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1 Hemodynamic impacts of various types of stenosis in the left coronary artery bifurcation:  
2 A patient-specific analysis

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21

22 **Abstract**

23 This study investigates the hemodynamic changes to various types of coronary stenosis in  
24 the left coronary artery bifurcation, based on a patient-specific analysis. Twenty two  
25 patients with left coronary artery disease were included in this study. All stenoses  
26 involving the left coronary artery bifurcation were classified into four types, according to  
27 their locations: A) left circumflex (LCx) and left anterior descending (LAD), B) LCx  
28 only, C) left main stem only, and D) LAD only. Computational fluid dynamics (CFD)  
29 was performed to analyze the flow and wall shear stress (WSS) changes in all  
30 reconstructed left coronary geometries. Our results showed that the flow velocity and  
31 WSS were significantly increased at stenotic locations. High WSS was found at >70%  
32 lumen stenosis, which ranged from 2.5 Pa to 3.5 Pa. This study demonstrates that in  
33 patients with more than 50% stenosis in the left coronary artery bifurcation, WSS plays  
34 an important role in providing information about the extent of coronary atherosclerosis in  
35 the left coronary artery branch.

36

37 **Keywords:** Atherosclerosis, coronary artery disease, hemodynamics, wall shear stress

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## 41 **Introduction**

42 Hemodynamic parameters cannot be directly measured in vivo; accordingly,  
43 computational fluid dynamic analysis has become established as a method to predict  
44 hemodynamically induced shear stress in the coronary arteries. Low shear stress normally  
45 occurs at the bifurcated region due to the coronary angulation [1]. Recently, wide angled  
46 bifurcations have been reported to lead to the development of atherosclerosis [2]. Studies  
47 using medical imaging techniques have revealed the distribution of coronary stenosis in  
48 the left main bifurcation, and evaluated the relationship between the bifurcation angle and  
49 development of coronary disease [3,4]. It is generally believed that the left coronary  
50 artery geometry is more complicated than the right coronary artery since the left side  
51 consists of two large main branches forming an angle, with many side-branches [2, 5, 6].  
52 The bifurcation stenosis has been classified and identification of the appropriate  
53 classification is a significant component in planning the appropriate treatment [7]. A  
54 stenosis of greater than 50% diameter results in significant flow changes to the coronary  
55 artery [8].

56 Early studies used computational fluid dynamics to analyze a >50% coronary stenosis  
57 distributed around the main bifurcation with promising results achieved [9-11]. Results  
58 showed the change of flow parameters at the bifurcated regions, with some effects on the  
59 hemodynamic factors in coronary side-branches. Recent studies investigated the coronary  
60 blood flow under normal and diseased condition, with an assumed degree of stenosis  
61 [12,13]. Despite the use of computer simulation in these studies to investigate the  
62 hemodynamic changes in coronary models, there have been no reports about the realistic  
63 bifurcation stenosis based on patient-specific models. In this study, we aim to investigate

64 the hemodynamic patterns and wall shear stress with detection and classification of the  
65 types of bifurcation stenosis based on a group of patients with suspected coronary artery  
66 disease (CAD). Research findings from this study could improve our understanding of  
67 hemodynamic effects of various stenosis distributions in the left coronary artery  
68 bifurcation with coronary artery disease.

## 69 **Material and Methods**

### 70 *Patient datasets*

71 Fifty consecutive patients presenting with typical chest pain indicative of CAD were  
72 screened for study participants over a period of 12 months. Out of these patients, 20  
73 patients were excluded either due to normal coronary artery identified on coronary CT  
74 angiography or because of renal insufficiency, hypersensitivity to iodinated contrast  
75 materials and known severe coronary artery disease. Eight patients with right coronary  
76 artery disease detected on coronary CT angiography were further excluded from the  
77 analysis as this study only focused on the left coronary artery disease. The remaining 22  
78 patients (15 males, 7 females) were included and subjected to invasive coronary  
79 angiography for further analysis of CAD extent. Patient's characteristics are shown in  
80 Table 1. Fig. 1 shows an example patient, with a stenosis at the left main stem branch. All  
81 patients underwent coronary CT angiography, which was performed on a 64-slice scanner  
82 (GE Medical Systems, Lightspeed VCT, 64x0.625 mm) with the following protocols:  
83 beam collimation 0.625 mm, pitch 0.2-0.26, reconstruction interval of 0.4 mm, with tube  
84 voltage of 120 kVp and tube current ranging from 300 to 650 mAs. Axial images were  
85 reconstructed with a slice thickness of 0.625 mm in 0.4 mm increments, resulting in  
86 isotropic volume data with a voxel size of 0.4 x 0.4 x 0.4 mm<sup>3</sup>. CT volume data was used

87 to reconstruct the actual 3D luminal models. Volume data post-processing was performed  
88 on a workstation equipped with Analyze 7.0 (Analyze Direct, Inc., Lexana, KS, USA).

