

Vascular endothelial ageing, heartbeat after heartbeat

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Abstract

The vascular endothelium starts to age at the first heartbeat. There is no longer a need to demonstrate that an increased resting heart rate—above 70 b.p.m.—is associated with the onset of cardiovascular events and reduces lifespan in humans. Each cardiac cycle imposes a mechanical constraint on the arteries, and we would like to propose that this mechanical stress damages the vascular endothelium, its dysfunction being the prerequisite for atherogenesis. Consequently, reducing heart rate could protect the endothelium and slow the onset of atherosclerosis. The potential mechanisms by which reducing heart rate could be beneficial to the endothelium are likely a combination of a reduction in mechanical stress and tissue fatigue and a prolongation of the period of steady laminar flow, and thus sustained shear stress, between each systole. With age, irreparable damage accumulates in endothelial cells and leads to senescence, which is characterized by a pro-atherogenic phenotype. In the body, the highest mechanical stress occurs in the coronary vessels, where blood only flows during diastole and even reverses during systole; thus, coronary arteries are the prime site of atherosclerosis. All classical risk factors for cardiovascular diseases add up, to accelerate atherogenesis, but hypertension, which further raises mechanical stress, is likely the most damaging. By inducing flow through the arteries, the heart rate determines shear stress and its stability: mechanical stress and the associated damage induced by each systole are efficiently counteracted by the repair capacities of a healthy endothelium. The maintenance of a physiological, low heart rate may be key to prolonging the endothelial healthy lifespan and thus, vascular health.

Keywords

Endothelium; Resting heart rate; Mechanical stress; Cellular maintenance; Cellular repair; Atherosclerosis

1. Context

Resting heart rate is a basic and simple physiological parameter of the physical examination which has important prognostic implications: there is a remarkable negative correlation between resting heart rate and life expectancy, in individuals free of disease and in patients with cardiovascular diseases.^{1,2} Resting heart rate is a strong predictor of cardiovascular

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mortality,^{3,4} independently of other known risk factors such as hypertension, diabetes, or smoking. Heart rate is a key determinant of coronary blood flow and myocardial O₂ consumption. Thus, an increased resting heart rate reduces the ischaemic threshold and cardiac performance. Because of myocardial mechanical and metabolic stimulation, heart rate likely imposes a stress not only on the myocardium but also on the vasculature, which could play an important role in determining cardiac and vascular damage to influence life expectancy.

High resting heart rate has been identified as a potential accelerator of atherosclerosis via its negative effects on the endothelium.⁵ More than five decades ago, Dr R. Altschul (1954) wrote: 'It has been said that one is as old as one's arteries. In view of the supreme importance of endothelium in arterial function, I should like to modify ...this statement by saying that one is as old as one's endothelium'.⁶ This was a visionary statement at a time when the endothelium was merely considered as an anti-coagulant sheet of cellophane. With age, the endothelium loses its ability to protect the arterial wall, promoting adhesion of platelets and infiltration of neutrophils, losing its smooth muscle cell anti-proliferative action, its dilatory function in favour of contraction, and expressing pro-inflammatory and oxidative markers.^{7,8} In this review, we will focus on trying understanding how heart rate reduction could be used as a means to slow the onset of atherosclerosis and thus to prolong vascular half life. The overall concept remains a hypothesis: unavoidable mechanical damage induced by each heartbeat starts *in utero*. It seems only logical that the addition of each risk factor for cardiovascular disease (including an elevated resting heart rate) will magnify the damage induced by each heartbeat and shorten vascular lifespan.

2. Healthy ageing and endothelial dysfunction or the natural history of atherosclerosis

With ageing, physiological functions decline.⁹ This is also true for endothelial functions.¹⁰ In short, endothelial ageing is first characterized by reduced endothelium-dependent dilation both *in vivo* and *in vitro* in all vascular bed tested.¹¹⁻¹³ To put it simply, this dysfunction (as we will refer to throughout this review) is due to a reduced production and release of nitric oxide (NO) in response to flow and agonists following an increase in inflammation and oxidative stress.¹¹ The consequences are not only functional, but also structural: the endothelium influences the structure of its underlying arterial wall, which becomes stiffer with age.¹⁴ An increase in arterial wall rigidity augments systolic and pulse pressure, and in turn strongly increases the risk of atherosclerosis, hypertension, myocardial infarction, and stroke.¹⁵

