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Editorial

Roberto Ferrari, MD, PhD
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SHIFT: HEARTBEAT WILL NEVER BE THE SAME AGAIN

Our life starts and ends with a heartbeat. The very first rhythm that we hear is the heartbeat of our own mother while we are still in the womb. This is the “primordial, binary rhythm of life,” tantamount to life itself, systole/diastole—the rhythm against which all other rhythms are defined and gauged: day and night, ebb and flow, the double-time beat of music, yin and yang.

We are unaware of our own heartbeat when it is normal, but it certainly makes itself felt when there is something unusual or wrong with it. We feel it as a thumping in our chest and a pulsing in our ears after intense exertion. We “skip” or “miss” a beat when, love-smitten, we suddenly catch sight of our sweet heart—ironically, the same word (skip or miss) is used to describe the perception of a ventricular premature beat, the “missed” beat being in fact an “extra” beat, in other words an extrasystole. And when our heartbeat goes haywire, say, because of a bout of paroxysmal supraventricular tachycardia, we experience this as highly disagreeable and distressing palpitations. Heart failure, for its part, is also characterized by palpitations, which, although less intense, are accompanied by increasingly incapacitating fatigue and shortness of breath.

All this, as well as the mechanics, physiology, biochemistry, pathophysiology, and what have you of the heartbeat, is well known, and has been so for so long that 30 years ago, it looked like nothing much new would be coming from the heartbeat front, save for a few stirrings in the field of electrophysiology.

And then, suddenly, something big happened in precisely that field: in 1979, the world of cardiac ion currents was rocked when Hilary Brown, Dario DiFrancesco, and Susan Noble started talking about a current in the sinus node cells of the right atria, whose unusual properties earned it the catchy moniker of “funny” current. This current, now named $I_h$, or “pacemaker” current, transports potassium and sodium and is responsible for the slow phase of the sinus node action potential and, consequently, for heart rate.
But it took another breakthrough, in 1994, to firmly put heart rate under the spotlights. That year saw the discovery of a drug capable of reducing this current—ivabradine—and hence of reducing the heart rate. What was most fascinating about this drug is that reducing heart rate was all it did, period—a property dubbed “pure heart rate reduction.” With this discovery, a major program was launched to assess ivabradine’s action in various pathological settings such as angina, coronary artery disease, and heart failure.

The ivabradine angina program—the most extensive program ever undertaken—yielded excellent results. As early as 2003, it was shown that heart rate reduction with ivabradine reduced angina symptoms and improved exercise tolerance. Then came the ASSOCIATE trial, which showed that the addition of ivabradine on top of atenolol achieved further heart rate reduction and improvement in exercise tolerance and angina symptoms. On the strength of these findings the European Medicines Agency (EMA) approved the use of ivabradine in angina. Kim Fox described ivabradine as “one of the most important advances in cardiovascular treatment over the last two decades.”

But that’s not the end of the story. The follow-up to the angina studies was the large-scale BEAUTIFUL trial in 2008, conducted on close to 11 000 patients. This was the first trial to assess the effect of heart rate reduction with ivabradine on the prevention of cardiovascular events in patients with stable coronary artery disease and left ventricular dysfunction. The trial somewhat “generously” enrolled patients with heart rates starting from 60 bpm. This resulted in a relatively low mean heart rate at inclusion, which probably explains why there was no change in the primary end point. However, in those prespecified patients with a heart rate of ≥70 bpm, there was a clear and significant benefit in terms of reduction of myocardial infarction incidence and reduction in need for revascularization. In addition, in 2009, the BEAUTIFUL angina substudy confirmed the benefits for those patients who suffered from angina at entry in terms of prognosis. This was the first clue that an antianginal drug could improve prognosis.

And so we come to the latest breakthrough. All along there had been hints that ivabradine would bring benefits in the context of heart failure, but this required solid proof, as the implications were immense. This is exactly what has now been provided by the just released findings from SHIFT on 29 August, 2010. SHIFT shows that ivabradine, given on top of guideline-based treatment for heart failure patients with heart rate ≥70 bpm, is able to reduce mortality and hospitalization for heart failure. There is no

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**ASSOCIATE** = evaluation of the Anti-anginal efficacy and Safety of the asSociation Of the If Current inhibitor IvabrAdine with a beTa-blockEr.

**BEAUTIFUL** = morBidity mortality EvAlUaTion of the If inhibitor ivabradine in patients with coronary artery disease and left ventricULar dysfunction.

**SHIFT** = Systolic Heart failure treatment with the If inhibitor ivabradine Trial.
beating about the bush: SHIFT is a landmark trial, which at long last is shaking off the
doldrums of the last 10 years, marked by the absence of any major medical advance in
terms of heart failure treatment above the standard use of ACE inhibitors, β-blockers,
and diuretics.

With the SHIFT trial, a new era has commenced. As one medical reporter covering the
event put it: “Developing ivabradine and showing its efficacy in a major trial with 6500
heart failure patients turned the funny current into serious medicine.”

Anticipating the interest that would be raised by SHIFT, nearly a year ago, we started
planning an issue of Dialogues that would coincide with the release of the SHIFT
findings and would provide a contextual update on the topic of “Heart Rate and Car-
diovascular Disease.” So although this issue of Dialogues does not reflect the actual
findings from the study, it is particularly timely, and takes on added weight in light of
what SHIFT has disclosed.

The contributions in this issue of Dialogues would have been impossible to write without
the efforts of the many scientists involved in the ivabradine program. Åke Hjalmarson
leads this issue by exploring the role of heart rate in cardiovascular disease. Gabriel
Steg discusses the role of increased heart rate in coronary artery disease, while José
López Sendón et al look at how it impacts acute coronary syndromes. The issue con-
cludes with Michael Böhm et al expounding the benefits of heart rate reduction.

As always, patient benefit is our primary goal, but understanding is also paramount.
Ivabradine has allowed us to gain a deeper understanding of the role of heart rate in
cardiovascular disease. And this is what this issue of Dialogues is all about.

In the months and years to come, the cardiological community will be digesting the
findings of SHIFT and translating into practice its implications: rest assured—Dialogues
will return to this topic in the very near future.

(See references on next page)
REFERENCES


The role of heart rate in cardiovascular disease

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A large number of epidemiologic studies have reported that elevated heart rate is an independent risk factor for mortality and morbidity in healthy individuals with or without hypertension and in patients with coronary artery disease, myocardial infarction, and congestive heart failure. In the present review, factors and conditions influencing heart rate, such as diurnal variations, mental and physical stress, obesity, smoking, alcohol abuse, diabetes, and depressed cardiac function, are discussed. Despite the large number of confounding factors, multivariate analyses have clearly demonstrated that elevated heart rate per se is a very powerful predictor, both in healthy individuals and in patients with cardiovascular disease. Elevated heart rate has also been found to be a powerful predictor in patients with depressed left ventricular function. Thus, heart rate should be recognized as an important risk factor both in primary and secondary prevention, in addition to hypertension, hyperlipidemia, smoking, and diabetes. Several large placebo-controlled trials of patients with acute myocardial infarction or congestive heart failure have demonstrated that β-blockers reduce mortality and morbidity. It seems reasonable to believe that heart rate reduction per se is of major importance for these effects of β-blockers in view of the BEAUTIFUL (morBidity-mortality EvAlUaTion of the I inhibitor ivabradine in patients with coronary disease and left venticULar dysfunCTion) trial on the sinus node inhibitor ivabradine. Heart rate reduction has recently been listed as an important variable in the European Guidelines on Cardiovascular Disease Prevention in Clinical Practice.

Cardiovascular (CV) disease is a leading cause of death around the world, including the Western industrialized world as well as more underdeveloped countries. In high- and middle-income countries there has been a marked reduction in morbidity and mortality from CV disease during the last few decades due to better management and treatment. Doctors are more concerned about optimizing therapies and following international and national guidelines. In patients with coronary artery disease (CAD), a majority of patients are given aspirin, statins, angiotensin-converting enzyme (ACE) inhibitors, and β-blockers, all treatments with proven effects on CV morbidity and mortality. Physicians are also already well aware of the importance of detecting and limiting various risk factors from an early phase in healthy and asymptomatic individuals by considering risk factors such as hyperlipidemia, hypertension, smoking, diabetes, and obesity. “Cardiovascular disease continuum” describes the set of progressive processes that start in healthy and asymptomatic humans and continue through different stages of CAD with the development of symptoms, ending up with heart attacks and heart failure, which lead to death.

A large number of epidemiologic studies have reported that elevated heart rate is an independent risk factor for mortality and morbidity in healthy individuals with and without hypertension and in patients with CAD, myocardial infarction, and congestive heart failure. Most physicians believe that elevated heart rate at rest is prognostically undesirable. However, a much smaller proportion of physicians recognize heart rate as an important prognostic factor and a potential therapeutic target. Considerable evidence suggests that heart rate is involved in all the steps along the CV continuum, and strong clinical epidemiological data for this have been obtained continuously since the early 1980s. The aim of this article is to review the pathophysiology of heart rate as a risk factor and the clinical and epidemiological evidence of the importance of heart rate as a risk predictor, and to discuss the clinical data supporting the idea that it is reasonable to modify this risk with treatment that reduces elevated heart rate.

Keywords: heart rate; risk factor; risk predictor; cardiovascular disease; atherosclerosis; β-blocker; selective If inhibitor
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NORMAL DETERMINANTS
OF HEART RATE ELEVATION

The resting heart rate of a healthy human being is approximately 50-75 beats per minute (bpm) depending upon age, sex, and lifestyle. Heart rate is determined by the activity of cardiac pacemaker cells of the sinus node and is influenced by the autonomic nervous system via vagal and noradrenergic sympathetic nerves. The heart rate in humans is lower than that of the pacemaker frequency (approximately 90 bpm) because of the dominant vagal influence on heart rate. Heart rate changes in response to a wide variety of physiological and pathological conditions in order to maintain cardiac output and preserve perfusion to vital body tissues. Individual fundamental determinants of heart rate as well as heart rate variability include: the activity of pacemaker cells and of ion channels; reflexes associated with respiration and the carotid sinus receptors, as well as central nervous system connections to the autonomic nervous system, plasma hormones, and thermoregulation; genetic factors, myocardial phenotype, and other receptors located in the sinoatrial (SA) node. Epidemiological and clinical studies show that resting heart rate is also determined by numerous fixed or nonmodifiable factors as well as certain potentially modifiable factors specific to individuals and certain populations.

The nonmodifiable factors include age and gender. Heart rate in neonates (130-140 bpm) falls throughout childhood to reach typical adult levels of 50-75 bpm at the age of 20 years. It is widely assumed among physicians that heart rate decreases with age, especially in the higher age groups. This has been reported in several large populations. The lack of consensus about decreasing heart rate with increasing age probably relates to different study populations and the methodologies used, the influence of illness and other confounding variables, and the age ranges studied.

Despite this lack of certainty, reviews have tended to persist with the assertion that heart rate negatively correlates with age. Studies showing a reduction in heart rate with increasing age have reported data with multiple regression analysis showing an independent influence of age, in contrast to most of the other studies. Confounding factors, such as CV disease, obesity, and diabetes, that elevate heart rate are more common with increasing age. Furthermore, it has been suggested that changes in the SA node, a decrease in the responsiveness of autonomic CV reflexes, a decline in intrinsic heart rate, and decreased adrenergic sensitivity may be the biological explanations for a decrease in heart rate with age. It is widely accepted that women have a higher resting heart rate than age-matched male counterparts.
The circadian variation of heart rate is well known, with a higher heart rate during daytime compared to the lower nighttime rate associated with sleep. Several investigators have also noted a rapid rise in heart rate in the early morning associated with waking, between approximately 6 AM and 8 AM.9 There is also the well-known influence of posture with an immediate response in healthy young adults when going from a supine to a standing position. There is a prompt rise in heart rate, which peaks after about 8 to 15 seconds.10

An acute fall in blood pressure is related to a rise in heart rate. In a situation of mental or physical stress, both heart rate and blood pressure are elevated. Heart rate and chronic elevation of blood pressure have consistently been shown to have significant correlation.7,8 High heart rate has emerged as one of the most potent precursors of hypertension independent of baseline blood pressure values.4 The probable explanation for the correlation between an increase in heart rate and blood pressure is that both are regulated by sympathetic and vagal tone.

Heart rate increases with physical activity to adjust the cardiac output to the extra demands of muscular exercise. Increasing exercise tolerance and endurance by physical training over a period of time is associated with a lower heart rate at rest.11 Obesity significantly correlates with heart rate in several studies, and there is an increase in resting heart rate with increased body mass index, for example.12 Cigarette smoking causes an acute increase in heart rate and seems to be a significant determinant of heart rate over the long term.13 The most likely mechanisms for the increase in heart rate with cigarette smoking include sympathetic stimulation by nicotine and increased myocardial oxygen consumption at rest. An overview of studies that included analyses of alcohol as a potential determinant of heart rate failed to show a consistent trend related to this lifestyle factor. However, isolated studies have shown that the use of alcohol may be associated with higher minimal and average heart rates,11 and one large-scale population study with a long-term follow-up period concluded that alcohol abuse can be considered a confounder related to high heart rate.14

It is well known that acute and chronic mental stress cause a “fight or flight reaction,” which is important for survival in animals and man. In acute stress, there is a prompt increase in heart rate; this falls over time with chronic and long-term stress, but nevertheless remains higher than under nonstressed conditions.15 There are a great number of stress factors that cause an increase in sympathetic activity and a fall in vagal activity, which elevate heart rate. Such factors include physical, psychological, and psychic abnormalities, “change of life” conditions, emotions, and social and genetic factors influencing stress reactions and sensitivity.16 Family studies have estimated that the heritability of resting systolic and diastolic blood pressure and heart rate are in the range of 15%-35%, for example.17

**PATHOLOGICAL CONDITIONS AND HEART RATE**

It is well known that patients with diabetes have a high heart rate compared to healthy subjects. This is due to autonomic neuropathy with widespread neurologi cal degeneration affecting the nerve fibers of the sympathetic and the parasympathetic branches of the nervous system. In a population study from the United States of 9940 individuals aged 45-64 years, the resting heart rate in the group with normal fasting glucose (<5.6 mmol/L) was 65 bpm, in those with elevated fasting glucose (5.6-7.0 mmol/L) it was 68 bpm, and in diabetic subjects heart rate was 71 bpm.18 High resting heart rate is strongly associated with impaired cardiac function and with poor cardiorespiratory fitness.19,20 Furthermore, in patients with normal cardiac function with supraventricular or ventricular tachyarrhythmias, including atrial fibrillation, resting heart rate is often pathologically rapid. A number of medications are known to reduce resting heart rate including digitalis, β-blockers, and calcium antagonists, such as verapamil.1 High cholesterol and triglyceride levels significantly and positively correlated with heart rate in a large general population survey.21 It can be concluded that heart rate is influenced by a variety of physiological processes mainly via effects on the balance of sympathetic and vagal tone. The factors and conditions which influence heart rate are summarized in Table I (page 182).

