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STATE-OF-THE-ART PAPER

Resting Heart Rate in Cardiovascular Disease

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The importance of resting heart rate (HR) as a prognostic factor and potential therapeutic target is not yet generally accepted. Recent large epidemiologic studies have confirmed earlier studies that showed resting HR to be an independent predictor of cardiovascular and all-cause mortality in men and women with and without diagnosed cardiovascular disease. Clinical trial data suggest that HR reduction itself is an important mechanism of benefit of beta-blockers and other heart-rate lowering drugs used after acute myocardial infarction, in chronic heart failure, and in stable angina pectoris. Pathophysiological studies indicate that a relatively high HR has direct detrimental effects on the progression of coronary atherosclerosis, on the occurrence of myocardial ischemia and ventricular arrhythmias, and on left ventricular function. Studies have found a continuous increase in risk with HR above 60 beats/min. Although it may be difficult to define an optimal HR for a given individual, it seems desirable to maintain resting HR substantially below the traditionally defined tachycardia threshold of 90 or 100 beats/min. These findings suggest that the potential role of HR and its modulation should be considered in future cardiovascular guidance documents. (J Am Coll Cardiol 2007;50:823–30) © 2007 by the American College of Cardiology Foundation

Heart rate (HR) is a familiar and accessible clinical variable. Based on epidemiologic data and inferences from clinical trials designed for other purposes, most physicians believe that tachycardia at rest is prognostically undesirable. However, the importance of HR as a prognostic factor and potential therapeutic target has not been formally explored, and therefore, despite suggestive evidence, is not generally accepted. The aim of this article is to review the data associating resting HR and mortality, the possible pathophysiological basis of this association, and the likelihood of therapeutic utility of HR slowing in improving cardiovascular outcomes for a wide range of patients. The profile of change in HR during and after exercise is also important prognostically (1), but will not be considered here.

Epidemiologic Data Associating HR and Outcome

A significant association between resting HR and all-cause and cardiovascular mortality has been reported in numerous epidemiologic studies over the last 25 years (see reviews by Palatini et al. [2,3]), and pertains in both the general population and in those with various cardiovascular diseases, including hypertension, acute myocardial infarction (AMI), and heart failure or left ventricular dysfunction. For example, in a recent study of 10,267 patients with acute coronary syndromes, mortality at 30 days and 10 months increased progressively and significantly with HR (4). Moreover, in many studies, multivariate analysis has shown HR to be an independent predictor of mortality after correction for demographic and clinical variables (including blood pressure).

Two recent large studies with particularly lengthy follow-up have extended our understanding of the prognostic importance of HR. In the first of these (1), resting and exercise HR were measured in 5,713 working men, age 42 to 53 years and without known or suspected cardiovascular disease, who then were followed up for a mean of 23 years.

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Abbreviations and Acronyms

AMI = acute myocardial infarction

HR = heart rate

All-cause mortality and sudden and nonsudden death from AMI each increased progressively with resting HR, and remained significant after adjustment for exercise capacity (evaluated by bicycle ergometry), age, diabetes, systolic arterial pressure, body mass index, level of physical activity, and other factors. The relationship was steepest for sudden death (Fig. 1).

The second study (5) involved 24,913 men and women with suspected or proven coronary artery disease who had been entered into the Coronary Artery Surgery Study registry. Median follow-up was 14.7 years. Both all-cause and cardiovascular mortality were directly related to resting HR at study entry. This predictive capacity was independent of concomitant hypertension, diabetes, and smoking, and also of left ventricular ejection fraction and number of diseased coronary vessels. Hazard ratios were similar for all-cause and cardiovascular mortality (Fig. 2), and among men and women, old (>65 years) and young patients, hypertensive and normotensive patients, diabetic and nondiabetic patients, those with left ventricular ejection fraction >50% and <50%, and those with a body mass index >27 and <27 kg/m^2.