The mechanisms leading to the progressive decline in endothelial function remain uncertain. During our life, damage to the endothelium will activate maintenance repair systems. A working hypothesis is that this damage stems from the daily pounding of the cycling pressure, a classical risk factor for cardiovascular diseases, but also viral infections, autoimmune diseases, and inflammatory diseases in general. If the damage is minimal or maintenance system efficient (as in young subjects), endothelial cells will likely correct the defect and keep going. If the damage is irreversible, the damaged cells senesce and are

eventually eliminated by a mechanism yet to be discovered, while a sister endothelial cell will divide and fill the gap. It is also proposed that circulating progenitor endothelial cells assume some repair function,¹⁶ although this has not yet been clearly demonstrated *in vivo*.¹⁷ Cell division for maintenance is likely the main response of an injured endothelium. In the long term, however, the regenerated endothelium is dysfunctional¹⁸ and endothelial cells can only undergo a finite number of divisions, after which they enter senescence and stop dividing.^{19,20} Senescence is a state of quiescence in which cells are still metabolically active and, most importantly, express a pro-inflammatory, pro-oxidative, and pro-atherogenic phenotype.²¹ The gradual accumulation of senescent endothelial cells leads to a progressive decline in endothelial function.²² Thus, while endothelial cell division contributes to repair and maintenance of endothelial function, this leads ultimately to senescence, and thus, endothelial dysfunction (Figure 1). Consequently, any condition that increases damage will accelerate endothelial cell division and so hasten dysfunction.^{23–25}

3. Risk factors for cardiovascular diseases accelerate endothelial dysfunction

At exhaustion of the endothelial repair capacities, atherosclerosis develops according to a process that has been very well reviewed.^{26,27} Briefly, atherosclerotic plaques associated with excessive expansive remodelling evolve to high-risk plaques in areas of low endothelial shear stress, a condition that promotes continued local lipid accumulation, inflammation, oxidative stress, matrix breakdown, and eventually further plaque progression and excessive expansive remodelling. In the endothelium of patients with severe coronary artery disease (CAD), and exposed to multiple risk factors, we observed that while the sum of all risk factors for cardiovascular diseases accelerates endothelial senescence in plaque-free arteries, hypertension is sufficiently damaging per se to accelerate endothelial cell turnover and lead to premature senescence (Figure 1), which is associated with atherosclerosis.²⁵ Hypertension likely magnifies the mechanical stress of each heartbeat by increasing peripheral resistance. In addition, hypertension-dependent endothelial dysfunction will accelerate large artery stiffening (see in what follows), thus magnifying further the stress of each heartbeat, and will increase pulse pressure, a risk factor for stroke, to name only one consequence. Therefore, elevated resting heart rate and high blood pressure have synergistic effects on cardiovascular mortality.¹

4. Causes for elevated resting heart rate

Tachycardia is a well-defined medical condition with resting heart rate above 100 b.p.m. Such condition can be the consequence of fever (18 beats per degree Celsius), sympathetic activation of the heart (shock or semi-shock, loss of blood), and toxic conditions to the heart such as weakening of the heart that elicits a sympathetic reflex to increase the heart rate.²⁸ In contrast, the origin of a higher-than normal resting heart rate, which is directly relevant to this review, is not clearly defined. Mental stress increases sympathetic drive in humans and increases resting heart rate.^{29–31} Obesity is associated with an increase in sympathetic drive in humans and can be at the basis of the associated hypertension and elevated resting heart rate.³² Interestingly, however, a recent 20 year prospective study demonstrates that an

increase in resting heart rate may predispose to obesity and diabetes mellitus,³³ suggesting that an early rise in sympathetic drive may promote these metabolic changes. Nagae *et al.*³⁴ demonstrated the importance of central oxidative stress in the regulation of blood pressure and heart rate and how obesity increases the sympathetic drive (also see the section on the regulation of the baroreflex sensitivity).

These observations lead us to consider the role of NO as a regulator of the sympathetic outflow, since a rise in reactive oxygen species (ROS) production favours the degradation of NO. Nitric oxide is known to depress the sympathetic activity, likely by increasing parasympathetic tone both centrally³⁵ and peripherally (for review, see Danson *et al.*³⁶). A rise in oxidative stress down-regulates this pathway and favours the sympathetic drive as shown in diabetes³² and hypertension.³⁶ In spontaneously hypertensive rats, L-arginine supplementation corrects local cardiac noradrenergic hyperactivity, probably via increased pre-synaptic substrate availability of the NOS pathway and reduced tyrosine hydroxylase levels, limiting noradrenaline production.³⁵ There is therefore a strong inhibitory effect of NO on the sympathetic drive, and thus the regulation of heart rate.

Finally, and to our knowledge, there are no genome wide association studies that tested the genetic association with resting heart rate. Overall, the central hypothesis for an increased resting heart rate below tachycardia but above normal range (>70 b.p.m.) is an increased sympathetic drive either directly or through a reduction in parasympathetic tone. Alternative hypotheses have yet to be defined but increased ROS production is emerging as an important mechanism activating the sympathetic drive.

5. High heart rate and the potential link with endothelial dysfunction

Cardiac contraction induces a pulsatile pressure and flow: it is accepted that the pulsatile increase in pressure leads to fatigue failure of the vascular wall in the long term, while the pulsatile rise in blood flow is beneficial to the endothelium.^{26,27} At normal low heart rate (between 60 and 70 b.p.m., based on the impact of resting heart rate on event rate;³⁷ Figure 2), mechanical stress-induced damage is likely efficiently counterbalanced by the protective function of the normal endothelium under physiological shear stress conditions.