**HEART RATE AND CV DISEASE**

Myocardial ischemia is due to an imbalance between myocardial metabolic demand and the coronary blood flow supply. Heart rate is the major determinant for both myocardial metabolic demand and supply of blood flow that mainly occurs during diastole.22 In patients with a flow-limiting stenosis of a coronary artery, an increase in heart rate during physical exercise or mental stress causes myocardial ischemia and well-known ischemic events, including pain, arrhythmias, and shortness of breath. Medications reducing heart rate, such
as β-blockers, verapamil, and sinus node inhibitors, have the expected favorable effects on ischemia. Furthermore, heart rate reduction causes an increase in the length of diastole, during which the major part of myocardial blood perfusion takes place. The effect of increased perfusion time is most apparent in the subendocardial region, where intravascular systems affected directly by myocardial contraction totally preclude blood flow during systole. In studies of dogs with experimental ischemia, an increase in heart rate reduces subendocardial flow and contraction, and this is accompanied by a reduction in subepicardial flow. Furthermore, experimental studies have shown that an increase in heart rate causes an elevation in oxygen demand even when the external work performed by the heart is kept constant, probably due to a greater oxygen requirement for excitation-contraction coupling. In patients with stable CAD, most ischemic episodes are preceded by an increase in heart rate. Furthermore, during ambulatory monitoring of such patients over 24 hours, the ischemic episodes are clearly related to the diurnal variation of heart rate, with a marked increase in the early morning hours (Figure 1). In this study, medications known to reduce heart rate, eg, propranolol, reduced heart rate over 24 hours and ischemic episodes in parallel.

Increase in heart rate is also known to cause more marked atherosclerosis, as demonstrated in experimental studies of monkeys. Heart rate reduction by either SA node ablation or with β-blocker treatment reduces the severity of atherosclerotic stenosis and the area covered by lesions within the coronary arteries and the area covered by lesions within the coronary arteries and the area covered by lesions within the coronary arteries. In human beings, higher heart rate is associated with more marked progression of coronary atherosclerosis and also with disruption of preexisting atherosclerotic plaque. It can thus be concluded that elevated heart rate plays an important role in the development and progression of coronary atherosclerosis and triggers ischemic events due to an increase in myocardial metabolic demand and a reduction of diastolic coronary perfusion.

![Table 1. Factors and conditions influencing heart rate.](image)

**Table 1. Factors and conditions influencing heart rate.**

<table>
<thead>
<tr>
<th>Factors and conditions</th>
<th>Heart rate increase/decrease (+/-)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nonmodifiable</strong></td>
<td></td>
</tr>
<tr>
<td>Increasing age</td>
<td>–</td>
</tr>
<tr>
<td>Female sex</td>
<td>+</td>
</tr>
<tr>
<td>Genetic</td>
<td>+/-</td>
</tr>
<tr>
<td><strong>Physiological</strong></td>
<td></td>
</tr>
<tr>
<td>Early morning hours</td>
<td>+</td>
</tr>
<tr>
<td>Nighttime</td>
<td>–</td>
</tr>
<tr>
<td>Supine to standing</td>
<td>+</td>
</tr>
<tr>
<td>Mental/physical stress</td>
<td>+</td>
</tr>
<tr>
<td><strong>Lifestyle</strong></td>
<td></td>
</tr>
<tr>
<td>Physical training</td>
<td>–</td>
</tr>
<tr>
<td>Obesity</td>
<td>+</td>
</tr>
<tr>
<td>Smoking</td>
<td>+</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>+</td>
</tr>
<tr>
<td><strong>Pathological</strong></td>
<td></td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>+</td>
</tr>
<tr>
<td>Obesity</td>
<td>+</td>
</tr>
<tr>
<td>Poor cardiorespiratory fitness</td>
<td>+</td>
</tr>
<tr>
<td>Heart failure</td>
<td>+</td>
</tr>
<tr>
<td>Medication (β-blockers/stimulants)</td>
<td>+/-</td>
</tr>
</tbody>
</table>

Increase in heart rate is also known to cause more marked atherosclerosis, as demonstrated in experimental studies of monkeys. Heart rate reduction by either SA node ablation or with β-blocker treatment reduces the severity of atherosclerotic stenosis and the area covered by lesions within the coronary arteries. In human beings, higher heart rate is associated with more marked progression of coronary atherosclerosis and also with disruption of preexisting atherosclerotic plaque. It can thus be concluded that elevated heart rate plays an important role in the development and progression of coronary atherosclerosis and triggers ischemic events due to an increase in myocardial metabolic demand and a reduction of diastolic coronary perfusion.

![Figure 1. The greatest heart rate reduction results in the greatest reduction in ischemia.](image)

Left panel: Heart rate measured over 24 hours with placebo, diltiazem, and propranolol (curves from top to bottom, respectively).

Right panel: Frequency of ischemic episodes in patients on placebo, propranolol, and diltiazem.

HEART RATE AS A RISK FACTOR IN CV DISEASE

A great number of studies in healthy and asymptomatic subjects as well as in patients with already established CAD have demonstrated that heart rate is a very important and major independent CV risk factor for prognosis. Table II summarizes the major epidemiological studies published between 1980 and 2005. This data comes from 14 studies of the general population and subjects with hypertension that included more than 155,000 patients followed up over a period of 8 to 36 years. In the well-known Framingham study that included 5070 subjects with a follow-up of 30 years, it was demonstrated in both men and women that all-cause mortality increased progressively and significantly in relation to heart rate (Figure 2). Later studies in healthy men reported that elevated resting heart rate is also an independent risk predictor of sudden cardiac death (Figure 3, page 184). In the last few years, a large number of studies have been published which provide further evidence for the role of resting heart rate as an independent risk predictor. These studies not only included healthy, normal individuals with or without hypertension, but also patients with hyperlipidemia, diabetes, and established CAD with or without hypertension.

### Table II. Epidemiological studies on the relationship between heart rate and cardiovascular mortality in general and hypertensive populations.

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Population</th>
<th>Follow-up (years)</th>
<th>Cardiovascular mortality RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chicago Gas Company (1980)</td>
<td>1233 M</td>
<td>15</td>
<td>&gt;94 vs ≤60 bpm</td>
</tr>
<tr>
<td>Chicago Heart Assoc Project (1980)</td>
<td>33 781 M+W</td>
<td>22</td>
<td>≥90 vs &lt;70 bpm M, 1.6; W, 1.1 (NS)</td>
</tr>
<tr>
<td>Framingham (1993)</td>
<td>4530 M+W HTN</td>
<td>36</td>
<td>&gt;100 vs ≤60 bpm M, 1.5; W, 1.4 (NS)</td>
</tr>
<tr>
<td>British Regional Heart (1993)</td>
<td>735 M</td>
<td>8</td>
<td>&gt;90 vs ≤90 bpm IHD death, 3.3</td>
</tr>
<tr>
<td>Spandz (1997)</td>
<td>4756 M+W</td>
<td>12</td>
<td>Sudden death 5.2 per 20 bpm</td>
</tr>
<tr>
<td>Benetos (1999)</td>
<td>19 386 M+W</td>
<td>18.2</td>
<td>&gt;100 vs &lt;60 bpm M, 2.2; W, 1.1 (NS)</td>
</tr>
<tr>
<td>Castel (1999)</td>
<td>1938 M+W</td>
<td>12</td>
<td>5th vs 3rd quintile M, 1.6; W, 1.1</td>
</tr>
<tr>
<td>Cordis (2000)</td>
<td>3257 M</td>
<td>8</td>
<td>≥90 vs &lt;70 bpm 2.0</td>
</tr>
<tr>
<td>Reunanen (2000)</td>
<td>10 717 M+W</td>
<td>23</td>
<td>M, 1.4 (&gt;84 vs &lt;60); W, 1.5 (&gt;94 vs &lt;66)</td>
</tr>
<tr>
<td>Thomas (2001)</td>
<td>60 343 M HTN</td>
<td>14</td>
<td>&gt;80 vs ≤80 bpm &lt;55 y, 1.5; &gt;55 y, 1.3</td>
</tr>
<tr>
<td>Matiss (2001)</td>
<td>2533 M</td>
<td>9</td>
<td>per 20 bpm: 1.5 ≥90 vs ≤60 bpm: 2.7</td>
</tr>
<tr>
<td>Ohasama (2004)</td>
<td>1780 M+W</td>
<td>10</td>
<td>M, 1.2; W, 1.1 (NS) per 5 bpm</td>
</tr>
<tr>
<td>Okamura (2004)</td>
<td>8800 M+W</td>
<td>16.5</td>
<td>per 11 bpm (1 SD): M, 1.3; W, 1.2</td>
</tr>
<tr>
<td>Jouven (2005)</td>
<td>5713 M</td>
<td>23</td>
<td>Sudden death from AMI, 3.92 (&gt;75 bpm)</td>
</tr>
</tbody>
</table>

Abbreviations: AMI, acute myocardial infarction; bpm, beats per minute; HTN, hypertension; IHD, ischemic heart disease; M, men; NS, not significant; RR, risk reduction; W, women.


![Figure 2. Resting heart rate and all-cause mortality in the Framingham Study.](image-url)
out heart failure. The largest study of patients with established CV disease is the CASS (Coronary Artery Surgery Study) register in a population of 24,913 patients with suspected or proven CAD. As can be seen in Figure 4A, a high resting heart rate at baseline markedly increased overall mortality as well as CV mortality over 14.7 years of follow-up. Furthermore, subgroup analyses clearly demonstrated that this was a very consistent finding in all groups regardless of age, sex, body mass index, β-blocker use, or the presence of hypertension, left ventricular dysfunction, or diabetes (Figure 4B).

In the study of the CASS register, it was suggested that risk increases around 83 beats/minute (bpm) and above. However, in the recently published INVEST (INternational VErapamil-trandolapril STudy) it was found that there was a significantly increased risk above 75 bpm, which is well below the conventional definition of tachycardia (>90 bpm). Furthermore, in the placebo arm of the BEAUTIFUL (morBidity-mor-tality EvAlUaTion of the i inhibitor ivabradine in pa-tients with coronary disease and left ventricULar dys-function) study, it was reported that patients with baseline heart rates of >70 bpm had a markedly increased risk of CV death, admission to hospital for heart failure, myocardial infarction, and coronary revascularization. These patients were men and women aged 55 years or more with CAD, left ventricular ejection fraction of <40%, and an end-diastolic short-axis internal dimension larger than 56 mm. The patients were in sinus rhythm and had a resting heart rate of 60 bpm or greater. At randomization, these patients were on optimal medication, including aspirin, ACE inhibitor or angiotensin II receptor blocker, β-blocker, statin, and aldosterone agents. Figure 5A and Figure 5B show the marked difference between patients with heart rate >70 bpm compared with those with heart rate <70 bpm. In the GISSI (Gruppo Italiano per lo Studio della Streptochinasi nell’Infarto miocardico) study of 11,020 patients with acute myocardial infarction, there was a tenfold increase in mortality after 6 months of follow-up between those with a baseline heart rate below 60 bpm and those with a heart rate above 100 bpm. Also, in large trials in patients with symptomatic congestive heart failure, baseline heart rate was an inde-
pendent predictor of all-cause mortality, CV mortality, and hospitalization for heart failure. Figure 6 shows the one-year all-cause mortality rates with changing baseline heart rate in the placebo arm of the CIBIS-II (Cardiac Insufficiency Bisoprolol Study II) trial.

**BENEFICIAL EFFECTS OF HEART RATE REDUCTION**

β-blockers and calcium antagonists are well-established therapies for providing symptomatic relief in patients with angina pectoris due to CAD and have been in use for more than 30 years. It is assumed that reduction in heart rate is the major mechanism of action for β-blockers and calcium antagonists, especially in exercise-induced ischemia with symptomatic angina pectoris. In a double-blind study of low- and high-dose calcium channel blockers given in addition to β-blockers, there was a close correlation between the improvement in time to ischemia during the bicycle exercise test and the reduction in exercise heart rate. The real evidence that heart rate reduction is of major importance in the treatment of angina pectoris with β-blockers and calcium antagonists was obtained with a new class of selective heart rate–lowering agents that act specifically on the SA node. A dose-dependent improvement in exercise tolerance and time to development of ischemia during exercise was obtained with ivabradine, which selectively and specifically inhibits the I_f pacemaker current. In contrast to β-blockers and calcium antagonists, ivabradine reduced heart rate with an improvement in exercise tolerance, despite having no effect at all on contractility. In the INITIATIVE (INternational Trial on the Treatment of angina with IvabradinE versus atenolol) study in 939 patients with stable angina pectoris, ivabradine was compared to atenolol for antianginal and anti-ischemic efficacy during an exercise stress test. Both treatments reduced heart rate and rate-pressure product compared to baseline. The decrease in heart rate at peak exercise was greater with atenolol (14 bpm) than with ivabradine (8.6 bpm and 10.3 bpm for the dosages 7.5 mg daily and 10 mg daily, respectively). Ivabradine induced similar or greater improvement in exercise capacity than atenolol for a comparatively smaller reduction in heart rate and rate-pressure product. This might be due
to ivabradine's lack of negative inotropic, peripheral, vascular, or coronary vasoconstrictive effects, which atenolol is known to have. Thus, it can be firmly stated that heart reduction per se, as found with ivabradine, is of major importance for the benefit of β-blockers and calcium antagonists.

β-Blockers were the first group of drugs that clearly demonstrated mortality reduction in patients with acute myocardial infarction using timolol, metoprolol, or propranolol. A reduction in total mortality, CV death, sudden cardiac death, and the number of hospitalizations was found. When pooling placebo-controlled β-blocking trials in patients with acute myocardial infarction, Kjekshus proposed that there was a significant relationship between reduction in resting heart rate and a decrease in all-cause mortality (Figure 7). β-Blockers that reduced heart rate by about 15 bpm reduced mortality by more than 30 percent, while β-blockers that produced a small or no reduction in heart rate (those with high intrinsic stimulatory activity) had no significant effect on mortality. It was first reported by Waagstein, Hjalmarson, and coworkers that patients with symptomatic heart failure could markedly improve with long-term use of a β-blocker, which reduced average heart rate from 98 to 69 bpm in 2-12 months. The same group later reported that stepwise withdrawal of chronic β-blockade with a resultant increase in heart rate from 71 to 88 bpm caused a marked deterioration in the patient’s cardiac function and symptoms. The target for dose titration of β-blockers in these early studies was to reduce heart rate down to 60-70 bpm. The first placebo-controlled trial in patients with symptomatic heart failure was the MDC (Metoprolol in Dilated Cardiomyopathy) trial comparing metoprolol and placebo in patients with idiopathic dilated cardiomyopathy. Metoprolol improved cardiac function and exercise capacity and reduced symptoms. Furthermore, there was a significant improvement in the combined end point of death or need for cardiac transplantation. Later, several large placebo-controlled trials were performed in patients with chronic heart failure, the MERIT-HF trial (MEtoprolol MR/XL Randomized Intervention Trial in congestive Heart Failure) with metoprolol, the CIBIS-II study with bisoprolol, and CAPRICORN (Carvedilol Post-infarct suRvival COntRol in left veNtricular dys-function) and COPERNICUS (Carvedilol ProsPective RaNdomized CUMulative Survival) with carvedilol, which all demonstrated a reduction of about 35 percent in all-cause mortality and good tolerability. The target for dose titration of β-blockers in these trials was to reduce heart rate to about 60-70 bpm or to find the highest tolerated β-blocker dose. In a review of studies on patients with chronic heart failure, Kjekshus and Gullestad proposed that in these patients the relationship between changes in heart rate and all-cause mortality does not only occur in conjunction with β-blockers, but also, for example, with ACE inhibitors.

