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Letter to the Editor

Gender differences in the interaction between heart rate and its variability — How to use it to improve the prognostic power of heart rate variability ☆

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Accelerated heart rate (HR) as well as reduced heart rate variability (HRV) are commonly recognized risk factors for different adverse outcomes in various diseases [1,2]. Yet, there is a growing body of evidence that elevated HR is mainly a significant predictor of such outcomes in men but not in women [3]. Moreover, HR and HRV are associated with each other but this relationship is both physiologically and mathematically determined [4–6]. Recently, we have shown that the association between HR and HRV may be mathematically modified, i.e. one may strengthen or weaken the HRV dependence on HR [7]. By using this method, we have demonstrated that HR contributes to the prognostic power of HRV in patients after myocardial infarction (MI), albeit, this contribution is different for different outcomes, i.e. it is positive for cardiac death but negative for non-cardiac one [8]. Indeed, if HRV becomes more dependent on HR, its predictive ability increases for cardiac mortality but decreases for non-cardiac one — conversely, when losing this dependence, HRV is losing its power for predicting cardiac death but gaining its power for non-cardiac one [8]. However, this phenomenon has never been tested in males and females separately. The goal of the study was to explore the HR impact on the prognostic value of HRV in different genders.

We analyzed the post-MI patients recruited between January 1996 and December 2000 (i.e. the exploratory sample, n = 1455; 1154 males) and then validated the results by studying another post-MI population recruited between January 2001 and December 2005 (i.e. the validation sample, n = 946; 782 males). Both cohorts took part in earlier studies and were followed up for 5 years—the details have been published elsewhere [9]. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee and all participants gave their informed consent.

Each of the patients underwent Holter recording during the second week after the index infarction. Spectral HRV indices were estimated from 512 RR interval segments and then averaged for every patient. Power spectra were calculated by means of the fast Fourier transform and the following indices were distinguished: very low frequency (VLF, 0.003–0.04 Hz), low frequency (LF, 0.04–0.15 Hz), high frequency (HF, 0.15–0.6 Hz) and total power (TP, 0.003–0.6 Hz). Seven classes of spectral HRV indices with different dependence on HR were obtained by either division or multiplication of average standard indices of each patient by different powers of the corresponding average RR interval (avRR), i.e.: hrv1—by division of standard HRV indices by avRR to the power 4; hrv2—by division of standard HRV indices by avRR squared; hrv3—consisted of standard HRV indices; hrv4—by multiplication of standard HRV indices by avRR squared; hrv5—by multiplication of standard HRV indices by avRR to the power 4; hrv6—by multiplication of standard HRV indices by avRR to the power 8; and hrv7—by multiplication of standard HRV indices by avRR to the power 16. Their respective average Spearman correlation coefficients with HR were: −0.001, −0.4, −0.64, −0.78, −0.85,−0.93, and −0.97 (all statistically significant except for hrv1). In the hrv1 and hrv2 classes the HRV dependence on HR was weakened, but it was strengthened in the hrv4, hrv5, hrv6 and hrv7 classes. During the follow-up period 135 patients (104 males) and 49 patients (42 males) died in the exploratory and validation group, respectively. The exact description of the method, analyzed population and protocol has been published elsewhere [7,8].

