Heart rate contribution to the clinical value of heart rate variability

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INTRODUCTION

Heart rate (HR) has been extensively investigated for many years and has been found to be a significant risk factor, especially for cardiovascular events [1–3]. Its predictive ability has been proven in different settings, i.e. both at rest and during or after exercise [1–5]. However, even resting HR is not a constant quantity but one that changes beat by beat, a phenomenon that is commonly called heart rate variability (HRV) [6]. Both HR and HRV are under the influence of the autonomic nervous system activity, and to some extent may reflect autonomic imbalance associated with different pathological states [6–8]. Years of investigations have shown that HRV is an important risk factor associated with adverse outcomes in various diseases [8–12]. However, HRV reveals a significant correlation with HR, and therefore HRV actually provides information on two quantities, i.e. heart rate and its variability [13–15]. The question arises as to which of these two really matters in HRV prognostic value; in other words, what is the HR contribution to the prognostic ability of HRV? This article summarises recent reports concerning this intriguing point as well as methodological aspects of such research.

HRV CORRECTION FOR AVERAGE HR

HRV is usually estimated from sequences of R-R intervals of electrocardiogram (ECG) and as such is negatively correlated with HR [6, 16]. However, the relationship between HRV and HR is both physiologically and mathematically determined [13–15, 17–20].

The physiological determination comes from the autonomic nervous system activity, especially from its parasympathetic branch, i.e. the higher the parasympathetic activity, the lower the HR and the higher its variability [6].

The mathematical determination is caused by the non-linear (inverse) relationship between R-R intervals and HRs. Consequently, the same changes of HR cause much higher fluctuations of R-R intervals for the slow average HR than for the fast one. Moreover, the fluctuations of R-R intervals for fast HR may not be as high as for slow HR because the R-R intervals should have become negative (Fig. 1) [13–15, 17–20]. Due to these facts, standard HRV analysis may be mathematically biased, particularly if patients exhibit different average HRs. To overcome this problem, one should calculate the variability of R-R intervals with respect to the average R-R interval, i.e. normalise the oscillations with respect to the mean value. One can do that by dividing the sequence of R-R intervals by the corresponding average R-R interval [15, 17–20]. Or, one may divide standard deviation of R-R intervals by average R-R interval (i.e. calculation of coefficient of variation), or divide HRV power spectrum (or its components) by the average R-R interval squared [15].

Such a normalisation is critical for investigations of HRV after different interventions which change HR because by employing this approach, one may differentiate between physiologically and mathematically mediated changes in HRV (i.e. one may exclude the mathematical bias) [15, 17–21]. For example, metoprolol-induced changes of HRV become insignificant after they are normalised to the same R-R interval, suggesting that the increase in HRV after beta-blockade can be explained by a change of HR [22]. Also, in an animal model, it has been shown that beta-adrenergic receptor blockade may reduce rather than increase R-R interval variability after correction for the drug-induced HR reductions [21]. Furthermore, an employment of this correction method has helped to demonstrate that HR is a better indicator of higher fitness than its variability — i.e. an association between HRV indices and maximal oxygen intake (VO_2max) exists mainly due to the relationship between HR and VO_2max [23]. On the other hand, the same method has shown that an increase in HRV following dengue viral infection does not result from the accompanying reduction in HR, but reflects a real improvement in cardiac autonomic nervous control [24].

Therefore, it is necessary to establish to what extent HRV changes associated with HR alterations are physiologically and