From these clinical studies, it is highly likely that heart rate reduction is of major importance for the beneficial effects on mortality and morbidity. The proof of the importance of heart rate reduction was obtained in a study using a canine model of left ventricular dysfunction, where it was demonstrated that β-blocker benefit on cardiac function was abolished by pharmacologically-induced bradycardia. Similarly, in patients with left ventricular dysfunction, reversal of β-blocker-induced bradycardia by pacing at 80 bpm, when compared with 60 bpm, had adverse effects on left ventricular volume and ejection fraction.

Due to the beneficial effects of β-blockers, it has been generally accepted and also stated in international guidelines that β-blockers should be used in patients suffering from acute myocardial infarction or chronic heart failure in order to reduce mortality and morbidity. Since more marked effects were seen in subgroups of patients with elevated heart rate, it has been assumed that heart rate reduction per se is of major importance for the effect of β-blockers on outcome. However, β-blockers do not only reduce heart rate, but in addition have a number of potentially beneficial effects caused by blocking, for example, the effects of sympathetic activation. It is well known that sympathetic activation and catecholamines increase the risk of seri-
ous ventricular arrhythmias and ventricular fibrillation in experimental animal models of acute myocardial ischemia. In large placebo-controlled clinical trials, both in patients with myocardial infarction and in those with chronic heart failure, β-blockers have been found to have a marked effect on sudden cardiac death. In fact, the effects on sudden cardiac death are in general more marked than the overall effects on all-cause mortality or on other modes of death. This may be due to a specific antifibrillatory effect of β-blockers.

To test the hypothesis that heart rate reduction per se is of major importance for the beneficial effects on outcome in patients with myocardial infarction or chronic heart failure, studies were designed using ivabradine. With this pure heart rate–lowering agent in patients with sinus rhythm, there is no effect on blood pressure, myocardial contractility, intraventricular conduction, or ventricular repolarization. Thus, treatment with ivabradine provides an opportunity to assess the effects of lowering heart rate without directly altering other aspects of cardiac function. The BEAUTIFUL trial was designed to test whether the addition of ivabradine to standard treatment to lower heart rate could reduce CV death and morbidity in patients who had stable CAD and left ventricular systolic dysfunction. A total number of 10 917 patients with CAD and left ventricular ejection fraction <40% were randomized. The patients on ivabradine were given an increasing dose from 5 mg to 7.5 mg twice daily compared to matching placebo, in addition to optimal CV medication. The primary end point was a composite of CV death, admission to hospital for acute myocardial infarction, and admission to hospital for new onset of or worsening of heart failure. Patients eligible for inclusion were males and females aged 55 years or older (18 years or older if diabetic) with CAD, left ventricular ejection fraction <40%, and an end-diastolic internal dimension no greater than 56 mm. Patients had to be in sinus rhythm with a resting heart rate >60 bpm. There was a prespecified statement in the protocol explaining that one should analyze the effects of ivabradine in a subgroup of patients with a heart rate >70 bpm. There was no significant effect of ivabradine on the composite primary end point in the total study population. In the prespecified subgroups with a heart rate >70 bpm, ivabradine tended to reduce a primary composite end point (9 percent; nonsignificant). However, as can be seen from Figure 8A and Figure 8B in the group of patients with heart rate >70 bpm, ivabradine significantly reduced admission to hospital for myocardial infarction (36 percent) and also admission to hospital for myocardial infarction or unstable angina (22 percent) and the need for coronary revascularization (30 percent). It can be concluded that heart rate reduction per se with ivabradine without other effects has a favorable effect on morbidity.

One major question is whether the heart rate reduction with ivabradine was too small to be effective on mortality. In the BEAUTIFUL trial, ivabradine reduced heart rate by 6 bpm at 12 months and 5 bpm at 24 months. The major β-blocker trials in myocardial infarction with timolol, metoprolol, and propranolol reduced heart rate by 12 to 15 bpm. In the two large β-blocker trials in heart failure, heart rate was reduced by about...
11 bpm. It should be noted that 87 percent of the patients in the BEAUTIFUL trial were on a β-blocker (84 percent of patients who had a baseline heart rate ≥70 bpm). Even if the β-blocker dose had been doubled (instead of adding ivabradine), it is most likely that further heart rate reduction would not have been more than 5-6 bpm (comparable to the effect of ivabradine). Are the patients in the BEAUTIFUL trial comparable to those in the β-blocker trials in heart failure? In fact, they were very similar to those of the CAPRICORN trial comparing carvedilol with placebo in patients after myocardial infarction with left ventricular dysfunction. 59 In this trial, baseline ejection fraction was 33 percent (age 63 years, follow-up 16 months) and all-cause mortality on carvedilol was 12 percent at 16 months. Corresponding figures for the BEAUTIFUL trial were ejection fraction of 32 percent, age 65 years, and mortality in the placebo group was 10 percent (87 percent were on β-blockers). In the CAPRICORN trial, all-cause mortality was reduced by 23 percent compared to no effect with ivabradine in the BEAUTIFUL trial. Two heart failure trials with β-blockers50,51 had a 19-month mortality rate in the β-blocker arms of around 10 percent, the same as in the BEAUTIFUL trial. However, in these trials the β-blockers metoprolol and bisoprolol reduced all-cause mortality by 35 percent and sudden cardiac death by 40 percent, and heart rate by about 11 bpm. The question is whether a further reduction in heart rate of 5-6 bpm (as provided by ivabradine in the BEAUTIFUL trial on top of β-blockers) obtained by increasing the dose of β-blocker causes any further reduction in mortality and morbidity. The most likely reason for the lack of significant ivabradine effect on mortality in the BEAUTIFUL trial is that optimal use of β-blockers had lowered heart rate and mortality. There is a study in progress of ivabradine in patients with symptomatic heart failure, SHIFT (Systolic Heart failure treatment with the I inhibitor ivabradine Trial). In this study, all patients will be on optimal medical treatment at baseline, including β-blockers, before the patients are randomized to ivabradine or placebo. At present, it seems clear that heart rate reduction per se is of major importance for the efficacy of β-blockers and the calcium antagonists verapamil and diltiazem on chest pain in patients with chronic stable angina pectoris and on morbidity and mortality in patients with myocardial infarction or chronic symptomatic heart failure. The data from the BEAUTIFUL trial, especially in the subgroup of patients with heart rate ≥70 bpm where heart rate was more markedly reduced, support the earlier findings suggestive of the importance of heart rate reduction in treatment with β-blockers.

In conclusion, heart rate is an independent risk predictor of the onset of acute coronary events, including all-cause mortality, CV mortality, sudden cardiac death, and acute coronary syndromes. This has been demonstrated in healthy subjects, patients with risk factors such as hypertension, hyperlipidemia, and diabetes, and also in patients with established CAD with angina pectoris, myocardial infarction, arrhythmias, and chronic heart failure. Elevated heart rate also plays a role in the development and progression of atherosclerosis and of CAD causing myocardial infarction, sudden death, and chronic heart failure. There is strong evidence that reduction of heart rate using β-blockers has a marked effect on the symptoms of CAD as well as on mortality and morbidity. It seems very likely that heart rate reduction per se is of major importance for the beneficial effect of β-blockers. Heart rate should be considered in all patients with CAD or at risk of CV disease in a similar way to other risk factors such as hypertension, hyperlipidemia, and smoking. The treatment target ought to be 60-70 bpm when adding a β-blocker, calcium antagonist, or ivabradine.

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Heart Rate and Cardiovascular Disease

Expert Answers to Three Key Questions

1

What is the role of increased heart rate in stable coronary artery disease?

P. G. Steg

2

What is the role of increased heart rate in acute coronary syndromes?

J. López-Sendón, R. Ferrari

3

What is the role of increased heart rate and why is it beneficial to reduce it?

M. Böhm, J.-C. Reil, R. Ferrari, H.-R. Neuberger
What is the role of increased heart rate in stable coronary artery disease?

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Coronary artery disease (CAD) is characterized by coronary stenoses, which hamper myocardial blood flow and limit maximal oxygen delivery to the myocardium. In situations of heightened flow demand, as with physical exertion or emotional stress, flow limitation—when myocardial oxygen demand exceeds available supply—can result in myocardial ischemia. Ischemia is often accompanied by angina pectoris, which remains the most common clinical manifestation of CAD. Indeed, it is estimated that in Europe and the United States 30 000 to 40 000 people per million of population suffer from angina.1-3 More than half the patients afflicted with angina are limited, often severely, in their daily activities. This limitation commonly results in premature retirement from work in people of working age. Though the presence and severity of angina are not determined solely by the severity of the underlying myocardial ischemia, angina nonetheless reflects ischemia and is, therefore, associated with major morbid and lethal outcomes. For example, in a study of 110 consecutive patients with typical angina who were prospectively followed, the combined rate of coronary death or nonfatal myocardial infarction was 10.9% within the first year after presentation.4 Indeed, angina is related to mortality even after adjustment for age, race, and clinical comorbidities, and mortality depends directly on symptom severity.5,6 The magnitude of risk associated with angina is of the same order of magnitude as that associated with diabetes or chronic heart failure.5

Results of the recent BEAUTIFUL (morBidity-mortality EvAlUaTion of the I_f inhibitor ivabradine in patients with coronary disease and left ventricULar dysfunction) study have underlined the importance of heart rate reduction in the management of stable coronary artery disease (CAD). The prospective analysis of data from the placebo arm of that trial demonstrated that elevated resting heart rate (≥70 bpm) is a strong independent predictor of clinical outcomes. Heart rate reduction is a primary therapeutic objective not only for preventing angina, but also for modifying the natural history of CAD and for preventing cardiovascular events and other CAD outcomes. Antianginal and anti-ischemic heart rate–lowering drugs may have wider applications than originally thought, due to their effects on myocardial oxygen consumption.

Keywords: heart rate; myocardial ischemia; antianginal therapy; ivabradine

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SELECTED ABBREVIATIONS AND ACRONYMS

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<th>Abbreviation</th>
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<td>ASIS</td>
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Myocardial ischemia in CAD results from a mismatch between myocardial oxygen demand and the supply of oxygen from coronary blood flow. In patients with stable CAD, heart rate is a primary determinant of both demand and supply: heart rate increase, caused by physical exercise or mental/emotional stress, adversely affects both sides of the demand/supply balance, increasing the likelihood of ischemia and angiina. Heart rate is known to play an important regulatory role in endothelial function and vascular tone. Heart rate regulates the release of nitric oxide and other vasoactive compounds from the endothelium, determining the degree of vasodilation and consequently the amount of blood and oxygen delivered to peripheral muscles, and thus their activity. In addition, there is clinical and experimental evidence on the role of increased heart rate in the development and progression of atherosclerosis. The strong relationship between resting heart rate, coronary artery disease (CAD), and mortality has been documented by several epidemiological studies, including in patients with stable CAD.

**INCREASED HEART RATE AS A TRIGGER OF MYOCARDIAL ISCHEMIA**

Heart rate is a primary determinant of cardiac work. When defining the metabolic requirements of the heart, heart rate is the single most important determinant of myocardial oxygen demand. Heart rate also modulates myocardial oxygen supply: since coronary blood flow is greatest during diastole, variations in heart rate will alter diastolic duration and hence the interval during which coronary flow can occur (Figure 1). Finally, in persons with normal coronary arteries, isolated increases in heart rate result in vasodilation with modest increases in coronary flow; while, conversely, in patients with coronary atherosclerotic plaques or stenoses, a heart rate increase results in a paradoxical loss in luminal volume and a decrease in coronary flow. Thus, in patients with CAD, tachycardia can affect coronary flow by inducing coronary constriction, potentially worsening the hemodynamic consequences of preexisting coronary artery stenosis, as demonstrated during cardiac pacing.

Acceleration of heart rate by exercise or pacing is frequently used in clinical practice to induce myocardial ischemia for the purpose of diagnosis or prognostication, and coincidentally triggers most unexpected ischemic events. Holter monitoring data have shown that most episodes of ambulatory ischemia are associated with substantial increases in heart rate; increased myocardial oxygen demand has therefore been suggested as the major determinant of ischemia. Several studies have consistently found that the vast majority (approximately 80% to 90%) of ischemic episodes in patients with stable CAD are preceded by increases in heart rate of ≥5 to 10 beats per minute (bpm). Furthermore, ischemic episodes occur 80% of the time when the heart rate reaches the ischemic threshold for exercise, with a strong correlation between heart rate and onset of 1-mm ST-segment depression (ischemic threshold) during exercise testing and during ambulatory electrocardiography (ECG) monitoring. These findings have been supported by a number of studies showing a positive correlation between heart rate and silent ischemia with ST-segment depression during ambulatory monitoring. In the Angina and Silent Ischemia Study (ASIS), patients with CAD, stable angina, and a resting heart rate of <60 bpm had an 8.7% risk of ischemia, which doubled to 18.5% in patients with a resting heart rate of >90 bpm. In addition, decreases in heart rate variability, reflecting changes in sympathovagal balance, precede ischemic ST-segment depression by 4 to 10 minutes, indicating that this imbalance is likely to be involved in triggering myocardial ischemia (Figure 2).
Investigations of the relation between heart rate and ischemia have generally examined the minutes immediately preceding onset of ST-segment depression. However, heart rate increases can affect ischemia even if they occur more remotely from the event. As an example, in a study of 212 episodes of ischemia in 21 patients undergoing continuous ambulatory monitoring, increases in heart rate occurring 5 to 30 minutes before each event were strongly associated with myocardial ischemia during daily life. These authors postulated that because the development of ischemia is determined by both the intensity of exercise and its duration, a modest rise in heart rate over a prolonged interval may explain the reduced heart rate threshold for ischemia commonly described in daily life. This finding may help to explain the well-recognized observation that ischemia commonly develops at lower heart rates during daily life than during standard exercise testing.

The circadian rhythm of ischemia correlates with that of heart rate. Indeed, the circadian pattern associating heart rate with all ischemic events has been confirmed specifically for silent events, 34% of which were reported between 6:00 AM and noon in one study in men with stable angina. In another study, ambulatory ECG monitoring during regular daily activity showed morning (8:00 AM) increases in heart rate; the number of ischemic episodes was linked to physical activity patterns.

