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Heart Rate, Autonomic Markers, and Cardiac Mortality

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“Current data leave little doubt that heart rate is a risk factor for cardiovascular mortality, independent of currently accepted risk factors and other potentially confounding demographic and physiological characteristics” (Fig 1).^{1,2} These words reflect the main conclusion of a recent state-of-the-art paper by the Heart Rate Working Group comprised of European and U.S. investigators. Support for the important role of heart rate as an independent prognostic risk factor is provided by numerous epidemiological studies^{1,2} and large post-myocardial infarction trials^{3,4} as well as by the sizeable morbidity-mortality evaluation of the selective I_f inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction (BEAUTIFUL) study.^{5,6}

Notwithstanding this body of evidence, an important caveat in evaluating the role of heart rate as a risk factor for cardiac mortality is the extent to which this physiologic variable is in the causal chain of events versus being a “fellow traveler,” reflecting other, more potent influences. Heart rate is mainly indicative of actions on the sinoatrial node and does not provide information concerning effects on the specialized conducting system and ventricular myocardium, which may be more directly linked to life-threatening arrhythmias. For example, the increase in heart rate associated with enhanced sympathetic nerve activity and decreased vagal tone may not adequately reflect the potent direct heart-rate independent actions of neurotransmitters⁷ on repolarization properties of the normal and diseased myocardial substrate.^{8,9} It is well established that enhanced adrenergic activity is arrhythmogenic and that efferent vagal tone is cardioprotective by opposing adrenergic influences through presynaptic inhibition of norepinephrine release and an action at the receptor level mediated by second messenger mechanisms.¹⁰

The present review addresses the following fundamental questions: (1) How is heart rate regulated? (2) How are autonomic tone and reflexes measured clinically? (3) What mechanisms mediate the cardiovascular pathology associated with elevated heart rates? (4) Does reducing heart rate independent of other factors protect against cardiovascular events?

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How is heart rate regulated?

Control of the sinoatrial node is achieved through both intrinsic and extrinsic mechanisms. Its intrinsic regulation is determined by the I_f pacemaker current, which establishes the slope of spontaneous diastolic depolarization. Sinoatrial node depolarization has been attributed to a “voltage clock” regulated by voltage-sensitive membrane currents, particularly the hyperpolarization-activated pacemaker current, I_f , which is regulated by cyclic adenosine monophosphate (cAMP). Recent evidence supports joint roles for membrane voltage and Ca^{2+} clocks in regulating the sinoatrial node, which result in a heart rate increase during beta-adrenergic stimulation.¹¹ The Ca^{2+} clock is mediated by calcium release from the sarcoplasmic reticulum, leading to diastolic depolarization through activation of the sodium-calcium exchanger current, which coordinates the regulation of sinus heart rate interactively with the voltage clock. The intrinsic heart rate of healthy individuals, as reflected by the heart rate observed during complete autonomic blockade, is ~100 beats/minute.¹² With advancing age, the intrinsic rate decreases, particularly in the latter decades of life.¹³

Extrinsic regulation of the sinoatrial node in response to physical and mental activity and sleep states¹⁴ is achieved through an influence on the tonic activity of both limbs of the autonomic nervous system, circulating hormones, and reflex regulation associated with cardiorespiratory and baroreceptor inputs. The neurocircuitry that influences the sinoatrial node is illustrated (Fig. 2).¹⁵ The main mechanisms for heart rate acceleration by autonomic function are steepening the slope of spontaneous diastolic depolarization and hypopolarizing the resting potential as a result of release of norepinephrine and epinephrine. An opposing influence of the vagus nerve in slowing heart rate involves a decrease in the slope of diastolic depolarization through an effect on I_f and through hyperpolarization due to increased potassium permeability. The sinus node is also responsive to nonautonomic influences including hypoxia, exercise, and temperature.