5.1 The pulsatile change in pressure

The pulsatile increase in pressure generated by cardiac contraction is the main cause of vascular stress. The conduit arteries are elastic because the heart is a reciprocating pump. Thus, during systole, a bolus of blood is ejected into the aorta and the pressure stretches the aortic wall to accommodate the bolus. At the end of systole, the aortic valve closes, the blood starts to flow through the systemic circulation driven by the elastic energy stored in the aortic wall, which returns to its end-diastolic diameter. This mechanical stress is therefore largely absorbed by the compliance of the conduit artery wall. If the aorta and other conduit arteries were not rubber-like but copper-like, the required systolic pressure would have to be greater to permit flow throughout the entire vascular tree and the heart rate would need to be much higher than 70 b.p.m. Hypertension, which increases peripheral resistance, imposes a greater pressure. This no doubt magnifies the mechanical stress and accelerates the damage induced by repeated cardiac cycles.³⁸ Likewise, while

conceptualizing a bridge, an engineer takes into account material strength and fatigue capacity, and thus resistance to stresses such as high winds, waves, and earthquakes. Any of these stresses, if higher than normal, will shorten the half-life of the construction.

5.2 The pulsatile change in flow

Before presenting the effects of heart rate on shear stress—the frictional (tangential) force per unit area created by flow of viscous blood over the inner vessel wall and the luminal surface of the endothelium—and endothelial function, we would like to summarize briefly the mechanisms by which flow mediates dilation and regulates eNOS expression.

A rise in flow induces a transient rise in intracellular Ca^{2+} necessary for calmodulin to interact with caveolin, which maintains eNOS inactive in the basal state. Following calmodulin activation, heat shock protein (Hsp) 90 binds to eNOS³⁹ favouring the recruitment of Akt leading to the phosphorylation of eNOS on ser-1177, its sustained enzymatic activation, production of NO, and dilation.^{40,41}

Haemodynamic shear stress also regulates eNOS expression in the endothelium. Recent data clearly point to a role for H_2O_2 in this process, and thus to the primary involvement of superoxide ($\text{O}_2^{\bullet-}$).^{42,43} In agreement with the concept that oxidative stress up-regulates eNOS expression is the demonstration that exercise increases the production of ROS together with eNOS.⁴⁴

The cardiac contraction is responsible for pulsatile flow and thus for haemodynamic shear stress. The latter is characterized by Poiseuille's law, which states that shear stress is proportional to blood flow and its viscosity, and inversely proportional to the third power of the inner diameter. Shear stress is low in the veins (1–6 dynes/cm²; 10 dynes/cm² = 1 Pa = 1 N/m²), high and pulsatile in conduit arteries (10–70 dynes/cm²), and averages 15 dynes/cm² in arterioles. Overall, in the arterial tree, shear stress averages 15–20 dynes/cm.^{2,26} Shear stress is important for three reasons. First, it is a strong endothelial stimulus. A physiological increase in shear stress stimulates the production of NO—and to a lesser extent prostacyclin—which immediately dilates brachial arteries in humans,¹³ except large conduit arteries, which are essentially elastic. Second, sustained shear stress maintains the expression of the NO-producing enzyme, which maintains basal release of NO, which is known to reduce platelet aggregation, neutrophil adhesion, inflammation, constricting factors, and free radical production.^{26,27} Third, conversely, a reduction in flow constricts small arteries, increases resistance, and thus further reduces flow locally. The response to shear stress of the endothelium therefore permits fine-tuning of nutrient delivery to accommodate metabolic demand.⁸

There are, however, two extreme conditions where shear stress no longer plays a regulatory role, i.e. low and even negative shear stress (–4 to +4 dynes/cm²) on the one hand, and extremely high shear stress (>70–100 dynes/cm²) on the other hand. The former occurs in areas of the coronary circulation at each cardiac cycle, but also in zones of recirculation of blood flow such as behind bifurcations or a plaque. Extremely high shear stress occurs in the aortic valve, but also at complex atherosclerotic plaques and stents, both of which are rigid and therefore do not dilate in response to systolic pressure or to shear stress. Thus, if one

compares shear stress in veins and arteries, it may not be its physiological level that contributes to the maintenance of a healthy endothelium, but rather its stability.