☆ All the authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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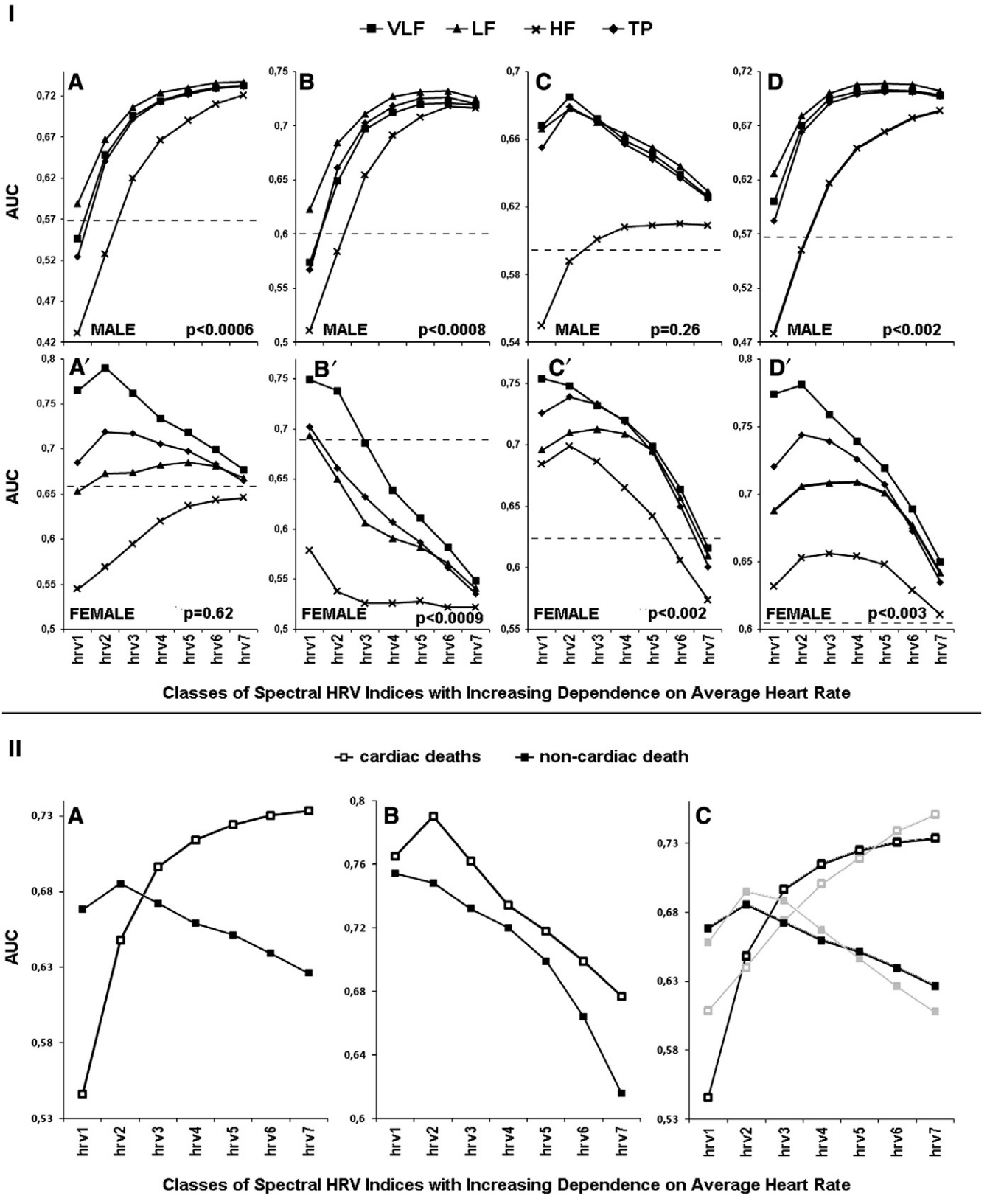

Fig. 1. Exploratory study: panel I presents the prognostic powers (AUC, area under receiver–operator characteristic curves) of spectral indices from various HRV classes for different modes of death in males and females, i.e.: cardiac death (A, A′); sudden cardiac death (B, B′); non-cardiac death (C, C′); and all-cause death (D, D′), (p-values refer to Friedman ANOVA test for differences between classes). All AUC above dashed lines are significantly different from 0.5, those below are not. Panel II depicts the predictive powers (AUC) of VLF for cardiac versus non-cardiac death in men (A) and women (B) from the exploratory sample, and in men from both exploratory and validation sample (C) — data corresponding to the exploratory sample are marked with black color but those of validation one with gray color. Of note, in men, VLF from hrv1 is a stronger predictor of non-cardiac than cardiac death and conversely, VLF from hrv7 is more powerful in predicting cardiac than non-cardiac death. However, in women VLF from hrv1, which is completely HR-independent, is as good in predicting cardiac death as non-cardiac one. The diagram in panel II C represents data from male subgroups in the exploratory and validation samples — one can see a very good correspondence between prognostic powers of VLF for cardiac and non-cardiac death in men from both samples (compare black and gray lines in panel II C). Such a comparison was not possible in women, since in the validation sample, only 3 of them died from cardiac causes and 4 from non-cardiac ones and consequently all AUCs were not different from 0.5.