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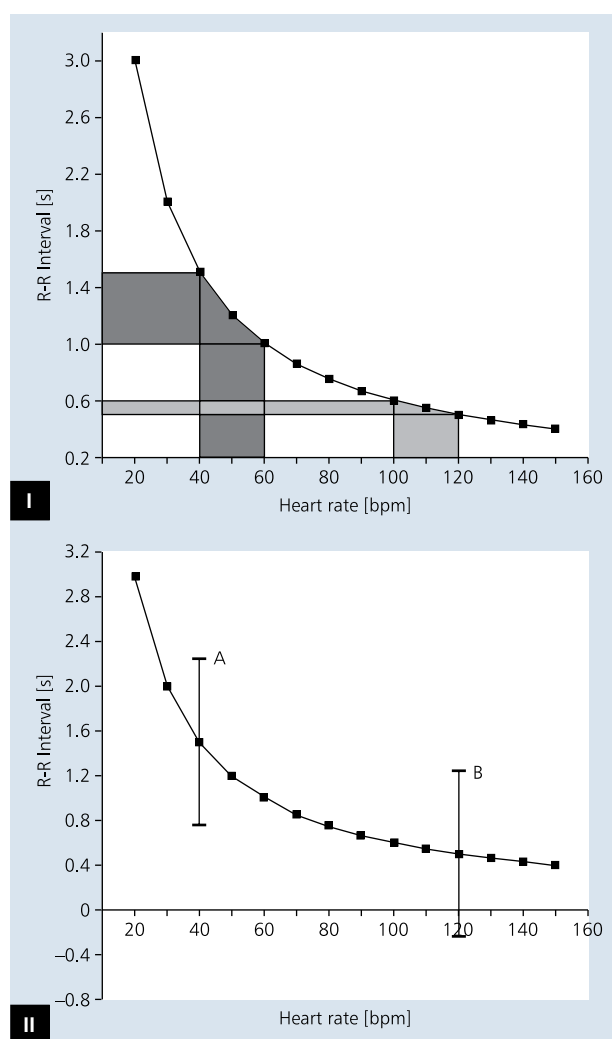
Figure 1. **Panel I**: The nonlinear (mathematical) relationship between R-R interval and heart rate (HR) is depicted. One can see that the oscillations of a slow average HR (x-axis, dark grey area) result in much greater oscillations of R-R intervals (y-axis, dark grey area) than the same oscillations of a fast average HR (light grey area). As a consequence, the variability of R-R intervals is higher for the slow average HR than for the fast one, despite the fact that the variability of HR is the same. **Panel II**: the relationship between R-R interval and HR with two hypothetical examples of R-R interval oscillations (i.e. A and B) are presented. It can be seen that the fluctuations of R-R intervals may be potentially quite high for a slow average HR (A); however, such fluctuations are not possible for a fast average HR (B) since the R-R intervals should have become negative. Owing to the above phenomena, the standard analysis of HR variability may be mathematically biased. Reprinted with modifications from Sacha [17]

mathematically determined — by the correction for average HR, one is able to differentiate these two essentially different effects [15]. It is also worth noting that HR influences the reproducibility of HRV measurements, i.e. HRV corrected for average HR is significantly more reproducible than standard HRV [25]. Therefore, differences in average HR should be taken into account when one compares HRV measurements in a given patient [25–28].

MODIFICATIONS OF THE RELATIONSHIP BETWEEN HRV AND HR

The modification method of the association between HRV and HR has been recently considerably developed, and now enables us to completely remove HRV dependence on HR (even the physiological one) or mathematically enhance this dependence [13]. Such an approach allows us to explore the HR contribution to the prognostic ability of HRV. In order to decrease or increase the HRV dependence on HR, one should respectively divide or multiply the sequences of R-R intervals (or HRV spectra) by different powers of the corresponding average R-R interval. The principle of such modifications is simple, i.e. by division by the average R-R interval, the HRV of slow HR is attenuated, while that of fast HR is relatively amplified and consequently HRV loses its dependence on HR; conversely, multiplication by the average R-R interval boosts the association between HRV and HR — the resulting HRV reveals much higher dependence on HR than standard HRV (Fig. 2) [13]. The higher the power of the average R-R interval is used, the stronger the effect on HRV/HR dependence is achieved (Table 1). Such a method may be employed for any HR dynamics analysis which parameters are significantly associated with HR — all details concerning this modification method have been published elsewhere [13, 15].

