79	92	113	97	94	90	97	1	3
32	105/63	114/55	98	116	81	98	94	81	3	5
33	112/50	114/55	81	108	82	93	86	82	1	3
35	115/85	115/84	112	127	100	100	94	100	0	1

BP: blood pressure; HR: heart rate; SpO_2: oxygen saturation. Dyspnoea = measured using the modified Borg scale[24]

Appendix 8 Statistical testing of assumptions conducted prior to the exploration of the predictive ability of 6-minute walk distance for ward length of stay and discharge destination (Study 1)

The relationship between the intensive care unit (ICU) length of stay (LOS) and ward LOS was explored to assess the impact of the critical illness on the 6-minute walk distance (6MWD). A delineation within ICU LOS of < 14 days and > 14 days was chosen to examine the effect of prolonged versus shorter duration ICU admission on both 6MWD and ward LOS. This point of delineation was chosen due to the plateauing of the diminishing strength in peripheral muscles that appears to occur between 10 and 14 days during a prolonged ICU admission.[40] The proportion of participants with acute lung injury (ALI) and critical illness who had an ICU LOS of > 14 days was similar (30% vs. 29%, $p = 1.00$). The ward LOS was similar for the participants with ALI and critical illness (0.79). The ward LOS was also similar, when the ALI and critical illness participants were combined as one group, for those with an ICU LOS < 14 days and > 14 days ($p = 0.49$). When the relationship between the ICU LOS and ward LOS was examined for the groups combined, there was no relationship ($r_s = 0.13$, $p = 0.38$).

The 6MWD of the participants with ALI and critical illness, (considered separately) who had a ward LOS < 2 weeks was greater than the 6MWD of those who had a ward LOS > 2 weeks ($p = 0.036$ and $p = 0.008$ respectively). With the ALI and CI groups examined as one group, the median 6MWD of those who spent < 2 weeks on the ward was greater than those who spent > 2 weeks on the ward (265 [174 to 332] vs. 60 [15 to 221] m, $p = 0.02$).

When a cox regression analysis was performed using 6MWD and ICU LOS as predictors of ward length of stay, only the 6MWD significantly contributed to the model ($p = 0.006$) with ICU LOS not contributing any further to the ward LOS ($p = 0.95$).

Appendix 9 Reference equations used to identify the predicted values for respiratory function (Study 1, 2 and 3)

Variable	Equations	
	Female	***Male***
FEV_1[316]	3.95 x height/100 – 0.025 x age – 2.6	4.3 x height/100 – 0.029 x age – 2.49
FVC[316]	4.43 x height/100 – 0.026 x age – 2.89	5.76 x height/100 – 0.026 x age – 4.34
MVV	FEV_1 x 40	FEV_1 x 40
TLC[316]	6.6 x height/100 – 5.79	7.99 x height/100 – 7.08
FRC[316]	2.24 x height/100 + 0.001 x age – 1	2.34 x height/100 + 0.009 x age – 1.09
RV[316]	1.81 x height/100 + 0.016 x age – 2	1.31 x height/100 + 0.022 x age – 1.23
VC[316]	4.656 x height/100 – 0.026 x age – 3.28	6.1 x height/100 – 0.028 x age – 4.65
D_LCO[364]	0.256 x height – 0.144 x age – 8.36	0.416 x height – 0.219 x age – 26.34
MIP[365]	Exp (3.89 – 0.22 – 0.004 x age + 0.52 x √ [(height x weight)/3600])	Exp (3.89 – 0.004 x age + 0.52 x √ [(height x weight)/3600])
MEP[365]	Exp (4.48 – 0.18 – 0.004 x age – 0.003 x age + 0.25 x √ [(height x weight)/3600]	Exp (4.48 – 0.004 x age + 0.25 x √ [(height x weight)/3600]

ALI: acute lung injury; D_LCO: diffusion capacity of carbon monoxide; FEV_1: forced expiratory volume in one second; FRC: functional residual capacity; Hb: hemoglobin; IC: inspiratory capacity; MIP: maximal expiratory pressure; MEP: maximal expiratory pressure; MVV: maximal voluntary ventilation; RV: residual volume; TLC: total lung capacity; VC: vital capacity. Height measured in cm; age measured in years; weight measured in kg.

