

Review

## Elevated heart rate and atherosclerosis: An overview of the pathogenetic mechanisms<sup>☆</sup>

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### Abstract

Several epidemiological studies have reported that an elevated heart rate is associated with coronary atherosclerosis independently of other risk factors. In this review we explore the pathophysiologic mechanisms involved in the pro-atherosclerotic effect of elevated heart rate, apart from its association with sympathetic tone. An elevated heart rate enhances the magnitude and frequency of the tensile stress imposed on the arterial wall and prolongs the exposure of coronary endothelium to the systolic low and oscillatory shear stress. Moreover, increased heart rate intensifies the pulsatile motion of the heart and, therefore, the frequency of the periodically changing geometry of the coronary arteries, thereby affecting the local hemodynamic environment. All these processes induce structural and functional changes of the endothelial cells, which are accumulated over the time in atherosclerosis-prone regions promoting atherosclerosis. Heart rate should be considered in every patient with coronary heart disease, especially since it is an easily measurable and reproducible parameter. Slowing the heart rate could potentially decrease the progression of atherosclerosis by reducing the local pro-atherosclerotic vascular environment. This effect may be involved in any beneficial role of heart rate lowering agents in preventing coronary heart disease.

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### 1. Introduction

Epidemiological evidence shows that elevated heart rate is associated with increased cardiovascular morbidity and mortality, an association that has been mostly attributed to the underlying sympathetic overactivity [1–14]. The sympathetic nervous system plays a key role in the pathogenesis of

atherosclerosis probably through induction of several hemodynamic (e.g. tachycardia, hypertension, increased blood viscosity) and metabolic (e.g. hyperinsulinemia, hyperglycemia, dyslipidemia, obesity) changes. Several large clinical studies have shown that high heart rate, is associated with atherosclerosis and cardiovascular morbidity and mortality, independently of other risk factors, such as age, gender, hypertension, hyperlipidemia, and diabetes [1,5,6,13,15,16] (Fig. 1). Experimental studies in animal models of atherosclerosis also demonstrated that high heart rate is associated with coronary and carotid atherosclerosis [17]. Monkeys with higher heart rates had more extensive coronary atherosclerosis than those with lower heart rate [18,19], whereas experimental lowering of heart rate

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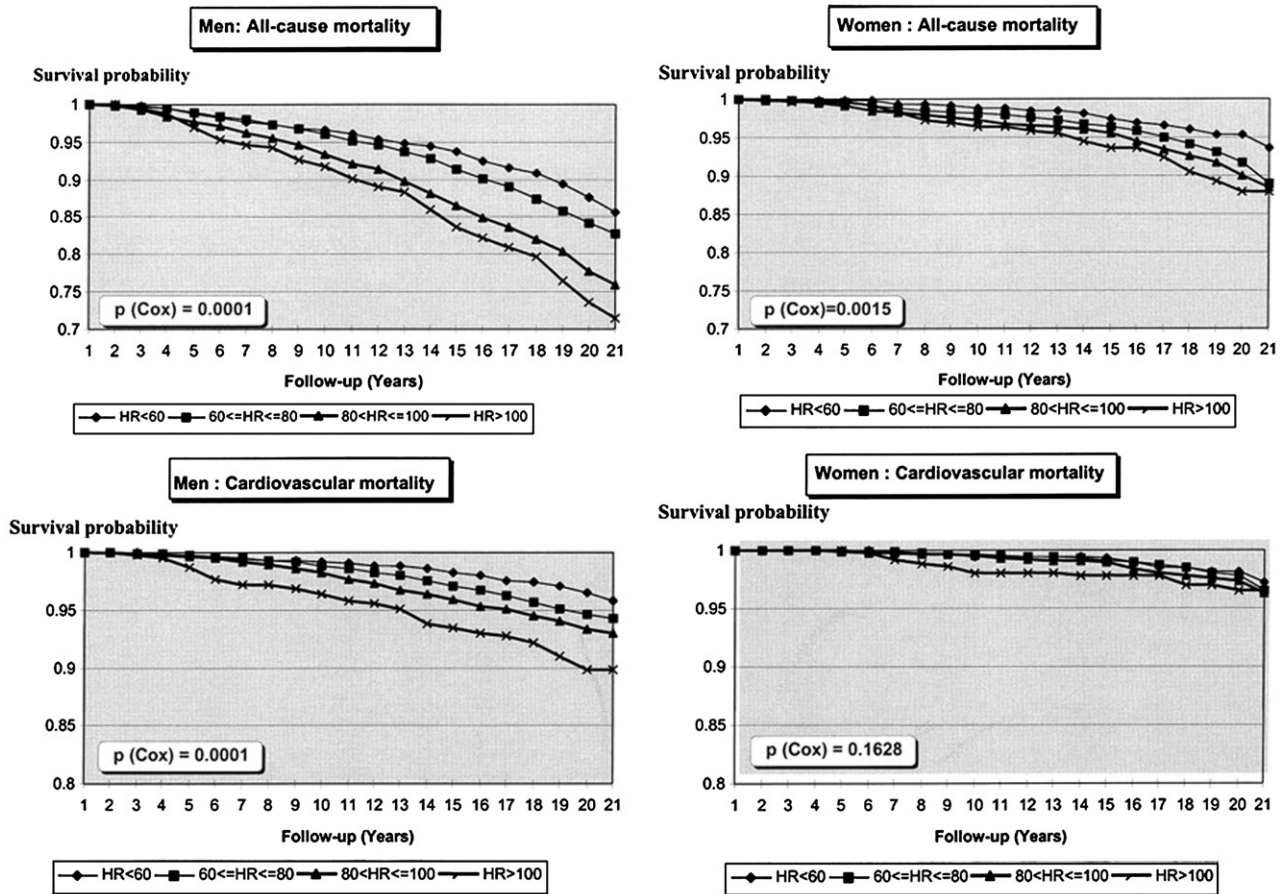


