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Abstract

The purpose of this study was to investigate the hemodynamic effect of variations in the angulations of the left coronary artery, based on simulated and realistic coronary artery models. Twelve models consisting of four realistic and eight simulated coronary artery geometries were generated with the inclusion of left main stem, left anterior descending and left circumflex branches. The simulated models included various coronary artery angulations, namely, 15°, 30°, 45°, 60°, 75°, 90°, 105° and 120°. The realistic coronary angulations were based on selected patient's data with angles ranging from narrow angles of 58° and 73° to wide angles of 110° and 120°. Computational fluid dynamics analysis was performed to simulate realistic physiological conditions that reflect the *in vivo* cardiac hemodynamics. The wall shear stress, wall shear stress gradient, velocity flow patterns and wall pressure were measured in simulated and realistic models during the cardiac cycle. Our results showed that a disturbed flow pattern was observed in models with wider angulations, and wall pressure was found to reduce when the flow changed from the left main stem to the bifurcated regions, based on simulated and realistic models. A low wall shear stress gradient was demonstrated at left bifurcations with wide angles. There is a direct correlation between coronary angulations and subsequent hemodynamic changes, based on realistic and simulated models. Further studies based on patients with different severities of coronary artery disease are required to verify our results.

Keywords: Coronary artery disease, angulation, computational fluid dynamics, wall shear stress, wall shear stress gradient.

Introduction

Atherosclerosis is the leading cause of morbidity and mortality in the advanced countries. The causes of atherosclerosis are multifactorial and identification of these factors could allow earlier detection and prevention of the disease. Hemodynamics and vessel geometry may play an important role in the cause of plaque formation, since atherosclerotic plaques occur frequently in well-recognized arterial regions of curvature, bifurcated area and vessel branches (Zarins et al., 1983; Asakura and Karino, 1990; Conner, 1994). Blood flow variations, particularly those related to the rate of change of stream-wise velocity perpendicular to the blood vessel wall, (known as the wall shear stress) has been reported to be related to the pathogenesis of atherosclerosis (Lehoux, 2006; Sabbah et al., 1986).

Early hemodynamic analysis of coronary artery disease performed using computational fluid dynamic (CFD) techniques has been typically performed using one of two approaches, either they were based on simulated models, or on realistic coronary artery geometry simulations (Lim et al., 2005; Katritsis et al., 2007; Shanmugavelayudam et al., 2010; Wellnhofer et al., 2010; Nordgaard et al., 2010). As far as we know, no systematic studies have been performed hitherto that relate bifurcation angles to flow instabilities predisposing to the formation of atherosclerotic lesions. The left coronary artery differs from the right coronary artery in terms of geometric appearance as the left side has a very short main stem, which quickly divides into left anterior descending and left circumflex with an angle formed between these two branches. Thus, the angulation between these two coronary branches induces local hemodynamic changes, which may pose a potential risk for development of atherosclerosis. The aim of this study was to investigate the

relationship between hemodynamics and angulations at the left coronary artery, based on simulated models and realistic patients' data. Various angles were simulated at the left coronary artery with the aim of identifying the effect of angulation on the subsequent hemodynamic changes to the left coronary artery.

Materials and Methods

Measurement of left coronary artery anatomical details

Four patients suspected of coronary artery disease underwent multislice CT angiography and were included in the patient datasets. This original DICOM (digital imaging and communication in medicine) data was transferred to a separate workstation equipped with Analyze version 7.0 (AnalyzeDirect, Inc., Lexana, KS, USA) for image post-processing and segmentation. Three-dimensional (3D) volume data was post-processed and segmented using a semi-automatic method with a CT number thresholding technique (Sun et al., 2003; Sun et al., 2004) and manual editing was performed in some slices to remove soft tissues and artefacts. Four models were produced with a special focus on the left coronary artery (LCA) and its branches. The 3D LCA models were saved as 'STL' stereolithography CAD format for further reconstruction purposes. Anatomic measurements were performed at the LCA location and its branches in the volumetric models so that these measurements could be used to provide suitable dimensions for the simulated LCA models, as shown in Table 1. Figure 1 shows anatomical details of the LCA with an angle formed between the left anterior descending (LAD) and left circumflex (LCx) branches.