Blood flows in the coronary arteries during diastole and reverses during systole as the contracting myocardium squeezes the subendocardial coronary arteries.⁴⁵ Nowhere else in the body is such mechanical stress imposed on an artery. Shear stress in coronary arteries is uneven, and its mean value is well below 10 dynes/cm². The consequence is a lower NO production and thus reduced protection against stresses. Not surprisingly the coronary circulation is the prime site for early endothelial dysfunction,⁴⁶ followed by atherosclerosis.⁴⁷ Conversely, cerebral arteries are better protected from such extreme mechanical stress and so are less prone to early atherosclerosis than the coronaries.⁴⁸ In cerebral arteries, shear stress is more stable, and pulsatility is quickly reduced by myogenic responses—the reduction in diameter induced by a rise in intraluminal pressure—leading to faster dampening of pulse pressure.⁴⁹ Therefore, a high resting heart rate shortens the diastolic coronary perfusion phase,⁴⁵ favours bi-directional changes in flow, and reduces the average shear stress, and thus the release of protective NO. Finally, this likely promotes endothelial dysfunction.

6. Heart rate and atherosclerosis

The first evidence of the prognostic importance of heart rate was presented by Levy *et al.*⁵⁰ in 1945. In this report, the authors showed that the rate of developing hypertension with age was more than doubled in the presence of transient tachycardia (Figure 3). Numerous epidemiological data now show that an increase in resting heart rate accelerates the atherosclerotic process.³ Accordingly, the reduction in resting heart rate by metoprolol slows endothelial cell replication (a marker of dysfunction/activation) in psychologically stressed monkeys,³⁰ while the reduction in resting heart rate by surgical ablation of the sinoatrial node slows the atherosclerotic process in monkeys fed a high fat diet.^{51,52} Regular exercise, which decreases resting heart rate, is beneficial to the cardiovascular system.⁵³ It increases the number of healthy life years,⁵⁴ slows the progression of atherosclerosis,⁵⁵ and a year of regular exercise that lowers resting heart rate from 71 to 65 b.p.m. even reduces the recurrence of cardiovascular events post-angioplasty.⁵⁶ Hence, lowering resting heart rate through exercise is beneficial even in secondary prevention. The benefits gained from regular exercise are, however, by far not limited to the reduction in heart rate but also due to the improvement in the endothelial function, the reduction in blood pressure and the better metabolic profile.⁵⁷

The discovery and clinical development of new drugs that selectively reduce heart rate without concomitant negative effects on myocardial contractility, relaxation, and conduction constitute a significant advance for the medical treatment of angina. To date, only the benzocyclobutane derivative ivabradine is available in medical practice in Europe.⁵⁸ This small molecule selectively inhibits the activity of the depolarizing pacemaker current I_f and thus slows heart rate without affecting blood pressure or cardiac contractility.⁵⁸ In other words, ivabradine slows heart rate by reducing the ‘steepness’ of the I_f current slope of diastolic depolarization in the sinoatrial nodes and thus increases diastolic duration. Ivabradine not only protects endothelial function,⁵⁹ but also slows atherosclerosis in apolipoprotein E-

deficient mice,⁶⁰ which is in complete agreement with the clinical data cited earlier. However, besides the reduction in resting heart rate, the underlying vascular protective mechanisms of ivabradine remain to be elucidated.

6.1 Clinical benefits of ivabradine

The pathophysiological basis and experimental data support the potential of heart rate reduction as an intervention to improve endothelial function, to attenuate progression of atherosclerosis and ultimately to prevent coronary events. Whether lowering heart rate with ivabradine in patients with stable CAD receiving optimal background therapy could result in reduction of cardiovascular events prompted the BEAUTIFUL (morBidity-mortality EvAIUaTion of the If inhibitor ivabradine in patients with coronary disease and left ventricULar dysfunction) study, the results of which have been recently reported.⁶¹ BEAUTIFUL is a large, international, randomized, placebo-controlled morbidity–mortality trial in a high-risk population of patients with CAD and left ventricular systolic dysfunction (mean left ventricular ejection fraction was 32.4%), conducted between December 2004 and December 2006. The study enrolled 10 917 eligible patients; 5479 patients were randomized to receive ivabradine on top of conventional cardiovascular treatments as recommended by guidelines, and 5438 patients were randomly assigned to the placebo group. The mean heart rate at baseline was 71.6 b.p.m.

Although the primary endpoint of the study (composite of cardiovascular mortality, admission to hospital for acute myocardial infarction, and admission to hospital for new-onset or worsening heart failure) was not met in the overall population, in the pre-specified subgroup of patients with resting heart rate \geq 70 b.p.m., ivabradine reduced significantly the risk of coronary events by 22%, fatal and non-fatal myocardial infarction by 36%, and reduced coronary revascularization by 30%. These benefits were observed despite the fact that 84% of these patients received beta-blockers.

The BEAUTIFUL evidence has extended current knowledge of the role of heart rate as a risk factor in CAD by also conducting a prospective analysis of the data from the placebo arm of the BEAUTIFUL study to assess the association of heart rate with different clinical outcomes.⁴ Patients with a heart rate of 70 b.p.m. or more had significantly increased risks of cardiovascular death (34%), admission to hospital for heart failure (53%), admission to hospital for myocardial infarction (46%), and coronary revascularization (38%) after adjustment for other predictors of outcome.

