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Review

Is left coronary system more susceptible to atherosclerosis than right? A pathophysiological insight

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Abstract

On the basis of pathological, angiographical, intravascular ultrasound and computed tomography data coronary atherosclerosis appears to be more prevalent in the left coronary arterial system compared to the right. However, the pathophysiological mechanisms implicated in this discrepancy largely remain uncertain. The hemodynamic or anatomical differences between the right and left coronary artery might play a key role. Physiologically, the right coronary flow is more uniform during the cardiac cycle compared to the left, which experiences a remarkable systolic decline accompanied by a significant diastolic increment. Thus, the oscillatory shear stress, that constitutes a proved atherogenic factor, is more intense in regions with disturbed flow in the left coronary system. Likewise, the wall stress is more oscillatory during the cardiac cycle in the left coronary artery. On top of that, several differences regarding the anatomical configuration (3D geometry, branching) and the phasic motion between the right and the left arterial system appear to play a critical role in the modulation of the local atherogenic environment. Therefore, it could be assumed that the flow characteristics along with the geometrical and phasic motion patterns generate an intense oscillation of the imposed to the arterial wall stresses, especially in the left coronary artery. Over the long-term, these augmented oscillatory stresses, in combination with the effect of systemic risk factors, might modulate a more atherogenic environment in the atherosclerosis-prone regions of the left coronary system.

Keywords: Coronary artery; Atherosclerosis; Blood flow; Hemodynamics; Coronary geometry

1. Introduction

According to large pathological observations in 600 male and 600 female human hearts coronary atherosclerosis seems to be more prevalent in the left coronary arterial system, in particular in the proximal segments, compared to the right [1,2]. In fact, this discrepancy has been found to be more prominent in the later decades in both genders. The increased susceptibility of the left coronary artery (LCA) and especially of the left anterior descending (LAD) to atherosclerosis has also been demonstrated in histopathology data derived from 2964 hearts [3]. Recent angiographic [4], intravascular ultrasound [5] and computed tomography [6] studies in 302, 262 and 111 patients, respectively, have also confirmed these findings.

Furthermore, existing clinical evidence supports indirectly the lesser prevalence of atherosclerosis in the right coronary artery (RCA). Isolated infarction of the right ventricle, which is almost exclusively perfused by RCA, is extremely rare; right ventricular infarction is usually noted in association with inferior–posterior left ventricular wall infarctions [7]. Also, isolated left posterior wall infarction is an uncommon condition; it varies within a 3–11% range among all patients with acute myocardial infarction [8]. Usually, the left posterior infarction is observed in the setting of acute lateral or inferior infarctions due to lesions at the left circumflex artery in a left dominant coronary circulation. When seen in isolation, the infarct-related artery is the posterior descending artery derived by RCA in patients with right dominant coronary circulation.

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Coronary hemodynamics has long been the subject of interest and has been studied both in humans and animals. Since Doppler guidewire system was introduced for the measurement of coronary flow more accurate and direct evaluation of coronary hemodynamics has come into practice [9]. As long as the local hemodynamic conditions are directly related with the development and progression of atherosclerosis [10], it would be of utmost clinical and therapeutic importance to investigate the exact hemodynamic regulatory determinants of left and right coronary flow, as well as their phasic distribution over the cardiac cycle.

The predominance of left coronary atherosclerosis in comparison to right constitutes an epidemiological finding that has not been explained pathogenetically yet. Possibly the hemodynamic or anatomical particularities of RCA could modulate a less atherogenic environment in this vessel. These particularities are being discussed in this review, attempting to provide at the same time their pathophysiological impact on the right and left coronary atherosclerosis.

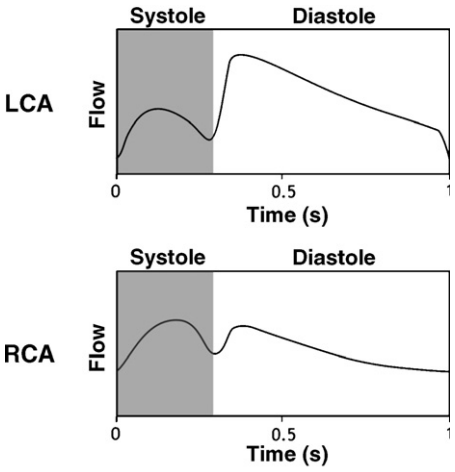

Fig. 1. The flow patterns at the epicardial segments of the left (LCA, upper panel) and right coronary artery (RCA, lower panel) over the cardiac cycle. The diastolic blood flow is less prominent in RCA than in LCA, whereas RCA has relatively systolic dominance in comparison to LCA.