Heart rate exhibits a distinct circadian pattern with a progressive rise in the early morning, which parallels the surge in sympathetic nerve activity, as has been shown in chronically instrumented canines (Fig. 3).¹⁶ During nighttime, there is relative vagal dominance in the regulation of heart rate, particularly during nonrapid-eye-movement sleep. This pattern is periodically interrupted by rapid eye movement sleep, when heart rate surges as vagus nerve tone is withdrawn and sympathetic nerve activity reaches levels higher than during waking.¹⁴

The presence or absence of respiratory sinus arrhythmia constitutes an important measure of cardiovascular health. This rhythmic change in heart rate during breathing is mediated largely through the Hering-Breuer reflex, which acts through the medullary cardiovascular regulatory centers.¹⁷ During inspiration, cardiac efferent vagal tone is inhibited and sympathetic efferent tone is enhanced, resulting in heart rate accelerations. During expiration, reciprocal changes in autonomic balance occur that slow heart rate (Fig. 4).¹⁷ Respiratory sinus arrhythmia appears to provide a “measure of biologic cardiac age,”¹⁸ as it is depressed with advancing age, reflecting decreases in cardiac and vascular elasticity and compliance or in the capacity of the pacemaker to be activated.¹³ It is unclear whether respiratory sinus arrhythmia is causally related to improved cardiac health or is a marker of beneficial autonomic influences.

It is well established that behavioral stress can significantly increase heart rate due to the attendant surge in catecholamines and withdrawal of vagal tone.¹⁰ Of note, is the recent observation¹⁹ that an exaggerated heart rate response in anticipation of exercise predicts sudden cardiac death in the general population.

How are autonomic tone and reflexes measured clinically?

Numerous techniques developed to evaluate autonomic function in health and disease have been extensively reviewed.^{7,20} They can be classified in two general categories as measures largely of tonic activity [heart rate, heart rate variability (HRV)^{7,21,22}] or reflex baroreceptor function [baroreflex sensitivity (BRS)^{22,23} or heart rate turbulence (HRT),^{3,24}]. Parameters that reflect the combined influence of autonomic tone and reflexes and hemodynamic factors have also been explored. These include heart rate recovery,^{1,25–27} deceleration capacity,²⁸ and tonic and reflex vagal activity (TARVA).²⁹ The latter two methods have been less extensively studied but are promising. Deceleration capacity²⁸ proved to be a better predictor of mortality in post-myocardial infarction patients than either left ventricular ejection fraction or standard deviation of normal RR intervals (SDNN), a conventional measure of HRV. TARVA, calculated as BRS X HF/LF ratio of HRV and thus incorporating both tonic activity and baroreceptor responsiveness, was demonstrated to predict ventricular fibrillation in canines with myocardial ischemia induced during submaximum exercise.²⁹

Heart Rate Variability

Autonomic nervous system tone has been studied in human subjects primarily by analyzing HRV. The underlying principle is that the pattern of beat-to-beat control of the sinoatrial node reflects autonomic influences on the cardiovascular system. Parasympathetic influences exert a unique imprimatur through rapid dynamic control by release of acetylcholine, which affects muscarinic receptors, and are therefore reflected in the high-frequency component of HRV. Sympathetic nerve activity, through the influence of norepinephrine on beta-adrenergic receptors, has a considerably slower influence and is manifest in the lower frequency components. Thus, HRV is an indirect measure of autonomic function, as it reflects influences on the sinoatrial node but not on the ventricular myocardium.

Nevertheless, HRV provides insights into general autonomic changes associated with disease states. Following an initial finding of its capacity to separate survivors from nonsurvivors of myocardial infarction, studies have demonstrated the utility of HRV to define autonomic status in patients with coronary artery disease,^{19,22,30} heart failure,^{31–33} cardiomyopathy,³⁴ early-stage hypertension, incipient diabetes, and following cardiac surgery. It also tracks autonomic changes during normal ageing and their improvement with exercise conditioning.