Ongoing and future clinical studies will provide further evidence on the extent of the cardioprotective benefits of heart rate lowering with ivabradine in cardiovascular disease. The SHIFT (Systolic Heart failure with the I_f -inhibitor ivabradine Trial) study, which is currently investigating the effects of ivabradine in congestive heart failure, will provide important information concerning importance of heart rate reduction with ivabradine in the management of heart failure. This large-scale, randomized, placebo-controlled trial has recruited over 7000 patients with moderate to severe heart failure and resting heart rate \geq 70 b.p.m. Throughout the study, all patients have continued their current standard treatments for heart failure and any other cardiovascular conditions. The results of these studies will extend current knowledge of the role of heart rate as a risk factor in heart failure.

7. By what mechanism pure heart rate reduction could slow age-related endothelial dysfunction?

Two possible mechanisms can be put forward, keeping in mind that first irregular shear stress and second mechanical stress are damaging. The first mechanism is well described in a recent review:⁶² by reducing heart rate, the interval of sustained blood flow during diastole increases. The second mechanism, also well described in a recent review,¹⁴ is only mechanical and is a direct consequence of a slower heart rate, which slows tissue fatigue. In addition to these mechanisms, it is also important to consider that a low heart rate has a positive regulatory consequence: the baroreflex sensitivity increases.³⁸

7.1 Shear stress

Exercise and ivabradine improve endothelial function and slow the onset and progression of atherosclerosis. But how do we know that shear stress is important in the response to heart rate? To answer this question specifically, one needs to study a vascular bed where the cycling mechanical stress imposed by each heartbeat is limited. In small, 100 μm diameter, mouse resistance cerebral arteries, the pulsatile nature of the flow is not eliminated, but is largely dampened by the myogenic contraction of upstream arteries. Consequently, blood pressure is lowered to 60 mmHg, compared with 100 mmHg in same size peripheral *gracilis* arteries.⁶³ Ivabradine was tested in mice with dyslipidaemia, in which endothelial function declines from the age of 3 to 6 months.^{12,59} A treatment with ivabradine, from the age of 3 to 6 months, reduced heart rate by 10% and prevented the decline in cerebrovascular endothelial function.⁵⁹ Since ivabradine did not affect blood pressure, only a slower heart rate accounted for this effect. By slowing heart rate, the diastolic perfusion time increases, and thus flow is more constant.^{45,62} A more constant shear stress in the physiological range, i.e. over 15 and below 70 dynes/cm², likely explains part of the benefit of a lower resting heart rate. The stability of shear stress is so important that the initial growth of an atherosclerotic plaque will promote an endothelium-dependent expansion of the vascular lumen to maintain shear stress within normal values, a response known as the 'Glagov phenomenon'.⁶⁴ This response is genetically programmed and demonstrates how a constant shear stress is fundamental to the overall regulation of arterial function.

7.2 Mechanical stress

Ageing is associated with a change in the structure of the wall, which becomes stiffer.¹⁴ The most damaging effect of the hypertensive phenotype is likely a magnification of the mechanical stress imposed on the wall by each heartbeat, which is reminiscent of an accelerated ageing process.⁶⁵ This has two consequences: the heart and the large conduit arteries hypertrophy to compensate for the increased resistance pressure. In the long term, cardiac hypertrophy turns into heart failure, while loss of arterial elasticity,⁶⁶ by magnifying mechanical stress, accelerates endothelial cell turnover,⁶⁷ promoting premature senescence of the endothelium²⁴ and atherosclerosis.⁶⁸ Not only does the endothelium lose its protective capacities, but very high shear stresses (>70 dynes/cm²) generated by the lack of elasticity during the systole activate platelets and favour thrombosis.^{23,26,27}

We observed the ‘age-retarding’ effect of a lower heart rate on conduit arteries in dyslipidaemic mice using ivabradine.⁵⁹ After 3 month treatment with ivabradine, the renal arteries of dyslipidaemic mice dilated to the same extent as healthy arteries. In these large conduit arteries, pulse pressure is at its maximum, as is the mechanical stress. Ivabradine, which slowed heart rate by around 10% from the age of 3 to 6 months, prevented the decline in endothelium-dependent dilations. Although we have no definite demonstration, it is possible that the reduction in heart rate minimized the damaging effect of the mechanical stress and consequently attenuated the deleterious effect of dyslipidaemia. In hypercholesterolaemic mice, ivabradine slowed the progression of atherosclerosis,⁶⁰ in agreement with the concept that each heartbeat generates damage. It may come to a surprise, however, that in the study by Custodis *et al.*,⁶⁰ high-fat fed ApoE^{-/-} mice had a lower resting heart rate compared with wild-type mice; yet, lowering further heart rate by 13% prevented the decline in endothelial function and development of atherosclerotic plaques. It was known that resting heart rate differed from one strain to another,⁶⁴ but there is also the possibility that high-cholesterol limits somehow heart function/rate. It would therefore have been informative to have a group of ApoE^{-/-} mice fed a normal diet. Finally, it has been suggested that ivabradine may have pleiotropic effects on cardiac infarct size and reperfusion injury.^{45,69} The mechanisms by which ivabradine could protect the heart post-ischaemia remain to be discovered. In isolated arteries, however, ivabradine has no direct acute effect on either contractions or dilations.⁵⁹