This investigation conforms to the principles outlined in the Declaration of Helsinki for use of human subjects (World medical association declaration of Helsinki, 1997.). Since

patients underwent routine CT scanning for clinical diagnosis of coronary artery disease, and only the DICOM images were used for generation of 3D coronary artery images, with patient's details being de-identified, thus there is no ethical issue involved in this study.

Generation of simulated left coronary artery models

The geometry of a simulated, perpendicular (90°) model was generated based on the anatomical details of LCA and standard dimensions measured based on Figure 1, using Blender version 2.48 (Blender Institute, Amsterdam, Netherlands). The surface of the 90° LCA model was used as a reference model, which was then converted into a solid model. A bifurcation angle of 80° is recommended as a cut off value to determine whether there is presence of coronary artery disease, as confirmed by previous reports studying the natural distribution of coronary bifurcation angles (Reig and Petit 2004; Pflederer et al 2006). Our simulation of different angles of the left coronary artery reflects the range of angulations from very small to large angles which enables us to perform an in-depth study of the relationship between angulation and development of atherosclerosis. Based on the reference model, seven other models were generated by changing the angle between LAD and LCx, these included 15°, 30°, 45°, 60°, 75°, 105°, 120°. All baseline models were saved as 'STL format' for producing mesh models. Figure 2 shows variable angles that were simulated in the left coronary artery models. Finally, the merging of side-branches within left main trunk generated sharp edges at the bifurcation regions, which could potentially have an undesirable impact on local flow simulation (He and Ku, 1995). Therefore, gentle B-spline smoothing was applied at the interface between branches and the trunk to reduce any potential non-physical behaviour

that could be induced by sharp edges. The splitting of flow rate at a symmetric bifurcation is defined by Zheng et al. (2006) and Lou and Yang (1993). Their flow rate system of equal diameter branches can be defined as a splitting ratio (Zhang et al, 2006):

$$Q_{LMS} = Q_{LCx} + Q_{LAD} \quad (1)$$

$$R_s = \frac{Q_{LCx}}{Q_{LAD}} \quad (2)$$

where $Q_{LMS} = \pi r_{LMS}^2 \vec{V}_{LMS}$ is flow rate in parent with r_{LMS}^2 and $\vec{V}_{LMS}$ being radius and velocity at main trunk, Q_{LCx} and Q_{LAD} are flow rate in daughter branches. However, in this study, the two left coronary artery branches are unequal in diameter and distance in regard to the main left coronary artery, as shown in Table 1. In our case, R_s (splitting ratio) of a 90°model is calculated as $R_s = (\pi r_{LCx}^2 \vec{V}_{LCx})/(\pi r_{LAD}^2 \vec{V}_{LAD}) = 9\vec{V}_{LCx}/16\vec{V}_{LAD}$.

Generation of realistic left coronary artery models

The patient 3D LCA models consisting of the ascending aorta, right and left coronary arteries were then imported into a computer-aided design program using Blender version 2.48. Four volume models were reconstructed into the surface models, which were then converted into solid models and saved as 'STL format' for generation of CFD mesh models. Figure 3 shows four sample realistic patient left coronary models with variable angulations. The realistic patient bifurcation angles ranged from 58° to 73°, 110°, 120°, respectively. These patients were selected to reflect the relationship between hemodynamics and angulations in the LCA. In summary, there were a total of twelve models consisting of four patient models and eight simulated models.

CFD simulation in the left coronary artery-generation of meshes

All of the above models were used to create hexahedral meshes with which to perform the CFD simulations (mesh details are shown in Table 2). The meshes were generated

using ANSYS ICEM CFD version 12 (ANSYS, Inc., Canonsburg, PA, USA), with details having been described in previous studies (Sun and Chaichana 2010; Sun and Chaichana 2009). Finally, the twelve 3D meshes were saved as 'GTM format' for CFD computation.