Finally, in the previously referenced study of Andrews et al., in which the frequency of ischemic episodes varied throughout the day, a multivariate model was constructed that included heart rate variables (baseline heart rate, and magnitude and duration of heart rate increase) and time of day. Heart rate–related variables alone, but not time of day, were independently related to the development of ischemia, suggesting that the circadian ischemic patterns observed are linked primarily to heart rate patterns.

**PROGNOSTIC VALUE OF ELEVATED RESTING HEART RATE IN PATIENTS WITH STABLE CAD**

The prognostic value of elevated heart rate has been clearly documented in patients with chronic CAD. Moreover, an important analysis from the large Coronary Artery Surgery Study (CASS), with a median follow-up of almost 15 years, has extended our understanding of the prognostic importance of heart rate in patients with stable CAD: in this study, elevated heart rate was an independent risk factor for total and cardiovascular (CV) death in patients with a heart rate ≥83 bpm versus those with a heart rate ≤62 bpm, with a hazard ratio (HR) for total mortality of 1.32 (99% confidence interval [CI], 1.19 to 1.47; P<0.0001), and an HR for cardiovascular mortality of 1.31 (99% CI, 1.15 to 1.48; P=0.0001). Rehospitalization due to any cardiovascular cause increased in line with increased heart rate. The association between heart rate and total mortality was remarkably consistent across all subgroups analyzed, regardless of gender, diabetes, hypertension, left ventricular ejection fraction, or finally (and importantly) treatment with β-blockers. Similar observations have been made in different populations. For example, a recent post hoc analysis from the International VERapamil-trandolapril STudy (INVEST) in CAD patients with hypertension demonstrated that a higher baseline resting heart rate was independently associated with a higher incidence of CV events. This was particularly evident for heart rates above 70-75 bpm.

The BEAUTIFUL (morBidity-mortality EvAilUaTion of the Iβ inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction) trial was the first to prospectively examine the association between elevated resting heart rate and cardiovascular outcomes in a large population with stable CAD and left ventricular dysfunction. An analysis in the placebo arm of BEAUTIFUL showed that elevated resting heart rate (≥70 bpm) was a strong predictor of clinical outcomes.
What is the role of increased heart rate in stable coronary artery disease? - Steg

in that population. Patients with an elevated resting heart rate (≥70 bpm) were 34% more likely to die from cardiovascular causes (P=0.0041) and 53% more likely to be hospitalized for new or worsening heart failure (P<0.0001) than those with values <70 bpm (Figure 3). Likewise, elevated heart rate was associated with a 46% increased risk of fatal and nonfatal myocardial infarction (P=0.0066) and a 38% increase in the need for coronary revascularization (P=0.037). These data were adjusted for all baseline differences, including β-blocker intake and other background therapy. The BEAUTIFUL study investigators also analyzed the effect of incremental increases in resting heart rate on cardiovascular outcomes in the placebo arm. Every 5-bpm increase in heart rate was associated with an 8% increase in the risk of coronary revascularization (P=0.034) and a 7% increase in fatal and nonfatal myocardial infarction (P=0.052).

The BEAUTIFUL study also clearly demonstrated that elevated resting heart rate places coronary patients at risk of cardiovascular events, even if they are apparently well treated according to current guidelines, including treatment with β-blockers. Indeed, a large majority of the BEAUTIFUL population received concomitant β-blocker therapy; 87% of patients in the placebo arm received β-blockers, which is a considerably higher rate than that observed in population surveys in patients with stable CAD.

There are several possible mechanistic explanations for why an elevated heart rate is deleterious in CAD. Apart from the important role of heart rate as a determinant of myocardial ischemia, increased heart rate is known to contribute to the progression of atherosclerosis. Experimental studies in monkeys have shown that heart rate exerts a direct atherogenic effect on arteries, increasing lesion area and stenosis percentage through increased wall stress. This finding is further supported by clinical studies that have shown that heart rate is an independent factor that correlates with the severity of coronary atherosclerosis in young patients after myocardial infarction and with the rate of progression of atherosclerosis. Increases in heart rate have also been shown to correlate with higher levels of atherogenic serum lipid fractions in the general population. Experimental data suggest the involvement of heart rate in endothelial dysfunction and in the progression of atherosclerosis. Briefly, pressure wave–derived vascular stress sensed by mechanoreceptors triggers a cascade of signaling molecules. Elevated tensile stress is thought to induce direct endothelial injury and to increase endothelial permeability to low-density–lipoprotein (LDL) particles and to circulating inflammatory mediators (Figure 4). An increased heart rate may also be involved in the later stages. Increased heart rate due to mechanical stress may promote the weakening of the fibrous cap, ultimately increasing the risk of plaque disruption and the onset of acute coronary syndrome. Logistic regression analysis has shown a positive correlation between atherosclerotic plaque disruption and a mean heart rate >80 bpm.

Given the importance of elevated heart rate in the pathophysiology of CAD, heart rate reduction is an important therapeutic target in coronary patients to improve symptoms and prevent ischemia, and, in the long term, to potentially prevent cardiovascular events.

HEART RATE REDUCTION IN THE MANAGEMENT OF STABLE CAD

Heart rate reduction is a well-recognized strategy for ischemia prevention in patients with CAD. Heart rate reduction decreases myocardial work and myocardial oxygen consumption, increases diastolic filling time and myocardial oxygen supply,
and, thus, minimizes the pathophysiological roots of angina. In studies examining the efficacy of antianginal agents in stable angina and silent myocardial ischemia, the greatest efficacy was achieved with agents producing the most sustained reductions in heart rate. For example, in ASIS in stable CAD, propranolol was more effective in relieving angina and preventing asymptomatic myocardial ischemic episodes than diltiazem, which has a lower propensity to reduce heart rate. When compared with placebo, only propranolol was associated with marked reductions in all manifestations of ischemia during ambulatory ECG monitoring.

Slowing heart rate has generally been accepted as an effective method for angina prevention, but this approach was rigorously evaluated recently, thanks to the availability in clinical practice of drugs that reduce heart rate selectively, such as ivabradine. Data from clinical studies with ivabradine, which selectively inhibits the pacemaker If current, are consistent with the importance of heart rate reduction in preventing angina and minimizing underlying ischemia. Clinical trials have established the potent anti-ischemic and antianginal effects of ivabradine. In randomized placebo-controlled trials, ivabradine demonstrated dose-dependent improvements in exercise tolerance and prevention of exercise-induced ischemia. In INITIATIVE (INternational Trial on the Treatment of angina with IvabradinE versus atenolol), ivabradine was compared to β-blocker therapy with atenolol, an established treatment for the prevention of exercise-induced angina, using stress tests, in 939 patients. In that study, ivabradine bid was compared to 100 mg atenolol od, all the parameters of the exercise treadmill test (ie, exercise duration, time to limiting angina, time to angina onset, and time to 1-mm ST-segment depression) of ivabradine fulfilled criteria for non-inferiority versus atenolol. In addition, when examining the increase in exercise capacity (measured by increase in total exercise duration) provided by each beat reduction in heart rate, the “efficiency” of heart rate reduction with ivabradine was greater than that achieved by atenolol (increase in total exercise duration of 10.1 s vs 5.6 s).

More recently, the ASSOCIATE (evaluation of the Antianginal efficacy and Safety of the aSsociation Of the If Current Inhibitor IvAbradine with a beTa-blockEr) trial examined the effects of ivabradine in patients with chronic stable angina pectoris already receiving β-blocker therapy. In this double-blind trial, 889 patients on 50 mg of atenolol daily were randomly assigned to additional treatment with either ivabradine (up to 7.5 mg bid) or placebo. Patients were then studied with exercise treadmill tests at the trough of drug activity 2 and 4 months later. Ivabradine improved total exercise duration and all the parameters of the exercise test, at 2 and 4 months. In addition, treatment was well tolerated, with less than 1% of patients stopping drug therapy because of side effects (generally bradycardia). Therefore, ivabradine reduces heart rate further, improves exercise capacity, and is well tolerated when added to chronic treatment with β-blockers.

Elevated heart rate may also play a role in the pathogenesis of atherosclerosis and promote coronary plaque disruption, which can exacerbate the effects of ischemia. This suggests that slowing heart rate may be uniquely suited to mitigate...
not only angina, but also these other consequences of CAD. Consistent with the prognostic value of increased heart rate, the BEAUTIFUL study demonstrated that reduction in heart rate with ivabradine in stable CAD patients with an elevated resting heart rate (>70 bpm) was associated with significant reductions in coronary outcomes: a 36% reduction in the relative risk of fatal and nonfatal myocardial infarction (P=0.001), a 30% reduction in the relative risk of coronary revascularization (P=0.016), and a 22% reduction in the relative risk of fatal and nonfatal myocardial infarction or unstable angina pectoris (P=0.023) (Figure 5).

These results provide evidence of the benefits of ivabradine beyond the mere control of anginal symptoms. It now belongs to the small group of drugs that has established prognostic benefits on hard clinical outcomes in patients with CAD, even when these patients are receiving excellent background medical therapy. Consistent with these findings, a recent post hoc analysis in the 1507 patients in BEAUTIFUL who had angina showed that ivabradine improved the primary outcome (the composite of cardiovascular death, myocardial infarction, and hospitalization for heart failure) by 24% (myocardial infarction alone by 42%) relative to placebo.43

These findings also have another important implication from a pathophysiologic standpoint: they provide evidence that a drug specifically slowing heart rate without affecting any other hemodynamic parameter confirms the observed relationship between elevated heart rate and adverse cardiovascular outcomes is not solely an association, but is, at least in part, causal. This is because ivabradine has no hemodynamic action other than slowing sinus rhythm.

The most recent European Society of Cardiology (ESC) guidelines for cardiovascular disease prevention highlighted the prognostic value of resting heart rate, which has been demonstrated in the general population and in patients with hypertension, diabetes, and/or CAD.44 The guidelines advocate the avoidance of raised heart rate in the general population through various lifestyle measures (ie, taking regular physical exercise, avoiding psychological stress, and discouraging high caffeine consumption). They also stipulate that in a clinical setting, of the pharmacotherapies available for heart rate reduction, β-blockers and selective If current inhibitors (eg, Procoralan) have shown marked pharmacological efficacy in the treatment of angina.44

**CONCLUSION**

Heart rate plays a key role in the pathophysiology of stable CAD. In patients with chronic stable CAD, heart rate increases due to exercise or mental/emotional stress, which increases myocardial oxygen consumption while decreasing oxygen supply, the roots of ischemia and angina. There is now a substantial body of evidence showing that sustained elevation in heart rate is associated with increased mortality in people with suspected or known CAD, in those with documented myocardial infarction or hypertension, and even in otherwise healthy individuals. This makes heart rate reduction a primary therapeutic objective for angina prevention in patients with CAD as well as an important strategy for modifying the natural history of CAD and for preventing cardiovascular events.

Heart rate–lowering drugs developed as antianginal and anti-ischemic agents, due to their effects on myocardial oxygen consumption, are now recognized as having wider applications due to their beneficial cardioprotective effects.
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Heart rate (HR) plays a major role in the pathophysiology of acute coronary syndromes (ACS). Epidemiological surveys report a direct relationship between HR and outcomes after myocardial infarction, and increased HR has been identified as an independent risk factor for ACS. Reducing HR is expected to be a valuable therapeutic strategy in ACS. The disadvantages of HR reduction with β-blockers in ACS include contraindications and tolerance issues, as well as mixed trial results, particularly in moderate- to high-risk patients; the beneficial effects of calcium channel blockers are also inconsistent. HR reduction with the selective If inhibitor ivabradine may have potential in this setting. This is currently being tested in VIVIFY (Evaluation of the IntraVenous If inhibitor ivabradine after ST-segment elevation myocardial infarction).

What is the role of increased heart rate in acute coronary syndromes?

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Heart rate (HR) plays a major role in ischemic heart disease. Increased HR has been identified as a risk factor for acute coronary syndrome (ACS). In patients with acute myocardial infarction, HR is directly related to prognosis and there is growing evidence that reducing HR improves outcomes. In spite of the epidemiological and clinical evidence, the role of increased HR and the potential benefit of its control are probably still neglected in this clinical setting.

POTENTIAL DETRIMENTAL EFFECTS OF ELEVATED HEART RATE IN ACS

ACS, which includes acute myocardial infarction, unstable angina, and ischemic sudden death, is triggered by plaque rupture and thrombus formation in a coronary artery. Endothelial dysfunction, increased oxygen supply to the myocardium further contribute to ischemia. HR has a major impact on some major factors related with the pathophysiology of ACS. Increased HR is associated with endothelial dysfunction, plaque instability and rupture, and a decreased threshold for ventricular fibrillation. A high HR in patients with ACS increases cardiac work and myocardial oxygen consumption, and reduces diastolic myocardial perfusion time. This can produce an imbalance between myocardial oxygen supply and demand, contributing to ischemia in patients with ACS. Finally, after an acute complete coronary artery occlusion, collateral circulation plays a crucial role and is related to prognosis.

In patients with coronary artery disease (CAD), collateral vessels are much more frequently visible on angiography when HR is below 60 beats per minute (bpm) than when HR is above 60 bpm.

HEART RATE AS A RISK FACTOR

In several large epidemiologic studies, resting HR has been clearly associated with acute coronary events, including sudden death and myocardial infarction. In the French population of the Paris Prospective Study I, in 5713 asymptomatic middle-aged men (42 to 53 years old) followed over 23 years, after adjustment for potential confounding variables, resting HR was significantly associated with an increase in both sudden death and nonsudden death from myocardial infarction. In other epidemiologic studies in different ethnic populations, resting HR was also found to be an independent predictor of coronary events (myocardial infarction or coronary death) in multivariable analysis. In one of the largest series, the Women’s Health Initiative study, in 129 135 postmenopausal women followed over a mean of 7.8 years, resting HR independently predict-
ed myocardial infarction or coronary death, but not stroke, with a relative 21% increase in risk in women with HRs from 70 to 76 bpm and a 68% increase in women with HRs over 76 bpm compared with the referent group of women with a resting HR below 62 bpm.

In patients with CAD, HR is a predictor of hospitalization for myocardial infarction and unstable angina. In 22,192 patients with hypertension and CAD followed over 2.7 years in INVEST (INternational VErapamil-trandolapril STudy), higher baseline and follow-up resting HRs were associated with increased adverse outcome risks, including all-cause death and myocardial infarction. In the placebo arm of the BEAUTIFUL (morBidity-mortality EvAlUaTion of the I_f inhibitor ivabradine in pa-tients with coronary disease and left ventricULar dysfunction) trial, which included 5438 patients with stable CAD and left ventricular systolic dysfunction, patients with a resting HR over 70 bpm were at increased risk of hospitalization for fatal or nonfatal myocardial infarction (46%) compared with the population with a basal HR below 70 bpm.