Fig. 1. Survival probability curves for all-cause and cardiovascular mortality in men and women across the entire heart rate spectrum. *P* values were obtained after adjustment for age, systolic blood pressure, diastolic blood pressure, cholesterol, body mass index, tobacco consumption, physical activity, antihypertensive treatment, and history of myocardial infarction. In men, high heart rate was associated with all-cause and cardiovascular mortality, whereas in women, this association was observed only for all-cause mortality (reprinted from [10]).

with propranolol [20] or sinus node ablation [21,22] reduced coronary or carotid atherosclerosis. In normotensive and spontaneously hypertensive rats, chronic heart rate reduction by ivabradine, a selective heart rate lowering agent, induced a significant decrease in thoracic aorta wall thickness, supporting the association of elevated heart rate with atherosclerosis [23].

In this review we explore the underlying mechanisms implicating high heart rate in atherosclerosis — independently of its association with sympathetic overactivity. We also consider the anti-atherogenic effect of heart rate lowering. Although the review focuses on the coronary vasculature similar mechanisms probably apply to the entire arterial bed.

## 2. Basics of coronary hemodynamics

### 2.1. Definition of shear stress and tensile stress

Histopathology combined with flow simulations, as well as in vivo animal and human studies have shown that atherosclerotic lesions are preferentially located in the vicinity of branch points, the outer wall of bifurcations and the inner wall

of major curvatures [24–27]. Local hemodynamic forces play a unique role in predisposing some arterial areas to atherosclerosis [28–34]; these forces include flow-generated shear stress (SS) and blood pressure-derived tensile stress (TS) (Fig. 2). SS is the tangential force derived by the friction of the flowing blood on the endothelial surface and is defined as the

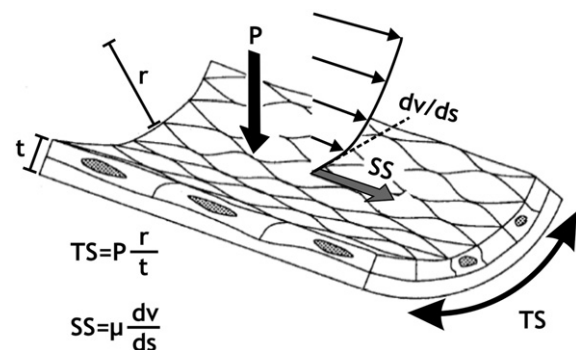


Fig. 2. The major hemodynamic forces include flow-derived shear stress (SS) and blood pressure-induced tensile stress (TS) imposed tangentially and circumferentially, respectively, on the arterial wall ( $P$ =blood pressure,  $r$ =lumen radius,  $t$ =wall thickness,  $dv/ds$ =shear rate at the wall,  $\mu$ =blood viscosity).