Application of physiological parameters

In order to ensure that our analysis reflects the realistic simulation *in vivo* conditions, realistic physiological boundary conditions were applied for 3D numerical analysis. The transient simulation was performed using accurate hemodynamic rheological and material properties, as described in a previous study (Frauenfelder et al., 2006). Figure 4 shows the pulsatile flow rates and pressure (Nichols and O'Rourke 2005) at the aorta and LCA, reconstructed using a Fourier series (Smith, 1997) in Matlab (MathWorks, Inc. Natick, MA, USA). This Fourier series was applied using ANSYS CFX Command Language (CCL) programming to define velocity and pressure boundary conditions. Pulsatile velocity was applied as an inlet boundary condition at the left main stem, and pulsatile pressure was applied at the left anterior descending and left circumflex outlet boundaries. Appropriate rheological parameters were applied with a blood density of 1060 kg/m3, blood viscosity of 0.0035 Pa s (Boutsianis et al., 2004; Milnor, 1989). The blood flow was assumed to be laminar and a no-slip condition was applied at the walls. Blood was assumed to be a Newtonian and incompressible fluid (Johnston et al., 2004; Johnston et al., 2006; Borghi et al., 2008).

Performance of CFD computation

The Navier-Stokes equations were solved using the ANSYS CFX CFD package (version 12 - ANSYS, Inc.), on a Microsoft Windows XP 32-bit machine, 4 MB RAM with a dual

core 2.4 GHz CPU. The CFD simulation was run for 80 time-steps, representing 1.0 second of pulsatile flow, (0.0125 seconds per time step), with each time step converged to a residual target of less than 1×10^{-4} by approximately 100 iterations. The CFD solution was fully converged by approximately 8,000 time iterations per LCA model. The calculation time for each LCA model was approximately 5 hours. The configuration of this simulation is similar to previously published simulations (Sun and Chaichana 2010; Sun and Chaichana 2009). Flow patterns, flow velocity, wall pressure, wall shear-stress (WSS), and wall shear-stress gradient (WSSG) were calculated and visualized using ANSYS CFD-Post version 12 (ANSYS, Inc.). The parameter used to characterise the impact of bifurcation angle on hemodynamic flow was calculated as the magnitude of local wall shear-stress gradient (Kleinstreuer et al, 2001) which is defined as:

$$\mathrm{WSSG} = \sqrt{\left(\frac{\partial \tau_{w,m}}{\partial_m}\right)^2 + \left(\frac{\partial \tau_{w,n}}{\partial_n}\right)^2} \quad (3)$$

where m is the temporal mean WSS direction, n is tangential to the surface and normal to m. $\tau_{w,m}$ and $\tau_{w,n}$ are WSS components along m and n directions, respectively. $\partial \tau_{w,m}/\partial m$ and $\partial \tau_{w,n}/\partial n$ are the off-diagonal components of $\nabla \tau_w$ tensor, which is obtained by computing a spatial derivative of WSS vector with respect to the Cartesian coordinates $(x, y, z \text{ directions})$. The local WSS is calculated as $\tau_w = \mu \times (\partial \vec{v}_t / \partial y)$, where μ is blood viscosity, $\partial \vec{v}_t$ is velocity near wall perpendicular to surface, ∂y is distance to the wall surface. The WSSG components demonstrated that localized cellular proliferation may coincide with sudden pronounced changes in WSS (LaDisa et al., 2004; Ojha, 1993; White et al., 2001; Lei et al., 2001). Therefore, the temporal WSSG is an alteration of WSS over a small period of time at the same location (White et al., 2001; Ojha, 1993), and can be obtained by taking the time derivative to the local WSSG, which

is considered as $\partial \tau_w / \partial t$ and this has been described before (Lei et al., 1996). The time-dependent alterations in WSS and temporal WSSG were determined to evaluate the impact of bifurcation angles upon the flow and the ANSYS CCL language was used to develop a code to compute the WSSG in ANSYS CFX-Post processing.

Results

The simulated and realistic left coronary artery models were successfully performed with CFD analysis under the *in vivo* physiological conditions during the systolic and diastolic phases. The analysis demonstrates a strong relationship between hemodynamics and angulations at the left coronary artery, as observed in both types of models.

Simulated left coronary artery models

Peak systolic velocity and pressure was reached at a time of 0.4 sec during the cardiac cycles. Velocity patterns measured with different angulations of the simulated models are shown in Figure 5. The CFD analysis showed that a small region of low-velocity blood flow distributed in the small angled models gradually became a large region of flow separation when the angulations were increased, and this is particularly apparent at the location of the left coronary bifurcation.

Low WSS regions occurred at bifurcations where the left coronary main stem branches into left anterior descending and left circumflex. Figure 6 demonstrates that WSS regions were found to reduce in wide angled models when compared to the narrowed models and this phenomenon is particularly obvious in the systolic phase.