HEART RATE AS A PROGNOSTIC FACTOR IN ACS

Increased HR during ACS is related to an increase in sympathetic tone and catecholamine discharge, with probable deleterious effects in the setting of acute ischemia. The first clinical observations were made in patients with acute myocardial in-
farction admitted to coronary care units in the 1980s. Kjekshus et al and Hjalmarson et al observed a direct relationship between HR and outcomes after myocardial infarction; both in-hospital and postdischarge mortality progressively increased with elevated admission HR (Figure 2). More recently, investigators from the GISSI (Gruppo Italiano per lo Studio della Streptochinasi nell’Infarto miocardico) trials made the same observations. In the extensive electrocardiography database of the GISSI studies of almost 20,000 patients, there was a progressive increase in hospital mortality with increased HR at admission.15

In contemporary series of patients with ACS with high rates of coronary revascularization and widespread use of statins, β-blockers, and anti-thrombotic therapy, the observations are similar. In the Global Registry of Acute Coronary Events (GRACE), which includes patients with ST-segment–elevation myocardial infarction (STEMI), non-ST-segment–elevation myocardial infarction (NSTEMI), and unstable angina, HR was an independent prognostic factor in an elaborated model, with an attributable risk for in-hospital and postdischarge mortality of 5% to 10% for each 10 bpm increase in HR.16-18 The CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the American College of Cardiology/American Heart Association Guidelines) registry investigators evaluated the relationship between presenting HR and in-hospital events in a cohort of 135,164 patients with non-ST-segment–elevation ACS. They found that the relationship between presenting HR and all-cause mortality and stroke followed a “J-shaped” curve, with an increased event rate at very low and high HRs even after controlling for baseline variables. However, there was no relationship between presenting HR and risk of reinfarction (Figure 3, page 206).19

RECOMMENDATIONS FOR REDUCTION OF HEART RATE

The GRACE registry was used to create a clinical “risk calculator” for the prediction of death or myocardial infarction before hospital discharge and in the 6 months following ACS.18 The presence of HR as an integral part of the GRACE risk prediction tool illustrates the importance of reducing HR in these patients to improve their prognosis. The performance of GRACE as a predictive tool was recently compared with two other risk calculators in ACS, the TIMI (Thrombolysis In Myocardial Infarction) risk score and the PURSUIT (Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy) risk score.20 Interestingly, the two risk scores that included HR as a component of risk (GRACE and PURSUIT) were found to be the best discriminators of mortality or hospitalization at 1 year. The importance of HR is also recognized in current European guidelines in the prevention of cardiovascular disease.21 While there is no fixed threshold for a target HR in ACS, the American Heart Association currently recommends the reduction of HR to values below 55 to 60 bpm in patients with stable angina.22 Despite this, a recent analysis from the Euro Heart Survey indicates that these patients rarely reach target HR,23 and we can only suppose that the same is the case elsewhere in cardiology. A recent observational study demonstrated that only a minority of post-ACS patients (5.3%) treated according to current guidelines reached the recommended level of HR during their hospital stay.24

BENEFIT OF REDUCING HEART RATE IN ACS

Reducing HR decreases oxygen consumption and increases coronary flow during diastole, two important determinants of ischemia in ACS.
Accordingly, reducing HR should be related to an improvement of ischemia and clinical outcomes. So far, interventions directed exclusively at reducing HR have not been conducted and the benefit observed in some studies when HR decreases may not truly reflect the role of direct intervention.

HR can be reduced using β-blockers, some calcium channel blockers (CCBs), and ivabradine. Both β-blockers and CCBs induce hypotension, but have significant inotropic and bathmotropic depressant effects that may limit their use or the use of the appropriate doses to obtain a sizeable reduction in HR. In addition, β-blockers can increase coronary vasomotor tone, in part because of unopposed α-adrenergic mediated vasoconstriction. These effects are not observed with ivabradine, which gives pure HR reduction.4,25,26

There is a huge amount of evidence for β-blockade in patients with ACS. Its beneficial effect appears at least in part to be secondary to the reduction in HR, with a direct relationship between HR reduction obtained and reduction in infarct size, reinfarction, and clinical outcomes, including mortality (Figure 4).13

On the other hand, the limitations of β-blockade were illustrated by COMMIT-CCS2 (ClOpidogrel and Metoprolol in Myocardial Infarction Trial—Chinese Cardiac Study 2), which tested the use of intravenous, followed by oral, β-blockers in 45,852 patients with suspected acute myocardial infarction.27 There was no impact on the composite of death, reinfarction, and cardiac arrest or all-cause mortality over the 28-day hospitalization. Overall, there was
a modest reduction in reinfarction and ventricular fibrillation (after day 1), which was counterbalanced by an increase in cardiogenic shock, which occurred early (in the first 24 hours). The increase in cardiogenic shock was observed primarily in those who were hemodynamically compromised, were suffering from heart failure, or were stable, but at high risk of developing shock.

In summary, the routine early use of β-blocker in STEMI does not appear to be beneficial, especially when treatment is started via the intravenous route. Very early use of β-blockers is clearly contraindicated in patients with clinical signs of hypotension or congestive heart failure. Early use may be associated with a modest benefit in low-risk hemodynamically stable patients, but in all other patients, it is prudent to wait for the patient’s condition to stabilize before the introduction of oral β-blockade.

The beneficial effect of HR-reducing CCBs in patients with ACS is less evident. Clinical trials with verapamil and diltiazem have failed to demonstrate consistent significant benefit in patients with ACS in studies conducted in the early 1980s with low use of antiaggregants, β-blockers, statins, and revascularization. In DAVIT-I (DAnish Verapamil Infarction Trial I), treatment was started with 0.1 mg/kg verapamil iv and 120 mg/day orally on admission followed by 120 mg three times daily po, or matched placebo. Mortality and reinfarction rates were similar in both groups of treatment during hospitalization and after the 6-month and 12-month follow-ups after continuous treatment.28 In the Multicenter Diltiazem Reinfarction Study, conducted in 576 patients recovering from acute non-Q-wave myocardial infarction treated with either diltiazem or placebo, treatment was initiated 24 to 72 hours after the onset of myocardial infarction and continued for 14 days. Active treatment did not modify total mortality, but reduced the early reinfarction rate compared with placebo (9.3% vs 5.2%, P<0.03).29 In INTERCEPT (Incomplete Infarction Trial of European Research Collaborators Evaluating Prognosis post-Thrombolysis), another prospective, randomized, double-blind, sequential trial in 874 patients with acute myocardial infarction, but without congestive heart failure, who first received thrombolytic agents, patients received either oral diltiazem or placebo, initiated within 36 to 96 hours of infarct onset, and then given for up to 6 months. Diltiazem did not reduce the cumulative occurrence of cardiac death, nonfatal reinfarction, or refractory ischemia during 6-months of follow-up, but the need for revascularization was lower in the diltiazem group.30 There is no information related to the possible benefit of CCB in patients with ACS treated according to contemporary strategies.

Ivabradine, a selective inhibitor of the If current, reduces resting and exercise HRs without affecting cardiac contractility or blood pressure. In experimental models, ivabradine reduced oxygen consumption, increased myocardial blood flow, improved endothelial and myocardial function, and reduced infarct size.4,26,31-33 In clinical studies, ivabradine has been found to be at least as effective as β-blocker or CCB in reducing myocardial ischemia in patients with stable ischemic heart disease.34-39 Ivabradine has been studied as monotherapy versus placebo39 and versus comparators, such as amlodipine and atenolol.34,36 Its antianginal and anti-ischemic efficacy has also been evaluated in combination with the β-blocker atenolol in patients with stable angina in the ASSOCIATE (evaluation of the Anti-anginal efficacy and Safety of the asSoCIation Of the If current inhibitor IvabrAdine with a beta-blockEr) study.37 ASSOCIATE showed that the combination of ivabradine 7.5 mg bid and atenolol 50 mg/day in patients with chronic stable angina pectoris provided additional anti-ischemic efficacy with no untoward effect on safety or tolerability.

Ivabradine also improves outcomes in patients with chronic ischemic disease and reduced left ventricular ejection fraction. In the BEAUTIFUL trial, ivabradine reduced the risk of myocardial infarction in patients with a HR of 70 bpm or greater.40 In the subgroup of 1507 patients with limiting angina, ivabradine improved the composite end point of cardiovascular mortality, myocardial infarction, and heart failure. The observed reduction in hospitalization for myocardial infarction in this subpopulation was 42%, and 73% in patients with a HR above 70 bpm.41 Notably, the majority of the BEAUTIFUL population, like the ASSOCIATE population,37 were receiving background treatment with β-blockers. In addition, patients with a lower baseline HR (between 60 and 70 bpm) or patients that could be considered to be on a maximal effective atenolol dose had similar benefits, although not significant, when ivabradine was added to their β-blocker therapy compared with the whole study population. Based on all this evidence, ivabradine has been approved for the treatment of angina patients in sinus rhythm with a contraindication to β-blockers, or in combination with β-blockers in patients with a HR >60 bpm inadequately controlled with an optimal dose of β-blocker.37 The positive clinical trial results in patients with CAD and/or stable angina pectoris are a promising sign for the application of this agent in ACS.
INTRAVENOUS HEART RATE REDUCTION IN AN EMERGENCY SETTING

Considering that HR is frequently elevated—and deleterious—in ACS, the use of intravenous HR-lowering agents in an emergency setting is appealing. HR reduction decreases oxygen demand and increases diastolic duration (thereby lengthening the time available for coronary perfusion). A rapid reduction in HR may therefore allow the myocardium to withstand longer durations of ischemia before irreversible myocardial necrosis occurs, and therefore increases the possible window for reperfusion therapy (with intravenous thrombolysis or primary percutaneous coronary intervention [PCI]) to achieve effective coronary recanalization and myocardial reperfusion.

Intravenous β-blocker may not be the best method to achieve rapid reductions in HR in the emergency room. For a start, they are contra-indicated or poorly tolerated in patients with obstructive pulmonary disease, hypotension, or pulmonary congestion, which complicates their use in an emergency setting. Secondly—and perhaps more importantly—the COMMIT trial results described above showed mixed results, particularly in moderate- to high-risk patients.

On the other hand, ivabradine, which reduces HR without affecting left ventricular inotropy and without the classic side effects of β-blockade, may be valuable in this setting. This possibility is currently being tested in VIVIFY (eValuation of the Intravenous If inhibitor ivabradine after ST-segment-elevation myocardial infarction), a phase 2 pilot, randomized, placebo-controlled blind trial, the first clinical study of intravenous ivabradine in the setting of ACS. VIVIFY sets out to compare the effects of intravenous ivabradine with placebo on HR, left ventricular dimensions and function, and infarct size in patients receiving primary PCI for STEMI. The study plans to enroll patients diagnosed with STEMI within the previous 9 h and treated with PCI less than 6 h after symptom onset. Participants also have to be in sinus rhythm, have a baseline HR >80 bpm, and a systolic blood pressure >90 mm Hg. Treatment will have to be initiated less than 9 hours from the onset of symptoms at a dose of 5 mg ivabradine or matching intravenous placebo over 30 seconds, followed by an 8-hour infusion of 5 mg ivabradine or matching placebo.

The main objective of VIVIFY is to determine the feasibility, safety, and potential value of intravenous ivabradine in the setting of ACS, which will hopefully pave the way for studies powered to assess its effect on clinical outcomes. Given the critical role of HR in oxygen consumption and the pathogenesis of myocardial ischemia, ivabradine has therapeutic potential that ranges from the acute ischemic setting of ACS to the long-term treatment of CAD patients, for whom the control of elevated HR has already been demonstrated to improve outcomes. 23 40

CONCLUSIONS

HR is strongly associated with the risk of cardiovascular events in patients with stable CAD as well as in healthy populations. In patients with acute myocardial infarction, HR is an independent predictor for short- and long-term outcomes. Indirect evidence suggests that control of increased HR is an excellent opportunity for benefiting patients with ACS, but this hypothesis should be tested in appropriate clinical trials. Ivabradine, a selective If current inhibitor, reduces HR without inducing hypotension, conduction disturbances, or negative inotropic effects. Its safety and efficacy are currently being investigated in patients with STEMI.

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What is the role of increased heart rate in acute coronary syndromes? - López-Sendón and Ferrari


What is the role of increased heart rate and why is it beneficial to reduce it?

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Increased heart rate is an independent risk factor for patients with cardiovascular disease, in particular those with arterial hypertension, myocardial infarction, coronary artery disease, heart failure, and extracardiac comorbidities like microalbuminuria. This relation is supported by a large number of animal studies as well as clinical trials, which are summarized in this article. These studies demonstrate the detrimental effects of increased heart rate on the structure and function of the cardiovascular system. Heart rate can be easily measured during physical examination of the patient, therefore allowing us to make a simple assessment of the prognosis and efficiency of therapy. Thus heart rate, which can selectively be reduced by \( I_f \) channel inhibition, seems to be a therapeutic target in cardiology.

Heart rate is regulated by activity of the autonomic nervous system and is the main mechanism for adapting cardiac output to the demands of the body. However, relaxation and contraction is associated with an extremely high utilization of energy and adenosine triphosphate (ATP), amounting to 300 mg of ATP per beat and 30 kg of ATP per day.\(^1\) The negative aspect of the high energy and ATP utilization of the heart is its association with high levels of oxidative stress, which in turn is involved in cellular aging as well as in the mechanisms of cardiovascular disease like atherosclerosis and heart failure.\(^2\) Therefore, a reduction of heart rate by 10 beats per minute, which saves 5 kg ATP per day,\(^1\) should be associated with a reduction in oxidative stress in addition to a reduction in myocardial energy demand. The proof of concept would be a treatment experiment that provides evidence that heart rate reduction is indeed associated with an increased life span. These experiments—treating mice with digoxin—have been done. Digoxin reduced heart rate in mice by 15% and prolonged survival time by 30% (Figure 1, page 212).\(^3\) This observation has been complemented by many investigations providing evidence for the predictive role of high heart rate on cardiovascular mortality throughout the cardiovascular continuum.\(^4\)

**EPIDEMIOLOGY**

In the general population, life expectancy is associated inversely with elevated heart rate.\(^5-7\) This association is independent of gender and genetic background. An increase in

### SELECTED ABBREVIATIONS AND ACRONYMS

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<th>Abbreviation</th>
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<tr>
<td>ATP</td>
<td>adenosine triphosphate</td>
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<td>HARVEST</td>
<td>Hypertension and Ambulatory Recording VEnetia STudy</td>
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<td>INVEST</td>
<td>InterNational VERapamil-trandolapril STudy</td>
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<td>BEAUTIFUL</td>
<td>morBidity-mortality EvAluATion of the ( I_f ) inhibito ivabradine in patients with coronary disease and left ventricULar dysfunction</td>
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risk is derived from data comparing individuals with heart rates <60 beats per minute (bpm) with those with heart rates of 90-99 bpm. In particular, there is an increase in coronary artery disease mortality and also an increase in sudden cardiac death.