The method has been recently tested in a large post myocardial infarction (MI) patient population, i.e. almost 1,500 patients who were followed up for five years [14]. Seven different classes of spectral HRV parameters with increasing dependence on HR were calculated, as described in Table 1. The hrv1 class was independent of HR, but in other classes the association between HRV and HR increased, up to a very high level for the hrv7 class (Table 1). During the follow-up period, 135 patients died (76 from cardiac causes and 59 from non-cardiac ones). The analysis of areas under the receiver-operator characteristic curves revealed that if HRV is becoming more dependent on HR, its predictive power increases for cardiac death, while it decreases for non-cardiac death. Conversely, when losing its dependence on HR, HRV loses its prognostic power for cardiac death, but gains its power for non-cardiac death (Fig. 3). Thus, the HR contribution to the HRV prognostic power turns to be different for different outcomes, i.e. positive for a cardiac death, but negative for a non-cardiac one. In such a context, HR may be treated as a cardiovascular factor of the HRV predictive value. Moreover, HRV highly dependent on HR (i.e. hrv7 in Fig. 3) presents much stronger predictive power for cardiac than non-cardiac death; therefore by using it one may potentially find patients being at higher risk of cardiac than non-cardiac
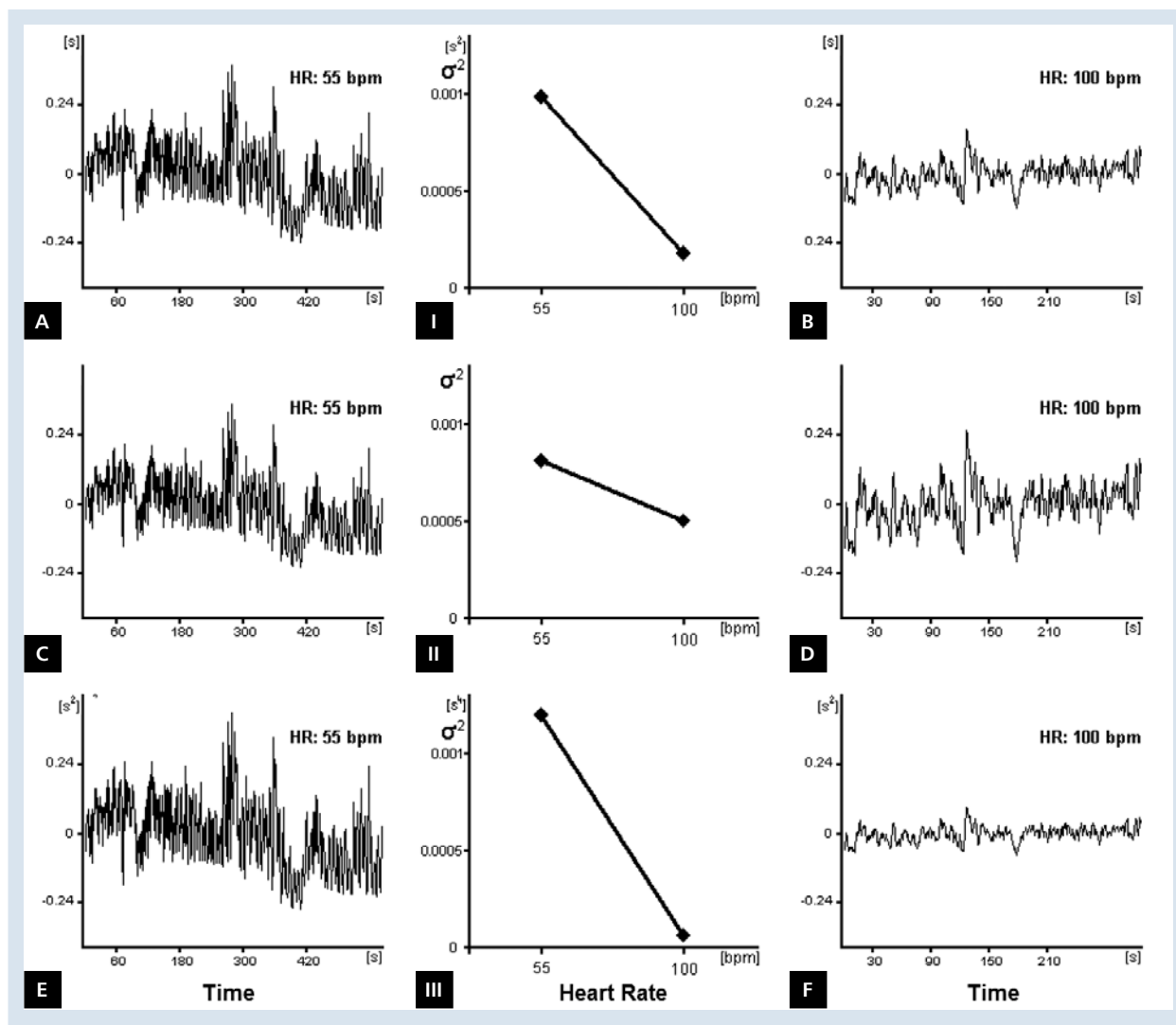
Figure 2. The mechanism of modifications of heart rate variability (HRV) dependence on heart rate (HR) is presented: the R-R interval tachograms with different average HR (i.e. 55 and 100 bpm) are shown: **A** and **B** standard tachograms; **C** and **D** tachograms after division by their corresponding average R-R intervals; and **E** and **F** tachograms after multiplication by their average R-R intervals. In panels **I**, **II**, and **III**, the dependencies of variance (σ^2) of the respective HRV tachograms on HR are exhibited, in other words the standard HRV dependence on HR (**I**); the weakened dependence (**II**); and the strengthened dependence (**III**). One can see that after the division by an average R-R interval, HR has little influence on HRV (**II**) and conversely, after the multiplication by an average R-R interval, HRV is more dependent on HR (**III**) than the standard HRV (**I**). The higher the power of average R-R interval is employed, the stronger the effect on HRV/HR dependence is achieved. By using the above modifications one may weaken or strengthen HR influence on HRV. To facilitate the comparison of the fluctuation amplitudes, the mean values have been subtracted from the respective tachograms in panels **A**, **B**, **C**, **D**, **E**, and **F**. Reprinted with modifications from Sacha et al. [13]