2. Left vs. right coronary artery hemodynamics

The coronary flow (Q) is defined as, $Q = \Delta P/R$, where ΔP is the pressure gradient (driving pressure) between the aortic root and the right or left ventricle and R is the vascular resistance [11]. Henceforth, the critical determinants of coronary flow are the driving pressure [12] and the intramyocardial resistance attributed to the compressive force of the contractile myocardium [13]. Physiologically, the coronary flow is not uniform; it varies not only between the left and right coronary artery, but also within the same artery both temporally and spatially [11]. Regarding the temporal variation of coronary flow, this is attributed to the periodic phenomena that occur during the cardiac cycle. In particular, the left sub-endocardial arteries experience a massive retrograde flow during systole due to the compressive resistance of the contractile left ventricular myocardium [14]. Contrary to the sub-endocardial arteries, the left sub-epicardial and epicardial segments maintain an anterograde but remarkably slow flow during systole. Although it would be anticipated that during systole the backward flow derived by the sub-endocardial arteries would induce a retrograde flow in the sub-epicardial and epicardial portions as well, in fact, this retrograde flow is concealed by the high capacitance of extramural epicardial arteries due to their elastic properties [13]. Conversely, in diastole, as the left ventricular myocardium relaxes and the intraventricular pressure significantly declines, the compressive impediment to sub-endocardial arteries reduces significantly. As a result, the dilated epicardial arteries discharge the stored blood through the microcirculation causing a massive anterograde and accelerated flow in the entire left coronary arterial bed in order to maintain the myocardial perfusion [11]. In fact, it has been found that 85% of coronary flow in the LCA occurs throughout diastole [11]. Thus, as it is illustrated in Fig. 1, the flow in the left epicardial segments exhibits a biphasic pattern with low values in systole until early diastole, when it abruptly rises and then declines gradually as aortic pressure falls during the rest of diastole.

However, the right epicardial coronary flow experiences some differences in comparison to the left (Fig. 1). In particular, the blood flow in RCA is less dominant than in LCA in diastole, while RCA has relatively systolic predominance compared to LCA [11,12,15–19]. Therefore, the ratio of peak systolic to peak diastolic flow velocity is substantially greater in RCA (approximately equal to 1) in comparison with LCA, where it is less than 1. The explanation of the right systolic dominance is twofold; first the right intraventricular pressure during systole is much lower, thus the systolic pressure gradient (ΔP) across the right coronary arterial bed is greater and secondly the intramyocardial resistance (R) within the thin right ventricular myocardium is markedly lower than the left [12,15]. Thus, during systole the compression of the sub-endocardial arteries and the subsequent retrograde flow are remarkably less in RCA than LCA, resulting in a lesser deceleration of the right epicardial and sub-endocardial flow. Interestingly, it has been found that the RCA branches that supply blood to the left ventricle such as the posterior descending artery exhibit a flow pattern similar to that of LCA, due to their exposure to the left ventricular hemodynamic conditions [15].

3. Role of shear stress

3.1. Vascular wall response to low and oscillatory shear stress

Shear stress (SS), the frictional force exerted by the flowing blood on the endothelial surface, comprises a