**ARTERIAL HYPERTENSION**

The association of arterial hypertension and increased heart rate was first demonstrated in soldiers returning from the First World War. Individuals with a transient increase in heart rate and a transient increase in blood pressure had increased rates of disability due to cardiac and renal disease. Moreover, this effect was further augmented when both conditions were present. These findings were later supported by the prospectively designed HARVEST (Hypertension and Ambulatory Recording VEnetia STudy) in individuals with mild hypertension.

Several studies and meta-analyses provided evidence that there was an increase in risk of 100% for cardiovascular complications when heart rate was 40 bpm higher. In addition, INVEST (INternational VErapamil-trandolapril STudy) has consistently shown that in hypertensives, heart rate is closely associated with cardiovascular death, myocardial infarction, and stroke.

**RENNAL DISEASE IN HYPERTENSION**

Renal disease is one of the most common complications in hypertension and reflected by microalbuminuria, which occurs very early during the development of end-organ damage. In a large registry of more than 20,000 hypertensive individuals, microalbuminuria was measured and its association with medication, coexisting disease, heart rate, and blood pressure was analyzed. It was shown that microalbuminuria was more prevalent in hypertensives with a cardiovascular risk profile when heart rate ≥80 bpm. The risk for developing heart rate–dependent microalbuminuria was higher in patients with atrial fibrillation than in patients in sinus rhythm. Since atrial fibrillation is an important comorbidity in hypertension and heart failure, heart rate—in addition to blood pressure—could also be involved in the comorbidity of other organs, like the kidney.

**ATHEROSCLEROSIS**

Stretching of human vascular smooth muscle cells enhances the frequency-dependent release of angiotensin II and thereby stimulates the production of procollagen mRNA, presumably leading to enhanced fibrosis in the vessel wall. Arterial stiffness of the aorta corresponded with these experimental results; it was closely associated with observed heart rate, in particular in patients with hypertension (Figure 2). Tachycardic pacing induced an increase in the stiffness of carotid arteries. However, a decrease in heart rate caused by sinus node ablation reduced atherosclerotic lesions in monkeys fed a cholesterol-rich diet. Finally, in ApoE
knockout mice fed a Western diet, treatment with the 
$I_f$ channel inhibitor ivabradine reduced heart rate
by 15% and atherosclerotic lesions by 42% in the aorta via a reduction
in oxidative stress and an improvement
in endothelial function.24

CORONARY ARTERY
DISEASE AND
MYOCARDIAL INFARCTION

High heart rate is closely associated
with events in patients with stable
coronary artery disease.25,26 Furthermore,
plaque rupture is closely associated with resting heart rate,
as is arterial hypertension, but the relative risk for individuals with heart
rates above 84 bpm is higher than
that for individuals with elevated
blood pressure.27 Consistently, after
myocardial infarction, an elevated
heart rate on admission, during the
clinical course of the condition, as
well as at discharge was associated with a poorer outcome.28 Evidence
for functional relevance of heart rate
in myocardial infarction is provided by 
$\beta$-blocker trials. After myocardial infarction, heart rate reduc-
tion with $\beta$-blockers is associated with a decrease in total mortality. However, other mechanisms, like antiadrenergic effects that reduce
the deterioration of myocardial function as well as antiarrhythmic
effects, cannot be ruled out.29-31
Recent evidence for the role of heart rate in these conditions comes from BEAUTIFUL (morBidity-mortality EvAlUaTion of the $I_f$ inhibi-
tor ivabradine in patients with coronary artery disease), which started recently.

Figure 3. Elevated heart rate and its potential influence on cardiovascular disease.

HEART FAILURE

One crucial feature of the failing
heart is the reduction of the force-
frequency relationship,34,35 which
is one of the crucial basic mecha-
nisms for regulating inotropy, which
was first characterized in 1871.36 In patients with pacemaker stimulation,
an increase in stimulated heart rate
during exercise is not accom-
panied by an increase in oxygen up-
take, indicating that in heart failure
patients elevated heart rate might
only produce myocardial load and
oxygen consumption without con-
tributing to an increase in exercise
performance.37 Furthermore, all
cardiovascular interventions that reduce heart rate, like $\beta$-blocker
treatment, have been shown to im-
prove outcomes in patients suffering
from heart failure, while others with
$\beta$-adrenoceptor agonists or va-
sodilators adversely effect survival
and morbidity.38

The answer to whether heart rate
reduction is beneficial for reducing
relevant end points in heart failure
patients will be provided by SHIFT
(Systolic Heart failure treatment
with the $I_f$ inhibitor ivabradine Trial).
However, it is noteworthy that in
BEAUTIFUL, heart failure–related
end points, like heart failure hospi-
talization or death, are not signifi-
cantly reduced by treatment with
ivabradine.32 Interestingly, there
are some case reports and circum-
stantial observations that ivabra-
dine-induced heart rate reduction is
able to improve hemodynamics in
patients with severe heart failure on
inotropic stimulation and in cardio-
genic shock.39,40 Further data are
necessary to characterize selective
heart rate reduction, which might
be one, but not the only, mechanism for the beneficial effects of therapy with \( \beta \)-blockers in heart failure.

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**PERSPECTIVES**

Many epidemiological studies have provided evidence that a high heart rate in a normal population, in hypertensives, and in patients with atherosclerotic vascular disease is associated with cardiovascular outcomes. This association of higher heart rates with events can already be detected in the high-normal range at a cutoff of about 84 bpm. Furthermore, experimental studies have provided evidence that heart rate reduction by sinus node ablation, \( \beta \)-blocker therapy, or treatment with ivabradine has beneficial effects on atherosclerotic outcomes. However, data in patients are rather sparse. Although heart rate reduction by ivabradine and \( \beta \)-blockers reduce ischemic symptoms, only some atherosclerosis end points were significantly reduced in BEAUTIFUL. It needs to be pointed out that the primary combined end point was not significantly reduced. Further studies in patients with stable coronary artery disease and heart failure will provide further knowledge about whether pure heart rate reduction using pharmacological intervention with ivabradine is able to improve outcomes. However, heart rate in high-risk cardiovascular patients should become a significant cardiovascular parameter for predicting complications because it is an integral sign of cardiovascular function and related to several complications at different stages of the cardiovascular continuum (Figure 3, page 213). Therefore, in all future cardiovascular studies, heart rate should be carefully monitored in order to improve our knowledge of this important physiological risk marker, or even risk factor.
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CARDIOLOGIST

In 1942, while teaching physics and, at the same time, in the gentle arms of academia as a PhD student in embryology at New York University, I entered the army to serve in a parachute-glider division.

There, I was a medic, not a medical doctor, and greatly impressed by the chest surgeons who performed miraculous lifesaving procedures, under combat conditions. Hearts had entered my field of vision in a powerful way.

Returning home after three years, I became a medical student at New York University College of Medicine. In 1946, I was treated to a memorable guest lecturer and a basic researcher, Otto Loewi. He exposed two beating frog hearts and stimulated the vagus nerve in the first heart, producing bradycardia. He then aspirated some pericardial solution from the first heart and introduced this on the second frog’s heart, which also demonstrated bradycardia. With a shrug, he said, simply and humbly, “I put the vagus stuff from here to here and for this they gave me a Nobel prize!” First lesson in humility.

I received clinical and medical training from 1947 to 1948 at Bellevue Hospital in New York City. At this time, four
services were shared by New York, Cornell, and Columbia Universities. An important part of this training was learning of the then new techniques of cardiac catheterization from Richard Bing and André Cournaud. Then, a rigorous internship at Mt Sinai Hospital was followed by a cardiology residency at the Bronx Veterans Hospital under the guidance of Arthur de Graff and Clarence de La Chapelle. I was then invited to join the laboratory of Drs Solomon Berson and Rosalyn Yalow, who were to receive together numerous awards, the Nobel Prize for their joint work on radioimmunoassay going alone to Yalow only because of Berson’s death two years previously. They were well organized, strict, and hardworking, and I learned a great deal about self-discipline and research ethics.

In 1952, radioactive labels were available for research and my first cardiac study with potassium 42 showed that potassium left and entered the heart at more than one rate, indicating more than one channel, and refuting earlier reports of single channels. At this time, in the late 1950s, research space was offered to me in the New York University–Veterans Hospital. My interest in cardiac metabolism was stimulated by the newly available amino acids labeled with carbon 14.

For the next 30 years, having the good fortune of steady support from the National Institutes of Health and the Veterans Administration, my efforts turned to the effects of stress on cardiac muscle protein turnover, using isolated guinea pig hearts in vitro. A response of ventricular muscle to increased pressure was rapid, and cardiac muscle protein synthesis was increased after 2 to 3 hours of this stress.

Further studies showed that pressure stress stimulated the formation of mRNA, tRNA, and tRNA, all of which are required for increased protein synthesis. Other researchers found, in studies using the electron microscope, that myocardial nuclei were crumpled in accordion-like fashion during contraction and assumed an elongated oval form in relaxation. Because of this changing configuration, we initiated experiments to study the effects of pulsating pressure on isolated myocardial nuclei. The result was an increase in polymerase activity, which formed mRNA. In all of the above studies, we had examined the effect of pressure on cardiac muscle and now approached the problem of flow-load compared to pressure-load. A perfusion technique...
A scientist explores his research and his art - Schreiber

was devised in which the right ventricle was subjected to the stress of pressure or flow-load with constant coronary perfusion. The results showed a rapid response of protein synthesis in cardiac muscle to pressure overload, but not to flow-load. This suggested the difference in cardiac hypertrophy due to hypertension, in contrast to that due to valve leakage with flow overload.

With the available radioactive labels, my major clinical activity turned to the field of nuclear medicine and I joined the Department of Nuclear Medicine at the New York University–Veterans Administration Hospital. The radioactive-labeled material injected into the patient outlined the coronary circulation of the heart and allowed evaluation of ischemia or myocardial damage. It was stimulating teaching students these techniques. The imaging in sharp colors approached an art form. Looking at the colors alone, it could be abstract art.

During the last 40 years, I was also active in cardiology care of private patients in addition to research and teaching. All of these activities blended together in a most rewarding way.

ARTIST

At the age of 14, I was fortunate to have a gifted teacher of art who encouraged my constant pencil-sketching and introduced me to the technical basics of drawing complicated forms with perspective and dimension. During my college years and, later, my military years in World War II, I worked on pencil sketches of deserts, Italian ruins, Normandy churches, Dutch bridges, and whatever was there.
As a medical intern in the 1950s, I visited a retrospective of the work of Vincent Van Gogh at the Metropolitan Museum of Art in New York City and recognized the evolution of the fine technical virtuosity of his early drawings leading to the creative visions of his paintings with their vibrant colors. My path-to-be in art hit me with the full force of sudden realization. Van Gogh’s colors spoke to my emotional core. The colors were mesmerizing and I was stimulated to start painting with oils. Freed from the details of pencil sketches, I wielded brushes and palette knives with abandon, clearly imprinted with impressionism.

Living in New York City, I was surrounded by great museums and was no stranger to new artistic forms, styles, and trends, but in the fifties, I found impressionists to be the easiest to understand and interact with. I have become enamored of many other painters since, but it was Van Gogh’s voice that spoke the loudest.

Painting became my private world of meditation and fantasy. I never sought instruction or recognition, not that the former wasn’t needed or the latter desired, but I had balanced the time in my life to be able to indulge in my two passions—the laboratory and painting. I have had showings at local galleries and sold some paintings and given paintings to those who showed an interest. I have even had the dubious compliment of having a painting stolen from my office. Incredibly, no one noticed the thief leaving the building and walking in the street carrying a 40×50-inch painting. However, because I had sold a number of paintings, my insurance company recognized me as a “painter” as opposed to a “hobbyist” and gave me a sum they deemed to be of market value. This reduced my anger, but I miss that painting!

In both areas of medicine and art, the products of one’s efforts are seldom satisfactory to the worker. In the laboratory, new questions arise and must be investigated further. In painting, new ways of expression appear, sometimes involuntarily, which are tempting and need further examination. A “next step” is always in mind. In the past, medical discoveries could be made by individual projects but now because of scientific instrumentation and the cost of research, working alone is no longer practical and teamwork is more prevalent.

Yet, to satisfy the creative side to research and medical diagnosis, some physicians may attempt to achieve an individual persona through their art or music. The paradox lies in this dual role for the scientist, but perhaps also identifies the human need for a personal identity.
After three years of active combat in World War II, I was fearful I could not become a student again. I was stunned and worried about attending medical school to which I had just been ad-

mitted (Self-Portrait). But I had started to paint and that and my intensive studies and a supportive wife put me on a normal path.

My painting over the next few years became more impressionistic (Pond With Autumn Leaves). Thinking to overcome my impatience with details, I had just completed a mosaic composed of small glass tesserae, but the opposite effect was achieved and, using the palette knife, I simply discarded details.

My discovery of the palette knife gave me great freedom in Beach Dune, a wild, unoccupied beach where our then-urban children could learn of the wonders of life near an ocean.

The blue color of a huge planting of delphinium in Regent’s Park in London was memorable. Hoping I had memorized the color well after a second and third visit to the park, an attempt was made to reproduce it at home. However, lacking delphinium as a model, I superimposed the well-remembered blue color on Digitalis (foxglove), which grow in profusion in my garden, although the painting remains entitled Delphinium. It was the blue I was interested in, and I was satisfied with it on my foxglove blooms.

Silver Birches was the first painting to use a counter-color method that highlighted the lighter colors. When the rough texture of the completed palette-knife-painted canvas was covered with an ultramarine oil and then quickly rubbed off, some blue remained in the deepest crevices, creating dimensional shadows and complementing the lighter colors.
Similarly, in *Grand Canyon*, with the palette knife and counter-coloring, an attempt was made to portray the strength and formidable power of a Grand Canyon gorge. But such magnificent structures could never be depicted either by painting or photography.

My vision had begun to steadily decline after 1990 owing to macular degeneration. I was declared legally blind in 1998 and I retired from medicine. I had less than 10 percent of total vision with minimal peripheral vision left, and there was an inability to see any detail in faces or objects. In 2000, in despair and anger, *Window* was painted in little more than an hour using diluted paints and a large brush, palette knife having become less useful. For the next year I made daily adjustments in a seriously altered life. Gradually despair was being replaced with small amounts of optimism. A companion piece to *Window*, entitled *Infinity*, sees a bit of the world opening up.

There has been an accelerated distillation of memories and now, using my mind’s eye, I record less of a picture and more of an emotion.

As my vision changes, so does my painting technique. A splash of color (*Poppies*) suffices for a bloom, stems no longer need to connect with the flower and are drawn using a pen, the vase is shaped by a dark brush stripe on one side and bare white canvas on the other. Being able to see only vague shapes, I am now mainly painting from memory. Still impressionistic, but simple, I feel *Poppies* is one of my better paintings. Simpler still is *Beach and Boat*, a sea-scape that yields only at the last moment to a small boat in the foreground. The evolution in my painting styles continues, dependent only on my imagination.
Heart Rate and Cardiovascular Disease

Summaries of Ten Seminal Papers

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Highlights of the years by Ian Mudway, MD
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Heart rate as a prognostic factor for coronary heart disease and mortality: findings in three Chicago epidemiologic studies


Am J Epidemiol. 1980;112:736-749

Prior to the present report, other studies that had examined the association between heart rate and incidence of coronary heart disease (CHD) had not yielded consistent findings. Some studies had noted a positive association between baseline heart rate and later CHD incidence. In contrast, several large studies had found no significant association between heart rate and the incidence of CHD. The present study examines the associations between heart rate and death from cardiovascular disease (CVD) and heart rate and death from CHD, sudden death from CHD, along with death from all causes and noncardiovascular causes for middle-aged white males from three epidemiological studies in Chicago.

