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STATE-OF-THE-ART PAPER

Vascular Pathophysiology in Response to Increased Heart Rate

Florian Custodis, MD,* Stephan H. Schirmer, MD, PhD,* Magnus Baumhäkel, MD,* Gerd Heusch, MD,† Michael Böhm, MD,* Ulrich Laufs, MD*

Homburg/Saar and Essen, Germany

This review summarizes the current literature and the open questions regarding the physiology and pathophysiology of the mechanical effects of heart rate on the vessel wall and the associated molecular signaling that may have implications for patient care. Epidemiological evidence shows that resting heart rate is associated with cardiovascular morbidity and mortality in the general population and in patients with cardiovascular disease. As a consequence, increased resting heart rate has emerged as an independent risk factor both in primary prevention and in patients with hypertension, coronary artery disease, and myocardial infarction. Experimental and clinical data suggest that sustained elevation of heart rate—independent of the underlying trigger—contributes to the pathogenesis of vascular disease. In animal studies, accelerated heart rate is associated with cellular signaling events leading to vascular oxidative stress, endothelial dysfunction, and acceleration of atherogenesis. The underlying mechanisms are only partially understood and appear to involve alterations of mechanic properties such as reduction of vascular compliance. Clinical studies reported a positive correlation between increased resting heart rate and circulating markers of inflammation. In patients with coronary heart disease, increased resting heart rate may influence the clinical course of atherosclerotic disease by facilitation of plaque disruption and progression of coronary atherosclerosis. While a benefit of pharmacological or interventional heart rate reduction on different vascular outcomes was observed in experimental studies, prospective clinical data are limited, and prospective evidence determining whether modulation of heart rate can reduce cardiovascular events in different patient populations is needed. (J Am Coll Cardiol 2010;56:1973–83) © 2010 by the American College of Cardiology Foundation

Resting heart rate is an easily accessible clinical parameter. From vascular risk factors to endothelial function, coronary blood flow to atherosclerotic plaque development, plaque rupture, and myocardial infarction, heart rate affects several stages of the cardiovascular disease continuum (1–5). The initiation of the heart beat by spontaneous sinoatrial node depolarization is determined by voltage-sensitive membrane currents, particularly the hyperpolarization-activated pacemaker current I(*f*), and by calcium release from the sarcoplasmic reticulum, leading to diastolic depolarization through activation of the sodium-calcium exchanger current. The I(*f*) current was first described almost 30 years ago (6); *f* stands for "funny" because of the unusual properties of I(*f*) relative to other systems known at the time. These properties comprise mixed permeability to sodium and potassium ions, activation by hyperpolarization, and slow activation and deactivation kinetics (7). The sinoatrial node responds to physical and mental activity or sleep states through the autonomic nervous system and circulating hormones, which integrate notably cardiorespiratory and baroreceptor, but also more complex inputs such as emotion, exercise, and stress (for review, see DiFrancesco [7] and Verrier and Tan [8]). Therefore, increased heart rate reflects increased sympathetic and/or decreased vagal tone and, indirectly, life-style such as psychosocial stress or lack of physical training.

Recent data are available from epidemiological studies and randomized clinical trials focusing on the prognostic value of heart rate. Experimental and clinical evidence suggests that sustained elevation in heart rate plays a role in the pathogenesis of atherosclerosis, affecting initiation and progression as well as the severity of the disease. Experimental studies demonstrate several vascular responses accounting for the detrimental effects of accelerated heart rate. However, available mechanistic molecular data are surpris-

From the *Klinik für Innere Medizin III, Kardiologie, Angiologie und Internistische Intensivmedizin, Universitätsklinikum des Saarlandes, Homburg/Saar, Germany; and the †Institut für Pathophysiologie, Universitätsklinikum Essen, Essen, Germany. This work was supported by the Universität des Saarlandes (Homburger Forschungsförderungsprogramm). Drs. Heusch, Laufs, and Böhm are supported by the Deutsche Forschungsgemeinschaft (DFG, KFO 196, and He 1320). The Universität des Saarlandes has received financial support from Servier (France) for basic research. Drs. Heusch and Böhm have received honoraria from Servier (France). Dr. Laufs has received grants (to institution) from Servier. All other authors have reported that they have no relationships to disclose.

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JACC Vol. 56, No. 24, 2010
December 7, 2010:1973–83

Abbreviations and Acronyms

Apo = apolipoprotein
eNOS = endothelial nitric oxide synthase
FMD = flow-mediated dilation
I(*f*) = hyperpolarization-activated pacemaker current
NADPH = nicotinamide adenine dinucleotide phosphate
VSMC = vascular smooth muscle cell

ingly sparse in the light of the importance of heart rate for vascular physiology. This article reviews the effects of heart rate on vascular homeostasis and hemodynamics that eventually lead to the phenotype of atherosclerotic disease.