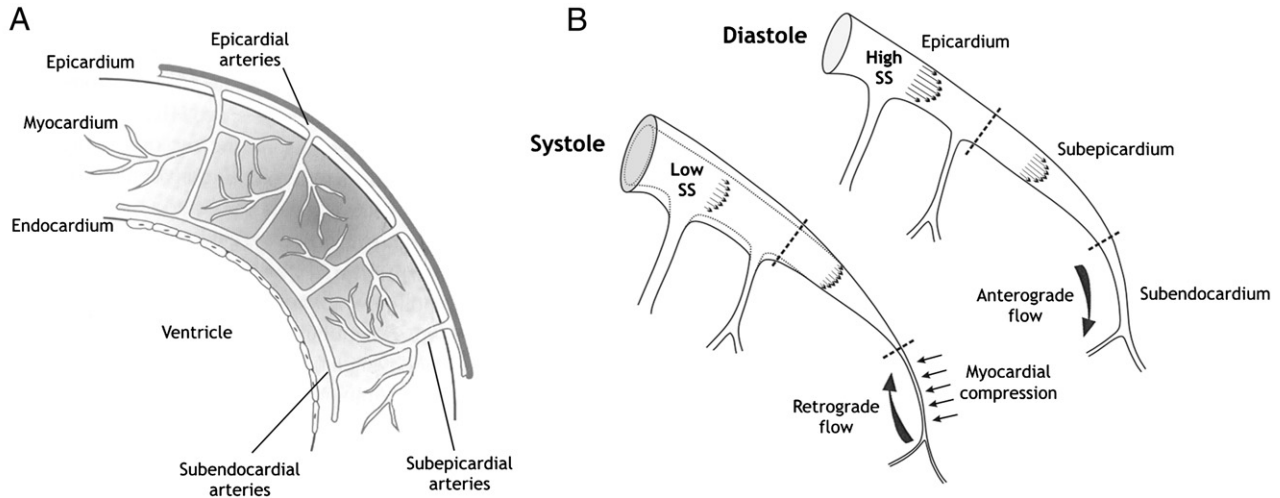


Fig. 3. A. The coronary vasculature is divided into three distinct territories, namely subendocardial, subepicardial and epicardial. In each of these territories a distinct flow pattern occurs. B. Phasic variation of coronary flow and shear stress (SS) during the cardiac cycle. In systole a retrograde flow (left black arrow) occurs in subendocardial arteries accompanied by decrease in their diameter. Contrary to subendocardial portions, the subepicardial and epicardial segments are dilated resulting in a slow systolic anterograde flow (dotted lines indicate the end-diastolic diameter of the epicardial coronary segments before their dilation in systole). In diastole, the flow in the entire coronary tree accelerates (right black arrow). As a result of these phasic changes, SS in epicardial coronaries experiences a low and oscillatory pattern during systole, and increases in diastole.

product of blood viscosity ( $\mu$ ) and shear rate at the wall ( $dv/ds$ ). The shear rate represents how fast the blood flow velocity changes when moving from the vessel wall towards the centre of the lumen.

TS, also known as circumferential stress, constitutes the blood pressure-derived force imposed circumferentially on the arterial wall [33]. Its magnitude can be approximated by the equation  $T=(P*r)/t$ , where  $P$  is the blood pressure,  $r$  is the lumen radius and  $t$  is the wall thickness.

### 2.2. Coronary blood flow

The major determinants of coronary flow are the compressive resistance of the ventricular myocardium and the driving pressure (i.e. the difference between aortic and intraventricular pressure) [35]. These forces create forward and backward compression waves (“pushing” effect) and expansion waves (“pulling” effect), which interplay with each other and determine the direction of flow at each time-point of the cardiac cycle [36,37] (Figs. 3 and 4).

In systole, the subendocardial arteries, especially in the left coronary system, experience a retrograde flow due to myocardial compression [38–45]. Unlike subendocardial arteries, the subepicardial and epicardial segments are mainly characterized by a slow systolic anterograde flow [39]. Although it would be anticipated that during systole the backward flow derived by the collapsed subendocardial vessels would induce a retrograde flow in subepicardial and epicardial arteries as well, actually, this retrograde flow is concealed by the high capacitance of the extramural epicardial arteries, which are dilated due to their elastic properties [41]. Forward compression waves derived by the increased aortic pressure also contribute to systolic forward

epicardial flow [36,37]. However, a small component of backward flow may occur, especially at the onset of systole, making the systolic flow in the coronary arteries more complex than in other vascular beds [37].

In diastole, as the ventricular myocardium relaxes, the compressive impediment in intramyocardial arteries resolves, and the dilated extramural segments discharge the stored blood through the microcirculation, resulting in a forward and accelerated flow in the entire coronary arterial bed to maintain myocardial perfusion [36,37].

### 2.3. SS and TS variation over the cardiac cycle

The pulsatile nature of the coronary blood flow in combination with the blood’s rheological properties and the

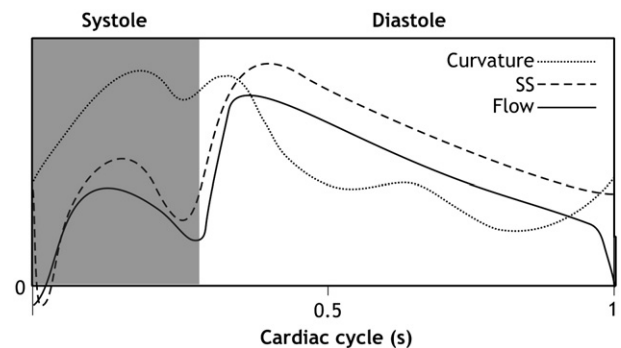


Fig. 4. Phasic variation of blood flow, shear stress (SS) and curvature in epicardial coronary arteries during the cardiac cycle [35]. In systole the vessel exhibits maximum curvature, while flow and SS experiencing low values. In diastole, the vessel curvature declines, whereas flow accelerates resulting in higher SS values.