The Chicago Peoples Gas Company study included 1233 white male employees aged 40-59 years, who were followed for 15 years. The Chicago Western Electric Company study followed 1899 white male employees aged 40-55 years for 17 years. Finally, the Chicago Heart Association Detection Project in Industry study recruited 5784 white males employed by 85 firms in the greater Chicago area with an average follow-up of 5 years. From initial examination, including resting electrocardiography (ECG), these men were considered free of CHD. The associations between heart rate and death from all causes, CVD, and CHD, sudden death from CHD, and death from non-CVD were analyzed in these three studies utilizing both cross-classification and Cox regression.

In order to fully understand the associations between heart rate and mortality, it was necessary to examine the associations between heart rate and other risk factors. Heart rate was found to positively correlate with systolic and diastolic blood pressure and cigarette use. For age, serum cholesterol, and body weight, the correlations were small or inconsistent. In univariate analysis, mortality from both cardiovascular and noncardiovascular causes generally increased with increasing heart rate. In the cross-classification analysis for each study, heart rate was divided into approximate quintiles, with the mortality rates then computed for each quintile. For all three studies comparing these five groups, increasing mortality with higher heart rate was highly significant ($P<0.001$). In two of the studies, the Chicago Peoples Gas Company study and Chicago Western Electric Company study, CVD and CHD death rates also increased with increasing heart rate. This correlation was not significant in the Chicago Heart Association Detection Project. In bivariate analysis using the Cox regression model to control for age, heart rate was significantly related to mortality from all causes and all CHD deaths, in each of the three studies.

In multivariate analysis using a Cox regression model to adjust for age, serum cholesterol, blood pressure, body weight, and cigarettes per day, the cohort coefficient for death from all causes continued to be statistically significant only in the Peoples Gas Company study, although the coefficients were nearly significant for the other two studies. The strength of this study is that it focused on heart rate as a prognostic factor for coronary heart disease and mortality. Although 3 independent Chicago epidemiologic studies showed consistent correlation between elevated heart rate and increased all-cause mortality, it was not certain whether heart rate is also an independent risk factor for death from CVD, CHD, and sudden cardiac death. The fact that the association between baseline heart rate and cause-specific cardiovascular death was not significant on multivariate analysis may, in part, be due to the associations between heart rate and other cardiovascular risk factors. The study raised the question of whether high heart rate may be an independent risk factor for cause-specific cardiovascular death and sudden cardiac death.
The Framingham study, a long-term prospective study of cardiovascular disease, began in 1948. This report focuses on the 5070 subjects who were free of cardiovascular disease at entry into the study. The specific objectives of the study were to examine the relationships between resting heart rate and overall and cardiovascular mortality, the effect of heart rate on cardiovascular death taking other risk factors into account, and the relationships with regard to sex and age.

Over 30 years of follow-up, there were 766 deaths among subjects under the age of 65 years and 1110 deaths among those over the age of 65. In both sexes, overall mortality rates increased progressively with resting heart rate. In both young (35-64 years at entry) and old subjects (65-95 years at entry), overall mortality increased with heart rate in both men and women ($P < 0.01$). The mortality risk gradients in relation to heart rate were substantially steeper in men than in women at any age. Cardiovascular death was also related to heart rate in both sexes and at all ages.

For coronary heart disease mortality, there was also a relationship to heart rate, but this was confined to men. Furthermore, in both young and old men the occurrence of sudden deaths increased substantially with heart rate, suggesting a specific relationship between rapid heart rate and the occurrence of sudden death. In multivariate analyses that included a number of cardiovascular risk factors, such as systolic blood pressure, serum cholesterol, blood glucose, cigarette smoking, and electrocardiographic (ECG) signs of left ventricular hypertrophy, cardiovascular mortality, coronary death, and sudden cardiac death were all independently related to heart rate. With regard to the overall mortality rate, a highly significant relationship with resting heart rate persisted in both sexes, adjusting for age and for all coexisting cardiovascular risk factors.

The Framingham study, a major epidemiologic study, analyzed the influence of various risk factors on cardiovascular morbidity and mortality. It clearly demonstrated that in both sexes and at all ages that all-cause, cardiovascular, and coronary mortality rates increased progressively in relation to heart rate at entry into the study. A more impressive association with cardiovascular disease was observed in men than in women, and this was independent of associated cardiovascular risk factors. The fraction of coronary deaths that were sudden death increased strikingly with heart rate in men aged 35 to 64 years.

The New Zealand government passes its Nuclear Free Zone, Disarmament, and Arms Control Act; the nonmigratory Dusky Seaside Sparrow of Southern Florida becomes extinct; and in a landmark legal case, Edwards v Aguillard, the Supreme Court of the United States rules that a Louisiana law requiring creationism to be taught alongside evolution is unconstitutional.
Epidemiological studies had addressed the issue of the importance of heart rate in healthy subjects and in patients with hypertension and metabolic syndrome prior to this study. There was, however, little information on the prognostic value of resting heart rate in patients with stable coronary artery disease (CAD). The objective of the current study was to evaluate the relationship between resting heart rate and future cardiovascular events in a large population of patients with suspected or proven CAD.

The Coronary Artery Surgery Study (CASS) was a multicenter research program consisting of a randomized trial of medical versus surgical therapies and a large registry of patients undergoing coronary arteriography for the presence of suspected or proven CAD. A total of 24,913 patients were included in this registry from 1975 to 1979, and there was a median follow-up time of cardiovascular events of 14.7 years. Quintiles of heart rates were chosen according to the resting heart rate, which was obtained manually from radial pulse, measured for 60 seconds, at baseline: (i) ≤62, (ii) 63-70, (iii) 71-76, (iv) 77-82, and (v) ≥83 bpm. Baseline characteristics differed significantly in the resting heart rate quintiles. With increasing heart rate from ≤62 bpm to ≥83 bpm, age fell significantly and there were fewer males, higher cholesterol, higher body mass index (BMI), lower ejection fraction, more patients with the diagnosis of hypertension and diabetes, and more current cigarette smoking (P<0.001). With increasing heart rate, there were also fewer patients on β-blockers and more patients on diuretics (P<0.001). In multivariate analyses, adjusting for the baseline characteristics, overall and cardiovascular mortality both increased with increasing heart rate (P<0.001). This was a consistent finding in all subgroups, regardless of age, sex, BMI, medical history, cigarette smoking, 1-3 vessel disease, ejection fraction, or use of β-blockers or diuretics. Rehospitalization due to angina or congestive heart failure (CHF) occurred more often with increasing heart rate, but this was not true for stroke.

Although this was a very large and well-performed study of patients with suspected or proven CAD, all of whom had a coronary arteriography, one possible limitation is that the measurement of resting heart rate was performed when patients were referred for cardiac catheterization, which is something that might not be applicable to all patients with CAD. However, the fact that the predicted power of resting heart rate remains independent of multivariable adjustment and potential methodological issues indicates the robustness of the associations with morbidity and mortality. It can be concluded that heart rate measured manually over 60 seconds at baseline from radial pulse is an independent risk factor for overall mortality, cardiovascular mortality, and for new cardiac events (angina or CHF).
Heart rate as a prognostic risk factor in patients with coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a subgroup analysis of a randomized controlled trial

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During the last 30 years, a large number of studies have been performed on heart rate as a prognostic factor for cardiovascular mortality and morbidity, including sudden cardiac death. This is a modifiable risk factor for cardiovascular disease. But at what level of resting heart rate does risk increase enough to justify the recommendation of treatment? From the Coronary Artery Surgery Study (CASS), it was suggested that risk increases around 83 bpm and above. The large population with coronary artery disease and left ventricular systolic dysfunction in the placebo arm of the BEAUTIFUL (morBidity-mortality EvaLUaTion of the I inhibitor ivabradine in patients with coronary disease and left ventricULar dysfunction) study allowed investigators to examine how elevated resting heart rate at baseline influences mortality and morbidity.

The BEAUTIFUL study included men and women aged 55 years or older with coronary artery disease, a left ventricular ejection fraction of less than 40 percent, and an end-diastolic short-axis internal dimension greater than 56 mm. Patients were in sinus rhythm and had a resting heart rate of 60 bpm or greater. Resting heart rate was measured at baseline in the supine position by 12-lead electrocardiography (ECG). It was prespecified in the protocol that the risk associated with elevated heart rate would be tested by comparing outcomes in patients with baseline resting heart rates of less than 70 bpm versus those with rates 70 bpm or greater. A second analysis involved division of the range of baseline heart rate into 6 groups: <65, 65-69, 70-74, 75-79, 80-84, and >84 bpm. A final analysis assessed heart rate as a continuous variable. Patients were on optimal medical treatment: 90 percent were on angiotensin-converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), or both, 87 percent were on a β-blocker, and 27 percent on an antialdosterone agent.

The baseline characteristics of patients with a heart rate of 70 bpm or greater differed to those of patients with a heart rate of less than 70 bpm: they were younger; they had a lower ejection fraction, a higher systolic blood pressure, and a higher NYHA (New York Heart Association) class; and were less likely to be treated with β-blockers. They were also at increased risk for all outcomes assessed. There was a 34 percent increase in the adjusted relative risk of cardiovascular death, a 53 percent increase in the risk for admission to hospital for heart failure, a 46 percent increase in the risk of admission to hospital for fatal and nonfatal myocardial infarction, and a 38 percent increase in the risk of coronary revascularization. When analyzing the six baseline heart rate groups, there seems to be an increase in the number of events with heart rates of 70 to 74 bpm or higher. Patients with a baseline heart rate of less than 65 bpm or 65 to 69 bpm seemed to have very similar levels of all the events assessed.

The major conclusion to be drawn from this prospective study is that elevated heart rate at baseline is a strong independent risk factor in patients with coronary artery disease and left ventricular dysfunction. This was seen despite the fact that all patients were on optimal treatment with β-blockers, ACE inhibitors, ARBs, and antialdosterone agents. It seems reasonable to suggest that patients with a resting heart rate of 70 bpm or higher should be more aggressively treated, in order to bring heart rate down below this level.

2008

Yasuo Fukuda, the 58th Japanese Prime Minister, resigns suddenly after less than a year in office; Darren Aronofsky’s film, “The Wrestler,” wins the Golden Lion for best film at the Venice Film Festival; and Roger Federer defeats Andy Murray to win the US Tennis Open for the fifth consecutive time.
Effect of chronic beta-adrenergic receptor blockade in congestive cardiomyopathy

F. Waagstein, Å. Hjalmarson, E. Varnauskas, I. Wallentin

Br Heart J. 1975;37:1022-1036

Before the publication of this study, it was generally thought that high heart rate in patients with acute myocardial infarction or in patients with congestive heart failure was due to a necessary compensation mechanism to maintain cardiac output in patients with depressed cardiac function. Beta-blockers were, in general, contraindicated in these patients. The authors of the present study found that all ischemic complications in patients with acute coronary syndromes, such as pain, ST-segment changes, arrhythmias, and dyspnea, could be reduced by intravenous injection of a beta-blocker, especially among patients with markedly elevated heart rates (>90 bpm). On the basis of these findings, it was considered that patients with chronic congestive heart failure from causes other than coronary artery disease might also respond well to reduction of tachycardia by beta-adrenergic receptor blockade.

Seven patients, 3 men and 4 women (aged 33-59 years with a history of congestive heart failure for 6 months to 6 years), were studied. The diagnosis of congestive cardiomyopathy (idiopathic) was based on the criteria given by Goodwin and Oakley. Patients with coronary artery disease, congenital heart disease, valvular disease, and hypertensive heart disease were excluded. The patients had a baseline resting heart rate of 83-115 bpm (mean 98±13 bpm). Six of the patients were given the beta-1-selective blocker practolol in dosages from 50 to 400 mg bid and one patient was given the nonselective alprenolol 50 mg bid. In addition, patients were on the conventional treatment of that time—digitalis and diuretics. All patients were either in a steady-state or were in a state of progressive deterioration at the start of beta-adrenergic receptor blockade.

Invasive investigations used included phonocardiogram, carotid pulse curve, apex cardiogram, and echocardiogram. Data of the present study indicated that beta-blockade given to these patients with congestive cardiomyopathy improved ventricular function in all cases. An improvement was seen in the patients’ clinical condition shortly after administration of the drugs, and continued treatment resulted in an increase in physical working capacity and a reduction in heart size. Heart rate before the start of beta-blockade was 98±13 bpm and after 3-7 days on beta-blockade, it had reduced to 79±14 bpm; after 2-12 months, it had reduced further to 69±16 bpm. Systolic blood pressure originally fell from 129±21 mm Hg to 118±20 mm Hg within 3-7 days of beta-blockade, and this reduction was seen in all seven patients. However, after 2-12 months on beta-blockade, systolic blood pressure had returned to its initial level in all patients. The physical work test on a bicycle improved in all patients after 2-12 months on beta-blockade. In most patients, there was a reduction in heart volume estimated from x-ray as well as from echocardiography (ECG). Improvements were noted in phonocardiograms (on diastolic extra sounds) and in apex cardiograms, indicating improvement of diastolic function.

The rationale for the study was the assumption that high heart rate was bad for the energy-starved, failing myocardium. This was the first report of a favorable effect of beta-blockers in patients with chronic congestive heart failure (idiopathic) and resting tachycardia. In the seven patients, beta-blockers caused a marked reduction in heart rate over 2-12 months, the average reduction being about 20 bpm. These effects were obtained when beta-blockers were added to the conventional treatment of the time—digitalis and diuretics—before the introduction of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or aldosterone antagonists. This helped change the view from one that advocated that beta-blockers should be contraindicated in patients with depressed cardiac function or heart failure to one that holds beta-blockers to be the drug of choice in modern treatment guidelines.

British actress Kate Winslet is born; five Australian-based journalists are killed by Indonesian forces during military incursion into Portuguese Timor; and Juan Carlos I of Spain becomes acting Head of State as Francisco Franco steps down due to ill health.
In 1981, three large trials were published on $\beta$-blockers and outcomes in patients with acute myocardial infarction: the Norwegian Timolol Trial, the Göteborg Metoprolol Trial, and the American BHAT (Beta blocker Heart Attack Trial). These studies convinced the authorities in most countries of the prophylactic use of $\beta$-blockers after myocardial infarction, which was generally accepted. They clearly demonstrate that $\beta$-receptor blockade offers protection against sudden cardiac death, death caused by heart failure, and recurrent acute myocardial infarction. The mechanisms of action were thought to be anti-ischemic, antiarrhythmic, or both. In various studies, it has been postulated that a marked reduction in heart rate is of great importance for the obtained effects.