Epidemiology of Elevated Heart Rate

In the Framingham study, cardiovascular and coronary mortality increased progressively with resting heart rate in a cohort of 5,070 subjects free from cardiovascular disease at the time of entry into the study. The effect of heart rate on mortality was independent of traditional cardiovascular risk factors (9–13). Other studies confirm the prognostic importance of resting heart rate for morbidity and mortality in patients with established coronary artery disease (14,15). The Coronary Artery Surgery Study registry assessed the relationship between resting heart rate and cardiovascular mortality in approximately 25,000 subjects with suspected or proven coronary artery disease over a median follow-up of 15 years. Multivariate analysis revealed that patients with a resting heart rate >83 beats/min had a significantly higher risk of cardiovascular mortality than subjects with a resting heart rate ≤62 beats/min (16). Recently, the analysis of a pre-specified subgroup of the BEAUTIFUL (morBidity-mortality EvAlUaTion of the I_f inhibitor ivabradine in patients with coronary disease and left-ventricULar dysfunction) trial demonstrated that in patients with coronary heart disease and left ventricular systolic dysfunction, a resting heart rate >70 beats/min was associated with an increased cardiovascular mortality as well as increased risk for hospitalization due to heart failure, myocardial infarction, or need for coronary revascularization (17). In subsequent analyses, the increased heart rate was largely associated with coronary vascular events, but not with heart failure (18,19). The INTRINSIC RV (Inhibition of Unnecessary RV Pacing With AV Search Hysteresis in ICDs) trial followed 1,530 patients after implantation of a dual-chamber implantable cardioverter-defibrillator and found that intrinsic (unpaced) heart rate was strongly and independently associated with the composite end point of heart failure hospitalization and total mortality (20). Taken together, there is compelling epidemiologic evidence that elevated resting heart rate is predictive of cardiovascular risk, independently of the other currently accepted risk factors or characteristics.

Pathophysiology of Elevated Heart Rate

Shear stress and vascular signaling responses. Shear stress is the tangential force in the direction of blood flow, generated by flow velocity over the vascular surface and expressed in units of force/unit area (dyne/cm^2) (for review, see Davies [21] and Chatzizisis et al. [22]). Local shear stress is sensed by endothelial mechanoreceptors, induces endothelial gene expression, and thereby determines vascular phenotypes that promote atherosclerosis susceptibility or atherosclerosis protection. High shear stress promotes adaptive vascular dilation (flow-mediated dilation), for example, by induction of endothelial nitric oxide synthase (eNOS) transcription and translation (23). Endothelial cells respond to variations in shear stress. Vascular regions with oscillating shear stress and flow reversal correspond with pathologic changes in the artery wall and are at risk for atherosclerosis, whereas sustained laminar flow and high shear stress conserve atheroprotective signaling (21,24).

Evidence for a close relation between shear stress and heart rate originates from in vitro studies that suggest that shear waveform, and in particular, shear frequency can influence endothelial cell gene expression profiles. Several studies compared the impact of steady laminar shear and "realistic" arterial (pulsatile) waveforms on endothelial metabolism and report an increased expression of proinflammatory, proapoptotic, and procoagulant transcripts (25,26) and a reduction of eNOS expression under pulsatile waveforms (27). Himburg et al. (28) examined the frequency-dependent response of aortic endothelial cells to pulsatile shear stress. A shear frequency of 2 Hz induced a proinflammatory phenotype characterized by up-regulation of monocyte chemoattractant protein-1, intercellular adhesion molecule-1, and vascular cell adhesion molecule-1, which was most pronounced under reversing and oscillatory shear. A "physiological" frequency of 1 Hz repressed inflammatory transcripts and induced several atheroprotective transcripts (28). In cultured endothelial cells, cyclic stretch was found to increase the endothelial expression of p22phox, a membrane-bound subunit of the superoxide-producing nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase, which is fundamental for the formation of reactive oxygen species. Endothelial cells treated with inhibitors of the NADPH-oxidase had reduced superoxide production in response to stretch (29).

Mechanical forces also play an essential role in vascular smooth muscle cells (VSMC) in the vessel media (30,31). In cellular models and in vitro studies using VSMC cultured on deformable substrates, the effect of cyclic strain on mechano- and signal transduction has been investigated, including altered cell proliferation, alignment, and protein expression. Among these, up-regulation of extracellular matrix proteins (fibronectin [32], collagen [33]), growth factors (34), and osteogenic markers (35) was linked to a vascular phenotype characterized by increased stiffness. Moreover, several studies have indicated that cyclic strain also amplifies oxidative stress in VSMC. In human coronary artery VSMC exposed to pulsatile strain, the observed time- and strain-dependent increase in superoxide production was inhibited by NADPH-oxidase inhibitors but not by xanthine

oxidase or cyclooxygenase inhibitors (36). In cultured vessels, stretch of 10% and 20% increased generation of reactive oxygen species in contrast to a 5% cyclic stretch (37).

In the context of these results, it could be speculated that persons whose arteries are chronically subjected to a particular range of shear frequencies, such as those with high resting heart rates, may be at greater risk for atherosclerotic lesion development. However, while the hypothetical association between shear stress and heart rate appears to be plausible, substantial experimental evidence is still lacking.

Endothelial dysfunction and increased heart rate. Because of its exposed location at the inner vessel wall, the endothelial monolayer acts as a mechanosensitive gatekeeper and a signal transduction interface for hemodynamic forces. These forces determine the shape and function of endothelial cells, allowing the vessel to cope with (patho-) physiological conditions (for review, see Berk [24] and Bundey [38]). Disturbance of endothelial function is considered a key event in the development of atherosclerosis and implies a change from the normally predominant release of nitric oxide to that of endothelium-derived contracting factors (39,40). Endothelial dysfunction has been identified as a common consequence of different cardiovascular risk factors and plays a pivotal role in the development, progression, and clinical manifestations of atherosclerotic disease (40,41).