In evaluating published data relating HR and outcome, the impact of gender requires comment. Although average life span is modestly longer in women than in men, it is well documented that, when adjusted for age, HR in women averages 2 to 7 beats/min higher than in men (6,7). Clearly, many factors in addition to HR influence survival duration; the effects of some of these factors certainly must differ in men and women. Nonetheless, within each gender, the relationship of HR and both all-cause and cardiovascular mortality rates is qualitatively similar (6).

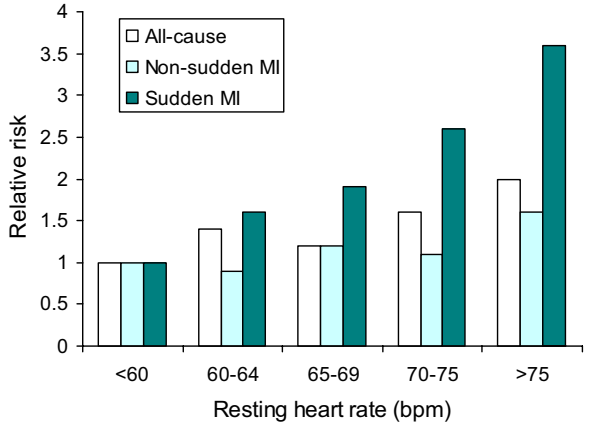

Figure 1 Heart Rate and Mortality in Healthy Men

Relative risk of death from any cause, nonsudden death from myocardial infarction (MI), and sudden death from MI by quintiles of resting heart rate in 5,713 men without known or suspected heart disease. Reprinted with permission from Jouven et al. (1). bpm = beats/min.

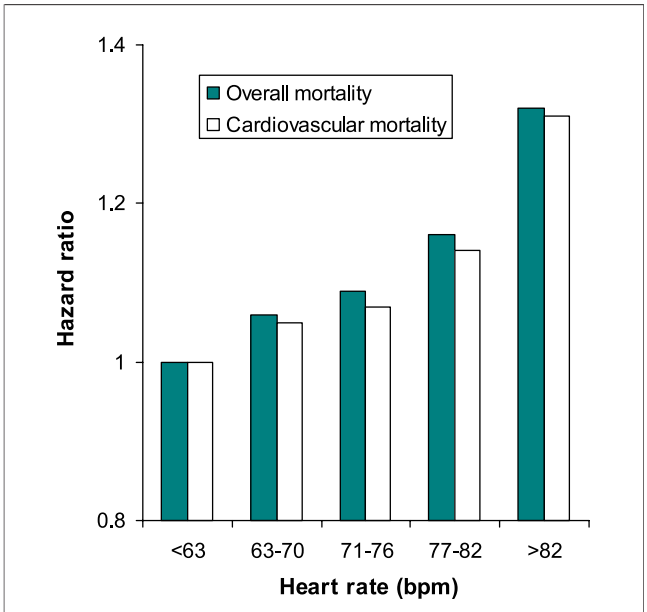

Figure 2 Heart Rate and Mortality in Coronary Artery Disease

Relationship between hazard ratio and resting heart rate for all-cause and cardiovascular mortality in 24,913 patients with suspected or proven coronary artery disease. Based on data from Diaz et al. (5). bpm = beats/min.

Resting HR currently is included in risk assessment indices for patients after acute coronary syndromes (e.g., the Global Registry of Acute Coronary Events risk prediction score [8]) and AMI (e.g., the Gruppo Itialiano per lo Studio della Sopravvivenza nell'Infarto Miocardico Prevenzione risk assessment model [9] and the Thrombolysis in Myocardial Infarction Risk Score [10]). Indeed, a model of only 3 variables (HR, age, and systolic arterial pressure) (11) has been validated in a large, unselected group of patients with ST-segment elevation AMI (12).

