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Short Title: Cardiorespiratory Fitness and CVD in RA

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Abstract

Objectives: This cross-sectional study investigated the association of different physical fitness levels (assessed by the maximal oxygen uptake (VO2max) test) with cardiovascular disease (CVD) risk factors in patients with rheumatoid arthritis (RA).

Methods: 150 RA patients were assessed for cardiorespiratory fitness with a VO2max test and based on this were split in three groups using the 33rd (18.1 ml.kg.min^{-1}) and 66th (22.4 ml.kg.min^{-1}) centiles. Classical and novel CVD risk factors (blood pressure, body fat, insulin resistance, cholesterol, triglycerides, high density lipoprotein-HDL, physical activity, C-Reactive Protein-CRP, fibrinogen and white cell count), 10-year CVD risk, disease activity (disease activity score 28-DAS28) and severity (health assessment questionnaire-HAQ) were assessed in all cases.

Results: Mean VO2max for all RA patients was 20.9±5.7 ml.kg.min^{-1}. Ten-year CVD risk ($p=0.003$), systolic blood pressure ($p=0.039$), HDL ($p=0.017$), insulin resistance and body fat (both at $p<0.001$), CRP ($p=0.005$), white blood cell count ($p=0.015$) and fibrinogen ($p<0.001$) were significantly different between the VO2max tertiles favouring the group with the higher VO2max levels. In multivariate analyses of variance, VO2max was significantly associated with body fat ($p<0.001$), HDL ($p=0.007$), insulin resistance ($p<0.003$) and 10-year CVD risk ($p<0.001$), even after adjustment for DAS28, HAQ and physical activity.

Conclusions: VO2max levels are alarmingly low in RA patients. Higher levels of VO2max associate with a better cardiovascular profile in this population. Future studies need to focus on developing effective behavioural interventions to improve cardiorespiratory fitness in RA.

Key messages

1. Cardiorespiratory fitness is alarmingly low in RA patients
2. Cardiovascular profile and 10-year CVD risk is worse in patients with low cardiorespiratory fitness
3. Cardiorespiratory fitness may be a good surrogate CVD marker in RA

Keywords: exercise, physical activity, cardiorespiratory fitness, cardiovascular disease, inflammation, rheumatoid arthritis, insulin resistance. body fat, cholesterol, risk factors

Introduction

Rheumatoid arthritis (RA) associates with an increased risk for cardiovascular disease (CVD) (1) attributed to both the deleterious effects of inflammation on the vasculature and to the increased prevalence of traditional CVD risk factors (2-5). Increased physical activity and/or exercise may associate with improved CVD risk profile in both healthy and diseased populations; this is indicated by the robust inverse relationship of CVD morbidity and mortality with cardiorespiratory fitness, as measured by the "gold standard" method, the maximal oxygen uptake (VO2max) test (6). Patients with RA have significantly lower levels of VO2max compared to healthy counterparts (7) but the association of VO2max and CVD risk has never been investigated in this population. The aim of the present cross-sectional study was to investigate the association of VO2max with both traditional and novel CVD risk factors and 10-year CVD risk in a well-characterised population of patients with RA.

Methods

Participants

One hundred and fifty patients were recruited from the Dudley Group NHS Foundation Trust, UK. The study was approved by the local NHS Research Ethics Committee and a detailed verbal and written description for the procedures involved was offered to all participants, according to the declaration of Helsinki. Patients' records were reviewed before requesting participation. Inclusion criteria were: fulfilling the American College of Rheumatology RA criteria and being on stable treatment for at least three months. Exclusion criteria were: previous/present CVD (e.g. cardiomyopathies, arrhythmias), cerebrovascular disease, diabetes, restrictive/obstructive lung disease, known malignancy, pregnancy, current infection, and hyper- or hypothyroidism, recent joint surgery (preceding six months), amputation, functional comorbidities incompatible with VO2max testing.