To investigate a potential mechanistic link between heart rate and endothelial function, cholesterol-fed apolipoprotein (Apo) $E^{-/-}$ mice, a disease model for endothelial dysfunction, were treated with ivabradine, an inhibitor of the I(*f*) channel in the sinoatrial node, which reduced heart rate by 13.4% and significantly improved endothelial-dependent vasorelaxation in isolated aortic ring preparations (Fig. 1). The improvement of endothelial function was independent of blood pressure or lipid levels (42). Experiments by Drouin et al. (43) add to these findings, showing that in dyslipidemic mice expressing the human ApoB-100, heart rate reduction with ivabradine prevented endothelial dysfunction in renal and cerebral arteries. Similarly, pharmacological reduction of heart rate improved endothelial function in isolated corpora cavernosa, where endothelial cell function determines erectile capacity. The treatment was effective both as prevention as well as treatment of erectile dysfunction (44). Taken together, these studies in different mouse models and different vascular beds consistently show that mild heart rate reduction (13% to 17%) protects endothelial-dependent vasorelaxation. In the study by Drouin et al. (43), the impairment of acetylcholine-induced, endothelium-dependent vasodilation of cerebral and renal arteries was restored by ivabradine, but not by metoprolol dosed to equally reduce heart rate. Therefore, it appears possible that ivabradine may exert vasoprotective effects in addition to heart rate reduction; however, this is a question of ongoing research (45).

An increased formation and/or release of reactive oxygen species appears to be a common denominator underlying endothelial dysfunction and is 1 of the key events in the pathogenesis of atherosclerosis (46). Indeed, ivabradine-induced heart rate reduction in $ApoE^{-/-}$ mice was associated with inhibition of NADPH-oxidase activity and superoxide release. In addition, vascular lipid peroxidation as a global marker of oxidative stress was decreased (42). The central characteristic of a dysfunctional endothelium is a reduced availability of NO. Restoration of impaired endothelial function by pharmacological interventions (e.g., statins) is associated with a restoration of endothelial NO production (47,48). However, aortic tissue of $ApoE^{-/-}$ mice treated with ivabradine did not exhibit a significant up-regulation of eNOS expression (42). In contrast, ivabradine treatment up-regulated eNOS expression in the corpora cavernosa of $ApoE^{-/-}$ mice (44). Even though a direct

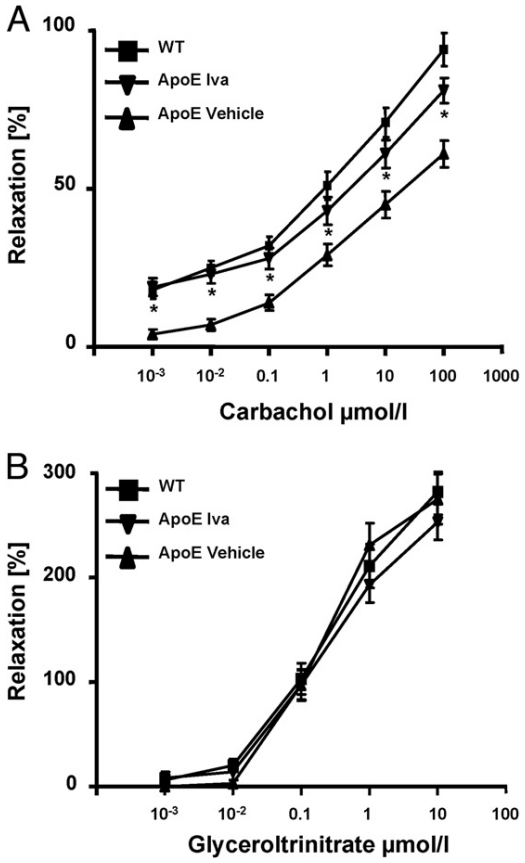

Figure 1 **Endothelial Function of Wild Type and $ApoE^{-/-}$ Mice**

In wild type (WT) mice **(squares)** and in apolipoprotein (Apo) $E^{-/-}$ mice after 6 weeks of treatment with cholesterol-rich diet with ivabradine (Iva), 10 mg/kg/day **(down-pointing triangles)** or vehicle treatment **(up-pointing triangles)**, aortic segments were isolated, and their functional performance was assessed in organ chamber experiments. Heart rate reduction improved endothelium-dependent vasodilation induced by carbachol **(A)**. Endothelium-independent vasorelaxation induced by glyceroltrinitrate was similar in all groups **(B)**. Both were expressed as percent of maximal phenylephrine-induced vasoconstriction. Mean ± SEM, n = 10 per group. $*p < 0.05$ versus ApoE vehicle. Adapted from Custodis et al. (42).

involvement of eNOS was not reported, Drouin et al. (43) showed in dyslipidemic mice that vasodilation of renal arteries induced by acetylcholine was sensitive to eNOS inhibition by N$^{\omega}$nitro-L-arginine, indicating at least a partial contribution of NO to ivabradine-induced improvement of endothelial function. Recchia et al. (49) also found a significant decrease of cardiac NO production after 3 weeks of rapid pacing in dogs with pacing-induced heart failure.