Appendix 10 Reference equations and normative values used to identify the predicted values for each participants' key physiological responses attained during the ICET (Study 2 and 3)

Physiological variable	Equation	
	Female	***Male***
Peak VO_2 (L/min)[368]	- 0.588 + 0.00913 x height + 0.0268 x weight – 0.01133 x age – 0.00012 x weight x weight	- 0.069 + 0.01402 x height + 0.00744 x weight + 0.00148 x age – 0.0002256 x age x age
AT (% of peak VO_2)[† 345]	44 – 48	42 – 48
Peak heart rate	210 – 0.65 x age	210 – 0.65 x age
Maximum work rate[369]	(204 x height – 8.74 x age – 288 - 1909) x 0.163	(20.4 x height – 8.74 x age – 1909) x 0.163
Peak O_2 pulse	(peak VO_2)/(peak heart rate)	(peak VO_2)/(peak heart rate)
Maximum VE[369]	(26.3 x VC) - 34	(26.3 x VC) - 34
Exercise breathing reserve	MVV – (max VE)	MVV – (max VE)
VE/VCO_2 @ AT[370]	27.9 + 0.106 x age – 0.0376 x age + 1	27.9 + 0.106 x age – 0.0376 x height
MVV[371]	FEV_1 x 40	FEV_1 x 40

AT: anaerobic threshold; ICET: incremental cycle ergometry test; MVV: maximal voluntary ventilation; max: maximum; O_2 pulse: oxygen pulse; VC: vital capacity; VCO_2: rate of carbon dioxide production; VE: minute ventilation; VO_2: rate of oxygen uptake; @: occurring at; † lower 95% confidence limit (mean). Height measured in cm; age measured in years; weight measured in kg.

Appendix 11 Strategies employed to enhance participant recruitment

Participant recruitment and completion of outcome measures occurred between March 2011 and December 2014 and was completed solely by the PhD candidate.

Strategies implemented prior to commencing participant recruitment

First, the same person (i.e. the PhD candidate) was responsible for gaining consent and all aspects of data collection throughout the entirety of the research program. This person was well known within the ICUs of John Hunter Hospital (JHH) and Calvary Mater Newcastle (CMN), having previously been employed in the JHH ICU for a number of years at a senior level. She was also available to recruit participants every day of the week (including weekends) between 0700hr and 2000hr. This minimised the likelihood of recruitment opportunities being missed.

Second, the research team decided a priori that screening for this research would not rely on a formal documented diagnosis of ALI made by clinicians. The under recognition of ARDS by clinicians has been reported recently in an international prospective study carried out in 459 ICUs in 50 countries in 5 continents. Approximately 40% of patients with ARDS (as measured using the Berlin definition and an algorithm from data entered daily by a research representative at each centre) in the entire cohort remained undiagnosed by clinicians.[87] The under diagnosis of ARDS/ALI has been reported using the AECC definition also.[486] All patients who were admitted to the JHH and CMN hospitals were screened by a clinician daily and the candidate notified of any participants who met the criteria. Further clarification if needed regarding the presence of atrial hypertension as a cause of the pulmonary changes, was sought from the ICU staff specialist. The final decision regarding inclusion into the study was made by the research team. The diagnosis of ALI was not necessarily reflected in the patient notes.

Third, all contact with participants (and their families) were made by the same researcher (i.e. the PhD candidate). This ensured that contact was made by someone who had established rapport. Reimbursement for travel was offered to participants, and dates/times for assessments and the exercise-based rehabilitation intervention were flexible within the working week ie. Monday to Friday and 0800hr to 1700hr.

Strategies implemented after recruitment had commenced

Once it was clear that recruitment was going to be challenging, the study criteria (for Study 2 and 3) were widened.

That is, the inclusion criteria was widened to include those who required an admission to an ICU, with the primary diagnosis of community acquired pneumonia (CAP). Community acquired pneumonia was chosen in order to minimise the heterogeneity inherent in studying critically ill patients,[487] and optimising the homogeneity inherent to primary respiratory pathology requiring mechanical ventilation.

Specifically, the inclusion criteria for CAP comprised: (i) > 18 years of age (ii) had an admission to intensive care and requiring intubation and ventilation (iii) diagnosis of CAP as per the following: evidence of new infiltrates on chest x-ray and one major criteria (cough, sputum, temperature > 37.8°C) or two minor criteria (pleuritic chest pain, dyspnoea, altered mental status, or leukocyte count > 12000/μL).[488]

Unfortunately, this strategy did not enhance recruitment to Study 2/3. Those patients who were screened in the ICU's during the recruitment period, and who met the criteria for CAP also met the criteria for ALI. Of the 10 participants with ALI recruited to Study 2, half of those participants had a primary diagnosis of CAP (n=5). In spite of the widening of the inclusion criteria the sample size required for adequate power as identified a priori (n=21) was not achieved. Recruitment was ceased in December 2014 with an ALI participant sample of n=10 and a healthy participant sample of n=21.