Baroreceptor Sensitivity

The classic studies by Schwartz and coworkers²³ focused attention on the importance of baroreceptor function in determining susceptibility to life-threatening arrhythmias associated with myocardial ischemia and infarction. They demonstrated that during exercise, canines with more powerful baroreflex responses were less vulnerable to ventricular fibrillation during myocardial ischemia superimposed on prior myocardial infarction. The protective effect of the baroreceptor mechanism has been attributed primarily to the antifibrillatory influence of vagus nerve activity, which presynaptically inhibits norepinephrine release and maintains heart rate low during myocardial ischemia. The latter effect improves diastolic coronary perfusion, minimizing the ischemic insult. La Rovere and coworkers²² subsequently documented the importance of BRS by demonstrating that post-myocardial infarction patients were less likely to experience sudden cardiac death if their baroreceptor function, evaluated with the pressor agent phenylephrine, was not depressed. Importantly, BRS analysis was capable of detecting the cardioprotective effect of exercise training in post-myocardial infarction patients (Fig. 5).³⁵ This protective effect probably resulted from multiple factors including a lower resting heart rate (by >8 beats/minute), enhanced vagal tone, and potentially favorable remodeling of the myocardium.

Heart Rate Turbulence

BRS can also be monitored noninvasively from routine ambulatory ECGs using the tool of HRT, which measures heart rate fluctuations after a single ventricular premature beat (VPB), which reflect the fall and recovery of blood pressure.³ These reactions of the cardiovascular system to a VPB are direct functions of baroreceptor responsiveness, as reflex activation of the vagus nerve controls the pattern of sinus rhythm. In low-risk patients, sinus rhythm exhibits a characteristic pattern of early acceleration and subsequent deceleration after a VPB. By contrast, patients at high risk exhibit an essentially flat, nonvarying response to the VPB, indicating an inability to activate vagus nerves and to enable their cardioprotective effect. The method has been found to be a promising independent predictor of cardiovascular and sudden death in patients with heart failure as well as of total mortality in the Multicentre Post-Infarction Program (MPIP) and in the placebo arm of the European Myocardial Infarction Amiodarone Trial (EMIAT) databases (Fig. 6).³

Heart Rate Recovery

Heart rate recovery following exercise, another marker of vagus nerve responsiveness, has proved to be highly predictive of cardiovascular mortality and sudden cardiac death in a variety of relatively low-risk cohorts including asymptomatic individuals.^{1,26,27} The reduction in heart rate during the first 30 to 60 seconds after exercise appears to be caused principally by reactivation of the parasympathetic nervous system but subsequently by withdrawal of sympathetic tone.²⁵ However, because the exponential deceleration in heart rate after exercise persists during blockade of both limbs of the autonomic nervous system with atropine and propranolol, Savin and coworkers²⁵ suggested that heart rate recovery may result to a significant degree from autonomically independent alterations in venous return with the attendant changes in stretch of atrial receptors of pacemaker tissue. The complex mechanisms underlying heart rate recovery require further elucidation.

What mechanisms mediate the cardiovascular pathology associated with elevated heart rates?

Elevated heart rates can influence the development of cardiovascular disease through a multitude of actions that can be classified both as longterm and acute effects. The underlying pathophysiologic mechanisms have been reviewed by the Heart Rate Working Group.² The longterm consequences of elevated heart rate can be subtle and insidious. Over the course of a lifetime, elevations in heart rate catalyze the atherosclerotic processes³⁰ and associated increases in arterial stiffness through pulsatile stresses and the underlying turbulence in blood flow, particularly at the bifurcations of arteries within the coronary and cerebral circulations. Over two decades ago, a 3-fold elevation in severity of diffuse coronary atherosclerosis and a doubling of development of distinct coronary stenoses was documented in young post-myocardial infarction survivors with higher resting heart rates.³⁶ These effects were independent of left ventricular ejection fraction, plasma cholesterol levels, and beta-adrenergic receptor blockade treatment. Experimental evidence also supports this mechanism, as lowering heart rate by surgical ablation of the sinoatrial node was found in adult male cynomolgus monkeys to retard development of coronary atherosclerosis.³⁷ The pulsatile stresses can also initiate proinflammatory responses that adversely affect the vascular endothelium.³⁸ In addition, there is evidence that ventricular wall stiffness can be augmented by elevated heart rates,³⁹ which can exacerbate left ventricular heart failure and predispose to adverse remodeling, thus providing a substrate for reentrant arrhythmias.