Similarly, wall pressure was affected to some extent with the change of angulations in different models. Figure 7 displays that wall pressure increased from narrow-angled models to wide-angled models, particularly near the left coronary bifurcation. This is

205 especially obvious in the model with a 15° angulation, as the results show significantly
206 reduced wall pressure when the blood flows through from the left main stem to the left
207 anterior descending and left circumflex braches.
208 Figure 8 presents the magnitude of temporal WSSG and the regions of low WSSG at the
209 left coronary bifurcations. A very low WSSG occurred in models with an angle of 120°,
210 105°, 90° and 75°, with the measured values ranging from 15.76 kg/m^2s^2 to 219.82
211 kg/m^2s^2. In contrast, low temporal WSSG was not significantly apparent in small angle
212 models such as 15° and 30° models. The temporal WSSG magnitude ranging 423.89
213 kg/m^2s^2 to 627.95 kg/m^2s^2 and 627.95 kg/m^2s^2 to 832.02 kg/m^2s^2 was only measured in
214 the models with an angle of 15°, 30°, 45°, 60° and 75°, respectively.
215 *Realistic left coronary artery models*
216 The analysis of realistic models is consistent with which was observed in the simulated
217 models, showing a direct correlation between hemodynamic effects and the angulation of
218 left coronary models. Figure 9 demonstrates that flow velocity was decreased at
219 bifurcation regions, and a small low-velocity region was observed in the small-angled
220 models, becoming a large separated region in the wide-angled models.
221 WSS was found to be related to blood flow velocity at bifurcating regions. Low WSS
222 was noticed in the bifurcated locations (angles between both left main artery branches
223 and side branches), as shown in Figure 10. The realistic coronary artery shapes
224 introduced complex wall geometry that directly affected the WSS and wall pressure.
225 However, our analysis showed that the impact on low WSS distributions at the left
226 bifurcation was largely in wide-angled models, and this reflects our similar observations
227 in the simulated models (shown in Figure 6).

Similarly, wall pressure was noticed to change with different angulations of realistic left coronary models. Wall pressure decreased from wide-angled models to narrow-angled models. This is particularly apparent in the model with a 73° angulation when compared to a 120° angulation, as shown in Figure 11. Again, this is consistent with that observed in the simulated models.

The magnitude of temporal WSSG is shown in Figure 12. The regions of low WSSG were distributed around the left coronary bifurcations. The magnitude of low WSSG was obviously demonstrated for bifurcations with 120° and 110° angulation, with measured WSSG values ranging from 15.76 kg/m^2s^2 to 219.82 kg/m^2s^2. Low WSSG also occurred at 58° angulation model due to the complex shape of the daughter branches. This indicates the difference between realistic models and simulated models as the realistic models represent the patient's actual arterial geometry, while simulated models do not reflect the complex wall geometry such as curved or tortuous appearance of the vessel wall. The temporal WSSG magnitude between 627.95 kg/m^2s^2 and 832.02 kg/m^2s^2 was only measured in the 58° model.

Discussion

Our results based on simulated and realistic coronary models showed that there is a direct correlation between angulations of the left coronary artery and subsequent hemodynamic changes. Low wall shear stress and wall shear stress gradient were noticed in wide-angled models, and this indicates the potential risk of developing atherosclerosis at the left coronary bifurcation.

It is believed that local hemodynamic forces play an important role in formation of atherosclerosis (Malek et al., 1999; Chien et al., 2007; Schroeder et al., 1995). Soulis et

al. (2006) explored the change of WSS in the reconstructed left coronary artery and its branches with inclusion of coronary bifurcation. The hemodynamic analysis in their study showed that the atherosclerosis plaques frequently occurred in bifurcation regions where WSS was low. This is confirmed in our study, as a large region of low WSS was noticed at wide-angled models, indicating the tendency to induce atherosclerotic changes. Early studies reported that atherosclerotic plaques tend to form at specific locations of the coronary artery such as the proximity branches, curvatures and bifurcations, where the flow separation occurred and WSS was low (Katritsis et al., 2007; Soulis et al., 2006; VanderLaan et al., 2004; Tarbell, 2010; Qi et al., 2008). Later reports further confirmed these early observations (Katritsis et al., 2007; Nordgaard et al., 2010). Katritsis et al. (2007) investigated the WSS oscillations based on the simulated artery bifurcation model comprising of a straight tube, and their results showed that low wall shear-stress occurred in the bifurcation locations. Nordgaard et al. (2010) in their recent report studied WSS in the remodelled left coronary artery and stated that low WSS was found in regions of low flow rate. Again, our analysis is consistent with these observations. Further to the simulated models, we included a number of models generated from patients' data with variable left coronary bifurcation angles, which is one of the advantages of the current study. Another advantage of our study is the direct comparison between two types of model, which showed consistent results. This indicates the additional value provided by this study.