Additional strategies considered (but not implemented) to enhance recruitment to Study 2 and 3

To further increase participant recruitment, it was considered to expand recruitment to sites outside of the Hunter, specifically Sydney. This was not implemented due to the extensive distance between Sydney and Newcastle (2.5 hours driving time) which would have made organisation, management of recruitment and data collection whilst ensuring protocol fidelity logistically impossible without additional funding.

Barriers to recruitment for Study 2 and 3

Recruitment to Study 2 was adversely impacted by a number of factors.

First, the incidence of ALI in the ICU populations of the JHH and the CMN hospitals was lower than the published incidence of ALI in Australia (3 vs. 86 per 100 000 person-years where ALI participants recruited over 4 years was n=99, estimated Hunter New England population was n=873 741).[88,489]

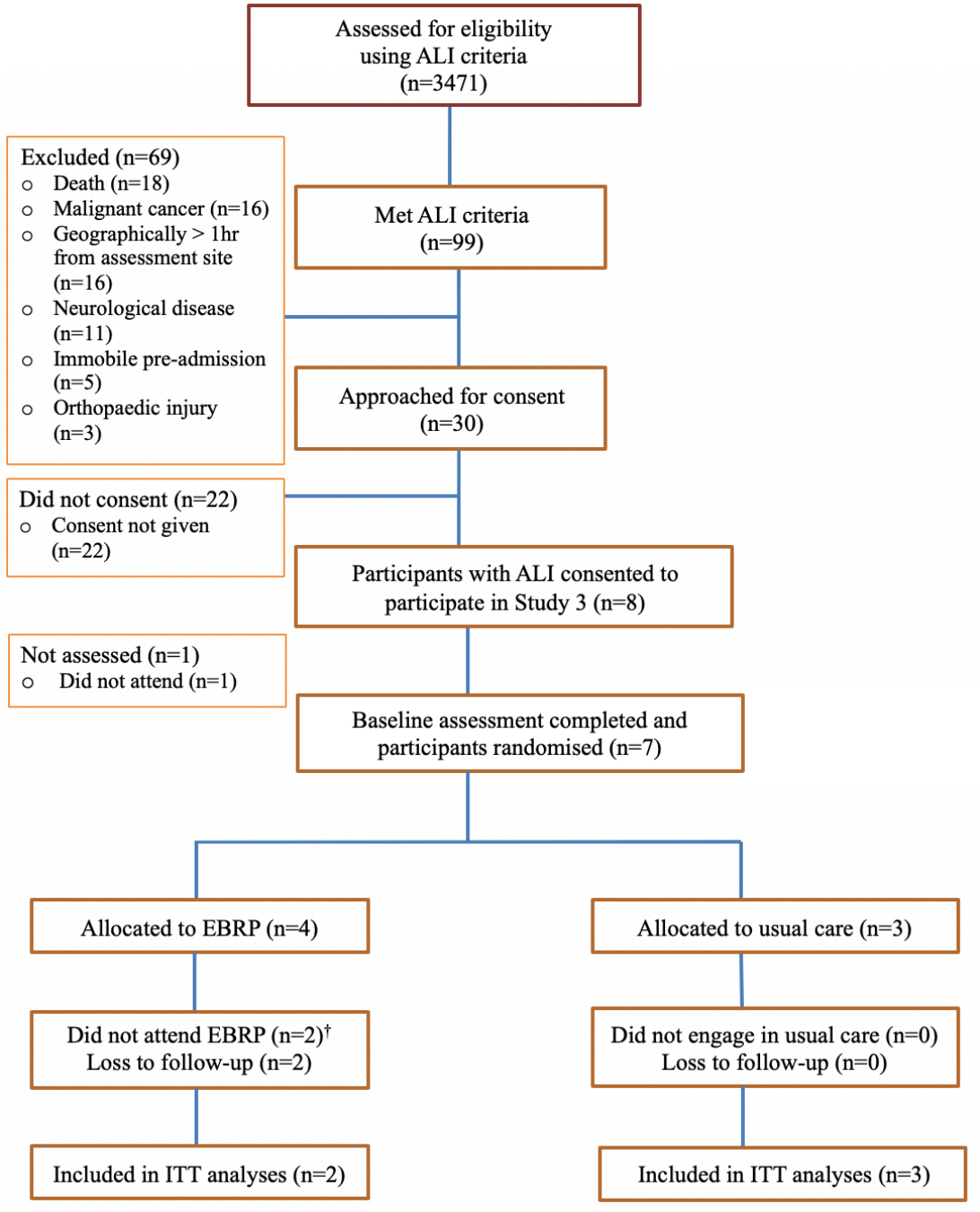
Second, participants were not prepared to return to John Hunter Hospital to participate in this study, after being discharged home. This is because some had returned to work, some had significant social issues (history of intravenous drug use), but people also cited that they did not want to be subject to more medical tests and/or wanted to 'get on with life'.