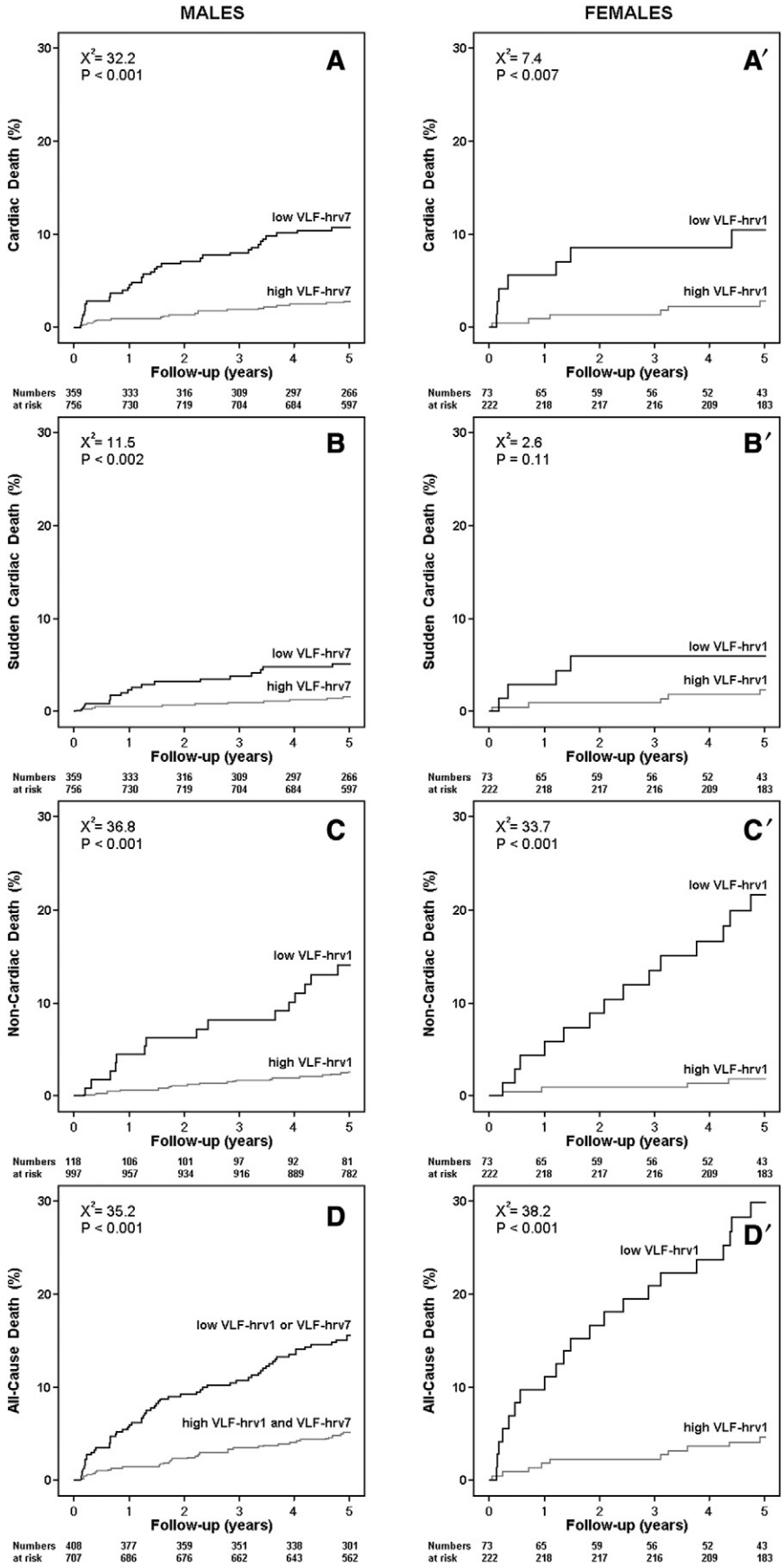

Fig. 2. Exploratory study: Kaplan–Meier curves of cardiac, sudden cardiac, non-cardiac and all-cause deaths for men (A, B, C, D) stratified according to VLF-hrv7 and VLF-hrv1 and for women (A′ B′, C′ D′) stratified with VLF-hrv1 are depicted. The cut-off values which best selected patients at risk of the respective modes of death are as follows: for VLF-hrv7 (i.e. 1.5E +50 ms[18]) and VLF-hrv1 (i.e. 6.61E −10/ms^2) in men and VLF-hrv1 (i.e. 7.0E −10/ms^2) in women. These cut-offs were determined by using the maximum logrank statistics. The logrank test was used to compare Kaplan–Meier curves.

In the male subgroup, as the HRV indices were becoming more dependent on HR (i.e. from hrv1 to hrv7) the predictive power of spectral indices progressively increased for cardiac death, sudden cardiac death and all-cause death, while it decreased for most of the indices for non-cardiac one (Fig. 1-panel I A, B, C, D). However, in the female subgroup, when HRV was getting more dependent on HR, the prognostic power of majority of indices decreased for all the outcomes (even for cardiac deaths) — Fig. 1-panel I A′, B′, C′, D′. One of the reasons for this phenomenon may be the fact that HR did not predict any kind of outcomes in females, i.e. AUCs (95% CI, p-value) for cardiac, sudden cardiac, non-cardiac and all-cause death were respectively: 0.64 (0.45–0.83, $p = 0.09$), 0.5 (0.28–0.73, $p = 0.97$), 0.52 (0.38–0.66, $p = 0.75$), and 0.58 (0.46–0.69, $p = 0.17$). Consequently, the exclusion of HR impact on HRV improved the HRV predictive ability in women. This was opposite to what we found in men where HR predicted all the outcomes, respective AUCs: 0.73 (0.67–0.8, $p < 0.001$), 0.71 (0.62–0.8, $p < 0.001$), 0.6 (0.51–0.69, $p < 0.05$), and 0.69 (0.63–0.74, $p < 0.001$).