death. On the other hand, HRV fully independent of HR (i.e. hrv1) is very specific for non-cardiac mortality (Fig. 3), so it allows the identification of patients predominantly burdened with extra-cardiac risk. In multivariate analysis, both hrv1 and hrv7 proved to be independent predictors of the respective mode of death — furthermore, of all other clinical risk factors, hrv1 turned out to be the strongest predictor for non-cardiac mortality [14]. The specific abilities of hrv1 and hrv7 for predicting a certain mode of death have been validated in other post-MI population (i.e. 946 patients followed up for five years) [14].

Currently, it is hard to understand why HRV completely independent of HR (i.e. hrv1) reveals such a high potential for the prediction of non-cardiac death. However, if standard HRV (i.e. hrv3 in Fig. 3) predicts all-cause mortality, the exclusion of HR influence (which seems to be a cardiovascular factor) may make HRV predominantly associated with extra-cardiac risk (i.e. hrv1 in Fig. 3) [14, 15].

Table 1. Spearman correlations between different classes of total powers of heart rate variability (HRV) spectra and heart rate

HRV class	CC	P
hrv1	−0.006	NS
hrv2	−0.44	$< 10^{-11}$
hrv3	−0.68	$< 10^{-11}$
hrv4	−0.81	$< 10^{-11}$
hrv5	−0.88	$< 10^{-11}$
hrv6	−0.94	$< 10^{-11}$
hrv7	−0.98	$< 10^{-11}$

CC — correlation coefficient; NS — non significant; Total powers (TPs) of HRV spectra were modified as follows: hrv1 — by division of standard TP by average R-R interval to the power 4; hrv2 — by division of standard TP by average R-R interval squared; hrv3 — standard TP; hrv4 — by multiplication of standard TP by average R-R interval squared; hrv5 — by multiplication of standard TP by average R-R interval to the power 4; hrv6 — by multiplication of standard TP by average R-R interval to the power 8; and hrv7 — by multiplication of standard TP by average R-R interval to the power 16. One can see that TP dependence on heart rate increases from hrv1 to hrv7; hrv1 is completely independent of heart rate, whereas in subsequent cases this dependence progressively increases, up to the extremely high level in the case of hrv7. According to Sacha et al. [13]