Nonetheless, HR is not included in some widely known indices for cardiovascular risk (Copenhagen Risk Score [13], European SCORE project [14]), but has been included in the recent Cooper Clinic risk index for overall mortality (15). In the latter study, involving 21,766 men, a stepwise proportional hazards model showed relatively high HR to be an independent predictor of all-cause mortality, even though cardiorespiratory fitness was also included in the model. Heart rate was assigned the same weighting as blood pressure and cardiorespiratory fitness in the overall score (15).

Pharmacological HR Reduction: Possible Benefits

At least 2 drug groups widely used in cardiovascular disease, beta-blockers and nondihydropyridine calcium channel blockers, have an HR-lowering action. Effects on mortality among some patient groups are evident with beta-blockers (patients with AMI or heart failure) and seem to be

associated, at least in part, with the drug-mediated HR reduction. Also, HR lowering has long been associated with prevention of exercise-induced angina and ischemia. Consumption of omega 3 fatty acids, found in fatty fish and fish oil, is associated with a modest (1 to 2 beats/min) reduction in HR, but a recent systematic review concluded that long-chain and shorter-chain omega 3 fats do not have a clear effect on total mortality, combined cardiovascular events, or cancer (16).

Mortality in patients with coronary artery disease/AMI. There is good evidence showing that the beneficial effects of beta-blockers after AMI are related to reduction in HR. Kjekshus (17) reviewed early randomized trials in which beta-blockers were given within 6 h of the onset of symptoms. For 6 trials for which estimates of infarct size and HR were available, involving 1,427 patients, the mean reduction in infarct size, relative to placebo, was directly related to the mean reduction in HR ($p < 0.001$).

Kjekshus (17) also reviewed long-term trials of beta-blockers after AMI. In 11 placebo-controlled trials involving more than 16,000 patients, a significant association was found between the reduction in HR and reduction in mortality (Fig. 3). The Norwegian Timolol Multicenter Study (18), published after the Kjekshus (17) analysis, showed similar results. In this study, HR during follow-up was a significant predictor of overall mortality. Timolol treatment was associated with a 41.6% reduction in mortality, but mortality at a given HR was similar in the timolol and placebo groups. In logistic regression analysis, HR remained predictive but treatment did not, indicating that the major effect of timolol on mortality could be attributed to its effect on HR. By contrast, the APSI (Acebutolol et Prévention Secondaire de l'Infarctus) study in high-risk patients with AMI suggested that low-dose treatment with acebutolol produced large reductions in all-cause and cardiovascular mortality (of 48% and 58%, respectively) in spite of only a modest effect on HR (19).

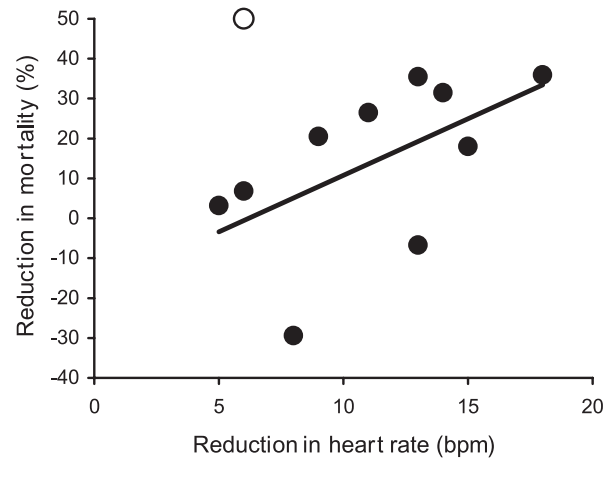

Figure 3 **Heart Rate Reduction and Mortality After Myocardial Infarction**

Relationship between the mean reduction in heart rate and the mean change in mortality (relative to placebo) in different randomized, placebo-controlled trials of beta-blockers after myocardial infarction. The linear regression line ($r = 0.6$, $p < 0.05$) was fitted excluding the smallest study **(open circles)**. Modified and based on data from Kjekshus (17). bpm = beats/min.