major modulator for the normal endothelial function and morphology [10,20,21]. Physiologically, in unbranched coronary segments, where laminar flow occurs, the SS forces vary within a normal range (10–70 dyn/cm^2) [20]. The endothelial cells (EC) contain several mechanosensors capable of detecting laminar SS and converting it into a biological signal (mechanotransduction) [22,23] (Fig. 2). To date, two models of mechanotransduction have been proposed, the "centralized", in which the mechanical stimuli are sensed and transduced by specific mechanoreceptors on the luminal surface, and the "decentralized", in which the mechanosensors are located away from the site of mechanical stimulus. In the former model several molecules (ion channels such as K^+-, Na^+-, Ca^{2+}- channel, G-proteins, tyrosine kinase receptors and caveolae) have been identified to be involved directly or indirectly into the transduction of SS [24,25]. However, recent in vitro studies have demonstrated that although SS acts on the luminal surface of the EC it activates several molecules located on the abluminal surface ("decentralized" mechanotransduction) [22]. The integrins, a family of more than 20 transmembrane glucoproteins anchored to the extracellular matrix proteins, have been shown to play a key role in this model [26,27]. Upon SS stimulus, the integrins experience a conformational change resulting in their activation. Following their activation, several kinases (FAK, Src, Fyn, PKC, PI3K, Flk-1) at focal adhesion sites of the EC are phosphorylated. These signaling molecules are associated with their adaptor proteins (Grb2, Shc, Crk) formatting complexes, which in turn activate the guanine nucleotide exchange factors (SOS, C3G) for a GTPase, called Ras, allowing it to discard GDP and bind GTP. Active Ras initiate a downstream intracellular cascade of protein kinases each of which phosphorylates and hence activates the next, culminating in kinases called mitogen-associated protein kinases (MAPKs). Three MAPKs have been identified so far, namely, ERK-1 and ERK-2, JNK and p38 [26,27]. Notably, caveolae, G-proteins, tyrosine kinase receptors and ion channels appear to play a complementary or synergistic role in the integrin-related mechanotransduction, suggesting an interplay between "decentralized" and "centralized" model [26]. All the above signaling pathways lead to the phosphorylation and subsequently activation of specific transcription factors [28] such as the nuclear factor kappa-B (NF-κB), the activator protein-1 (AP-1) and the early SS responsive genes *(*c-*fos,* c-*jun,* c-*myc),* which encode the corresponding transcription factors. The NF-κB [28] is activated in the cytoplasm where it forms with its inhibitor IκB an inactive heteromeric complex. After phosphorylation and degradation of the IκB the active molecule of NF-κB is released and translocates to the nucleus. The abovementioned transcription factors bind positive or negative shear stress responsive elements (SSRE) at the promoter regions of several genes inducing or suppressing their expression [10,29]. Ultimately, the laminar SS maintains an atheroprotective phenotype of the ECs by decreasing their proliferation and apoptosis, increasing the secretion of vasodilatory (prostacycline, NO), growth inhibitor (TGF-β), anti-coagulant (prostacyclin, thrombomodulin), fibrinolytic (TPA) and anti-oxidant (SOD, NO) substances and inhibiting the production of vasoconstrictors (ET), growth promoters (PDGF, VEGF), chemotactic factors (MCP-1) and adhesion molecules (VCAM-1, ICAM-1, E-selectin) [10,20,21,24,25,27,29].

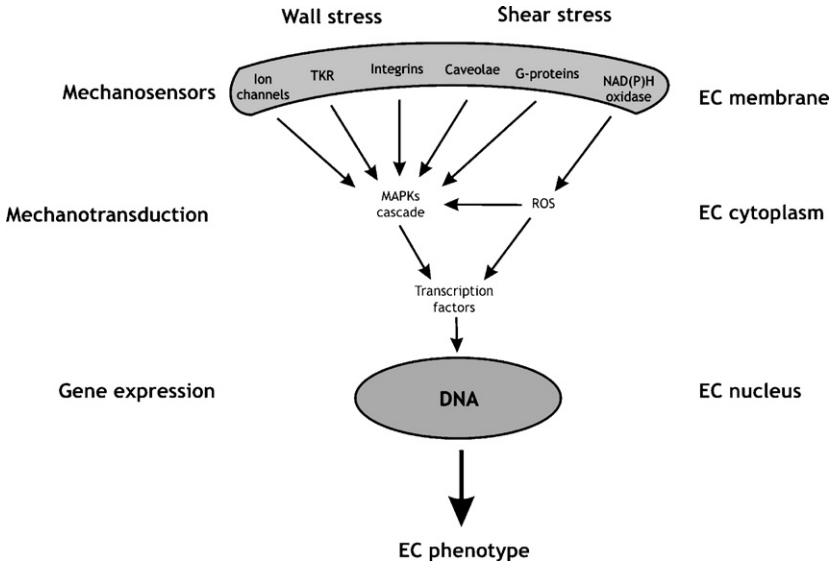

Fig. 2. The mechanical stimulus (shear stress or wall stress) stimulates several mechanosensors located either at the plasma membrane or away from the site of stimulus, initiating an intracellular network of reactions which eventually end up to the activation of MAPKs or the production of ROS. Ultimately, through the induction of several transcription factors and upregulation or downregulation of the expression of specific genes, the EC morphology and function are modulated appropriately (EC, endothelial cell, TKR, tyrosine kinase receptors, MAPKs, mitogen-activated protein kinases, ROS, reactive oxygen species).

Unlike straight arterial segments, near branch points, bifurcations and major curves disturbed flow occurs generating low or oscillatory SS (<4 dyn/cm^2) [20]. It is in these regions where, according to clinical and experimental observations, the atherosclerotic lesions are preferentially generated and progress [10,20,21,30]. It seems that low and oscillatory SS regulate the aforementioned mechanotransduction and gene expression processes so that they shift the EC from its atheropotective and quiescent state to its atherogenic phenotype [20].