The acute effects of heart rate surges have also been well characterized. Among the most important are the disruptive effects on plaques, which become more prone to rupture,⁴⁰ and

worsening of myocardial ischemia⁴¹ due to increased metabolic demand and reduced diastolic perfusion time.² Elevated heart rates can worsen heart failure through impaired ventricular relaxation and can increase the frequency of ischemic episodes.⁴²

In terms of arrhythmogenesis, heart rate has been implicated in diverse mechanisms, including sympathetic nerve activity and enhancement of reentrant mechanisms due to a disruption of the relationship between refractoriness and conduction time.⁴³ When heart rate is elevated during ischemia, the compromise of diastolic perfusion time worsens the ischemic insult and thereby contributes to development of ventricular tachycardia and fibrillation. Indeed, heart rate is more strongly related to sudden cardiac death than to nonsudden death from acute myocardial infarction.¹ Low resting heart rates, along with relatively low BRS, have been found to be protective factors in patients with the long QT syndrome attributable to KCNQ1 mutations and reduced I_{Ks} .⁴⁴

Elevated heart rate can be an important factor in generating arrhythmogenic T-wave alternans (TWA). This phenomenon, defined as a beat-to-beat fluctuation in the amplitude and shape of the T wave, can occur when the capacity of the sarcoplasmic reticulum to reuptake calcium from the cytosol is disrupted. This mechanism has been demonstrated with fluorescent dyes, which indicate that calcium transients alternate in synchrony with action potential duration alternans. The elicitation of discordant TWA, wherein neighboring cells alternate out of phase, can establish steep electrical gradients that are highly conducive to life-threatening arrhythmias.^{9,45} These arrhythmogenic effects are compounded when heart rates are excessively high, particularly in patients with ischemic heart disease, myocardial infarction, or heart failure. However, TWA magnitude is also affected by heart-rate independent influences including enhanced sympathetic nerve activity, exercise, and changes in myocardial substrate associated with ischemic and nonischemic heart disease.^{9,46–50} A representative example of TWA and its predictive capacity in the clinical setting is shown (Fig. 7).^{46,49}

Does reducing heart rate independent of other factors protect against cardiovascular events?

Because of mounting epidemiological evidence and plausible physiologic mechanisms for a cardioprotective role of lowered resting heart rate, in recent years there has been strong interest in using heart rate as a therapeutic target to reduce risk for cardiovascular mortality and sudden cardiac death. Multiple favorable and unfavorable countervailing effects are likely to play a role in the outcome (Table 1). A net benefit of pharmacologic interventions that reduce heart rate is documented in a variety of trials enrolling patients with chronic heart failure or survivors of acute myocardial infarction.⁴ Specifically, Hall and Palmer⁴ determined that a 2% reduction in death was associated with each 1 beat/minute reduction in heart rate. Over two decades ago, it was noted that reduction by beta-adrenergic receptor blockade of infarct size was linearly related to the agents' capacity to reduce heart rate.⁵¹ In a meta-analysis of 25 studies enrolling more than 30,000 patients, Cucherat⁵² identified an independent relationship between resting heart rate reduction by beta-adrenergic receptor and nondihydropyridine calcium channel blocking agents and the clinical benefits bestowed, including reduction in cardiac death ($p < 0.001$), all-cause death ($p = 0.008$), sudden death ($p = 0.015$), and non-fatal myocardial infarction recurrence ($p = 0.024$). Each 10-beat/minute reduction in the heart rate was estimated to reduce the relative risk of cardiac death by 30% and the risk of sudden cardiac death by 39%. Reduction in resting heart rate was a major determinant of clinical benefit.