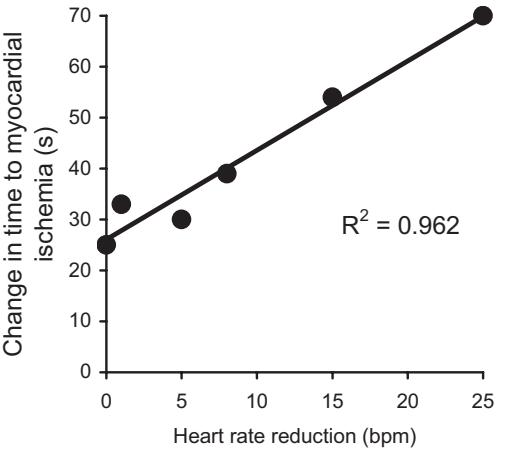

Figure 4 **Heart Rate Reduction and Myocardial Ischemia**

Relationship between the improvement in time to myocardial ischemia during bicycle exercise and the reduction in exercise heart rate achieved in stable angina patients after treatment with 2 doses of 3 different calcium channel blockers (amlodipine, diltiazem, and mibefradil). Reprinted with permission from van der Vring et al. (22). bpm = beats/min.

Exercise-induced angina and ischemia. When HR-lowering drugs have been used, angina reduction is related to HR reduction in patients with chronic coronary artery disease (20,21). Reduction in underlying ischemia also can be attributed to HR reduction. In a double-blind study comparing low and high doses of 3 different calcium channel blockers in 335 stable angina patients, the improvements in time to ischemia during bicycle exercise tolerance tests were directly related to the reductions in exercise HR (Fig. 4). Regression analysis showed that the beneficial anti-ischemic effect of the drugs was largely dependent on their effect on HR (22).

Mortality in patients with heart failure. Kjekshus and Gullestad (23) analyzed the relation of treatment to HR and outcome in patients with heart failure. Here, as for AMI, a relationship was found between reduction in HR and in mortality; in addition, agents that increased HR tended to increase mortality (Fig. 5).

Results of most recent studies in heart failure have been consistent with this finding. For example, in the CIBIS (Cardiac Insufficiency Bisoprolol Study) trial, treatment with bisoprolol reduced HR by approximately 15 beats/min relative to placebo; HR reduction was the most powerful predictor of survival in multivariate analysis (24). The relationship between log hazard for mortality and HR change was almost linear over the range −40 to +10 beats/min. In the larger CIBIS II trial (25), baseline HR