The clinical data on endothelial function affected by heart rate are not yet conclusive. In a large cohort of Framingham Study participants, heart rate was positively associated with brachial artery flow-mediated dilation (FMD) (50). Several studies that explicitly looked at heart rate and FMD showed an inverse relation between heart rate and FMD but are severely limited by the small number of subjects examined (51–54). Therefore, prospective clinical studies to determine the role of resting heart rate in FMD and to test the effect of randomized heart rate reduction on FMD are needed.

Increased levels of circulating markers of inflammation such as high-sensitivity C-reactive protein are associated with endothelial dysfunction and future cardiovascular risk (55). Two population-based studies reported a positive correlation between increased resting heart rate and markers of inflammation (C-reactive protein, white blood cell count, and fibrinogen) in apparently healthy subjects (56,57). Thus, increased heart rate may contribute to endothelial dysfunction by up-regulation of inflammatory cytokines. Microalbuminuria is a marker of generalized endothelial injury and correlates with renal and cardiovascular end organ damage (58,59). In a recent analysis of the I-SEARCH (The International Survey Evaluating Microalbuminuria Routinely by Cardiologists in Patients with Hypertension) study, an observational study in hypertensive patients, heart rate was a strong predictor for the prevalence of microalbuminuria, even after adjustment for hypertension and risk factors such as pre-existing cardiac disease, diabetes mellitus, age, and sex (60,61). In summary, the data show an association of heart rate with circulating markers of vascular inflammation; however, the underlying molecular mechanisms are not known.

Vascular structure and increased heart rate. Blood vessels adapt to mechanical demands and remodel by changing their geometry, structure, and elastic properties. Compliance, defined as change in volume (dV) for a given change in distending pressure (dP), or dV/dP, decreases steadily with vascular aging (62). Aortic stiffness, namely, the inverse of compliance, predicts cardiovascular morbidity and mortality in patients with essential hypertension, end-stage renal failure, or diabetes mellitus (63,64). Experimental evidence for a link between arterial compliance and heart rate was presented by Mangoni et al. (65), who demonstrated that progressive increases in heart rate caused by atrial pacing in rats led to marked reductions in carotid artery compliance. The stiffening effect of tachycardia was shown to be independent of sympathetic tone (66). Sa Cunha et al. (67) found a significant positive link between high heart rate and arterial stiffness measured at the site of central and lower limb arteries by pulse wave velocity measurements and high-resolution echo tracking. These findings are in line with a study of Giannattasio et al. (68), who showed that radial and carotid artery distensibility (an index of arterial stiffness measured by vascular echo tracking) was decreased during pacing-induced increase of heart rate. In treated hypertensive patients, high heart rate was associated with an accelerated progression of arterial stiffness, as estimated by carotid/femoral pulse wave velocity (69). Other investigations report opposite heart rate-induced effects on vascular wall mechanics. Wilkinson et al. (70) used pulse wave analysis to calculate an augmentation index as a measure of pressure wave reflection that accounts for arterial stiffness in patients with permanent cardiac pacemakers. Incremental pacing led to a linear reduction in the augmentation index and revealed an inverse relationship between heart rate and systemic arterial stiffness (70). Similar results are reported by an earlier study showing increased aortic distensibility, measured invasively by aortic pressure recordings, by pacing induced increases in pulse rate (71). Apparently, differences may evoke from different methods (ultrasonic echo tracking vs. pulse wave analysis) and parameters (arterial distensibility vs. augmentation index) that were applied. What is noticeable is that the majority of studies reporting a positive association between heart rate and vascular stiffness applied direct measurements of vascular compliance (e.g., by echo tracking) rather than pulse wave velocity or augmentation index.

At least, the reported observations suggest synergistic effects of heart rate and arterial blood pressure on the vasculature and the progression of atherosclerotic disease. Predominantly at the sites of atherosclerosis-prone areas, mechanical stress may result in pathological alterations and even vascular "fatigue." The concept of cumulative vascular injury caused by fatigue was introduced by Thubrikar and Robicsek (72) and describes a phenomenon deduced from nonbiological materials that occurs in vessels exposed to pulsatile pressure. At sites of stress concentration (e.g., vascular orifices), an accelerated heart rate potentiates the spatial mechanic load—defined by blood pressure—and accelerates vascular injury. Such a hypothesis was taken into account by Bassiouny et al. (73), who used a rate-pressure product (mean blood pressure × mean heart rate) to quantify hemodynamic load in cynomolgus monkeys and reported a positive relationship between hemodynamic stress and the extent of atherosclerotic lesions in the infrarenal aorta. Mechanistically, again, there is likely a disturbed endothelial-dependent vasorelaxation (74,75).

Heart rate reduction by I(f)-channel inhibition in spontaneously hypertensive rats reduced heart rate by as much as 30%, mediated antihypertrophic effects in terms of reduction of medial cross-sectional area in the thoracic aorta, and reduced wall stress (76). However, whereas chronic ivabradine treatment attenuated maladaptive alterations, an acute

pharmacological intervention by repetitive intravenous boluses of ivabradine did not affect arterial stiffness (77).