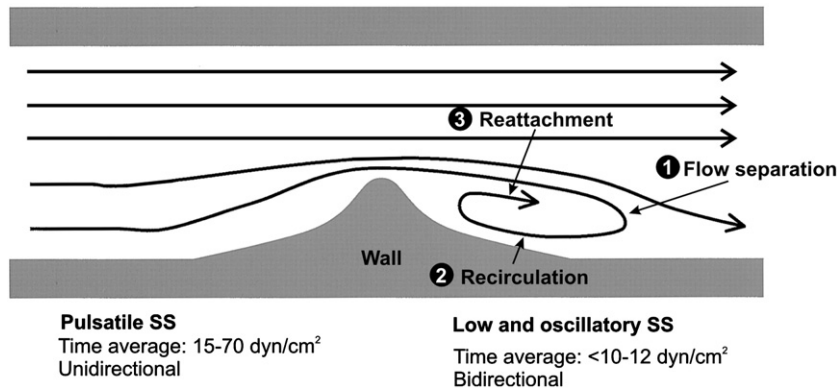


Fig. 5. In straight arterial segments pulsatile shear stress (SS) occurs, whereas in geometrically irregular regions, where secondary flows develop (i.e. flow separation, recirculation and reattachment to forward flow), SS acquires a low and oscillatory pattern.

complex geometric configuration of the coronary arteries determines the SS patterns, which are characterized by direction and magnitude [28] (Fig. 5). In relatively straight arterial segments, SS is pulsatile and unidirectional with a magnitude that varies within a range of 15–70 dyn/cm<sup>2</sup> over the cardiac cycle and yields a positive time-average.

In contrast, in geometrically irregular regions, where disturbed laminar flow occurs, pulsatile flow generates low and/or oscillatory SS. Low SS refers to SS which is unidirectional at any given point with a fluctuating magnitude during the cardiac cycle that results in a significantly low time-average (<10–12 dyn/cm<sup>2</sup>). Low SS typically occurs at the inner areas of curvatures, as well as upstream of stenoses.

Oscillatory SS is characterized by significant changes in both direction (i.e. it is bidirectional) and magnitude between systole and diastole, resulting in a very low time-average, usually close to zero. Oscillatory SS occurs primarily at the lateral walls of bifurcations, in the vicinity of branch points and downstream of stenoses.

Similarly to SS, following periodic changes in blood pressure, TS undergoes phasic variation over the cardiac cycle between a systolic maximum and a diastolic minimum.

### 3. Local hemodynamic environment and atherosclerosis

Endothelial cells are capable of sensing the local hemodynamic conditions, transducing them into biochemical signals, ultimately shifting endothelial gene expression, and phenotype to a pro-atherosclerotic state. This process is called mechanotransduction and has been extensively reviewed elsewhere [28,46–50].

Low SS stimulates specific mechanosensors located on the surface of endothelial cells, such as membrane integrins, ion channels, tyrosine kinase receptors, caveolae and G-proteins to convert SS stimuli into biochemical signals. These signals activate multiple downstream signaling cascades, thereby activating several transcription factors, such as nuclear factor-kappa B (NF-κB) and activator protein-1 (AP-1). Binding of these factors to shear stress responsive elements (SSREs) of the

endothelial DNA upregulates numerous pro-atherogenic genes, while downregulating the expression of several atheroprotective genes [51]. Ultimately low SS promotes reduced nitric oxide (NO) synthesis and increased NO degradation [52–54], increased LDL uptake [55], generation of reactive oxygen species (ROS) [56], expression of adhesion molecules [e.g. vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1)], chemoattractants [e.g. monocyte chemoattractant protein-1 (MCP-1)] and cytokines [e.g. tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6)] [57], and secretion of pro-thrombotic molecules [46]. In addition to functional changes, low SS affects the endothelial cytoskeleton provoking permanent structural changes of endothelial cells [58]. These structural changes in combination with endothelial cell apoptosis, which is also promoted by low SS [28,59], make the endothelium more permeable to circulating LDL and inflammatory cells (e.g. monocytes, T-lymphocytes, mast-cells) [50,60,61]. Blood stagnation that occurs in low blood flow regions further facilitates the infiltration of LDL and inflammatory cells into the intima [62].