7.3 The contrasting effect of β -adrenergic receptor blockade

While β -adrenergic receptor antagonists reduce heart rate, atenolol and most of the selective β -blockers impair endothelial function, decrease insulin sensitivity, and increase lipid levels,⁷⁰ conditions that increase the burden of cardiovascular risks. New generation of ‘vasodilating’ β -blockers (such nebivolol and carvedilol)⁷¹ have been reported to improve metabolism and endothelial function.⁷² It is clear that this new generation of agents are better at reducing central aortic blood pressure,⁷³ which may explain their apparent better efficacy, but large clinical trials are needed to validate these early findings.

The endothelium expresses β -adrenergic receptors and their activation by circulating catecholamines has been proposed to activate a survival pathway.⁷⁴ Although this remains an hypothesis, this may explain why the LIFE (Losartan Intervention For Endpoint) study showed that for an equal resting heart rate, there was a 28% greater cardiovascular risk associated with pulse pressure in atenolol-treated patients with hypertension and left ventricular hypertrophy than in patients treated with the angiotensin II receptor antagonist losartan. Most importantly, an even greater risk (84%) of stroke was reported in patients treated with atenolol compared with losartan.^{75,76} In the MORE (Multicentre Olmesartan atherosclerosis Regression Evaluation) study, when the baseline plaque-volume was greater than 33.7 μ L, atenolol did not promote its regression in contrast to the angiotensin II receptor antagonist olmesartan.⁷⁷ In this latter study, heart rate was not reported but the two receptor antagonists reduced blood pressure similarly. Meta-analyses have shown that despite lowering blood pressure and heart rate, β -adrenergic receptor blockage was not effective in reducing cardiovascular events when compared with either placebo or other antihypertensive agents.⁷⁸

Activation of endothelial β -adrenergic receptors stimulates NO release,⁷⁹ and a reduced bioavailability of NO is linked to increased arterial stiffness.⁸⁰ Arterial stiffness is so damaging to the cardiovascular system that restoring arterial elasticity would be of great therapeutic benefit.⁸¹ In our study,⁵⁹ pure heart rate reduction by ivabradine protected both cerebral and renal endothelial function. We also tested the effects of metoprolol, a β -adrenergic receptor antagonist, which reduced heart rate similarly to ivabradine without reducing blood pressure. Metoprolol partially protected renal but not cerebral arterial dilation. This suggests that a reduction in resting heart rate limits mechanical stress in conduit renal arteries, a beneficial effect that may be partially counterbalanced by inhibition of the protective endothelial β -adrenergic receptor survival pathway. Mechanical stress being of less impact in cerebral arteries, inhibition of endothelial β -adrenergic receptors likely negated the beneficial effects of an improved shear stress profile. As mentioned previously, this remains however, a working hypothesis to be tested.

7.4 The baroreflex

By reducing heart rate, the sensitivity of the baroreflex increases.^{38,82} This is confirmed in humans using β -adrenergic receptor antagonists^{83,84} but not with all of them.⁸⁵ The autonomic nervous system is perhaps the most important defender of homeostasis. Thus, by reducing heart rate and increasing baroreflex sensitivity, there is a better match between blood pressure and sympathetic activity, favouring greater parasympathetic tone, as observed with the non-selective β -adrenergic receptor antagonist carvedilol in heart failure patients.⁸⁴ This also means better long-term regulation of the rennin–angiotensin–aldosterone system, as suggested by a reduced level of circulating angiotensin-II in ivabradine-treated rats.⁸⁶ Parasympathetic tone, however, decreases with age and this is associated with a reduction in resting heart rate variability between night and day and a lower beat-to-beat adaptation to physiological haemodynamic stimuli.⁸⁷

Long-term regulation of blood pressure is highly dependent on the kidney via blood volume regulation.^{88,89} Blood pressure increases with age, but this is directly proportional to daily salt consumption: in societies where salt intake is high, blood pressure rises by 1 mmHg per year after the age of 30.⁹⁰ In this context, what could be the role of the baroreflex? The relationship between short-term baroreflex, sympathetic activity, heart rate, and blood pressure is obvious, but the link with hypertension is not, because it is generally accepted that the baroreflex is not an important regulator of blood pressure in the long term. Baro-denervation in animals does not change blood pressure over a 24 h period.⁹¹ Total peripheral resistance and cardiac output do not change, but mean blood pressure variability increases enormously between 50 and 140 mmHg compared with 80 and 125 mmHg in controls. This therefore supports the accepted idea that the baroreflex is a short-term regulator of blood pressure. There are, however, indications to the contrary. In baro-denervated animals, a high-salt diet increases blood pressure dramatically.⁹² In addition, chronic activation of the baroreflex causes sustained reduction in blood pressure in normotensive animals, with little evidence that there is activation of renal mechanisms to increase blood volume and thus, normalize pressure.⁹³ It has been shown that sympathetic activity increases with age and obesity, which raises blood pressure.^{94–96} Importantly, NO synthesis blockade impairs the cardiovascular autonomic adaptations induced by physical training in rats that might be, at