Appendix 12 Health-related quality of life domains: comparison between ALI participants proxy and ALI participants collected at 6 weeks after hospital discharge (Study 1 and 2)

Domain	ALI participant proxy (n = 10)	ALI participant (n = 10)	*p*-value
Physical functioning	45 [35 to 76]	53 [35 to 75]	0.81
Physical role	44 [23 to 63	34 [23 to 52]	0.49
Pain	22 [20 to 77]	32 [19 to 54]	0.69
General Health	52 [10 to 72]	39 [27 to 60]	0.23
Vitality	31 [27 to 53]	34 [25 to 50]	0.72
Social functioning	63 [34 to 75]	69 [47 to 75]	0.68
Emotional Role	50 [38 to 100]	46 [42 to 100]	0.90
Mental Health	63 [33 to 71]	65 [68 to 71]	0.18

Data are median [interquartile range]. Comparison of data conducted using paired samples Wilcoxon-signed rank test. ALI: acute lung injury.

Appendix 13 CONSORT diagram for the randomised controlled trial (Study 3)



ALI: acute lung injury; EBRP: exercise-based rehabilitation program; ITT: intensity to treat; †: reason for non-attendance not specified, participant did not respond to numerous attempts to contact the participant by the physiotherapist conducting the EBRP or by the candidate regarding the post-EBRP assessments.

Appendix 14 Exercise data for the control group, collected during the ICET measured before and after the intervention period (Study 3)

Measurement	Participant with ALI 1			Participant with ALI 4			Participant with ALI 8		
	Before	After	Change	Before	After	Change	Before	After	Change
Maximum work rate (W)	120	120	0	90	90	0	100	110	+10
Peak VO_2 (L/min)	2.04	2.17	+0.13	1.44	1.59	+0.15	1.35	1.52	+0.17
Peak VO_2 (mL/kg/min)	16.90	16.80	-0.1	14.1	14.3	+0.2	19.3	21.8	+2.5
AT (L/min)	1.10	1.30	+0.20	0.87	1.05	+0.18	0.75	1.0	+0.25
Peak heart rate (bpm)	146	149	+3	107	101	-6	167	176	+11
Peak O_2 pulse (mL/beat)	14.0	14.6	+0.6	13.5	15.7	+2.2	8.2	8.6	+0.4
Peak VE (L/min)	113.3	105.0	-8.3	59.2	59.0	+0.2	60.1	70.0	+9.9
Exercise breathing reserve (L/min)	30.7	42.6	+13.3	74.4	77	+2.6	26.5	22.8	-3.7
VE/VCO_2 @ AT or lowest	36.4	34.1	-2.3	32.2	29.2	-3.0	32.4	31.1	-1.3
Blood pressure (rest, peak) (mmHg)	140/-, 150/-	140/90, 160/84	-	110/60, 130/60	150/78, 180/90	-	127/75, 155/85	132/85, 170/90	-
Symptoms at test end (legs, dyspnoea) (Borg)	9†, 8	9†, 5	-	5†, 2	7†, 5	-	8†, 7	7†, 4	-

ALI: acute lung injury; AT: anaerobic threshold; ICET: incremental cycle ergometry test; O_2 pulse: oxygen pulse; VCO_2: rate of carbon dioxide production; VE: minute ventilation; VO_2: rate of oxygen uptake; WR: work rate; @: occurring at; †: limiting symptom to continuing ICET.

Appendix 15 Calculation of walk work on the treadmill using first principles (Study 3)

Walk work is defined by the equation: (distance walked [km] x force [N]) where force = body weight [kg] x gravity [m/s^2] x $\sin\theta$, and where θ is the angle of incline. Where there is a ramp incline, 2 vectors of force are acting upon the participant, therefore the equation to calculate walk work is: (distance walked [m] x body weight [kg] x 9.8 x sin90°) + (distance walked [m] x body weight [kg] x 9.8 x sin10°).

Appendix 16 Number of participants who met the criterion for ARDS according to the Berlin definition (Study 1, 2 and 3)

AECC definition for ALI[1]	**Berlin definition for ARDS[3] (n, %)**		
Study No. (n)	Mild	Moderate	Severe
Study 1 (22)	3 (14)	12 (54)	7 (32)
Study 2 (10)	1 (10)	7 (70)	2 (20)
Study 3 (2)	1 (50)	1 (50)	0 (0)

AECC: American and European Consensus Conference; ALI: acute lung injury; ARDS: acute respiratory distress syndrome.