The current study was based upon a review of all $\beta$-blocker trials in patients with acute myocardial infarction or post-myocardial infarction. The 8 early randomized intervention trials with $\beta$-blockers examined enrolled patients early enough to have the chance to change infarct evaluation (eg, within 6 hours of onset of symptoms). These trials studied infarct size reduction, estimated by serial creatine kinase analysis, which was shown to correlate closely with morphometrically determined infarct size. The reduction in heart rate obtained differed widely among the trials, from 10.5 to 22.8 percent. By relating the difference in heart rate between the treatment groups to percentage reduction of infarct size, an almost linear relation was obtained ($P<0.001$). The data suggest that a reduction in infarct size of 25-30 percent can be obtained if heart rate is reduced by 14 bpm or more and that a reduction of <8 bpm has no effect on infarct size.

Long-term placebo-controlled trials in patients surviving acute myocardial infarction have convincingly shown that $\beta$-blockers reduce overall mortality, in particular, sudden cardiac death and death due to pump failure. Data were available from 11 large placebo-controlled trials with a follow-up of 3 to 84 months. The average mortality changes ranged from −50 percent to +29 percent. The present review demonstrated that there was a very clear association between the reduction in resting heart rate and the changes in long-term mortality by treatment. $\beta$-Blockers with intrinsic stimulatory activity (practolol, oxprenolol, and pindolol) were much less effective in reducing heart rate than $\beta$-blockers without such effects, and the overall effect on mortality was not significant. Three major studies were performed on $\beta$-blockers without intrinsic stimulatory activity. Timolol, metoprolol, and propranolol were used in these studies. The average reduction in heart rate was about 15 bpm, and the mortality reduction was around 35 percent. In studies using practolol and sotalol, mortality reduction was nonsignificant and in the order of 20 percent.

This important review suggests that heart rate reduction with $\beta$-blockers is the most important factor for the favorable effects on both morbidity and mortality. But that's not all. In fact, the more marked the reduction of heart rate, the better the effect on infarct development, reinfarction, all-cause mortality, sudden death, and death due to congestive heart failure. This observation has had a very strong impact on our clinical judgment, choice of pharmacological therapy, and future research progress.

1986

Hailstones weighing 2.2 lb (1 kg) fall on the Gopalganj district of Bangladesh, killing 92; Japan celebrates the Diamond Jubilee of Emperor Showa (Hirohito) at the Kokugikan in Tokyo; and IBM unveils the world's first laptop computer, the PC Convertible.
Heart rate and cardiac rhythm relationships with bisoprolol benefit in chronic heart failure in CIBIS II trial

P. Lechat, J-S. Hulot, S. Escolano, A. Mallet, A. Leizorovicz, M. Werhlen-Grandjean, G. Pochmalicki, H. Dargie; on behalf of the CIBIS II Investigators

Circulation. 2001;103:1428-1433

IBIS II (Cardiac Insufficiency Bisoprolol Study II) and MERIT-HF (MEtoprolol MR/XL Randomized Intervention Trial in congestive Heart Failure), two major studies demonstrating the benefit of treatment with β-blockers in heart failure, were published in 1999. These two studies included both patients with ischemic and nonischemic etiologies of heart failure. The use of β-blockers in heart failure was first suggested in 1975, and the first placebo-controlled trial was published in 1994. This trial, the MDC (Metoprolol in Dilated Cardiomyopathy) trial, examined the effect of metoprolol in 383 patients with idiopathic dilated cardiomyopathy. The 2 studies of 1999 were larger: CIBIS II included 2647 patients with symptomatic heart failure in NYHA (New York Heart Association) classes III and IV, while MERIT HF included 3991 patients in NYHA classes II-IV. Overall mortality reduction in the two studies was 36 percent. The major purpose of CIBIS II was to investigate whether the benefit of β-blockade in heart failure was related to baseline heart rate and to treatment-induced heart rate reduction, which had not been studied before.

Heart rate was measured at baseline and during follow-up visits by pulse rate measurement (especially in atrial fibrillation) or by electrocardiography (ECG) recording at rest in the supine position. Two months after inclusion, the heart rate decrease was 0.2 bpm in the placebo group and 9.8 bpm in the bisoprolol group (P<0.0001). Baseline heart rate and heart rate change after the first two months of treatment were both significantly related to further survival in both univariate and multivariate analyses. The best prognosis was obtained in patients with the lowest baseline resting heart rate and with the greatest heart rate reduction after two months of follow-up. Benefit with bisoprolol was obtained only in patients with sinus rhythm and was questionable in patients with atrial fibrillation.

Patients were split into three tertiles of baseline heart rate and heart rate change at two months. The limits of the tertiles were ≤72 bpm, 72-84 bpm, and >84 bpm for baseline heart rate, and for heart rate increase, the three tertiles were <0, 0-10, and ≥11 bpm. Bisoprolol-induced mortality reduction was similar at all levels of heart rate reduction. These results demonstrate that for a given heart rate reduction, bisoprolol treatment further reduced mortality to a similar extent, whatever the amplitude of heart rate reduction. Furthermore, bisoprolol-induced survival improvement was significant and similar, whatever the level of baseline heart rate. With increasing baseline heart rate, one-year mortality, both in the placebo group and the bisoprolol group, increased.

The results confirm that heart rate reduction per se in patients with heart failure is associated with improvement in survival. For a given heart rate reduction and for any level of baseline heart rate, bisoprolol further improved survival compared with placebo. It was, however, also observed that heart rate reduction was not the only mechanism responsible for β-blocker-induced benefit in heart failure, since such benefit was present even without heart rate reduction.

In conclusion, baseline heart rate and heart rate reduction with time have prognostic value in patients with symptomatic heart failure. One interesting finding was that patients with heart failure and in sinus rhythm who had the lowest initial heart rate at baseline and then the greatest heart rate reduction with time (at 2 months) had the best prognosis. Another was that the greater the reduction of heart rate without marked systolic blood pressure decrease, the better the survival effect.

2001

This study is the first large clinical trial of the selective $I_f$ inhibitor ivabradine in patients with chronic stable angina pectoris. Ivabradine belongs to a new class of selective heart rate-lowering agents that acts specifically on the sinoatrial node and that has no effect on myocardial contractility.

This is a randomized double-blind placebo-controlled parallel-arm trial to investigate the effect of ivabradine 2.5, 5, or 10 mg twice daily on time to 1-mm ST-segment depression and time to limiting angina during standardized bicycle exercise tolerance test. There was a placebo washout of antianginal medications, including β-blockers, calcium channel blockers, and long-acting nitrates, prior to the placebo-controlled study. The patients were then randomly assigned in double-blind fashion to receive ivabradine or placebo for two weeks followed by a 2-3-month open-label extension phase during which all patients received a higher dose of 10 mg of ivabradine twice daily. Inclusion criteria included age ≥18 years and ≥3-month history of chronic, stable, effort-induced angina pectoris.

In the 2 weeks of the double-blind phase, resting heart rate fell significantly and proportionally at trough and at peak of drug activity. The fall in heart rate was about 6, 12, and 20 bpm with ivabradine at doses of 2.5, 5, and 10 mg bid, respectively. Significant effects were seen in time to 1-mm ST-segment depression, time to limiting angina, time to angina onset, and on total work performed. The rate-pressure product at peak exercise decreased stepwise and significantly with ivabradine. Angina attacks and the consumption of short-acting nitrates were reduced by ivabradine during the double-blind dose ranging, although these changes did not reach statistical significance. However, for those patients who continued with the open-label extension on ivabradine 10 mg twice daily, there was a highly significant reduction in angina attacks and the consumption of short-acting nitrates ($P<0.001$). The incidence of adverse events during double-blind dose-ranging was low and generally similar to that of placebo in all treatment groups. The only exception was visual symptoms, which were reported by no patients in the placebo group, 1 patient in each of the lower-dosage ivabradine groups, and by 13 patients in the 10 mg ivabradine group. All visual symptoms resolved spontaneously during or after drug discontinuation.

This first, large clinical trial of the novel selective $I_f$ inhibitor ivabradine in patients with chronic stable angina pectoris showed that reduction in resting and exercise heart rate per se significantly improve exercise tolerance, increase time to pain, and reduce frequency of angina attacks and consumption of short-acting nitroglycerin.

The Indian Government begins a program to inoculate 160 million children against polio within 6 days; the London congestion charge zone is introduced to reduce traffic density and encourage the use of public transport; and Norah Jones receives 8 awards, including best female singer, at the 45th Grammy Awards ceremony in New York.
Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a randomised, double-blind, placebo-controlled trial

K. Fox, I. Ford, G. F. Steg, M. Tendera, R. Ferrari; on behalf of the BEAUTIFUL Investigators

*Lancet.* 2008;372:807-816

In 2008, it was not known whether heart rate reduction per se could improve outcomes in patients with either post-myocardial infarction or symptomatic heart failure. Ivabradine, a specific inhibitor of If current in the sinoatrial node, had been found to have beneficial anti-ischemic and antianginal effects in short-term studies. The present study was designed to test whether the addition of ivabradine to standard heart rate-lowering treatment could reduce cardiovascular death and morbidity. Patients with chronic stable coronary artery disease with and without symptomatic angina pectoris and with impaired left ventricular function in addition were randomized in a double-blind placebo-controlled trial in 781 centers in 33 countries.

After a run-in period of 14 days without study treatment, all patients were assigned to either ivabradine or placebo. The starting dose of ivabradine was 5 mg twice daily, which was increased to 7.5 mg twice daily in patients with a resting heart rate of 60 bpm or greater. All patients continued to receive conventional, optimal cardiovascular medical treatment throughout the study. The primary end point was a composite of cardiovascular death, admission to hospital for acute myocardial infarction, and admission to hospital for new onset of or worsening heart failure. The planned study duration was 3 years. It was prespecified that the effects of ivabradine in a subgroup of patients with a heart rate of 70 bpm or greater would be analyzed. A total of 12 473 patients were screened and 10 917 eligible patients were randomized.

At 6 months after randomization, the mean differences between the treatment groups from baseline resting heart rates was 7.2 bpm; and at 24 months, this was 5.6 bpm. For the subgroup with heart rates of 70 bpm or more, the differences between the treatment groups from baseline heart rates were 9 bpm at 6 months and 6.9 bpm at 24 months.

The main finding was that 15.4 percent of the ivabradine group experienced a primary end point compared with 15.3 percent of the placebo group (*P*=0.94). Similar findings were seen in all prespecified subgroups, with the exception of the subgroup of patients with heart rates of 70 bpm or more. In these patients, 17 percent of the ivabradine group experienced a primary end point compared with 19 percent in the placebo group (*P*=0.17). For this subgroup, treatment groups did not differ in terms of rates of cardiovascular death or of admission to hospital for heart failure. In contrast, the rates of admission to hospital for acute myocardial infarction (fatal and nonfatal) were reduced by 36 percent (*P*=0.001). A similar positive effect was seen on the combined end point rates of admission to hospital for acute myocardial infarction or unstable angina, which was reduced by 22 percent (*P*=0.023). Furthermore, ivabradine caused a reduction in coronary revascularization of 30 percent (*P*=0.016).

This was the first observation that pure heart rate reduction with ivabradine can reduce the incidence of end points related to coronary artery disease, namely admission to hospital for fatal and nonfatal acute myocardial infarction and the need for coronary revascularization. Ivabradine can be given safely to patients with coronary artery disease and impaired left ventricular systolic function, and can be used in conjunction with β-blockers. Furthermore, a combination of ivabradine with β-blockade improved coronary artery disease outcomes in patients with heart rates of 70 bpm or more.
Various aspects of heart rate as a prognostic risk factor and their possible underlying pathophysiological mechanisms are summarized in this state-of-the-art paper. Multivariate analyses from most of the larger studies performed indicate that heart rate is an independent predictor of mortality. It is a very consistent finding among all subgroups, regardless of age, sex, hypertension, cholesterol levels, diabetes, blood pressure, ejection fraction, or concomitant medication.

Heart rate is an important and modifiable risk factor. A large number of studies have demonstrated that long-term treatment with β-blockers reduces mortality in acute myocardial infarction, postmyocardial infarction, and heart failure patients. It has been suggested that there is a significant correlation between heart rate reduction and reduction in mortality after myocardial infarction, and that the same also holds true for the pharmacological treatment of patients with symptomatic heart failure. It has even been suggested that heart rate reduction per se improves survival in patients with symptomatic heart failure.

An increase in heart rate causes an imbalance between myocardial metabolism and oxygen supply and demand. Heart rate is the primary determinant of myocardial oxygen demand, which increases as heart rate increases. At the same time, a higher heart rate causes a shortening of the diastolic perfusion period, which worsens myocardial ischemia. During Holter monitoring, most episodes of myocardial ischemia are preceded by an increase in heart rate. It has also been demonstrated that exercise-induced regional contractile dysfunction in dogs with experimental coronary stenosis is reduced by β-blockade. However, when pacing to pre-β-blockade levels this improvement is prevented.

In epidemiological studies, heart rate correlates more strongly with sudden death from acute myocardial infarction than with nonsudden death. In most studies of β-blockers in patients with myocardial infarction or in patients with symptomatic heart failure, there is a more marked reduction with β-blockade of sudden cardiac death than of nonsudden death. Experimentally, abrupt onset of myocardial ischemia is more likely to result in ventricular fibrillation in animals with higher heart rate than in those with lower heart rate.

In experimental models of heart failure, β-blockers and a sinus node inhibitor have been found to improve left ventricular function and normalize structure in patients with heart failure. Heart rate reduction by β-blockade reduces oxygen requirement, but this effect is abolished if heart rate is kept constant by atrial pacing. In heart failure patients with permanent pacemakers, pacing at 80 bpm as opposed to 60 bpm, reversed the beneficial effects of β-blockade on left ventricular volume and systolic function.

A number of studies have been performed to find out whether there is an optimal heart rate for different populations. Several studies indicate that there seems to be a cutoff point around 60-70 bpm. Subgroups of patients with a heart rate below this level seem to have a similar, low event rate in a number of studies, while there is a steep increase above this cutoff point. The clinical implication is, of course, that it is more reasonable to recommend interventions against elevated heart rate above 70 bpm.

International guidelines have recently underlined the potential role of heart rate reduction in the prevention of cardiovascular disease progression and outcome.

New Zealand launches its first commercially available biofuel, “Gull Force 10,” using bioethanol made from cows’ milk; Mongolian sumo wrestler Asashoryu becomes the first yokozuna to be suspended from competition; and Mexican archeologists announce the discovery of the tomb of Aztec Emperor Ahuitzotl.
Heart Rate and Cardiovascular Disease

Bibliography of One Hundred Key Papers

selected by Åke Hjalmarson, MD, PhD
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Gothenburg - SWEDEN (e-mail: ake.hjalmarson@gu.se)

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