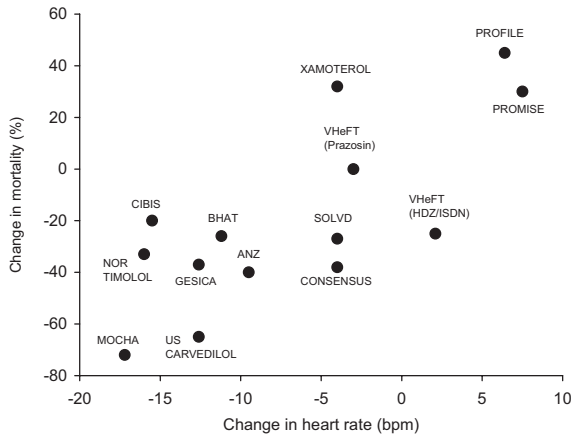

Figure 5 Heart Rate Reduction and Mortality in Heart Failure

Relationship between mean change in heart rate and mean change in mortality in studies of patients with chronic heart failure. Reprinted with permission from Kjekshus and Gullestad (23). ANZ = Australia/New Zealand Heart Failure Research Collaborative Group; BHAT = Beta Blocker Heart Attack Trial; bpm = beats/min; CIBIS = Cardiac Insufficiency Bisoprolol Study; CONSENSUS = Cooperative North Scandinavian Enalapril Survival Study; GEISCA = Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina; HDZ/ISDN = hydralazine/isosorbide dinitrate; MOCHA = Multicenter Oral Carvedilol Heart Failure Assessment; NOR TIMOLOL = Norwegian Multicentre Study Group; PROFILE = Prospective Randomized Flosequinan Longevity Evaluation; PROMISE = Protection Devices in PCI-Treatment of Myocardial Infarction for Salvage of Endangered Myocardium Study; SOLVD = Studies of Left Ventricular Dysfunction; US CARVEDILOL = U.S. Carvedilol Heart Failure Study Group; VHeFT = Vasodilator in Heart Failure Trials; XAMOTEROL = Xamoterol in Severe Heart Failure Study Group.

and HR change both were significant predictors of mortality. The best prognosis was obtained in patients with the lowest baseline HR and with the greatest HR reduction, and as expected, these conditions were met more frequently in the bisoprolol group than in the placebo group.

In an analysis of data from the COMET (Carvedilol or Metoprolol European Trial) study, HR achieved during beta-blocker therapy was a significant independent predictor of mortality, although HR did not influence the greater survival benefit with carvedilol compared with metoprolol (26). In the MERIT-HF (Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure) study, however, the benefits with metoprolol were independent of the change in HR achieved (27), suggesting that HR reduction is not the only mechanism of benefit of beta-blockers in heart failure.

Pathophysiological Mechanisms

Atherosclerosis and Arterial Stiffness

In cynomolgus monkeys, naturally occurring differences in HR are related to the extent of coronary artery atherosclerosis (28); HR reduction by sinoatrial node ablation reduces both severity of individual atherosclerotic stenoses and the area covered by lesions within the coronary arteries (29). In humans, HR is directly associated with progression of coronary atherosclerosis (30), and also has been significantly related to the likelihood of disruption of pre-existing atherosclerotic plaque (31).

Increases in HR induced by electrical pacing in rats are accompanied by progressive and marked reductions in arterial compliance and distensibility (32). Similarly, HR is strongly and directly associated with arterial rigidity in hypertensive patients, after adjustment for age and blood pressure (33).

These results suggest that HR impacts directly on the status of the arterial wall, probably because of mechanical pulsatile stress, and also possibly involving the proinflammatory actions of oscillatory fluid shear stresses acting on the vascular endothelium (34).

Myocardial Ischemia

The basis of myocardial ischemia is disordered balance between myocardial oxygen demand and supply. Heart rate importantly influences both factors, as the primary determinant of myocardial oxygen demand and as controller of supply. Experimental studies have shown that increasing HR increases oxygen demand even when the external work performed by the heart is kept constant, partly because of a greater oxygen requirement for excitation-contraction coupling (35).

Myocardial perfusion occurs predominantly during diastole, and the fraction of the cardiac cycle occupied by diastole increases as HR decreases. Therefore, HR reduction improves diastolic perfusion time. Furthermore, increasing HR by atrial pacing in patients with coronary artery disease produces coronary vasoconstriction, potentially further impairing oxygen supply (36).

In patients with stable coronary artery disease, most episodes of ambulatory or exercise-induced myocardial ischemia are preceded by an increase in HR (37). The likelihood of developing ischemia is related to the baseline HR and the magnitude and duration of the increase (38). The frequency of ambulatory ischemic episodes in treated patients with coronary artery disease is related to their mean HR: patients with HR >80 beats/min experience ischemia almost twice as often as those with HR <70 beats/min (39).

In dogs with experimental coronary stenosis, exercise-induced regional contractile dysfunction is reduced by beta-blockade, but the improvement is prevented if HR is kept at pre–beta-blockade levels by atrial pacing (40). Similarly, in patients with angina pectoris, beta-blockade does not reduce myocardial oxygen demand or ischemia if angina is induced by atrial pacing (41).

