Contribution of heart rate variability to long-term risk stratification after myocardial infarction

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Total mortality during the first year after non-lethal myocardial infarction is about 15–20%. Cardiac mortality represents the major cause of death (10–15%), mainly due to progressive heart failure (4–6%), sudden (arrhythmic) cardiac death (3–4%) and lethal reinfarction (3–4%)\(^1\)\(^–\)\(^3\). In addition, the occurrence of serious arrhythmic events (5–7%), such as sustained ventricular tachycardia or cardiac arrest due to ventricular fibrillation, are factors that determine prognosis. Predictors of hazard used for post-infarction risk stratification should reflect pathophysiological mechanisms and should be feasible in clinical practice allowing the screening of large post-infarction populations.

Among the various arrhythmogenic mechanisms, there is increasing awareness about the autonomous nervous system as a triggering factor of mechanical and electrical complications during myocardial infarction. Heart rate variability is a measure of autonomic input to the heart which is related to the occurrence of cardiac death and arrhythmic events. Heart rate variability has been identified as of prognostic value after myocardial infarction. The positive predictive value of measure of heart rate variability at a follow-up of 1 year is in the range of 10–15% for all-cause mortality and 12–16% for cardiac mortality as an end-point\(^4\). Few data are available on the...
prognostic value of heart rate variability for the prediction of arrhythmic events, such as sustained ventricular tachycardia or sudden cardiac death, showing a positive predictive value in the range of 15–20%[6]. In general, the prognostic value of parameters for risk stratification is strongly related to the prevalence of events. In particular, a high proportion of event-free patients is usually related to a relatively high number of false-negative classifications, which leads to a low positive predictive value.

The study by Quintana et al.[5] in this issue presents data of a long-term follow-up of 74 patients after myocardial infarction. Heart rate variability was obtained from 24-h ambulatory ECGs a few days after hospital admission. Parameters of heart rate variability were assessed both in the time and frequency domain. In addition, standard resting ECGs and left ventricular ejection fractions from echocardiograms were analysed. During 3 years of follow-up, 18 patients (24%) died and 19 (26%) were lost or censored. Eighteen (24%) new infarctions occurred and 20 (27%) revascularization procedures (PTCA, coronary artery bypass surgery) were performed. Information about the sudden cardiac death rate and incidence of serious arrhythmic events was not given. Focusing on all-cause mortality and reinfarction, Quintana et al.[5] found time and frequency domain measures of heart rate variability to be significantly lower in non-survivors. Cox analysis was performed including frequency domain parameters as well as clinical data. Parameters of heart rate variability did not provide additional prognostic information for all-cause mortality when compared with left ventricular ejection fraction, which was the strongest predictor. The predictive values of time domain parameters of heart rate variability were not further investigated. Sensitivities and specificities for cumulative survival based on frequency domain measures were in the range of 44–50% and 81–82%, respectively. These values, combined with the death rate, yield positive and negative predictive values of 50–56% and 73–77%, respectively.

Quintana et al.[5] present the first 3-year follow-up study to assess the prognostic value of heart rate variability for all-cause mortality. The main findings confirm previous results of studies with shorter follow-up periods in which left ventricular ejection fraction was strongly related to survival[6]. Reduced left ventricular function after myocardial infarction is known to cause changes in the autonomic regulation of the heart, which may also be responsible for the modifications in heart rate variability. Assuming a strong dependency of heart rate variability and ejection fraction, independent predictive information for mortality could be carried by left ventricular ejection fraction measures, whereas heart rate variability could represent a dependent variable. Quintana et al.[5], however, mention a 'moderately good correlation' between ejection fraction and heart rate variability measures in this study, but did not present the actual correlation coefficient. Thus, the independent prognostic value of heart rate variability in long-term follow-up was not entirely clarified.

An important result of this study can be obtained from the survival functions shown in the figures: during the first 12–14 months after myocardial infarction, the population defined as high risk in terms of frequency domain parameters of heart rate variability presented a markedly higher hazard compared to those at low risk. However, after this period, both subpopulations showed similar hazards until the end of follow-up. These findings suggest that heart rate variability may be particularly useful for risk stratification in the first year after myocardial infarction but may lose its significance thereafter. Various explanations might be possible: (1) In the first year of follow-up, mainly those patients in the high risk group who have a very low heart rate variability may die. This would shift the distribution of heart rate variability measures in the surviving patients to higher values, leaving a population at decreased hazard for further long-term follow-up. (2) Heart rate variability may have changed during the myocardial infarction healing process. This is supported by Lombardi et al.[7] and Bigger et al.[8] who have shown that in survivors after myocardial infarction, time domain parameters of heart rate variability changed towards normal values during one year of follow-up. (3) The pathophysiological mechanisms leading to cardiac death may have changed during follow-up.

The last argument is supported by previous findings of large post-infarction trials. Sudden cardiac death and serious arrhythmic events largely occurred in the first 6 to 12 months after myocardial infarction, whereas the incidence of deaths caused by progressive heart failure increased gradually over time and the proportion of lethal reinfarctions remained constant after some months. The influence of heart rate variability on the prediction of cardiac death is expected to be most powerful in the first year after infarction, because heart rate variability is a measure of the autonomous inputs to the heart, which acts as a trigger for the development of arrhythmias. After the first year of survival, heart failure, lethal reinfarctions and other modes of mortality, which are only marginally expressed by means of heart rate variability, may become predominant, thus lowering the prognostic value of heart rate variability. The survival functions for all-cause mortality presented in the paper of Quintana et al.[5] confirm these suggestions.
showing a parallel course for both, low- and high-risk populations after 14 months until the end of follow-up. Unfortunately, data on the incidence of sudden cardiac death and serious arrhythmic events in this long-term followed population have not been presented. This would provide a better understanding of the pathophysiological mechanisms leading to the decreased predictive power of heart rate variability after one year of survival.

The predictive value of heart rate variability described by Quintana et al.\[5\] differs considerably from previously published data. This may be based on obvious differences in mortality and event rates compared to previous studies, but not necessarily on the extended follow-up period, as mentioned by the authors. These findings need further explanation with regard to the amount of thrombolysis, beta-blocker therapy or a potential bias due to the large proportion of screened but lost patients.

Despite the valuable results obtained by the study of Quintana et al.\[5\] the evaluation of the independent prognostic value of heart rate variability for long-term risk stratification still needs further investigation.

**References**


**Treatment of mild heart failure: the place of diuretics and ibopamine**

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Chronic heart failure is a progressive disorder which carries high morbidity and mortality. In recent years, it has become increasingly clear that disease progression in chronic heart failure is not only related to haemodynamic, but also to neurohumoral factors[1]. Treatment which favourably affects both factors is attractive and should be initiated as early as possible. In the present issue, Andrews et al.[2] emphasize (again) the importance of diuretics in this patient group and provide new clinical information on the oral dopamine agonist, ibopamine, which was recently found to increase mortality in severe chronic heart failure (ref. [21] of Andrews et al.).

As fluid retention and congestion are hallmarks of chronic heart failure, diuretics are often the first drugs to be prescribed. In the acute phase of cardiac decompensation with pulmonary congestion, the value of these agents, particularly loop diuretics such as furosemide and bumetanide, is unquestioned. During long-term use in chronic heart failure, however, monotherapy with these drugs may be less appropriate, because of activation of neurohumoral systems, induction of electrolyte disturbances, and other side effects (refs [4] and [5] of Andrews et al.).