The finding that the augmentation index is influenced by heart rate is supported by population data from a cross-sectional study (78) and recent data from the CAFE (Conduit Artery Function Evaluation) study (79,80). The major finding of the CAFE study was that the beta-blocker atenolol was less effective than amlodipine in lowering central aortic systolic pressures, despite similar control of brachial blood pressure. The CAFE heart rate study focused on the importance of heart rate as a determinant of this effect and showed that a lower heart rate induced by beta-blockade was associated with higher aortic systolic pressure and pulse pressure, an effect that was primarily attributed to increased central pressure wave reflections at lower heart rates (Fig. 2) (81). As possible mechanisms that account for the inverse relationship between heart rate and aortic pressure, the authors discuss an increase of central systolic pressure attributable to a shift of the reflected wave into late systole due to the reduction in ejection duration by heart rate reduction, and an increased stroke volume secondary to heart rate reduction and better diastolic filling (Frank-Starling mechanism), which is then ejected into the proximal aorta with its windkessel function. Furthermore, the vasoconstrictor effects of beta-blockers on the peripheral circulation that increase pulse wave reflection have to be considered. The CAFE heart rate analysis adds relevant findings as it represents the first clinical trial assessing hemodynamic effects of a pharmacological heart rate reduction in a large number of patients. In the light of the CAFE study data, the net clinical effect of a beta-blocker–induced heart rate reduction in hypertensions remains controversial.

Atherosclerosis and increased heart rate. Pioneering experiments were conducted by Beere et al. (82,83), who established the first evidence for a direct connection between heart rate and lipid-induced atherogenesis in cynomolgus monkeys with reduced heart rate after ablation of the sinoatrial node, which exhibited reduced coronary and carotid atherosclerosis compared with sham-operated littermates. Subsequently, Kaplan et al. (84) demonstrated that naturally occurring differences in casual heart rate in monkeys were related to coronary atherosclerosis; monkeys with high heart rate exhibited atherosclerotic lesions more than twice as extensively as low heart rate littermates. In another study, the same authors reported a significant association between the extent of heart rate response to psychological stress and the degree of coronary atherosclerosis in the same species (85). Korshunov and Berk (86) characterized carotid outward remodeling and intima-media thickening in different inbred mouse strains. Vascular remodeling was highly dependent on genetic determinants and hemodynamic factors (86). Among these, heart rate, but not systolic blood pressure, was predictive for increased intima-media thickening. Recent data in ApoE$^{-/-}$ mice established that heart rate reduction by ivabradine decreased atherosclerotic plaque size in the aortic root and in the ascending aorta (42). Ivabradine prevented atherogenesis when given simultaneously with a high cholesterol diet but also was effective to reduce plaques size when given to animals 4 weeks after initiation of a high-cholesterol diet (44). In this model, pharmacological heart rate reduction led to a reduction of the vascular expression of monocyte chemoattractant

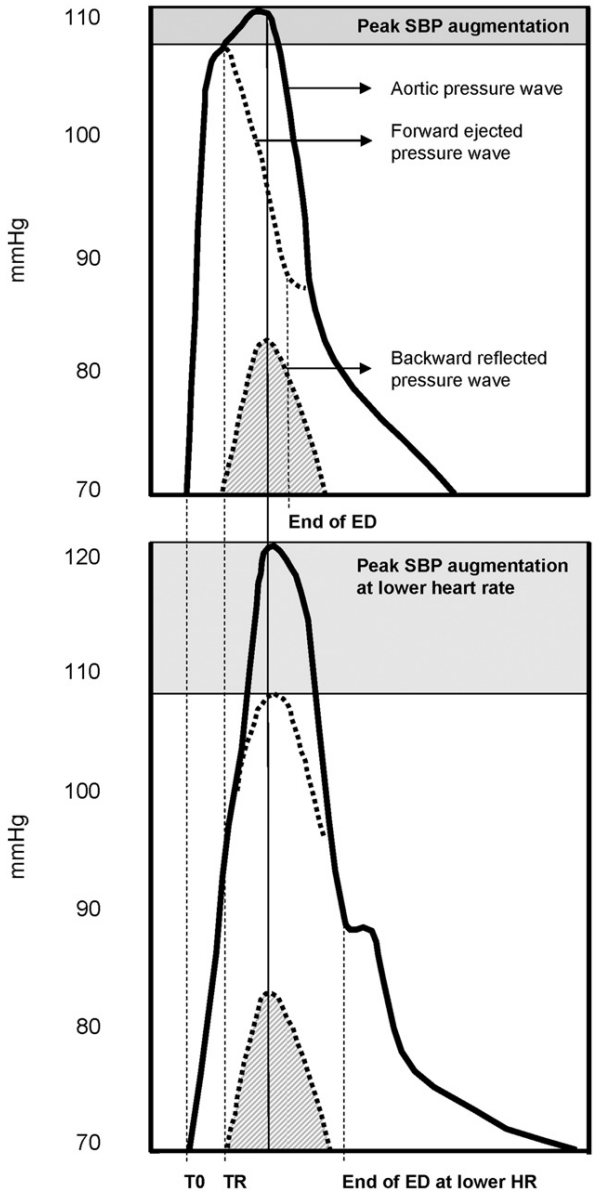

Figure 2 **Changes of Vascular Physiology in Response to Heart Rate Reduction**

Heart rate reduction increases central systolic blood pressure (SBP) augmentation for an identical pulse height of the forward-ejected pressure wave and the same reflected pressure wave. ED = ejection duration; T0 = onset of the forward-ejected wave; Tr = time to return at the aorta of the backward-reflected wave from T0. Adapted from Safar et al. (81).