least in part, ascribed to a decreased baroreflex sensitivity,⁹⁷ a mechanisms that has been confirmed in rabbits with congestive heart failure due to an augmentation in the vagal tone.⁹⁸ In fact, NO has more impact on the regulation by the baroreflex of heart rate than on the renal sympathetic nerve activity.⁹⁹ In leptin-deficient mice, which are diabetic, hypertensive, and with an elevated resting heart rate, the rennin–angiotensin system is activated and could be responsible for the greater sympathetic and decreased parasympathetic tone in these mice.¹⁰⁰ These observations have important implications for prematurely ageing and obese western populations: since ageing, hypertension, and obesity increase arterial stiffness and reduce baroreflex sensitivity, any way to increase this sensitivity is likely to be beneficial for the cardiovascular system and its longevity. A reduction in heart rate does so, and a better baroreflex control doubtless accounts for the long-term beneficial effects of exercise on the endothelium, the vascular wall, and thus cardiovascular longevity.

8. Concluding remarks

In this review, we have described evidences suggesting that resting heart rate, if elevated, is deleterious to the cardiovascular system. Our working hypothesis is that each heartbeat imposes a mechanical stress on the endothelium, and clearly over time, billions of them can induce damage. Mechanical stress is unavoidable, but its magnitude varies from one individual to another. We propose that this mechanical stress is magnified by additional stress factors, such as hypertension, as well as smoking, dyslipidaemia, and diabetes. If this hypothesis was validated, it would be essential to detect and treat cardiovascular risk factors—elevated resting heart rate being one of them—as early as during childhood.¹⁰¹ Stress and repair start *in utero*¹⁰² and atherosclerosis develops soon after childhood, as discovered in young US soldiers killed during the Korean War. Early control of risk factors will therefore benefit the patient. Reducing an abnormal elevated resting heart rate would be a way of increasing the number of healthy years of life by minimizing the primary stress imposed on the vascular endothelium and wall.

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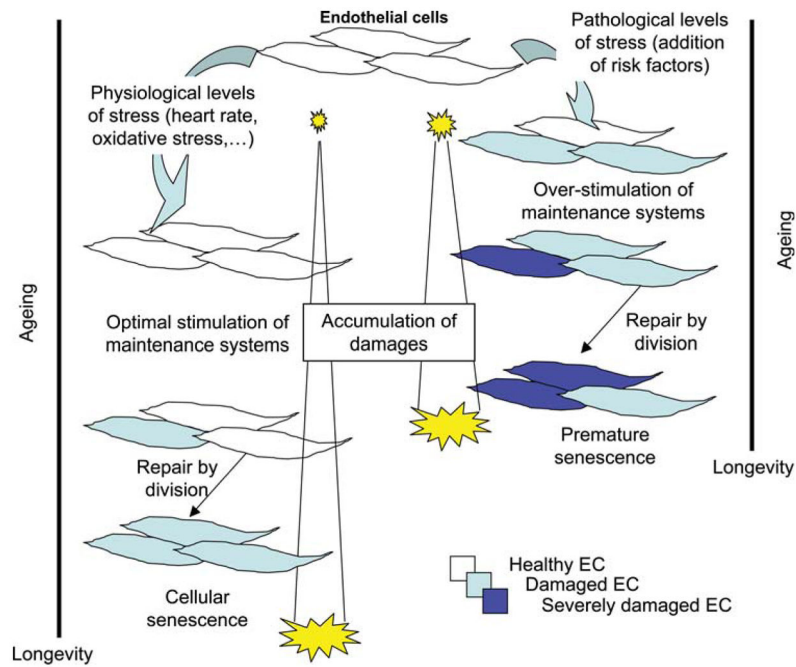


Figure 1. A model for the mechanisms of age-dependent endothelial dysfunction. Physiological levels of stress on the endothelium are generated by heartbeats and metabolic oxidative stress. Upon addition of a risk factor such as hypertension, damage increases, augmenting endothelial cell turnover and thus senescence.²⁵ Exponential accumulation of senescent endothelial cells is pro-atherogenic.

