

Resting heart rate and cardiovascular events: time for a new crusade?

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This editorial refers to ‘The association of admission heart rate and in-hospital cardiovascular events in patients with non-ST-segment elevation acute coronary syndromes: results from 135 164 patients in the CRUSADE quality improvement initiative’[†], by S. Bangalore et al. on page 552

Heart rate and cardiovascular risk factors

Acute coronary syndromes (ACS) include ST-elevation myocardial infarction (STEMI) and non-ST-elevation myocardial infarction (NSTEMI). ACS accounts for >1.5 million yearly hospitalizations in both Europe and the USA. In the vast majority of these, the rupture of an atherosclerotic plaque causes these events. Looking back into the history of medicine, ACS has only recently, shortly after the Second World War, been recognized as a ‘cardiovascular disease epidemic’.

The ‘Western’ scientific community initiated research associated with an increased risk for developing cardiovascular disease and coined the term ‘cardiovascular risk factor’. One should realize that a risk factor is a statistical association between a factor candidate and an increase in the probability of risk in the population under scrutiny. It is nevertheless important to distinguish a risk factor from a risk marker: in the first case, a ‘factor’ is at least partially responsible for the risk. Controlling the factor leads to a decrease in risk. In the second scenario, the ‘risk marker’ describes a simple correlation between the ‘marker’ and the risk, and a decrease in this marker will not change the risk.

In human medicine, this distinction requires control of the factor candidate and an effect that this control would have on the disease. For atherosclerosis, this observation requires a lot of patients and a long follow-up period.

So far, we have learned that atherosclerosis is a multifactor disease process that has several distinct pathways (Figure 1).

The first period of the disease may be long and asymptomatic, which can be summarized by plaque growth. During this period the plaque evolves gradually from the ‘fatty streak’ to the advanced plaque under the influence of the risk factors fighting against protective mechanisms.

Since the first Framingham study launched in 1948,^{1,2} several modifiable risk factors have been recognized, such as diabetes mellitus, arterial hypertension, dyslipidaemia, smoking, a sedentary lifestyle, or a diet rich in saturated fats. Controlling these risk factors separately will slow down the progression and the extent of the atherosclerotic disease. The second period is variable in both its duration (some patients die after the first plaque rupture) and its symptomatology (some ruptures remain silent): this is the ‘vulnerable’ period. Risk factors for plaque rupture are summarized in Figure 1, but, to date, remain only incompletely identified. It is not known whether some risk factors act during both periods or whether different factors are more prevalent in one or the other period. This is undoubtedly the case with high resting heart rate.

From the initial observational studies—such as those from Framingham or the French IPC^{1–4}—we know that a high resting heart rate is associated with an increase in cardiovascular mortality in the general population. Although these studies have been statistically corrected for many confounding factors by using multivariate analyses, these data may not definitively prove that ‘high heart rate’ is a cardiovascular risk factor. Nevertheless, several pieces of scientific evidence identified high resting heart rate as a risk factor for the pathogenesis of atherosclerosis and showed that reducing the resting heart rate will decrease vascular oxidative stress and atherogenesis in animal models.^{4,5}

More interestingly—and also more convincingly—an increase in cardiovascular mortality associated with high resting heart rate was found in patients with known coronary artery disease. This was shown among patients having stable coronary artery disease, e.g. in the majority of the 24 913 patients included in the CASS study⁶ and among patients having an ST-segment elevation myocardial infarction (STEMI).^{7–10} As shown in small angiographic studies, it is possible that an increase in shear stress due to a high resting heart

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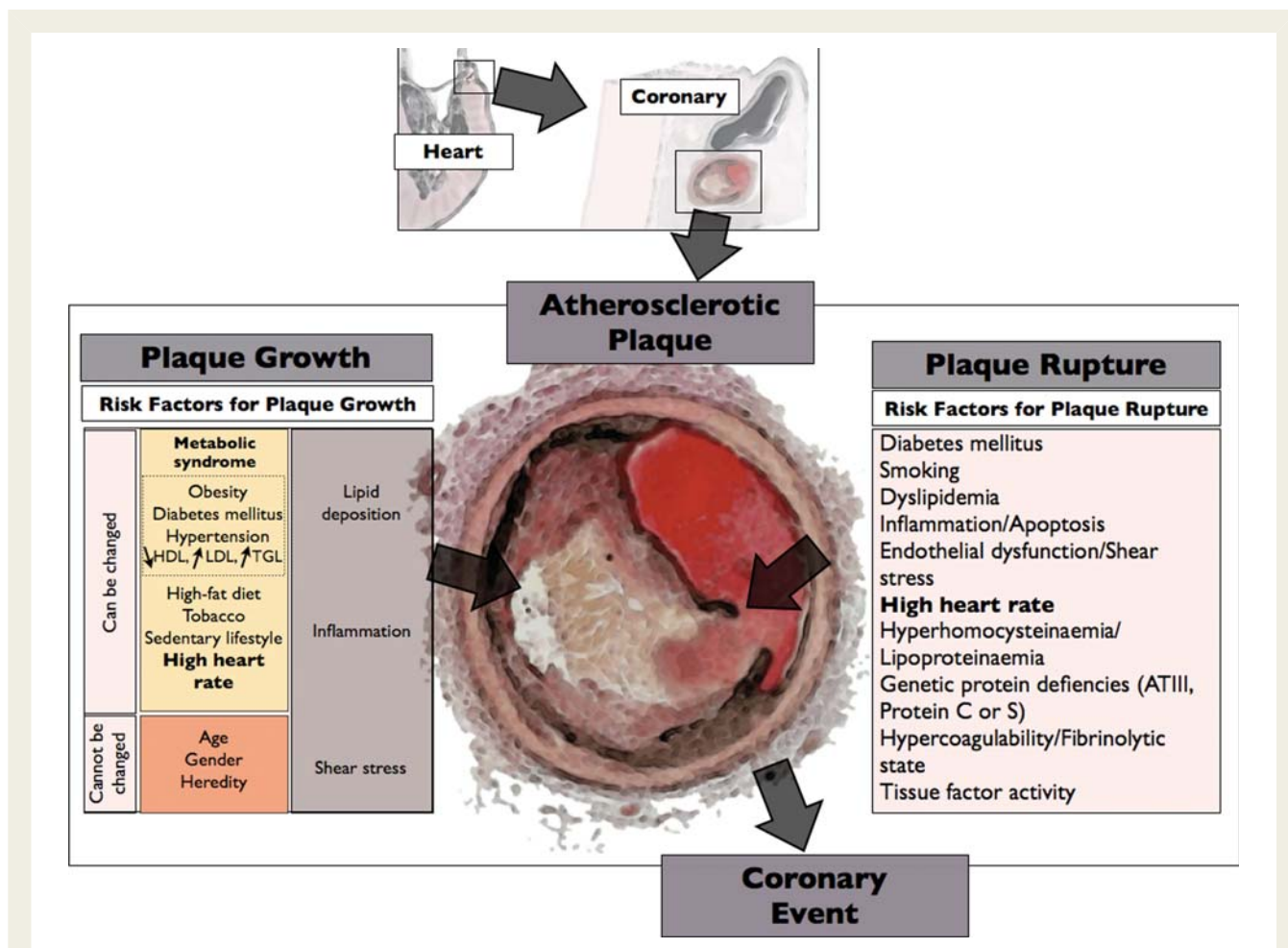