Also, it has been proposed that low and oscillatory SS lead to the activation of intracellular signaling pathways ending in the production of reactive oxygen species (ROS) and impairment of anti-oxidative systems [24,31] (Fig. 2). These processes eventually bring the EC to a state of high oxidative stress. Physiologically, NAD(P)H oxidase is a plasma membrane-bound oxidative enzyme found in the ECs, vascular smooth muscle cells, monocytes and fibroblasts. It has been postulated that NAD(P)H oxidase comprises a potential mechanosensor that transduces the low SS stimulus into biological response [23,24,31]. In an in vitro study the ECs exposed to oscillatory shear stress showed a marked increase in NAD(P)H oxidase activity and concomitant ROS production in contrast to the anti-oxidative state induced by laminar flow [31,32]. The generated ROS are implicated in the initiation of several atherogenic processes including the activation of transcription factors (NF-κB, AP-1) [29,33], the increased expression of inflammatory and adhesion molecules (VCAM-1, ICAM, MCP-1) [23,31], the release of matrix metalloproteinases (MMPs) [31] and the induction of EC apoptosis [31]. Furthermore, ROS reduce the bioavailability of intracellular NO by either degrading it or impairing its production [24,31]. In addition to the upregulation of NAD(P)H oxidase, low and oscillatory SS increase the EC oxidative stress by downregulating the anti-oxidative enzymes [24]. Glutathione constitutes a key factor in the regulation of the redox state of EC by providing reducing equivalents in several intracellular biochemical reactions. It has found to be decreased when exposed to disturbed flow [24]. Also, low SS appears to reduce the mRNA expression of Cu/Zn superoxide dismutase (SOD) which comprises another potent anti-oxidant enzyme [34].

3.2. Shear stress differences between RCA and LCA

Since SS is defined as the product of the flow velocity gradient near the endothelium and blood molecular viscosity, the phasic SS oscillations between systole and diastole follow the same pattern with flow [21,30]. Henceforth, like velocity, the oscillatory SS is less prominent in the susceptible to atherosclerosis regions of remodeling RCA compared to those of LCA, which experiences a significant systolic SS decline accompanied by a steep diastolic increment. Given the well-established involvement of oscillatory SS in atherogenesis, the augmented SS oscillation that occurs in LCA during the cardiac cycle could provide a substantial explanation for the increased susceptibility of this artery in atherosclerosis.

Intriguingly, it has been demonstrated that in patients with chronic lung diseases the prevalence of right coronary artery atherosclerosis and subsequent right ventricular myocardial infarction is greater as compared to those without obstructive lung disease [8,35]. It is well evidenced that the right ventricular hypertrophy occurs in patients with chronic lung disease due to chronic pressure overload. As a result, the driving pressure (ΔP) in RCA decreases while at the same time the myocardial resistances (R) increases. In other words, the hypertrophic right heart develops gradually over the time hemodynamic conditions similar to those that occur at the left heart. In such an environment, the flow in the RCA experiences a significant reduction in its systolic component, which in turn might increase the magnitude of SS oscillations between systole and diastole modulating eventually a more atherogenic environment [12,19].

4. Role of wall stress

Beside SS, the hydrostatic blood pressure generates another hemodynamic force, namely the wall stress (WS) [10]. The increased WS has long been suggested to be an atherogenic factor [36–38]. Like SS, several studies have demonstrated that WS instigate various signal transductions by stimulating several mechanoreceptors (ion channels, integrins, tyrosine kinase receptors) on either ECs or vascular smooth muscle cells [38,39] (Fig. 2). Many of the signaling events induced by WS are similar to those by SS e.g. the increased tyrosine phosphorylation of FAK leading to activation of MAPKs cascade and concomitant induction of transcription factors (NF-κB, AP-1) [28,39]. These signals promote in turn the remodeling of vascular wall by up-regulating smooth muscle cell growth and matrix degrading enzymes production [40]. Also, the EC function and morphology is mediated by the regulation of genes encoding vasoactive substances, growth and apoptotic factors, pro-inflammatory, chemotactic and coagulation molecules [28,39]. Another mechanism [41] involves the direct effect of mechanical stress on the ECs by stimulating the NAD(P)H oxidase to produce ROS leading to the formation of intracellular oxidative stress (Fig. 2). The generated ROS reduce the NO biovailability in the ECs by either degrading it or impairing its production, resulting in the loss of endothelium-dependent vasodilation. Furthermore, ROS contribute to vascular inflammation by stimulating transcription factors (NF-κB) and upregulating pro-inflammatory molecules and to vascular remodeling by inducing the smooth muscle cell growth and MMPs overexpression. Ultimately, all these processes confer a predisposition to atherosclerosis.