An increased TS is sensed by several mechanoreceptors such as integrins, stretch-sensitive ion channels, tyrosine kinase receptors and G-proteins, which in turn trigger a downstream cascade of signaling molecules resulting in the activation of NF-κB or AP-1 [48,63–67]. These transcription factors in turn are associated with certain strain-sensitive elements located at the promoter regions of several pro-atherogenic genes, thereby upregulating them. Such genes encode potent vasoconstrictors [e.g. endothelin-1 (ET-1)] [63], adhesion molecules (e.g. VCAM-1, ICAM-1), chemoattractants (e.g. MCP-1), and cytokines (e.g. TNF-α, IL-6) [68], oxidative enzymes, such as nicotinamide adenine dinucleotide phosphate oxidase (NADPH) and xanthine oxidase [69], growth promoting factors [e.g. platelet derived growth factor, (PDGF)], and matrix degrading enzymes [e.g. matrix metalloproteinases (MMPs)] [70]. Elevated TS was also proposed to induce direct endothelial injury thereby increasing the endothelial permeability to LDL and circulating inflammatory mediators [71,72].



#### 4. Mechanisms responsible for the pro-atherosclerotic effect of high heart rate

##### 4.1. Increased magnitude and frequency of the mechanical load imposed on the arterial wall

Mean blood pressure is given by the equation  $Blood\ Pressure = (Stroke\ Volume \times Heart\ Rate) \times Peripheral\ Resistances$ , in which the product of stroke volume and heart rate corresponds to the cardiac output [35]. Blood pressure does not change linearly in relation to heart rate for the entire spectrum of heart rate values. At rates above 120 beats per min (bpm), the stroke volume reduces due to the shortening of the diastolic phase, thereby reducing the cardiac output. However, for moderate tachycardia or even for resting heart rate close to 100 bpm, the moderately increased heart rate compensates for the reduced stroke volume, resulting in a positive gain of the cardiac output and accordingly in an increase of blood pressure and TS. Increased magnitude of TS imposed on the wall, upregulates the expression of pro-atherosclerotic genes by the endothelial cells [73] (Fig. 6). In keeping with that Bassiouny et al. [74] used the term stress index, defined as the product of mean blood pressure and heart rate, in order to study the effect of the increased mechanical load on atherosclerosis in the infrarenal aorta and iliac arteries of monkeys. A strong positive correlation between high stress index and was found revealing the importance of this parameter that encompasses the synergistic effect of high heart rate and hypertension on the formation of atherosclerotic plaque. This observation was further supported by other studies in which psychosocial stress induced endothelial injury and subsequent atherosclerotic lesion formation in coronary arteries of monkeys, an effect that was modulated through  $\beta_1$ -receptor activation [75,76].

In addition to the increased magnitude of the mechanical load, the frequency of this load, a factor that is greatly determined by heart rate, appears to play a central role in the pathophysiology of coronary atherosclerosis [71] (Fig. 6). As mentioned, TS undergoes significant temporal fluctuations over the cardiac cycle between a systolic maximum and a diastolic minimum. Conceivably, an elevated heart rate could increase the frequency of these fluctuations, thereby exerting an intensive stress (“fatigue effect”) on the endothelium, ultimately leading to endothelial dysfunction [71]. However, the pathophysiologic mechanisms responsible for high heart rate-induced cumulative endothelial injury need to be further elucidated with more analytical experimental studies.

##### 4.2. High heart rate prolongs the exposure of endothelium to low and oscillatory SS

By applying sophisticated Computational Fluid Dynamics in realistic arterial models, we and others showed that SS attains a low and oscillatory pattern during systole, whereas in diastole it exhibits an initial steep increment up to its diastolic maximum, and then it slowly declines throughout the rest of diastolic phase until the initiation of the next systole [62,77–80] (Fig. 4). Given the involvement of low and oscillatory SS in atherosclerosis, one could speculate that the systolic period favors the pathophysiological processes responsible for the onset and development of atherosclerosis [77], whereas the steep increase of SS, appearing in diastole, modulates an atheroprotective milieu, compensating for the atherogenic systolic SS values (Fig. 6). Under resting conditions (i.e. 60–80 bpm), in a typical cardiac cycle of 1000 ms, 700 ms correspond to diastole and the rest 300 ms to systole (i.e. diastole vs. systole duration