Figure 3. The predictive powers (AUC, area under receiver--operator characteristic curves) of heart rate variability (HRV) (i.e. very low frequency component of HRV spectrum) modified with respect to heart rate (HR) are depicted. The case of hrv3 corresponds to standard HRV; in the cases of hrv1 and hrv2, the HRV dependence on HR was weakened, but it was strengthened in the cases of hrv4, hrv5, hrv6, and hrv7 — HRV was modified according to the method described in Table 1. As HRV is getting more dependent on HR (i.e. from hrv1 to hrv7), its predictive power increases for cardiac death, while it decreases for non-cardiac death. Of note: hrv1 (which is completely HR independent) is a stronger predictor of non-cardiac than cardiac death and conversely hrv7 (which is highly HR dependent) is more powerful in predicting cardiac than non-cardiac death, but hrv3 (which is a standard HRV) is equally effective in both modes of death, thus it actually predicts all-cause mortality. Reprinted with modifications from Sacha et al. [14]

An excellent example of the importance of risk stratification of a specific mode of death is primary prevention with an implantable cardioverter-defibrillator (ICD). In this kind of treatment, it is crucial to identify patients whose risk of sudden cardiac death (SCD) significantly exceeds their risk of other modes of death — such patients may fully benefit from ICD therapy [14, 29, 30]. However, almost all commonly recognised risk factors of SCD (including low left ventricular ejection fraction [LVEF]) are associated with all-cause mortality, and therefore patients stratified with these risk factors are under threat of all-cause death, but not specifically cardiac or SCD. As a consequence, the benefit from ICD in terms of the reduction of SCD may be completely offset by the increased mortality from non-arrhythmic causes [29, 31, 32]. In such a circumstance, the specific ability of the modified HRV (i.e. hrv1 and hrv7) to predict non-cardiac and cardiac death is very promising. The employment of these modified parameters among post-MI patients with LVEF ≤ 35% has revealed that almost one fifth of them may not benefit from ICD due to their high non-cardiac risk [14].

New insight into the interaction between HR and HRV has been given by its investigation in different genders. Namely, it turns out that if HRV is becoming more dependent on HR, its predictive power increases for cardiac and decreases for non-cardiac death; but only in men, because in women it decreases for either outcome (Fig. 4) [33]. This is probably caused by the fact that in the female subgroup, HR is a very weak risk factor of adverse outcomes [1, 33–36], and the exclusion of its impact improves the HRV predictive power (Fig. 4) [33]. This is a very important observation because it seems as if
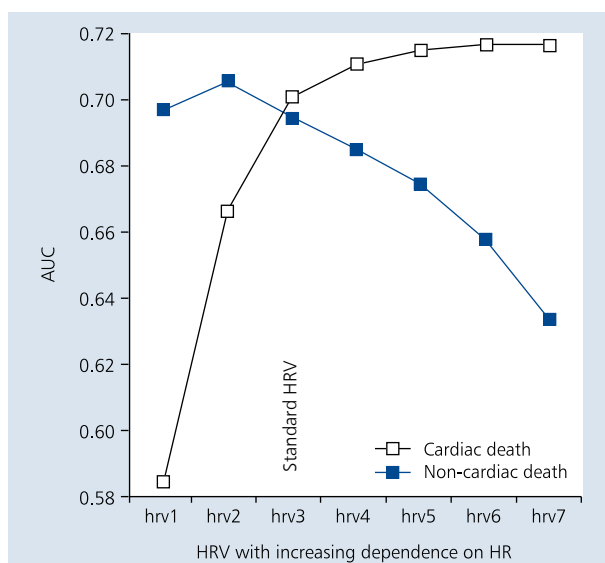
HR has a detrimental effect on the HRV prognostic value in females — therefore, it is possible that variability, but not average HR, reflects the prognosis in this population [15, 33].

In general, it is likely that for outcomes and populations where HR is not a risk factor, the exclusion of its influence may improve the HRV prognostic value; however, if HR is a risk factor, the enhancement of its impact makes HRV a better predictor [15]. This concept has been recently confirmed by Pradhapan et al. [37] who has examined the HR impact on the HRV after exercise test. The authors found that HR immediately before exercise is not a risk factor of death, and the removal of its influence improves the HRV predictive power. Conversely, HR during the recovery phase is a significant mortality predictor, and consequently the enhancement of its impact increases the HRV predictive ability.