Procedures

Patients visited our laboratory after a 12h overnight fast for collection of blood samples, demographic, anthropometric and disease-related characteristics: standing height was measured with a Seca Stadiometer, body mass and composition via bioelectrical impedance (Tanita BC418-MA, Japan), disease activity via the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and the 28 joint Disease Activity Score (DAS28), and disease severity via the Stanford Health Assessment Questionnaire (HAQ). Classical and novel CVD risk profile included: triglycerides, total cholesterol, high- and low-density lipoprotein (HDL and LDL) (Vitros® 5.1, USA), physical activity (International Physical Activity Questionnaire), glucose and insulin (Immunolite 2000 Analyser, USA) from which the homeostasis model assessment (HOMA) was calculated, blood pressure, family history, smoking, CRP (Vitros® 5.1 FS, USA), haemoglobin and white cell count (ADVIA® 120, Germany) and fibrinogen (IL Futura Advance analyser, UK). 10-year CVD risk was calculated using the Framingham score.

Participants returned within three days to perform an individualised VO2max test protocol with electrocardiography (ECG) after taking into account their physical abilities and the American Heart Association guidelines using a previously published protocol (8) and specific contraindications for terminating the test (9). The VO2max test was performed on a treadmill using a calibrated breath-by-breath system (Metalyzer 3B, CORTEX, Germany). Based on the results of the VO2max test, participants were divided into three groups using the 33^{rd} (18.1 $ml.kg.min^{-1}$) and 66^{th} (22.4 $ml.kg.min^{-1}$) centiles (10). To determine the number of participants needed per group, we used RA (8) and age-matched normal population VO2max data, and calculated that 44 patients were needed (90% power and 5% alpha error level). To account for potential drop-out we recruited 150 patients. Given the relevant VO2max data

from the general population (9) these groups reflected unfit vs. moderately unfit vs. average fitness groups, respectively.

Statistical Analyses

Kolmogorov-Smirnov tests were performed to investigate the distribution of all variables. Chi-square analyses were conducted to investigate differences amongst the VO2max tertiles for categorical variables (e.g. gender and medication). One-way analyses of variance (ANOVA) with Bonferroni correction for adjusting the number of multiple comparisons or Kruskal-Wallis tests were utilised, according to distribution, to investigate differences between VO2max tertiles. After controlling for age, gender and physical activity, multivariate ANOVA (MANOVA) with Sidak correction were initially utilised to investigate the association of VO2max levels (as a categorical variable with the three groups) with CVD risk factors. Thereafter, disease activity and severity variables were also utilised in the same models to investigate whether the association of VO2max with CVD factors and 10-year CVD risk persisted. For the MANOVAs, log transformations were conducted on all the variables that were not normally distributed. The adjusted mean differences [with confidence intervals (95% CI)] were also reported for the variables that were significantly different. The level of significance was set at $p<0.05$.

Results

Of the 150 patients that agreed to participate, six did not attend. Mean VO2max for the entire cohort was 20.9±5.7 $ml.kg.min^{-1}$ and was significantly different between the tertiles, i.e. unfit:15.4±1.9 vs. moderately unfit:20.2±1.3 vs. average:27.1±4.7 $ml.kg.min^{-1}$, ($p<0.001$). Significant differences were detected in age between the tertiles (Table 1, $p=0.035$) but not gender [Table 1, $p=0.095$] or physical activity [Table 2, $p=0.051$]. The anthropometric and disease-related characteristics of the three RA groups appear in Table 1.

Table 1 near here

Associations between cardiovascular profile and VO2max

Significant differences between the three groups were detected in systolic blood pressure, HDL, insulin resistance and body fat, CRP, fibrinogen, and white blood cell count, as well as 10-year CVD risk (Table 2).