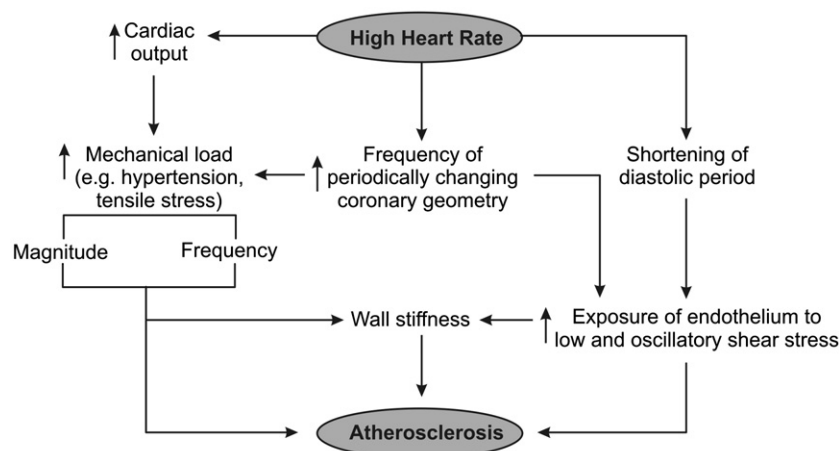


Fig. 6. Overview of the potential pathogenetic mechanisms, by which high heart promotes atherosclerosis. High heart rate increases the magnitude and frequency of the imposed on the wall mechanical load (i.e. hypertension, tensile stress). Also, due to the relative shortening of the diastolic time high heart rate increases the total time spent on systoles per minute, thereby prolonging the exposure of endothelium to the atherogenic effect of low and oscillatory shear stress. Furthermore, elevated heart rate intensifies the pulsatile motion of the heart, thereby increasing the frequency of the periodically changing geometry of the epicardial coronary arteries. This effect reinforces the periodic variations of tensile stress and shear stress over the cardiac cycle. The enhanced mechanical load, as well as the intensified low and oscillatory shear stress induce vascular smooth muscle cell growth and collagen deposition, resulting in vascular stiffening. Ultimately, all these processes confer a predisposition to atherosclerosis.

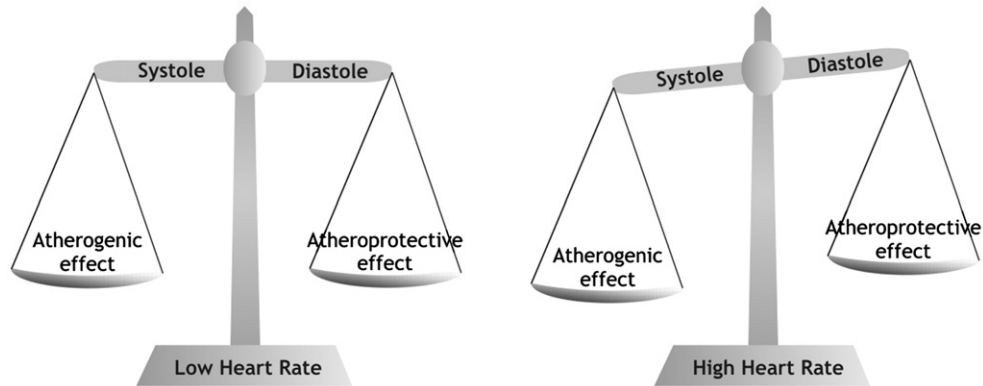


Fig. 7. Conceptual mechanism for the atherogenic effect of high heart rate: In low heart rate diastole lasts longer than systole, compensating for the pro-atherogenic effect of systolic low shear stress. As the heart rate increases diastole undergoes shortening and the total time spent on systoles per minute relatively to diastole increases; thus in regions susceptible to atherosclerosis the endothelium is exposed to the atherogenic effects of systolic low SS for longer periods.

ratio 2:1) [35]; therefore as diastole lasts longer than systole, it compensates for the systolic low SS values (Fig. 7). However, as the heart rate increases, the diastolic time gradually decreases, resulting in an increase of the total time spent on systoles per minute relatively to diastole; of note in severe tachycardia the duration of diastole may even become equal to that of systole [74,77]. As a result, in regions susceptible to atherosclerosis high heart rate attenuates the atheroprotective effect of diastole, exposing the endothelium to the atherogenic effect of the systolic low and oscillatory SS for longer periods.

#### 4.3. High heart rate induces wall stiffness

Another potential mechanism implicating high heart rate in atherosclerosis involves the induction of coronary wall stiffness [15] (Fig. 6). It was shown that experimental tachycardia instigates wall stiffness in the coronary arteries and femoral arteries of rats [81]. An association between high heart rate (>80 bpm) and stiffness of aorta or large peripheral arteries has also been demonstrated in studies performed in humans [82–84]. This effect was attributed to the elevated mechanical load, which was found to increase arterial wall viscosity, making the arteries stiffer [85]. However, whether the heart rate-dependent stiffening effect occurs in the coronary arteries remains elusive.

Physiologically, the epicardial arteries are elastic-type conduit arteries containing collagen and elastin in their wall [86]. Collagen provides integrity and tensile strength to the wall, whereas elastin regulates vascular elasticity. Both proteins determine the ability of the arteries to distend, so-called compliance. Under normal conditions, the relative content of collagen and elastin remains stable through a dynamic and constant process of synthesis and breakdown, thereby maintaining a normal wall compliance. Low and oscillatory SS, as well as phasic TS, which are both enhanced by the elevated heart rate, constitute potent stimuli for vascular smooth muscle cells to grow, migrate from the

media to intima, proliferate and secrete MMPs. These endopeptidases impair the established balance between collagen and elastin, progressively contributing to vascular stiffness. It could be hypothesized that since the stiff atherosclerotic epicardial arteries lose their elastic properties their ability to absorb the retrograde flow derived from the collapsed subendocardial segments during systole is limited [87]. As a result, a systolic retrograde flow could occur in the epicardial segments (not only in the subendocardial ones), followed by a diastolic anterograde flow, resulting in a more intense temporal SS and TS variation over the time, which may further promote the atherosclerotic process.