Ventricular Arrhythmias

In epidemiologic studies, HR is more strongly related to sudden death than to nonsudden death from AMI (1). Experimental studies suggest that HR not only is important in the development of ischemia, but also influences whether ischemic episodes trigger serious arrhythmias. Experimentally, abrupt-onset myocardial ischemia is more likely to

result in ventricular tachycardia and fibrillation among dogs with a high spontaneous HR than in those with a lower HR (42,43). In open-chest pigs with experimental coronary artery occlusion, beta-blockade raises the threshold for ventricular fibrillation, an effect abolished if HR is kept constant by pacing (44). These experimental studies suggest that HR modulation can reduce the risk of life-threatening arrhythmias during ischemic episodes; the beneficial effect of beta-blockade in this context may be mediated primarily by HR reduction.

Depressed HR variability is associated with the risk of life-threatening arrhythmias in patients after AMI (45). There is some suggestion that HR variability assessed very early after AMI may not add prognostic information beyond that of HR alone (46). However, others have shown that HR variability is strongly predictive after AMI (47,48), even when assessed during the first 7 days (49).

Other Rhythm Disturbances

Sinus node disease. Severe sinus bradycardia may be a feature of sinus node disease, and in turn related to underlying cardiovascular disease and ageing. In these circumstances, any gain in cardiovascular survival related to the low HR would most likely be offset by the negative consequences and the causes of the sinus node disease.

Atrial fibrillation. In atrial fibrillation, HR is often pathologically rapid. It may be controlled pharmacologically by beta-blockade, calcium antagonists, and digitalis glycosides, and reduction of HR is generally assumed to be associated with improved survival. However, this has only been convincingly shown in atrial fibrillation patients in the post-myocardial infarction or heart failure setting with some beta-blockers such as carvedilol (50), but pharmacological actions other than HR reduction also may play a part (51). In large rate versus rhythm control trials in patients with atrial fibrillation, HR reduction tended toward improved survival when compared with a rhythm control strategy (52). However, there is no evidence showing that strict HR control was superior to less stringent rate control (53). Atrial fibrillation is a pathological cardiac arrhythmia, and the optimal degree of HR reduction in this situation is unknown.

Left Ventricular Dysfunction and Heart Failure

In dogs, left ventricular dysfunction caused by surgically induced mitral regurgitation is substantially ameliorated by beta-blocker treatment, but the amelioration is largely prevented by electrical pacing to the pre–beta-blockade rate (54). In a rat model of heart failure, prolonged HR reduction with an HR-lowering agent that has no direct action on myocardial contractility or the autonomic nervous system improves left ventricular function and normalizes structure, including increasing capillary density (55). In patients with heart failure, HR reduction by beta-blockade reduces oxygen requirement for nonmechanical work and increases mechanical efficiency, benefits that are abolished if HR is kept constant by atrial pacing (56). In a recent study (57) in patients with heart failure fitted with permanent pacemakers and treated with beta-blockers, pacing at 80 beats/min as opposed to 60 beats/min attenuated or reversed the beneficial effects of beta-blockade on left ventricular volume and systolic function.

Heart Rate: Independent Causative Factor or Merely an Epiphenomenon?

Although the association of HR and outcome is suggestive, it does not, by itself, prove causality. High HR also is associated with poor cardiorespiratory fitness (58) or impaired cardiac function. Indeed, exercise capacity itself is a powerful predictor of mortality (59), and resting HR is lower in individuals who undertake vigorous leisure activities or participate in sports (60,61). Therefore, in recent studies significantly relating HR and mortality, adjustments have been made for the effects of physical activity and cardiac function (1,5). In the Cooper Clinic Mortality Risk Index, high HR and low cardiorespiratory fitness were both independent predictors of mortality (15).