JACC Vol. 56, No. 24, 2010
December 7, 2010:1973–83

protein-1. Monocyte chemoattractant protein-1 has been shown to be regulated by hemodynamic properties such as shear stress and cyclic strain (up-regulated by proatherosclerotic shear patterns) (87,88). While animal studies provide growing mechanistic evidence for the link between heart rate and an atherosclerotic phenotype, clinical data are limited. Perski et al. (89,90) studied the progression of coronary artery lesions in men who survived a myocardial infarction before the age of 45 years and reported a significant correlation between heart rate and the severity and progression of coronary atherosclerosis.

The contribution of heart rate reduction to the clinical effects of beta-blockers and calcium-channel blockers has been analyzed in several studies. A meta-regression analysis of 25 randomized clinical trials (21 with beta-blockers and 4 with calcium-channel blockers; n = 30,904 patients) performed by Cucherat (91) suggests that the beneficial effect of beta-blockers and calcium-channel blockers in post-myocardial infarction patients is proportionally related to the reduction of resting heart rate. Sipahi et al. (92) recently reported a post-hoc analysis of data from 4 intravascular ultrasonography studies showing that beta-blocker treatment is associated with a reduction of the progression of coronary atherosclerosis. The beta-blocker group showed a heart rate reduction by 2.7 beats/min (4%) but no difference in blood pressures compared with placebo (92). The association of beta-blockers with a reduced progression rate remained statistically significant after adjustment for average heart rates during treatment. The investigators suggest that reduced heart rate may not be the only mechanism responsible for the beneficial effects of beta-blockers on atherosclerosis and propose that reduced affinity of low-density lipoprotein cholesterol to vessel wall proteoglycans and blunting of the catecholamine-induced increases in endothelial permeability to lipoproteins may be alternative mechanisms of action. Bangalore et al. (93) analyzed 9 randomized studies evaluating beta-blockers for hypertension. In contrast to the findings in patients with myocardial infarction or heart failure, the meta-analysis found that beta-blocker–associated reduction in heart rate increased the risk of cardiovascular events and death for hypertensive patients. This analysis is driven by atenolol, which was used as beta-blocker in 78% of patients and has an inferior hemodynamic and metabolic profile compared beta-blockers with vasodilating properties. However, the existing data do not provide evidence for a beneficial effect of heart rate reduction using beta-blockers. In addition to the limitations of the retrospective clinical analyses of this question, the importance of heart rate reduction is difficult to interpret because of the very significant vascular effects of these drugs in addition to their impact on heart rate. Although beta-blocker treatment was reported to exert antiatherosclerotic effects in different species (for review, see Kaplan and Manuck [94] and Bondjers [95]), the molecular mechanisms were not studied, and possible negative effects of comparators such as hydralazine are not excluded (96). Therefore, to assess the importance of a pharmacological heart rate reduction for the prevention of atherosclerosis progression in patients with coronary heart disease, a prospective clinical trial with an I(*f*) inhibitor, for example, using intravascular ultrasonography may be an important next step.

Heart rate and myocardial oxygen supply. In the coronary arteries, blood flow is determined by the pressure gradient between the diastolic pressure in the aortic root, the right atrial pressure, and the duration of the diastole (1). Both the driving pressure gradient and the duration of diastole are integrated into the diastolic pressure-time integral reflecting the driving force for coronary blood flow. Due to its mechanical determinants, largely the phasically-contracting myocardium, coronary blood flow is pulsatile and occurs mostly during diastole (1). Increases in heart rate are associated with over-proportionate decreases in diastolic duration and, as a consequence, coronary perfusion and myocardial oxygen supply are reduced. Increases in coronary blood flow through metabolic coronary vasodilation in normal, nonstenotic coronary arteries act in concert with the reduction of blood flow in post-stenotic myocardium, secondary to abbreviated diastolic duration; in consequence, the driving gradient for collateral blood flow is reduced, and a marked reduction in post-stenotic blood flow ensues (Fig. 3) (1). Conversely, reduction of heart rate favorably redistributes myocardial blood flow toward the ischemic region (97) and finally reduces also infarct size (98,99). Clinically, precipitation of myocardial ischemia becomes eminent in diseased coronary arteries, where an increase in heart rate may lead to angina and myocardial ischemia (100–102).

Heart rate and coronary plaque instability. The characteristics of coronary shear stress are determined by the pulsatile nature of coronary flow. Shear stress attains a low and oscillatory pattern during systole followed by a diastolic increase to a diastolic maximum (103,104). In regions of low shear stress, progressive atherosclerosis and outward remodeling develop (105). Although an experimental and definite verification is lacking and a direct effect of heart rate on shear stress has not been investigated, one could speculate that as a consequence of a shorter diastole in regions susceptible to atherosclerosis, protective diastolic shear stress is reduced, resulting in longer periods of systolic shear stress.