89 Image segmentation was used with a semi-automatic method with CT number  
90 thresholding, and scan-related artifacts and soft tissues were manually removed in 2D  
91 axial slices [14,15]. The segmented 3D luminal models were created with an emphasis on  
92 the left main coronary bifurcation, which is composed of left main stem (LMS), left  
93 anterior descending (LAD), left circumflex (LCx), and its side branches. The 3D luminal  
94 models of twenty two patients were saved in 'STL format' for the generation of  
95 computational geometries. Blender version 2.48 (Blender Institute, Amsterdam,  
96 Netherlands) was used to reconstruct the 3D computational models. The twenty two  
97 geometries of arteries around the LMS, LAD and LCx were obtained from the patient  
98 datasets.

99 The stenosis boundaries were kept in original form from all anatomical structures that  
100 were shown on the CT images at left main bifurcation and its side-branches. The luminal  
101 surface geometries, consisting of stenosis boundaries, were converted into solid  
102 geometries and saved in 'STL format' for the meshing methodology.

### 103 *Types of stenosis in the left coronary artery bifurcation*

104 The coronary CT angiography images were used to classify the type of bifurcation  
105 stenosis at the left coronary artery in all patients [3]. These twenty two patients were  
106 classified according to the types of bifurcation stenosis: A) stenosis involving the ostium  
107 of the LCx and LAD branches; B) stenosis involving the ostium of the LCx branch; C)  
108 stenosis involving the LMS branch; D) stenosis involving the ostium of the LAD branch.

109 The percentage of stenosis lumen was calculated based on measurements on CT images,  
110 as shown in Table 1. The diagram of stenosis classification of different types based on the  
111 patient datasets was shown in Fig. 2.

### 112 *Flow computation and solution*

113 All realistic left coronary geometries were reconstructed with inclusion of the stenosis  
114 boundaries. The sample of four patients, with the different types of bifurcation stenoses in  
115 the left coronary artery is shown in Fig. 3. Meshes were created for these geometries,  
116 with resolutions ranging from  $9 \times 10^5$  to  $9.8 \times 10^5$  cells. Mesh independence tests were  
117 performed for all coronary geometries. ANSYS ICEM CFD version 12 (ANSYS, Inc.)  
118 was used for the meshing process, with details having been described in previous studies  
119 [2,16,17]. Transient flow replicating systolic and diastolic phase at the left coronary  
120 artery was applied as an inflow boundary condition at LMS [18]. The outflow boundary  
121 condition was applied with the flow ratio through the side-branches at the LAD and LCx  
122 [19]. Murray's law was used to define the flow relationship between inflow and outflow  
123 planes [20]. Rheological parameters were applied, with a blood density of  $1060 \text{ kg/m}^3$ ,  
124 blood viscosity of  $0.0035 \text{ Pa s}$  [21]. Blood flow was assumed to be laminar. The blood  
125 was assumed to be a Newtonian and incompressible fluid [21]. Blood vessels were  
126 assumed to be rigid, and a no-slip condition was applied at the walls [22]. The Navier-  
127 Stokes equations were solved using the ANSYS CFX version 12 (ANSYS, Inc.) on a  
128 Microsoft Windows 7 32-bit machine, 6 GB of RAM with a Xeon W3505 2.53 GHz  
129 CPU. Each timestep was converged to a residual target of less than  $1 \times 10^{-4}$ . ANSYS CFD-  
130 Post version 12 (ANSYS, Inc.) was used to calculate and visualize flow velocity and wall  
131 shear stress (WSS).