Adjusted associations between cardiovascular profile and VO2max

Classical CVD risk factors: After correction for age, gender and physical activity, VO2max levels significantly associated with body fat ($F_{1,107}$=16.7, p<0.001), HOMA ($F_{1,107}$=6.0, p=0.003) and HDL ($F_{1,107}$=5.3, p=0.007) but not systolic blood pressure (p>0.05). After further adjustment for DAS28 and HAQ, VO2max significantly associated with: a) body fat ($F_{1,107}$=15.7, p<0.001), which was related to the differences reported between the average vs. unfit groups [mean difference (95% CI)=10.9(6.1 to 15.7)%, p<0.001] and average vs. moderately unfit groups [mean difference (95% CI) =6.8(2.2 to 11.3)%, p=0.001], and b) HOMA ($F_{1,107}$=4.4, p=0.016) and HDL ($F_{1,107}$=5.6, p=0.005) which was related to the differences that were observed in average vs. unfit group [mean difference (95% CI): HOMA=0.52(0.09 to 0.95), p=0.012 and HDL=0.23(0.05 to 0.41)mmol/L, p=0.007].

Novel CVD risk factors: After correction for age, gender and physical activity, VO2max levels revealed significant associations with CRP ($F_{1,109}$=3.8, p=0.025) and fibrinogen ($F_{1,109}$=18.5, p<0.001) but not white blood cells (p=0.087). For CRP, this association was related to the differences between the average vs. unfit group [mean difference (95% CI) =0.78(0.09 to 1.47)mg/L, p=0.021]. Further correction for DAS28 and HAQ, did not eliminate the significant association between VO2max levels and fibrinogen (p<0.001): these

associations were related to the differences between the unfit vs. average [mean difference (95% CI)=1.2(0.64 to 1.80)g/dL, p<0.001] as well as the moderately unfit vs. average groups [mean difference (95% CI)=0.64(0.06 to 1.22)g/dL, p=0.024].

10-year CVD risk: After adjustment for age, gender and physical activity, the levels of VO2max significantly associated with the 10-year CVD risk ($F_{1,123}$=11.2, p<0.001) while further correction for DAS28 and HAQ in this model did not alter this association ($F_{1,123}$=10.8, p<0.001). This was related to the differences that were detected between the average vs. unfit [mean difference (95% CI)=1.23(0.58 to 1.88)yrs, p<0.001] as well as the average vs. moderately unfit patients [mean difference (95% CI)=0.81(0.18 to 1.45)yrs, p=0.007].

Table 2 near here

Discussion

RA patients with higher VO2max had better CVD risk profile and lower 10-year CVD risk compared to those with lower VO2max levels. Substantial evidence demonstrates a strong inverse association between CVD morbidity and mortality with VO2max (11, 12) highlighting the important role of fitness for health and longevity. RA patients repeatedly demonstrate significantly lower VO2max levels compared to healthy counterparts, most likely related to their low levels of physical activity (7, 13) and increased disease activity/severity; for example, a fit RA patient may stop the test potentially because of disease-related pain and physical dysfunction and not cardiorespiratory limitations. The low overall VO2max levels observed in this study, is an alarming finding that could be linked with the increased incidence of CVD-related death in RA, however, appropriate longitudinal studies are necessary to confirm this. Our results suggest significant differences between RA patients, classified according to fitness level, in a variety of classic and novel CVD risk

factors, as well as the 10-year CVD risk. As such, it seems reasonable to suggest that increased cardiorespiratory fitness may provide a protective role against CVDs in this population, which is similar to what is seen in the normal population (14, 15) or other rheumatic diseases (16).

Further analyses demonstrated that, after controlling for disease activity and severity, VO2max levels significantly associated with body fat, HDL and insulin resistance. RA patients experience a condition termed rheumatoid cachexia which is characterised by a significant increase in adiposity and decreased muscle mass; as such at the same weight a patient with RA may have an altered body composition compared to a health normal individual that favours an inferior cardiovascular profile (17). This condition seems to be mediated by both inflammation and physical inactivity (17). Studies in RA have previously shown that obesity associates with both low HDL and insulin resistance (18). Moreover, inflammation which is overexpressed in both obesity and RA, affects glucose metabolism and enzymes fundamental to HDL metabolism, promoting the development of insulin resistance and atherosclerosis (19). The interplay of these factors with physical inactivity may be one of several factors that explain the increased incidence of CVD and CVD death in RA.