To test more directly the effect of relatively pure reduction in heart rate independent of other pharmacologic actions, the BEAUTIFUL study investigators conducted a randomized, double-blind placebo-controlled trial of ivabradine in patients with stable coronary artery disease and left ventricular dysfunction.^{5,6} This agent is a current-dependent blocker of the I_f current, the

main determinant of the slope of diastolic depolarization in the sinoatrial node. It is a specific, use-dependent agent with substantial heart rate-reducing effects.⁵³ Ivabradine does not alter myocardial contractility or coronary vasomotor tone.⁵⁴ The BEAUTIFUL study, which enrolled >10,000-patients, determined that in the prespecified subgroup of >5,000 patients whose resting heart rate was ≥ 70 beats/minute, ivabradine reduced hospital admissions for fatal and nonfatal myocardial infarction and for coronary revascularization while reducing heart rate by 6 beats/minute. The reduction in revascularization is coordinate with evidence that ivabradine affords relief from angina.^{55,56} In this subgroup, the agent did not affect the cardiovascular death rate or hospital admissions for heart failure. The placebo arm of the BEAUTIFUL study indicated that elevated resting heart rate is a marker for subsequent cardiovascular death and morbidity, as a continuous rise in mortality and heart failure outcomes paralleled heart rate increases above 70 beats/minute.⁵ In this group, each 5 beat/minute increase in heart rate was associated with 8% increase in cardiovascular death, as well as increases in hospital admission for heart failure, myocardial infarction, and coronary revascularization. The drug was found to be safe in this patient cohort when given independently or in conjunction with beta-adrenergic receptor blocking agents.

Conclusions

Heart rate is a pivotal variable that is precisely regulated in health but disrupted in disease. The influence of altered heart rate is multifactorial, affecting the progression of coronary vascular and myocardial disease. Whereas there is evidence that elevated heart rate is prognostic of cardiovascular events, the precise utility of targeting this variable pharmacologically or by vagus nerve⁵⁷ or spinal cord stimulation⁵⁸ remains to be determined.

Finally, it should be emphasized that heart rate primarily reflects influences on sinus node activity and does not provide assessment of direct influences on ventricular electrical properties. This fact underscores the potential merit of analysis of measures of autonomic function, including HRV, BRS, HRT, and deceleration capacity, in combination with indicators of repolarization abnormalities such as TWA for improved diagnosis and monitoring therapeutic interventions.

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ABBREVIATIONS

BEAUTIFUL trial, morBidity-mortality EvAIUaTion of the If inhibitor ivabradine in patients with coronary disease and left ventricULar dysfunction
 BRS, baroreceptor sensitivity
 cAMP, Cyclic adenosine monophosphate
 EMIAT, European Myocardial Infarction Amiodarone Trial
 HRT, heart rate turbulence
 HRV, heart rate variability
 MPIP, Multicentre Post-Infarction Program
 SDNN, standard deviation of normal RR intervals
 SGNA, stellate ganglion nerve activity
 TARVA, tonic and reflex vagal activity
 TWA, T-wave alternans
 VPB, ventricular premature beat

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Fig. 1.

Relative risks of death from any cause and of nonsudden and sudden death from myocardial infarction, according to the quintile of resting heart rate. The reference group was subjects with a resting heart rate <60 beats/minute (lowest quintile). The numbers over the bars indicate the numbers of subjects. Comparisons were performed with the Mantel-Haenszel chi-square test for trend. The test for trend showed a significant difference among quintiles with respect to the risk of death from any cause ($p<0.001$), nonsudden death from cardiac causes ($p=0.02$), and sudden death from cardiac causes ($p<0.001$). Adjustments were made for age, use or nonuse of tobacco, level of physical activity, presence or absence of diabetes, body-mass index, basal systolic blood pressure, cholesterol level, presence or absence of a parental history of sudden death or myocardial infarction, and exercise duration. Data are missing for five subjects who died of any cause, including one who died suddenly from myocardial infarction. (Republished with permission from the Massachusetts Medical Society from Jouven et al.¹)

Fig. 2.