CONCLUSIONS

HR significantly contributes to the HRV clinical value, although this contribution may be different for different outcomes
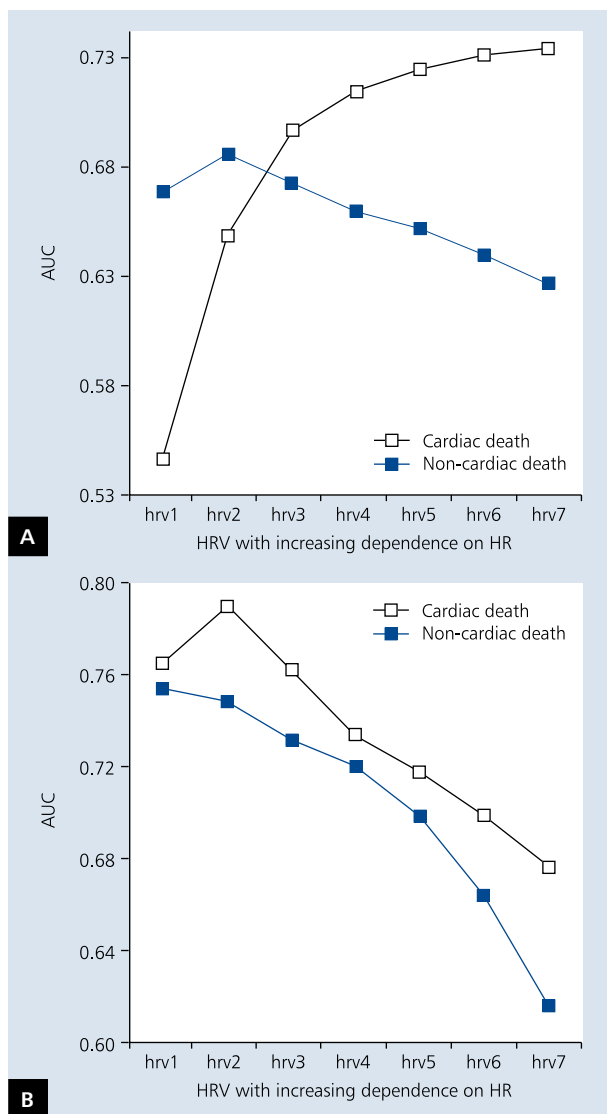
Figure 4. The predictive powers (AUC, area under receiver-operator characteristic curves) of heart rate variability (HRV) (i.e. very low frequency component of HRV spectrum) modified with respect to heart rate (HR) in men (**A**) and women (**B**) are depicted. The case of hrv3 corresponds to standard HRV; in the cases of hrv1 and hrv2, the HRV dependence on HR was weakened, but it was strengthened in the cases of hrv4, hrv5, hrv6, and hrv7 — HRV was modified according to the method described in Table 1. As HRV is becoming more dependent on HR (i.e. from hrv1 to hrv7), its predictive power increases in men for cardiac death, but decreases for non-cardiac death. In women, it decreases for both outcomes. Reprinted with modifications from Sacha et al. [33]

and populations. The interaction between HRV and HR is determined by two distinct mechanisms, i.e. physiological and mathematical ones — either of these mechanisms may be mathematically modified. Currently it is hard to conclude how to practically employ analyses of the HRV/HR interac-

tion, yet a separate approach to HR and its variability should enable us to judge which of the two quantities presents the highest clinical value for a given population and outcome. The analyses with modification methods show us that if HR is clinically relevant in a given clinical context, the amplification of its influence makes HRV a better predictor; nevertheless, if HR is not clinically significant, the exclusion of its impact allows HRV to become a stronger risk factor. In future, it will probably be feasible to determine specific therapeutic targets, i.e. HR or HRV, in order to overcome different adverse outcomes.

Therefore, the interaction between HRV and HR not merely requires but deserves further investigation. Ultimately, it should be stressed that all aspects described in this article could also refer to any other heart rate dynamics analysis which parameters are significantly correlated with HR.

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