Exercise is the predominant intervention to increase VO2max. Even in a disease such as RA which is characterised by significant disability, pain and fatigue, exercise is recommended and in fact, can even ameliorate disease-related symptoms (20) and the calculated risk for CVD. Therefore, RA patients can and should exercise but they consistently report lower levels of fitness compared to the healthy population (7, 16). The effects of exercise on improving disease activity and cardiovascular risk factors have also been shown in axial spondyloarthritis, another chronic inflammatory joint disease (21). Research investigating ways of increasing and maintaining physical activity and reducing sedentary behaviour is necessary in RA patients.

Deleted: this population

This study is limited by not evaluating VO2max levels of an equivalent age-gender matched population, its cross-sectional design, and the non-inclusion of patients with pulmonary fibrosis/nodules or other significant extra-articular features (as well as keeping a detailed record of non-included patients). Patients with poor mobility were also excluded, possibly introducing a positive bias in the present study. This would suggest that we have selected the "fittest" RA patients herein who still demonstrated that their VO2max levels are alarmingly low. Nevertheless, this is the first study that has explored the associations between VO2max and CVD risk factors with such a large sample of RA patients using appropriate power calculations and adjustment for several potential confounders. We conclude that overall VO2max levels are low in both female and male RA patients, and that lower VO2max levels associate with inferior CVD profile and higher 10-year CVD event risk.

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Conflict of Interest Statement

There authors declare no conflict of interest.

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Table 1. Anthropometric and disease-related characteristics [either in mean±std or median(interquartile range)] of the total population and fitness sub-groups.

	Total RA (n=144)	Unfit (n=47)	Moderately Unfit (n=48)	Average Fitness (n=49)	**P**
VO2max (ml.kg.min^{-1})	20.9±5.7	15.4±1.9**	20.2±1.3**	27.1±4.7	**<0.001**
Age (yrs)	54.4±11.7	54.7±13.4	57.3±10.3	51.2±10.6	**0.035**
Gender-females (n)	101	37	35	29	0.095
Anthropometric					
Height (cm)	1.71(1.63-1.71)	1.66(1.59-1.71)	1.64(1.59-1.73)	1.66(1.61-1.72)	**0.018**
Weight (kg)	76.8(65.5-90.0)	86.3(70.5-97.7)	77.5(70.5-86.8)	69.2(59.3-82.0)	**<0.001**
Fat-Free Mass (kg)	49.0(42.0-58.0)	49.0(42.2-59.7)	47.0(42.0-58.0)	49.0(42.0-60.0)	0.944
RA characteristics					
Disease Duration (yrs)	6.0(3.0-10.0)	5.0(2.0-6.5)	7.0(4.0-14.5)	5.0(3.0-7.5)	**0.046**
DAS28	3.2(2.3-4.5)	3.2(2.1-4.6)	3.0(2.3-4.0)	3.3(2.3-4.5)	0.817
ESR (mm1st hr)	11.0(5.0-21.0)	19.0(12.0-32.7)	10.0(7.0-21.5)	5.0(2.0-10.2)	**<0.001**
HAQ	0.58(0.13-1.12)	0.79(0.17-1.13)	0.52(0.16-1.21)	0.35(0.1-1.0)	0.617
Medication n(%)					
DMARDs	73(50%)	24(33%)	28(38%)	21(29%)	0.414
Anti-TNFa	22(15%)	10(45%)	5(23%)	7(32%)	0.350
NSAIDs	50(35%)	17(34)	15(30%)	18(36%)	0.948
Analgesics	57(40%)	20(35%)	18(32%)	19(33%)	0.709

P = differences between groups detected using ANOVA
Significantly different from the Average fitness group (ANOVA with Bonferroni): ** $p<0.001$ and * $p<0.05$
Significant values are highlighted in bold.