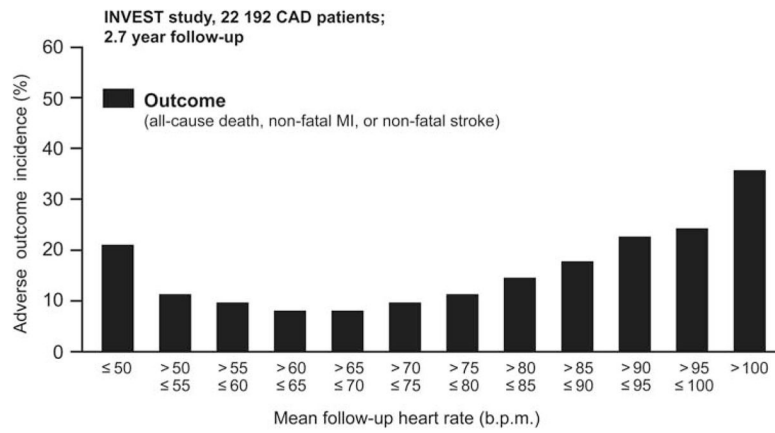


Figure 2. Relationship between follow-up resting heart rate for all patients and incidence of adverse outcomes. Among all patients, the nadir for follow-up resting heart rate was 59 b.p.m. Adapted from Kolloch *et al.* Impact of resting heart rate on outcomes in hypertensive patients with coronary artery disease: findings from the INternational VERapamil-SR/trandolapril STudy (INVEST). *Eur Heart J* 2008;**29**:1327–1334.³⁷

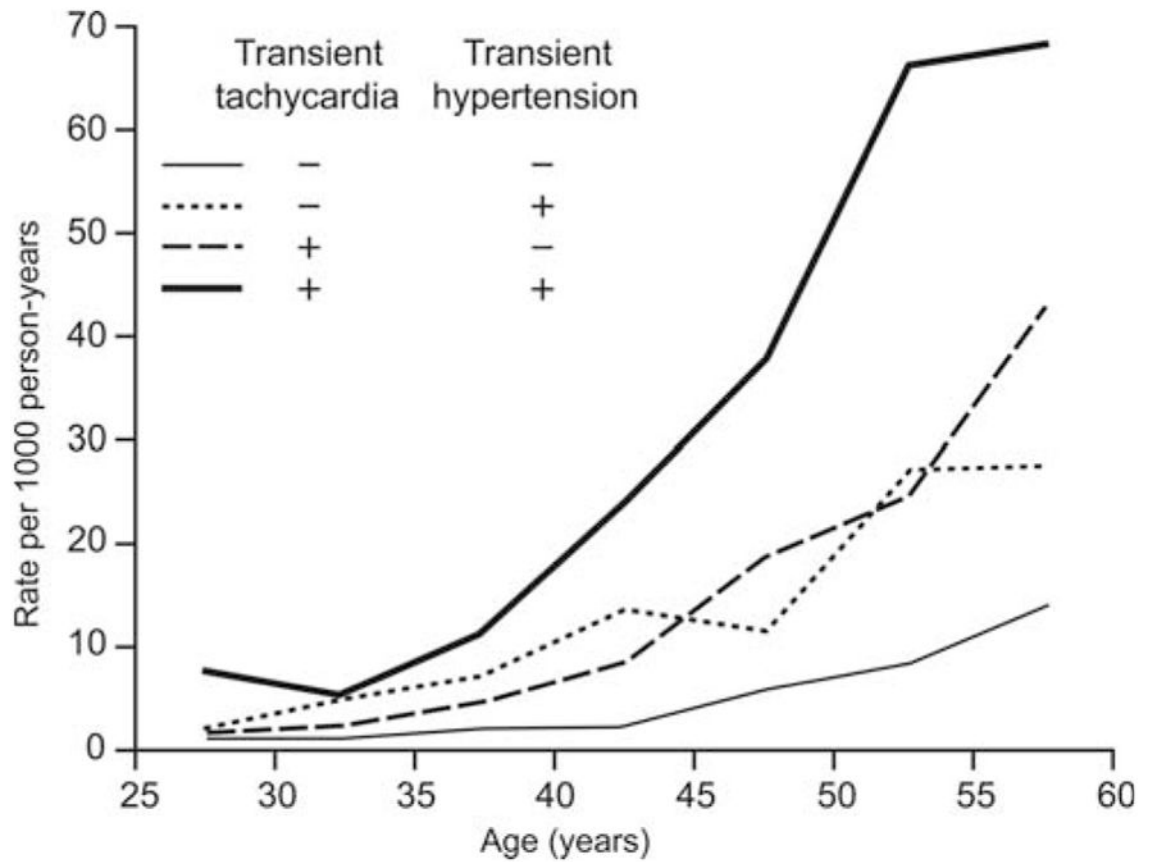


Figure 3. Rate of developing sustained hypertension by age according to the presence or absence of transient tachycardia and transient hypertension. Adapted from Levy *et al.* Transient tachycardia: prognostic significance alone and in association with transient hypertension. *JAMA* 1945;**129**:585–588.⁵⁰