In addition to the conventional CFD analysis, quantitative analysis of the impact of bifurcation angulations on hemodynamic flow was performed in this study by analysing the WSSG. The magnitude of wall shear stresses causes elongation and alignment of

endothelial cells, while the WSSG has direct effects on intercellular tension. The strong correlation between averaged low WSS and the localization of atherosclerotic lesions in arterial bifurcations has been well established (Katritsis et al., 2007; Soulis et al., 2006). However, WSS analysis topographically restricts the corresponding regions of low WSS at the vicinity of the coronary artery branches (Farmakis et al., 2004). Thus, low WSS regions appear to cover smaller surface area than the corresponding regions prone to developing atherosclerosis (Montenegro and Eggen ., 1968). In contrast, low WSSG has been reported to clearly describe the regions where atherosclerosis prevails (Kleinstreuer et al, 2001). Hence, WSSG analysis seems to better depict these regions than WSS analysis does. Our analysis showed that the WSSG distribution tends to form a large area of low magnitude at wide-angled models, particularly at the region of bifurcation, while this was not apparent at narrow-angled models, as shown in Figure 8 and Figure 12. Consequently, the wide- angled bifurcations at left coronary artery may have a higher possibility to promote the atherosclerotic formation and progression than the narrow-angled bifurcations.

There are some limitations in our study which should be addressed. Firstly, the simulated and realistic left coronary models were assumed to have a rigid wall rather than elastic wall, therefore, the simulation does not fully reflect the realistic physiological situation as coronary wall moves during cardiac cycles. Secondly, no pathological changes such as presence of plaques or coronary stenosis were simulated in this study, since our focus was simply to investigate the relationship between angulation and hemodynamic changes. Thirdly, the assumption of a Newtonian blood model has limitations on the biological effects of prolonged contract of blood flow with the cells of vascular wall, for example,

297 platelet deposition (van Zanten et al., 1994) and leukocyte rolling (Sequeira et al., 2009).
298 Additionally, a non-Newtonian blood model becomes important especially in low flow
299 and low wall shear stress regions. However, previous studies have showed that the
300 assumption of a Newtonian model is reasonable in this configuration (Johnston et al.,
301 2006; Pedley, 1980). Fourthly, although cardiac CT has been increasingly used in the
302 diagnosis of coronary artery disease with its improved diagnostic accuracy due to
303 technological developments (Sun and Ng 2011; Sun et al., 2008), the real CT patient data
304 with representation of these coronary artery branches is limited for computational fluid
305 dynamics analysis. Only four selected CT cases were included in this study, which limits
306 our analysis. Although no significant coronary stenosis is demonstrated on these CT
307 images, potential atherosclerotic changes in the coronary artery tree cannot be excluded,
308 given the fact that these patients are at high risk of developing atherosclerosis. However,
309 the representative angles in these cases reflected the ranges from normal to abnormal
310 coronary arteries, thus, this limitation can be compensated for to some extent. Finally,
311 although the geometry of simulated coronary models were based on patient's anatomical
312 details, there are still inadequacies in the representation of realistic geometry, as most of
313 the coronary arteries, especially at the left bifurcation follow a curved, as opposed to a
314 straight path. Thus, future studies will use coronary models with a more realistic
315 idealised geometry.
316 In conclusion, we studied the effect of various angulations of the left coronary artery on
317 hemodynamics, based on simulated and realistic coronary models. There is a direct
318 relationship between wide angulation in the left coronary bifurcation and hemodynamic
319 changes such as disturbed flow and low wall shear stress and wall shear stress gradient,

indicating the possible inducement of atherosclerosis. Further studies including patients with different risk factors or severity of coronary artery disease should be performed to verify our results.

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