VO2max=maximal oxygen uptake, BMI=body mass index, DAS28=disease activity score, ESR=erythrocyte sedimentation rate, HAQ=health assessment questionnaire, DMARDs=disease-modifying anti-rheumatic drugs, anti-TNFa=anti tumour necrosis factor alpha, NSAIDs=non-steroidal anti-inflammatory drugs

Table 2. Classical CVD risk factors and 10 year CVD risk [either in mean±std or median(range)] of the total population and fitness groups studied .

	Total RA (n=144)	Unfit (n=47)	Moderately Unfit (n=48)	Average Fitness (n=49)	**P**
Classical Risk Factors					
SBP (mmHg)	132.6±15.9	134.4±15.0	135.6±17.0*	127.9±14.7	**0.039**
DBP (mmHg)	81.0±9.8	80.4±10.3	82.8±10.4	79.6±8.5	0.4
Triglycerides (mmol/L)	1.1(0.8-1.6)	1.1(0.8-2.1)	1.1(0.0-1.7)	1.1(0.8-1.4)	0.46
Cholesterol (mmol/L)	5.0±1.0	5.1±1.1	5.1±1.1	5.0±0.9	0.916
HDL (mmol/L)	1.4(1.1-1.7)	1.2(1.1-1.6)*	1.3(1.2-1.6)	1.5(1.2-1.8)	**0.017**
LDL (mmol/L)	3.1(2.5-3.6)	2.7(2.4-3.7)	3.1(2.5-3.6)	3.1(2.6-3.5)	0.847
Glucose (mmol/L)	4.6(4.4-5.0)	4.6(4.3-5.1)	4.7(4.3-5.0)	4.6(4.4-5.0)	0.772
HOMA (mmol/L)	1.5(0.9-2.3)	2.0(1.4-2.4)*	1.5(1.2-2.1)*	0.9(0.6-1.7)	**<0.001**
BMI (kg/m^2)	27.8(24.2-31.5)	30.0(26.0-35.0)	27.9(25.3-31.0)	24.5(22.1-27.8)	**<0.001**
Fat Mass (%)	35.0(30-0-42.0)	41.0(34.8-46.2)	38.0(32.2-42.7)	30.0(25.5-33.9)	**<0.001**
Physical Activity (MET-min/week)	3109.0 (1085.0-5812.5)	2102.5 925.5-4447.5)	2830.5 (946.5-6018.7)	3549.0 (1782.0-9759.0)	0.051
Smoking (n)	17	6	4	7	0.912
Family history of CVD (n)	62	23	20	19	0.995
Novel Risk Factors					
CRP (mg/L)	3.6(2.6-8.6)	7.3(3.0-10.7)	4.5(2.7-9.8)	3.0(1.7-4.5)	**0.005**
vWF (IU/dL)	136(108-181)	138(120-180)	143(103-193)	129.0(88-170)	**<0.001**
White cell count (b/L)	6.7±2.1	7.3±2.4	6.8±1.9	6.0±1.8	**0.015**
Hemoglobin (gm/dL)	13.3±1.2	13.1±1.0*	13.4±1.2	13.4±1.4	0.519
10 year CVD risk (%)	7.0 (3.0-13.0)	8.0 (4.0-15.2)	7.0 (4.0-12.9)	4.0 (2.0-7.0)	0.003

P = differences between groups detected using ANOVA
Significantly different from the Average fitness group (ANOVA with Bonferroni): ** $p<0.001$ and * $p<0.05$
Significant values are highlighted in bold.
SBP=systolic blood pressure, DBP=diastolic blood pressure, HDL=high density lipoprotein, LDL=low density lipoprotein, HOMA=homeostatic model assessment, CRP=c reactive protein, vWF=von Willebrand factor, CVD cardiovascular disease