132 The WSS is a commonly used factor in hemodynamic analysis; endothelial cells have  
133 been shown to align themselves with the flow direction that corresponds to the local  
134 WSS. The coordinates of the wall surface elucidate the interaction of instantaneous WSS  
135 vectors and endothelial cells [23]. The WSS is defined as:

$$136 \quad \text{WSS} = \frac{1}{T} \int_0^T \left| \mu \frac{\partial v_t}{\partial n} \right| dt \quad (1)$$

137 where  $\mu$  is blood viscosity,  $v_t$  is velocity vector near wall perpendicular to surface and  
138  $n$  is distance to the wall surface,  $T$  is pulsatile period,  $dt$  is the time derivative of the  
139 local shear stress. In addition, the time-averaged WSS (TAWSS) [23] for one cardiac  
140 cycle was calculated to include the range of WSS. The range of WSS was calculated  
141 during one cardiac cycle, and the minimum WSS values are approximately 0 Pa and  
142 maximum WSS values are around 3.5 Pa at the left coronary artery bifurcation.

## 143 **Results**

144 The classification types of realistic bifurcation stenosis among twenty two patients are  
145 represented in Table 1. Fig. 3 shows patients with these four types of stenosis. Ten  
146 patients had type D stenosis (LAD branch) and seven patients had stenosis type A (LAD  
147 and LCx branches). Three patients had stenosis type B (LCx branch) and remaining two  
148 patients had stenosis type C (LMS branch).

### 149 *Hemodynamic patterns in the left coronary artery bifurcation*

150 Flow patterns were calculated and compared in all types of bifurcation stenosis, as shown  
151 in Fig. 4. The velocity contour levels ranged from 0 mm s<sup>-1</sup> to 30.50 mm s<sup>-1</sup> with 2.18  
152 mm s<sup>-1</sup> between levels. Fig. 4A shows the bifurcation stenosis at the LCx and LAD, and

153 this case revealed a type A stenosis. The high velocity surrounding the bifurcated location  
154 was found at the LCx and LAD, which ranged from  $6.54 \text{ mm s}^{-1}$  to  $10.89 \text{ mm s}^{-1}$  and  
155  $13.07 \text{ mm s}^{-1}$  to  $17.43 \text{ mm s}^{-1}$ , respectively. The type B stenosis was shown in Fig. 4B,  
156 and a high velocity near the bifurcation was reached, from  $8.71 \text{ mm s}^{-1}$  to  $13.07 \text{ mm s}^{-1}$  at  
157 LCx branch. Fig. 4C shows the stenosis involving the LMS branch (type C) and a high  
158 velocity was reached, ranging from  $6.54 \text{ mm s}^{-1}$  to  $8.71 \text{ mm s}^{-1}$ , which is close to the  
159 bifurcation region. Type D stenosis represented patients who had stenosis at the LAD,  
160 and a high velocity close to the bifurcation ranging  $17.43 \text{ mm s}^{-1}$  to  $19.61 \text{ mm s}^{-1}$ . In this  
161 analysis the velocity change was found to be high at the stenosis located near the  
162 bifurcation areas. The flow variation during diastolic phase was similar to the systolic  
163 phase, as the stenosis resulted in high velocity surrounding the bifurcation locations.

#### 164 *Wall shear stress in the left coronary artery bifurcation*

165 Wall shear stress was calculated and compared in all patients with the various bifurcation  
166 stenoses, as shown in Table 2 and Fig. 5. TAWSS for all comparisons in one cardiac  
167 cycle was calculated in addition to the range of WSS, as shown in Table 2. WSS  
168 distributions were mainly plotted to present the effects of lumen stenosis at the left  
169 coronary artery bifurcations. Calculated WSS values during cardiac cycle ranged from 0  
170 Pa to 3.50 Pa. Fig. 5A shows the impact of stenosis at the LCx and LAD close to the  
171 bifurcation, representing patient who had type A stenosis. WSS values were found, to  
172 range from 1.75 Pa to 2.0 Pa and 2.25 Pa to 2.5 Pa, at LCx and LAD branches  
173 respectively. Fig. 5B demonstrates that the WSS values at LCx ranging from 3.25 Pa to  
174 3.5 Pa, which represented the type B stenosis. In addition, the stenosis at LMS had minor  
175 effects on WSS changes, which values ranged from 0.75 Pa to 1.0 Pa near the bifurcation

176 region, as shown in Fig. 5C. Fig. 5D shows stenosis located at LAD branch with WSS  
177 were found to range from 3.25 Pa to 3.5 Pa.