As mentioned, during systole the dynamic storage of blood that retrogrades from the collapsed sub-endocardial segments occurs almost exclusively in the left coronary

epicardial segments. As a result, these segments are exposed to more intense WS during systole compared to the corresponding RCA segments, while in diastole the imposed WS declines markedly. Consequently, the LCA portions experience greater WS oscillations during the cardiac cycle, which might constitute an atherogenic stimulus. In fact, this effect could be intensified over the long-term—the so-called "chronic fatigue effect" [37]. However, this hypothetical mechanism needs to be further elucidated with more analytical experimental studies.

5. Role of coronary geometry and phasic motion

Apart from the hemodynamic differences, the RCA and LCA exhibit geometrical and motion particularities. Overall, the coronary arteries are considered as the most susceptible vessels to atherosclerosis in the entire human vasculature [42]. This observation could be merely explained by the extremely complex three-dimensional (3D) geometry they have in combination with the periodic changes this geometry experiences during the cardiac cycle, two unique characteristics that differentiate the coronary arteries from the rest of the human vessels. The major factors that characterize the 3D coronary geometry are curvature and torsion, which determine the straightness and the plainness of the artery, respectively [42]. In particular, the higher the curvature and torsion is, the higher the departure from straightness and plainness of the coronaries, hence more complex the geometry. Apart from the static 3D geometry, as long as the epicardial segments of coronary arteries are closely attached to the beating heart they sustain two main types of motion during the cardiac cycle, namely the in-plane bending (changing curvature) and the out-of-plane twisting (changing torsion) [42]. As with the coronary flow, both coronary geometry and coronary motion vary between the left and the right coronary artery, as well as within the same artery both axially and temporally. In the recent years, the development of new imaging techniques and novel computer algorithms made the in vivo tracking of coronary motion during the cardiac cycle reasonable [42]. Additionally, the integration of intravascular ultrasound, which provides information about the coronary wall, with these methods, facilitated the study of the implication of phasic coronary motion in the formation and development of atherosclerosis [42].

Ding et al. [43] investigated the dynamics of human coronary motion and correlated the parameters of that motion with the presence of atherosclerosis. It was found that the total displacement of RCA throughout the cardiac cycle is approximately twice than that of LAD, a phenomenon attributed to the different locations of the coronary arteries on the cardiac surface. This finding has also been confirmed by other computed tomography-based studies [44]. It was also found that LAD exhibits twice the torsion of RCA, while RCA experiences much greater curvature than the LAD [43]. A human autopsy study showed that the angiographically diseased coronary portions experienced significantly higher torsion; therefore it was postulated that there might be an association between high torsion and the development of atherosclerosis [45]. Furthermore, significant SS and WS oscillations have been found in arterial segments experiencing high twisting [43]. Thus it could be hypothesized that the above geometrical and motion differences between RCA and LCA might be implicated in their different susceptibility to atherosclerosis. The specific geometrical characteristics along with the phasic coronary motion could cause a periodic oscillation of the imposed to the arterial wall mechanical (e.g. WS) and fluid (e.g. SS) stresses, in addition to the periodic effect of pulsatile flow, modulating an atherogenic environment over the long-term. However, which precise patterns of coronary motion and which geometrical particularities facilitate the formation and progression of atherosclerotic lesions need to be elucidated.

Another important geometrical characteristic of the left coronary system is the increased number of branches, which play a key role in the generation of disturbed flow [10,21]. Since the disturbed flow comprises a proved atherogenic factor, it seems reasonable to adopt the hypothesis that the increased branching of LCA makes it more susceptible to the development of atherosclerosis by conferring more atherosclerosis-prone regions than RCA.

6. Conclusions

In conclusion, on the basis of epidemiological data the left coronary arterial bed seems to be more susceptible to atherosclerosis than the right. However, the precise pathogenetic explanation of this finding still remains uncertain. The hemodynamic and geometrical differences in combination with the effect of the systemic risk factors over the years might constitute a potential perspective for the explanation of this discrepancy (Table 1). Additional, patient-based follow-up studies, estimating the coronary hemodynamic conditions and the 3D geometry along the cardiac cycle, should be conducted in order to provide further insight.

Table 1
The major differences between the left and right coronary artery regarding hemodynamics, 3D geometry and phasic motion

	Left coronary artery	Right coronary artery
Hemodynamics		
Phasic flow	Predominantly diastolic	Predominantly systolic
Shear stress	More oscillatory	Less oscillatory
Wall stress	More oscillatory	Less oscillatory
3D Geometry		
Static geometry	Higher torsion	Higher curvature
Branching	More	Less
Phasic motion	Lesser phasic displacement	Greater phasic displacement

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