#### 4.4. High heart rate amplifies phasic geometric changes of coronary arteries

The coronary arteries are considered as the most susceptible vessels to atherosclerosis in the entire human vasculature due to their complex three-dimensional geometry in combination with the dynamic changes that this geometry undergoes during the cardiac cycle [88]. The epicardial segments of coronary arteries are closely attached to the beating heart and as a result they sustain two main types of phasic motion: (a) the periodically changing curvature which represents the changing bending of the coronary arteries during the cardiac cycle and (b) the periodically changing torsion, which refers to the changing twisting of the coronary arteries during the cardiac cycle [89]. It was demonstrated that the pulsatile motion of the heart affects the coronary geometry, and this in turn influences the local hemodynamic environment, initiating a self-perpetuating vicious cycle [90,91]. Human in vivo data revealed that the average curvature of the left anterior descending artery exhibits its highest values in systole, whereas relatively low and constant curvature occurs in diastole [89] (Fig. 4). By applying this pattern of periodically changing curvature on the left anterior descending artery it was demonstrated that in areas with high curvature low SS occurs at systole, whereas the same areas

experience higher SS values in diastole, possibly due to the fact that the coronary artery exhibits lesser curvature. This observation implies that the increased curvature may create a local low SS environment, thereby promoting atherosclerosis.

Also, periodically changing torsion has been proposed as a potential modulator of the local hemodynamic environment [87]. A human autopsy study demonstrated that angiographically diseased coronary artery portions experience significantly higher torsion compared to normal segments, suggesting that there may be an association between high torsion and the development of atherosclerosis [92]. Significant SS oscillations were also found in arterial segments exhibiting intense phasic changes in torsion [91].

In addition to the effect of changing coronary geometry on SS, the coronary motion during the cardiac cycle could augment the phasic TS variations [87,93].

Taking the aforementioned observations into account, it could be hypothesized that phasic changes of coronary geometry instigate a periodic fluctuation of the imposed on the arterial wall hemodynamic stresses, accentuating the local atherogenic environment. In this setting, an increased heart rate could increase the frequency of phasic changing coronary geometry [92], which in turn could augment the phasic SS and TS variations, ultimately accelerating the atherosclerotic process (Fig. 6).

## 5. Involvement of high heart rate in the natural history of atherosclerosis

Beside the implication of high heart rate in atherogenesis and early atherosclerosis, its role throughout the natural history of atherosclerosis, culminating to the formation of vulnerable atherosclerotic plaque prone to rupture, is also critical. Once an atherosclerotic plaque acquires characteristics of vulnerability it encounters several biomechanical factors (e.g. increased TS, low and oscillatory SS, radial compression, longitudinal bending, circumferential bending), which are generated mostly by the pulsatile nature of the blood flow, blood pressure and heart motion [94]. As the elevated heart rate accentuates blood flow, blood pressure and heart motion, it may promote and expedite the weakening of the fibrous cap, ultimately increasing the risk of plaque disruption and the onset of an acute coronary syndrome. This perspective is supported by an angiographic 6-months follow-up human study, which showed that high heart rate (>80 bpm) facilitates coronary plaque disruption; an effect, which could be prevented by beta-blockers [95].

## 6. Clinical perspectives

### 6.1. High heart rate: a new independent risk factor for atherosclerosis and cardiovascular mortality?

To date, the impact of raised heart rate in atherosclerosis has been underestimated; increased heart rate has been considered as a secondary effect of sympathetic over-

stimulation rather than an independent risk factor. Given that the underlying mechanisms for the vulnerability to develop atherosclerosis are still elusive since only about half of its causality is credited to established risk factors [88], the European Society of Hypertension Consensus Meeting recently suggested the inclusion of high heart rate — an easily measured, quite reproducible and modifiable factor — into the list of risk factors. Of note, it was proposed that the heart rate could be used for the stratification of the risk for development of future atherosclerosis [3,96].

### 6.2. Should the upper and lower normal limits of heart rate be revisited?

The absence of a standard widely accepted way to measure heart rate increases the uncertainty regarding the normal and pathologic range of this parameter. Resting (normal) heart rate is a generalized term encompassing a broad spectrum of heart rate values, between 60 and 100 bpm, which have been established on the basis of previous epidemiological and statistical evidence. However, the dynamic and changing nature of epidemiological data dictates the dynamic nature of the reference intervals. For example, although traditionally the threshold for systolic and diastolic hypertension has been set to 140 mmHg and 90 mmHg, respectively, new epidemiological evidence raised the need for these limits to be reconsidered. In this context, new terms, such as borderline systolic and diastolic pressure for readings within the range 130–140 and 85–90 mmHg, respectively, were introduced [97]. Similarly, new terms such as high resting heart rate and low resting heart rate have been recently introduced having the potential not to substitute the classical terms of tachycardia and bradycardia, respectively, but to stratify the risk of cases with resting heart rate [98]. Although there is no objective cut-off point between high and low resting heart rate, strong clinical evidence favors that values in the range of 80–100 bpm determine the high resting heart rate, while low resting heart rate varies between 60 and 80 bpm [3]. Corroborative clinical trials support this cut-off point showing that it corresponds to the treatment threshold at which the benefits of treatment outweigh the risks [98].