Figure 1 Schematic illustration of atherosclerotic plaque growth and plaque rupture. See text for explanation.

rate will increase plaque vulnerability and can cause plaque rupture.¹¹ Recently, and more compellingly, a decrease in high resting heart rate in patients suffering from coronary artery disease (with β -blockers or ivabradine, a selective heart rate-reducing agent) has been found to lower cardiovascular mortality rates.¹² Consequently, a high resting heart rate is a cardiovascular risk factor.

So what is the heart of the crusader?

Research on ACS is crucial for a better understanding of the transition from the advanced but stable to the vulnerable but unstable plaque. Observational surveys—such as the CRUSADE National Quality Improvement Initiative study¹³—make it possible to target a specific patient population and to offer a cross-sectional view of putative risk factors. With >500 participating centres and >200 000 patients, this study is very much appreciated to determine cardiovascular risk factors for a poor clinical outcome. In contrast to epidemiological trials mentioned earlier, the CRUSADE study was mainly focused on factors being ‘strong’ enough to influence early cardiovascular mortality. Strong risk

factors will cause a fast progression of the disease and will rapidly impact clinical outcome.

If high resting heart rate is a key risk factor for plaque rupture, then one should find an association between resting heart rate and cardiovascular mortality. Bangalore and colleagues¹³ tried to address this specific question. In those of the 139 194 patients having an NSTEMI and a blood pressure >90 mmHg, 8819 suffered a primary cardiovascular event (death or re-infarction) during the hospital stay. A clear J-shaped correlation was found between resting heart rate and all-cause mortality. The lowest mortality rates were found in patients with resting heart rates between 50 and 70 beats per minute (bpm) but doubled, when the resting heart rate decreased to <50 bpm. Moreover, mortality rates were lowest when a heart rate of 50–60 bpm was observed without β -blockers, but doubled when a heart rate reduction was obtained with β -blockers. This is an important point, which probably reflects a trivality: A ‘natural’ low heart rate signals a ‘healthier’ heart while a similar low heart rate achieved with a heart rate-reducing drug indicates a more ‘damaged’ heart.

In contrast, ‘natural’ tachycardia (>100 bpm) was associated with an increase in mortality, which was consistently decreased by the use of β -blockers. This has been recently described in

the BEAUTIFUL trial in patients with coronary artery disease and systolic dysfunction.¹²

Where are we now?

Who would consider a resting heart rate of 83 bpm to be a cardiovascular risk factor compared with 68 bpm? According to the Framingham study, the relative risk reduction by the lower heart rate is 47% for heart failure and 82% for sudden cardiac death.^{1,2} From the evidence accumulated so far, we know that a high resting heart rate is associated with an increase in cardiovascular and all-cause mortality in the general population, as well as in hypertensive patients, patients with diabetes mellitus, patients with stable coronary heart disease or those with a STEMI. The CRUSADE study of Bangalore *et al.*¹³ increases our knowledge and extends this concept to patients suffering from an NSTEMI. Although the lack of information concerning the underlying cardiac rhythm (mainly the presence of atrioventricular block or atrial fibrillation) in the CRUSADE study is unfortunate, one can still agree with the results presented. They point towards 'good clinical sense' showing that heart rates at the extremes (<50 bpm and >100 bpm) are associated with a poor in-hospital outcome and that drug-lowering therapy to attain a resting heart rate of <70 bpm but >50 bpm will reduce patient mortality.

Should we now start a new crusade and aggressively lower the heart rate in every patient? It is clearly too early to say what we should do, but we must remain vigilant and receptive to this new concept.

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