178 Fig. 5 shows the patient with a long LMS branch and a 30% stenosis displayed minor  
179 WSS change at the stenosis locations (arrows in Fig. 5C), while other patients showed  
180 WSS to be high at locations close to the bifurcations (Fig. 5A, B and D). In all patients at  
181 the locations of stenosis, low WSS was defined as  $< 1$  Pa, intermediate WSS as  $\geq 1$  Pa  
182 to  $< 2.5$  Pa, and high WSS as  $\geq 2.5$  Pa. High WSS was found in coronary branches  
183 where a  $>70\%$  stenosis was present, and in the group of patients who presented with high  
184 WSS at stenosis regions (Fig. 5B and D, arrows). The range of WSS in each type of  
185 bifurcation stenosis that was detected in all patients with CAD, can be grouped into 4  
186 categories based on our study population. TAWSS changes were similar to WSS changes  
187 in all types of stenosis but the averaged WSS values for all time steps of computation  
188 varied about 0.25 Pa of WSS values which reached at time of 0.2 s in systolic phase  
189 during one cardiac cycle. The WSS demonstrated changes during both systolic and  
190 diastolic phases, and the WSS levels were dependent on the stenosis types and degree of  
191 lumen stenosis, as shown in Fig. 2.

192 Table 3 represents the range of WSS in each type of bifurcation stenosis that was detected  
193 in patients CAD, which can be grouped into 4 categories. Stenosis type A showed a large  
194 WSS change of 0.715 Pa, and patient who had 30% stenosis represented WSS change of  
195 0.50 Pa. Stenosis type B and D showed small WSS change of 0.25 Pa, and most of the  
196 patients in these two types had stenosis  $\geq 50\%$ . Stenosis type C demonstrated the WSS  
197 change of 0.50 Pa. Therefore, the WSS variation in stenosis type A demonstrated the  
198 highest WSS values changes when compared to other types of stenosis.

199 **Discussion**

200 This study investigated the flow change and WSS distribution in the left coronary, based  
201 on different types of stenosis from a group of patients presenting with coronary artery  
202 disease. The datasets used consisted of reconstructions of the realistic left coronary  
203 geometries of 22 patients. Our results showed the various hemodynamic changes due to  
204 different types of stenosis, mainly due to the involvement of different left coronary  
205 branches. Thus, our study has potential value for improving the understanding of the  
206 impact of various types of bifurcation stenosis, and accordingly, the coronary artery  
207 disease.

208 Coronary artery disease generally forms near the bifurcation, due to the blood vessel's  
209 inherent angulation and tortuosity, leading to low WSS [2,3,8]. Medical imaging  
210 techniques such as CT angiography provides excellent anatomical details of the coronary  
211 lumen changes, however, they are unable to provide hemodynamic factors such as WSS  
212 distribution and flow variation. Recent studies have used computational fluid analysis to  
213 overcome the limitations of imaging modalities by characterizing hemodynamic changes  
214 in the situation of coronary disease [9-13]. Many studies reported in the literature paid  
215 attention to the degree of stenosis and the effects of stenosis originating in the left  
216 coronary artery bifurcation and side-branches and subsequent hemodynamic changes [9-  
217 13]. There is very little research being conducted, correlating hemodynamic change with  
218 the various types of bifurcation stenosis in the left coronary artery. This study was  
219 conducted to fill in the gap in the literature.

220 This study focuses on two important factors: velocity and WSS, and the characterization  
221 of the flow patterns and WSS variations at stenotic locations in left main coronary

222 bifurcation. The velocity was found to increase at stenotic locations in all types of  
223 bifurcation stenoses (as indicated with arrows in Fig. 4). Factors that influence the  
224 velocity increase, include vessel diameter, bifurcation angle, vessel tortuosity [2, 5, 6, 9-  
225 11]. In the coronary arteries, flow is highly pulsatile, with reversing flow in systole, and  
226 high forward flow in diastole. The left coronary artery consists of two main branches,  
227 LAD and LCx, which feature curvature in multiple phases. The likelihood of low WSS is  
228 high, depending on the individual geometry [24]. It has been reported in a previous study  
229 involving 17 casts of left coronary bifurcation that there is considerable variability in the  
230 left LAD and LCx geometries among patients, with the proximal segments of the LAD  
231 and LCx being the most predisposed sites to atherosclerotic disease [25]. Zhu et al  
232 characterized the normal geometry in 32 LAD and 35 right coronary arteries, and their  
233 results further confirmed the presence of considerable geometric variability in the  
234 coronary vasculature, particularly in the LAD [26]. Our analysis is consistent with these  
235 reports, showing that the geometric parameter in the left coronary artery induces a  
236 corresponding variability in the mechanical environment of the vessel, which would most  
237 likely to be responsible for individual differences in disease susceptibility and  
238 localization.