Traditional concepts focused on afferent tracts (dashed lines) arising from myocardial nerve terminals and reflex receptors (e.g., baroreceptors) that are integrated centrally within hypothalamic and medullary cardiostimulatory and cardioinhibitory brain centers and on central modulation of sympathetic and parasympathetic outflow (solid lines) with little intermediary processing at the level of the spinal cord and within cervical and thoracic ganglia. More recent views incorporate additional levels of intricate processing within the extraspinal cervical and thoracic ganglia and within the cardiac ganglionic plexus, where recently described interneurons are envisioned to provide new levels of noncentral integration. Release of neurotransmitters from postganglionic sympathetic neurons is believed to enhance

excitation in the sinoatrial node and myocardial cells through norepinephrine binding to beta-1 receptors, which enhances adenylyl cyclase (AC) activity through intermediary stimulatory G proteins (Gs). Increased parasympathectomy outflow enhances postganglionic release and binding of acetylcholine to muscarinic (M2) receptors, and through coupled inhibitory G proteins (Gi), inhibits cAMP production. The latter alters electrogenesis and pacemaking activity by affecting the activity of specific membrane Na, K, and Ca channels.¹⁵

Fig. 3. Circadian variation of heart rate and normalized stellate ganglion nerve activity (SGNA) at baseline. A, B: Average heart rate and normalized SGNA, respectively, over a 24-hour period. Vertical bars at each data point represent standard deviation. SGNA in panel B shows left SGNA in dogs 1–3 and right SGNA in dogs 4–6. SGNA was normalized to the midnight (0–1 o'clock in the morning) value.¹⁶

Fig. 4.

Respiratory sinus arrhythmia. During inspiration, the Hering-Breuer reflex is stimulated to inhibit the medullary cardiovascular regulatory centers. The latter normally depresses the sinus heart rate and its inhibition results in a relative increase in adrenergic activity. Consequently, there is a transient sinus tachycardia during inspiration and a subsequent slowing during expiration. NE = norepinephrine; SA = sinoatrial node. (Republished with permission from Dr. Opie and from Lippincott Williams & Wilkins.¹⁷)

Fig. 5. Cardiac mortality estimated by the Kaplan–Meier method among the patients with a training-induced increase in baroreceptor sensitivity (BRS) $\geq$ 3 ms/mm Hg and patients who trained without the same BRS increase or did not train. (Republished with permission from the American Heart Association from La Rovere et al.³⁵)

Fig. 6. Stratification of patients enrolled in Multicentre Post-Infarction Program (MPIP) study and in the placebo group of the European Myocardial Infarction Amiodarone Trial (EMIAT) comparing those with both factors normal (turbulence onset <0 and turbulence slope ≥ 2.5 ms/RR interval) to those with one of the two factors normal and to those with neither factor normal. (Republished with permission from Elsevier from Schmidt et al.³)

Fig. 7. Survival curves from the FINnish CArdioVAScular (FINCAVAS) study, which enrolled >1000 consecutive patients referred for routine exercise testing.⁴⁶ Inset is a high-resolution QRS-aligned template from a FINCAVAS patient illustrating the separation between successive T waves.⁴⁹

Table 1

Conceptual considerations relevant to heart rate as a therapeutic target for prevention of sudden cardiac death

Probable reasons for favorable outcomes	<ul style="list-style-type: none">•••	Reduced longterm effects on atherosclerosis and vascular compliance Reduced ischemic burden Reduced arrhythmogenic effect of intracellular calcium overload
Limitations	<ul style="list-style-type: none">••	Lacks rate-independent cardioprotective effects that are associated with muscarinic receptor activation and reduced beta-adrenergic input No improvement in respiratory sinus arrhythmia
Negative effects	<ul style="list-style-type: none">••	Potential proarrhythmic effects of bradycardia, e.g., early after-depolarization and torsades des pointes Action potential and QT interval prolongation