Of all spectral indices, VLF exhibited the largest AUC for most of the outcomes in both genders. Of note, VLF from hrv1 class (VLF-hrv1) and VLF from hrv7 class (VLF-hrv7) presented the biggest difference in their predictive powers for cardiac and non-cardiac deaths in men (Fig. 1-panel IIA). This may potentially help to differentiate men at risk of different modes of death, i.e. by using VLF-hrv7 one may find the men at risk of cardiac death but with VLF-hrv1 one can select those at risk of non-cardiac one. It seems that HR constitutes a cardiovascular factor of the HRV prognostic power in men, i.e. its influence on the HRV predictive ability is positive for cardiac deaths but negative for non-cardiac one. Such a phenomenon was not observed in women (Fig. 1-panel IIB), i.e. VLF-hrv1, which was completely HR-independent, revealed the strongest predictive power for all modes of death — indeed, VLF was losing its predictive power as it was becoming more dependent on HR. Thus, HR had a detrimental effect on HRV prognostic value in women. Fig. 2 shows cumulative mortality curves of different modes of death for the males classified by VLF-hrv7 and VLF-hrv1 and females classified according to VLF-hrv1.

To determine the independent predictors of cardiac and non-cardiac deaths in males and females, the multivariate analyses (adjusted for age ≥65 years, left ventricular ejection fraction [LVEF] ≤35%, presence of diabetes mellitus, history of previous MI, arrhythmia [≥10 ventricular premature complexes/h or non-sustained ventricular tachycardia on Holter], mean HR of >75 bpm and standard deviation of normal-to-normal heartbeat intervals [SDNN] ≤70 ms) [8] were performed with the Cox proportional-hazards model. Because of the relatively small number of events, the number of covariables had to be limited especially in women, i.e. one variable per 5 events [10]. The selection of parameters to be entered in the multivariable models was based on univariable statistical significance. Based on these considerations, we found the following independent predictors (hazard ratio [95% CI, p-value]), for cardiac death in males: LVEF 4.1 (2.2–7.5, $p < 0.0001$), VLF-hrv7 2.1 (1.05–4.4, $p < 0.05$), age 2.0 (1.1–3.3, $p < 0.05$), arrhythmia 1.9 (1.1–3.4, $p < 0.05$), diabetes 1.9 (1.07–3.3, $p < 0.05$); and in females: LVEF 8.4 (2.4–28.9, $p < 0.001$), VLF-hrv1 2.7 (0.8–8.4, $p = 0.09$ — borderline, probably due to small number of events); for non-cardiac death in males: VLF-hrv1 3.9 (1.9–8.1, $p < 0.0001$), LVEF 2.5 (1.1–5.7, $p < 0.05$); and in females: age 5.9 (1.3–26.3, $p < 0.05$), VLF-hrv1 4.5 (1.3–15.3, $p < 0.05$), diabetes 3.7 (1.4–9.8, $p < 0.01$).

The validation study was feasible only in males, since the number of events was too small in females in the validation sample (i.e. only 3 women died from cardiac causes and 4 from non-cardiac ones). However, there was a very good correspondence of the VLF prediction abilities between the exploratory and validation groups observed in males (Fig. 1-panel II C). Moreover, the validation analysis confirmed principle findings of the exploratory study in men, i.e.: VLF-hrv1 significantly predicted non-cardiac death (logrank test, $p < 0.01$), VLF-hrv7 stratified cardiac death ($p < 0.001$) and with borderline significance sudden cardiac death ($p = 0.07$), whereas the combination of VLF-hrv1 and VLF-hrv7 predicted all-cause death ($p < 0.001$)—the cutoff points for both indices were pre-specified on the basis of the exploratory study (see the legend of Fig. 2).

Conclusion: for the first time, it has been demonstrated that HR has a different impact on the HRV prognostic value in different genders. Indeed, HR has a detrimental effect on the clinical value of HRV in women, however, this problem may be solved by the mathematical removal of the HR influence on HRV. Yet, males should be treated with different approaches, i.e. by strengthening the HRV dependence on HR one may learn more about cardiac prognosis but by weakening it, more information on non-cardiac risk may be obtained. Finally, it should be stressed that the above methods can be employed to every analysis of heart rate dynamics where the indices are significantly correlated with HR [7].

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