In a retrospective analysis, Heidland et al. (106) investigated data from 106 patients who underwent subsequent coronary angiographies within 6 months. They analyzed 53 patients with initially smooth stenotic lesions in which plaque disruption developed by the time of the second coronary angiogram, and compared these patients with matched subjects exhibiting smooth stenoses without angiographic signs of plaque disruption. Logistic regression analysis identified positive associations between plaque disruption and a mean heart rate >80 beats/min and a negative association with the use of beta-blockers (106). This important clinical finding may be at least partially explained by

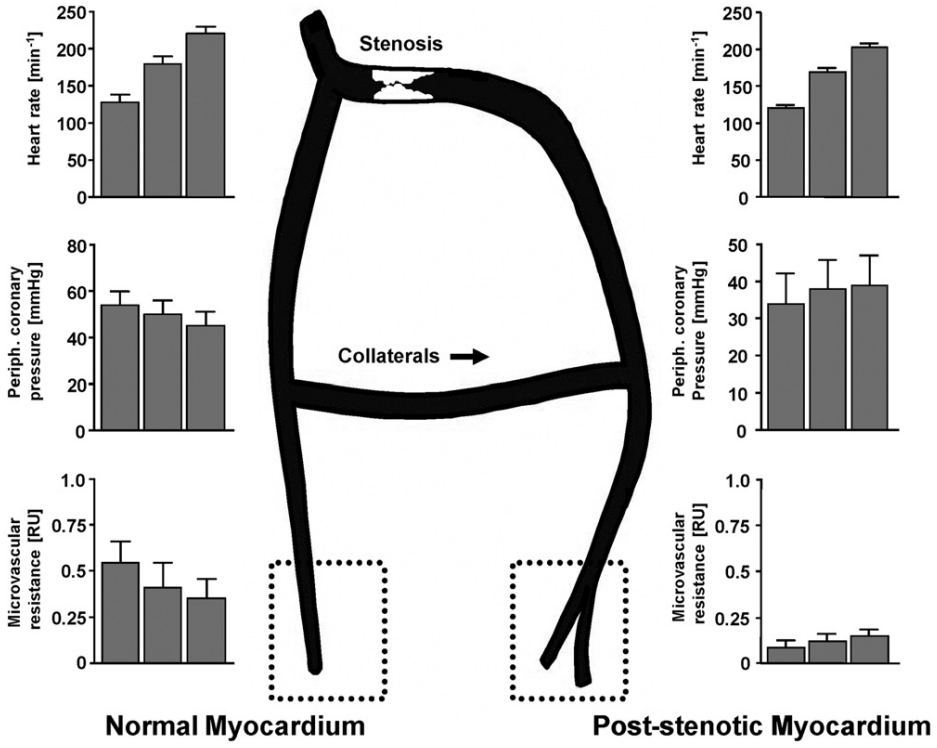

Figure 3 **Change in Driving Pressure Gradient for Collateral Blood Flow and Microvascular Resistance**

Schematic representation of changes in the driving pressure gradient for collateral blood flow and of microvascular resistance in normal myocardium **(left)** and in post-stenotic myocardium **(right)**. There is an autoregulatory decrease in microvascular resistance of the post-stenotic myocardium. With increasing heart rate, metabolic vasodilation and a decrease of microvascular resistance occur in healthy myocardium, resulting in decreased pressure at the origin of collaterals. In contrast, in post-stenotic myocardium, no further dilation is possible, and the reduction in diastolic duration prevails; subsequently, microvascular resistance and the pressure at the orifice of collaterals into the post-stenotic coronary vasculature are increased. Periph. = peripheral. Adapted from Heusch (1).

a dynamic coronary geometry and alternating dynamic changes imposed on the vessel during the cardiac cycle that may contribute to the initiation and development of coronary atherosclerosis (107). The motion of the coronary arteries during the cardiac cycle—primarily of the epicardial segments—is characterized by phasic bending of the curvatures and periodically changing torsion of the vessel directly affecting hemodynamic properties (107). Yang et al. (108) applied computational MRI-based models to characterize mechanical stress imposed on coronary atherosclerotic plaques and identified cyclic bending as a relevant stressor in rupture-prone areas. Other types of mechanical stress affecting plaque morphology are circumferential wall stress and repetitive tensile stress, which have been shown to facilitate and to trigger coronary plaque rupture (109). At least tensile stress was shown to stimulate matrix metalloproteinase-1—a key player in extracellular matrix degradation and plaque rupture—in coronary artery lesions (110). Consistently, hemodynamic factors that may precipitate plaque disruption are characterized by pulsatility and frequency of mechanical stress and are at least defined by the duration/length of the cardiac cycle.