Relatively high HR often is found together with other cardiovascular risk factors, notably hypertension, an atherogenic blood lipid profile, blood glucose and insulin levels, and overweight (62). Indeed, HR correlates with the number of cardiovascular risk factors presenting in an individual (63). Nonetheless, in most recent epidemiologic studies, when adjustments are made for accepted risk factors, HR still independently predicts risk.

The depolarization rate of the sinoatrial node is largely determined by the activity of the autonomic nervous system. Therefore, HR unquestionably is directly related to sympathetic activity or autonomic imbalance. An important unresolved issue is the extent to which HR mediates the deleterious effects of sympathetic hyperactivity. It is clear that the majority of the benefit of beta-1-adrenergic blockade is mediated via HR reduction, but beta-blockers have numerous other actions, some beneficial, some undesirable. Understanding the contribution of HR per se is likely to be particularly useful in managing the large number of patients who might expect to benefit from HR reduction but who do not or cannot receive intensive beta-blocker therapy. Absolute and relative contraindications, physician concerns, and medication intolerance, among the major reasons for low doses or nonprescription of beta-blocker therapy (64,65), may preclude optimal management for many patients.

In summary, it seems likely that relatively high HR is both causative and indicative of important pathophysiological processes. Clarification of the utility of HR modulation may come from the use of specific HR-reducing drugs that do not act via the autonomic nervous system. One such agent has shown antianginal and anti-ischemic benefits in patients with stable angina (66,67), but its effect on mortality is not yet known.

Is There an Optimal Heart Rate?

Heart rate at rest varies widely, but a pattern of distribution seems to exist. Thus, Palatini et al. (68) explored the shapes of the frequency distributions of HR in 3 populations, identifying 2 subgroups, 1 larger, representing those with "normal" HR, and 1 smaller, with a "high" HR. The segregation value between the subgroups varied between 75 and 85 beats/min in the different populations. From the epidemiologic data presented previously, it seems desirable to maintain HR in the normal rather than in the high range, and specifically, to maintain resting HR substantially below the traditionally defined tachycardia threshold of 90 or 100 beats/min.

Indeed, in recent large studies, there seems to be a continuous increase in risk with HR, at least for values above approximately 60 beats/min, with no evidence of a threshold (1,5). However, data from the GUSTO-1 (Global Utilization of Streptokinase and TPA for Occluded Arteries) study suggest an increasing risk below 60 beats/min (69). Thus, it may be possible to define an HR at which cardiovascular risk is optimized, although if it exists, such an HR may be expected to differ with underlying the physiological or pathophysiological state.

When considering a desirable or optimal HR for an individual patient, demographic and measurement factors also must be taken into account. The HR has been reported to decrease with age (3), although this has not been seen in all studies (7), and HR is higher in women than in men (7). The HR shows a clear circadian rhythm, being substantially higher during waking hours, but the variations are relatively small between 10 AM and 6 PM (70). Finally, HR also changes with posture, being some 3 beats/min higher in the sitting compared with the supine position (71). A recent consensus meeting recommended measurement of HR by pulse palpation during two 30-s periods, performed in a sitting position, after 5 min sitting in a quiet room (72). Clinic HR seems to carry as much prognostic information as ambulatory measurements (6).

Conclusions

Current data leave little doubt that HR is a risk factor for cardiovascular mortality, independent of currently accepted risk factors and other potentially confounding demographic and physiological characteristics. However, until now it has been difficult to determine whether modulation of HR can beneficially alter risk; currently available interventions that lower HR, such as beta-blockers, certain calcium channel blockers, and physical conditioning have multiple additional actions. Nonetheless, the data we have presented suggest that improved understanding of the relationship between HR, its modification, and cardiovascular health is important and potentially beneficial for patient care. To realize this benefit, awareness of the potential importance of HR must be enhanced. Currently, HR is not recognized as a factor for cardiovascular risk assessment or risk reduction in U.S. and European guidelines (14,73,74). Emerging data presented herein suggest that the potential role of HR and its modulation should be seriously considered in future cardiovascular guidance documents.

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