239 WSS affects biological signals to mechanoreceptors in endothelial cells, and it can affect  
240 gene expressions causing changes to the cellular functions of vessel walls [27,28]. In our  
241 analysis, WSS levels (low, intermediate and high) are in line with previous reports [27-  
242 29]. High WSS is also indicated as a contributor to the rupture and thrombosis of  
243 advanced atherosclerotic in human coronary artery [29-31]. Therefore, it could be

244 assumed that patients having stenosis at LAD branch (Fig. 5B) could lead to the plaque  
245 rupture, although this needs to be verified in further analysis.

246 Several limitations in this study should be addressed. Firstly, the walls of vessels were  
247 assumed to be rigid, a reasonable assumption in this case, supported by previous studies  
248 [22]. Secondly, the blood was assumed to be Newtonian, and this assumption is also  
249 supported by previous studies [7,21]. Thirdly, the study population was restricted to a  
250 small number of patients that can only be classified into the four types of bifurcation  
251 stenosis at the left coronary artery. In this study, we aim to characterise the stenosis type  
252 only based on the location of stenosis in the left coronary artery and to report the effects  
253 of the stenosis type with quantitative analysis of main hemodynamic factors such as  
254 velocity and wall shear stress. Therefore, future studies will use more patient's data,  
255 representing various types of actual stenosis, including all possible disease conditions in  
256 the left main coronary artery.

257 In conclusion, this study investigates the effects of stenosis on WSS and flow variation at  
258 bifurcated regions, and the patients' datasets were classified into the four types of  
259 bifurcation stenosis. WSS and flow velocity was found to change at different stenosis  
260 locations. WSS at >70% stenosis was significantly different from that observed at <30%  
261 of stenosis. Stenosis type A demonstrates large WSS changes, while stenosis type B and  
262 D show small WSS changes. Our results complement the former studies and have the  
263 potential of providing new insights and additional information about the hemodynamic  
264 effects of plaque location and coronary stenosis, thus, improving the understanding of the  
265 hemodynamic characterization of realistic bifurcation stenosis, although further studies  
266 based on a larger cohort are needed to confirm our results.

267 **Conflict of interest statement:** All authors declared that that they did not have any  
268 financial and personal relationships with other people or organisations that could  
269 inappropriately influence their work.

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369 **Figure legends**

370 Fig. 1. 2D medical imaging shows significant stenosis at left main stem due to calcified  
371 plaque, (arrow in A); corresponding virtual endoscopy confirms the lumen stenosis  
372 by demonstrating intravascular appearance (arrows in B).

373 Fig. 2. The diagram shows classification system of bifurcation stenosis in the left  
374 coronary artery with stenosis involving LAD and LCx (A), LCx (B), LMS (C), and  
375 LAD (D).

376 Fig. 3. The selected geometries of realistic left coronary models with bifurcation stenosis  
377 based on the classification system in Fig. 2, (A) stenosis type A in patient No. 1, (b)  
378 stenosis type B in patient No. 7, (c) stenosis type C in patient No. 16 and (d) stenosis  
379 type D in patient No. 10. Arrows reveal the stenosis locations.

380 Fig. 4. Flow patterns of velocity change surrounding bifurcation were reached at time of  
381 0.2 s in systolic phase during one cardiac cycle in patients who had (A) stenosis type  
382 A, (B) stenosis type B, (C) stenosis type C and (D) stenosis type D. Arrows identify  
383 the velocity to be high at stenosis positions near the bifurcations.

384 Fig. 5. WSS distributions of WSS change surrounding bifurcation were reached at time of  
385 0.2 s in systolic phase during one cardiac cycle in patients who had (A) stenosis type  
386 A, (B) stenosis type B, (C) stenosis type C and (D) stenosis type D. Arrows identify  
387 the WSS to be high at stenosis positions nearby bifurcations.