Vascular growth and increased heart rate. Angiogenesis and arteriogenesis are natural defense mechanisms to compensate for arterial stenosis or occlusion (97,111). Thus, stimulating vascular growth is a promising therapeutic goal in arterial occlusive disease (112,113). Using bradycardic pacing in a rabbit model, a proangiogenic effect of heart rate reduction was described as early as 1981 (114). More recently, enhanced vascular endothelial growth factor expression was shown to be critical in bradycardia-induced angiogenesis (115). Up-regulation of vascular endothelial growth factor is thought to be induced by cardiac myocyte stretch (116). In a dog model of gradual coronary occlusion, bradycardia increased arteriogenesis, which was accompanied by an up-regulation of Tie-2 and vascular endothelial growth factor (117). Again, longer duration of diastole with increased shear stress as well as myocardial stretch are discussed as responsible mechanisms. However, no data on the effects of bradycardia and reduced pulse pressure frequency on vascular growth in the peripheral circulation are available. Collateral artery growth is a NO-dependent process (118). Conceivably, improved endothelial function and

JACC Vol. 56, No. 24, 2010
December 7, 2010:1973–83

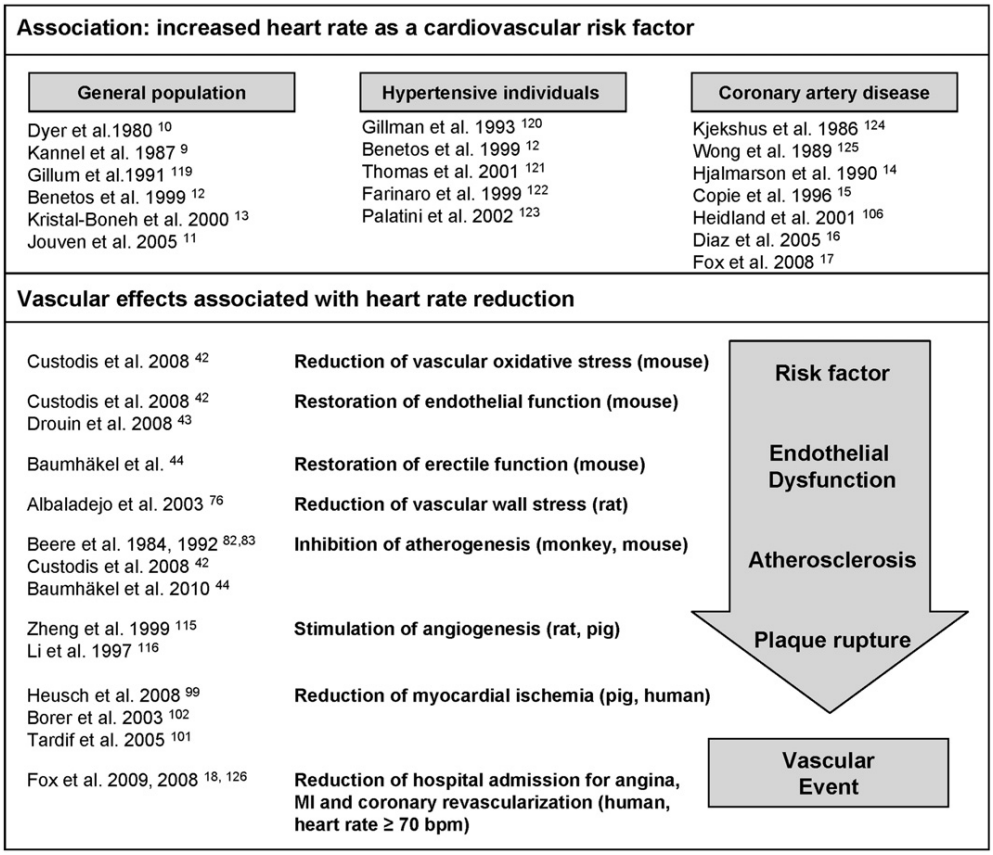

Figure 4 Heart Rate as a Cardiovascular Risk Factor and Vascular Effects of Heart Rate Reduction

(Top) Clinical evidence for the potential role of heart rate as a cardiovascular risk factor in the general population and in individual persons affected by cardiovascular disease. **(Bottom)** Evidence for vascular effects of heart rate reduction from animal and clinical studies. bpm = beats/min; MI = myocardial infarction.

up-regulation of NO may also stimulate arteriogenesis in the noncoronary vascular bed.

Conclusions and Perspective

Heart rate has emerged as an independent risk factor both in primary prevention and in patients with hypertension, coronary artery disease, and myocardial infarction (Fig. 4) (119–126). Available data support a strong association between elevated heart rate and negative cardiovascular effects. Increased heart rate impairs endothelial function in animal models and may contribute to reduced shear stress and vascular compliance. Heart rate reduction by sinus node ablation or pharmacological intervention by I(f)-channel inhibition reduces the formation of atherosclerotic plaques in animal models of lipid-induced atherosclerosis. By prolonging diastole and improving endothelial function, reduced heart rate stimulates vascular growth. While these experimental data provide considerable descriptive evidence of the pathophysiological concept, the current mechanistic understanding of the underlying molecular mechanisms warrants further investigation. However, prospective clinical evidence regarding the effects of heart rate reduction on cardiovascular events is lacking. Importantly, transition from experimental results to clinical evidence has to be further established, particularly to clarify whether pharmacological heart rate reduction might be beneficial for the prevention of atherosclerotic disease. Ongoing clinical trials and registries will further consider the role of heart rate and heart rate reduction in patients with coronary artery disease (127–129).

Reprint requests and correspondence: Dr. Florian Custodis, Klinik für Innere Medizin III, Kardiologie, Angiologie und Internistische Intensivmedizin, Universitätsklinikum des Saarlandes, Homburg/Saar 66424, Germany. E-mail: florian.custodis@uks.eu.

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