### 6.3. Anti-atherogenic perspective of heart rate lowering agents

Large clinical trials showed that traditional heart rate lowering agents including beta-blockers and non-dihydropyridine calcium antagonists (e.g. verapamil and diltiazem) are beneficial for the secondary prevention of coronary heart disease. More specifically, beta-blockers were found to reduce morbidity and mortality in patients with myocardial infarction or heart failure [98–101], whereas verapamil and diltiazem were shown to be beneficial after myocardial infarction, but not in heart failure [102,103]. However, the specific mechanisms responsible for this effect are not well

understood. In addition to the anti-arrhythmic and anti-ischemic effect of beta-blockers and calcium antagonists, the pathways mentioned above regarding the effect of high heart rate on atherosclerosis could provide a reasonable pathway of action for these heart rate lowering agents, suggesting that the intensive reduction of heart rate could decelerate the progression of atherosclerosis through reduction in the frequency and magnitude of mechanical load and prolongation of the atheroprotective diastolic phase [44]. Lowering the heart rate could also alleviate the mechanical loading imposed on the vulnerable atherosclerotic plaques, thus reducing the risk of plaque rupture [94].

On the other hand, the short-term adverse effects of beta-blockers (e.g. dyslipidemia) and the long-term ones (e.g. diabetes), as well as their potential effect on blood viscosity (e.g. by influencing circulating fibrinogen levels) [104] and haemostasis [105] may limit the overall benefit of these agents, reducing their efficiency in primary prevention of coronary artery disease [99,106]. As far as the calcium antagonists are concerned, although they reduce the heart rate to a lesser degree compared with beta-blockers, they are free of the adverse metabolic effects, which are common to the latter [3].

Recently, ivabradine has been introduced, a new selective heart rate lowering agent, which affects only the heart rate without exerting any inotropic or antihypertensive action. Although ivabradine has promising anti-atherosclerotic properties its efficacy in reducing atherosclerosis and related clinical outcomes needs to be tested in large clinical trials [107].

Beside heart rate lowering agents, lipid lowering drugs may indirectly modulate the harmful effect of a high heart rate by altering blood vessel stiffness (e.g. statins) or by lowering plasma fibrinogen levels (e.g. fibrates or statins), thus alleviating the atherogenic load of increased blood viscosity [108,109–112]. In this context, differences between lower and higher heart rates in terms of risk may need to be reconsidered in populations taking lipid lowering agents.

#### 6.4. Heart rate lowering role of exercise

Apart from pharmacological heart rate lowering, aerobic exercise has gained considerable interest [113]. Its beneficial role is mediated through several pathways including the periodically increased flow and concomitantly SS, especially in atherosclerosis-prone regions, resulting in enhanced synthesis, release and duration of action of NO [33,114,115]. NO is not only responsible for endothelium-dependent vasodilation, but also has anti-inflammatory, anti-proliferative and anti-thrombotic activity [54,69]. Although the heart rate lowering effect of aerobic exercise remains elusive, several epidemiological studies showed that exercise is effective in controlling the sympathetic nervous system and, as a result, high heart rate and blood pressure, thereby alleviating the local atherogenic load [3,116]. The chronic adaptation that athlete's hearts undergo with increased blood flow and lowered heart rate

could serve as a representative example of the salutary role of exercise. In addition to heart rate regulation, regular exercise may also help control weight, insulin resistance and lipid profile [117]. Furthermore, people who exercise on a regular basis are more likely to have a healthy lifestyle, including smoking cessation, which, among other adverse effects, has been shown to be associated with small and intermittent rises in heart rate [118].

## 7. Conclusions

Elevated heart rate appears to be implicated in coronary atherosclerosis in an independent manner by increasing the magnitude and frequency of the mechanical load imposed on the arterial wall, enhancing the exposure of endothelium to low and oscillatory SS and intensifying the periodically changing coronary geometry, which in turn affects the local hemodynamic environment. High heart rate-mediated induction of coronary wall stiffness may also play a role. All these changes modulate an atherogenic microenvironment, which in conjunction with the effect of systemic risk factors promotes atherosclerosis in atherosclerosis-prone regions. Heart rate should always be considered in patients with coronary heart disease, given that it constitutes an easily measurable and reproducible parameter.

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