Is heart rate a better risk predictor than heart rate variability?

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Although some publications in the past showed the good predictive power of the heart rate at rest, it did by far not achieve the attention compared with the parameters of heart rate variability. In addition, it is commonly believed that heart rate and heart rate variability are statistically independent parameters. Particularly the latter seems not to be true, as investigations show findings that will be presented here. The observable range of the standard deviation of heart rate variability decreases with increasing heart rate at rest as well as for a larger ensemble of patients who are undergoing a stress test. Thus, even if the correlation between heart rate and heart rate variability is poor, it is a fact that at high heart rates, the possible standard deviation of heart rate variability becomes low. In other words, heart rate variability is not independent of heart rate. Thus, an increased risk for patients with high heart rate means automatically that they have a low standard deviation of the heart rate variability.

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Dispersion of APD restitution quantified from the surface ECG

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Dependence of repolarization duration on heart rate has been shown to provide relevant information for arrhythmic risk stratification. A way of characterizing the relationship between the action potential duration (APD) and the RR interval is by the APD restitution (APDR) curve. Heterogeneities in ventricular myocardium make the APDR curve present spatial variations, and some studies propose transmural dispersion of restitution to act as a potent arrhythmogenic substrate. Also, increments in restitution dispersion have been associated with greater propensity for ventricular tachycardia/fibrillation. The main limitation on the usability of APDR dispersion is that its quantification requires invasive procedures. We have developed a method to estimate dispersion of the APDR curves by making only use of the surface electrocardiogram (ECG, specifically based on the dynamics of the distance from T-wave peak to T-wave end (Tpe)). The underlying hypothesis of this work is that changes of Tpe reflect changes in spatial dispersion of repolarization, in some studies related to transmural dispersion. We measure differences in Tpe normalized by differences in the RR interval, that is, ΔTpe/ΔRR, between 2 different stationary states separated by a transient heart rate change as in a tilt test trial. If we restrict spatial to transmural dispersion of APD restitution, then it is possible to estimate the dispersion increase as Δα = (αmid−αepi), where αmid and αepi denote the midmyocardial and the epicardial slopes of the restitution curves, respectively, and are computed for a specific RR range as: αi = ΔAPDmid/ΔRR and αepi = ΔAPDepi/ΔRR. Noting that in this study, ΔTpe represents ΔAPDmid − ΔAPDepi we propose that Δα can be estimated as: Δα = ΔTpe/ΔRR.

We have evaluated our index on ECG recordings of healthy subjects performing the tilt test, by using selected ECG segments presenting stable heart rate. In our study, mean and SD values of ΔTpe/ΔRR were 0.0371 ± 0.0327 ms/ms, which are in very good agreement with differences in dynamic APDR slopes evaluated for the same RR range using an electrophysiologically detailed human ventricular model (ten Tusscher 2006), where Δμ is 0.0364 ± 0.0217. The mean ± SD value of the individual differences is −7.3E−4 ± 0.0256, where SD quantifies the inaccuracy variability. This comparison considers the spatial dispersion represented by Tpe to be transmural, and then modelling including connections and a more complete geometry will be the next step to evaluate the extrapolation of these results to more realistic conditions.

In brief, the method proposed in this study allows estimating dispersion of the dynamic APD restitution slopes along the ventricular wall by...
making only use of the surface ECG. A potential application of this method is to identify drugs that alter restitution curves in such a way that they increase dispersion of restitution and lead to cardiotoxicity.

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Gender differences in regional action potential durations and repolarization times
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Longer QT in women than in men despite shorter QRS is thought to predispose women to adverse effects of cardioactive agents. We used a novel repolarization model in 4992 normal men and women with normal ventricular conduction to estimate regional repolarization times (RTs) and action potential durations (APDs), with the objective to elucidate their possible role as a mechanism for generating the sex differences in global QT. The model uses global rate-adjusted QTpeak time for RTepi and QRpeak time (QRp) for excitation time (ETepi) of the left lateral wall, with specific adjustments for other regions. Endocardial RT was determined by the algorithm: RTendo = RTepi − λ (ETendo − ETepi), where the regression coefficient λ = −0.25 was obtained by an iterative procedure to maintain the normal left ventricular repolarization reversed and to keep APD gradients within normal limits.

| Parameter estimates for repolarization times and action potential durations by sex* |
|-----------------|--------|--------|--------|--------|-------|-------|
|                 | RTepi | APDepi | APDendo | APDgrad | Te-Tp | QT  |
| Men             | 320   | 275    | 316     | 41     | 95    | 415  |
| (21)            | (21)  | (21)   | (7.4)   | (19)   | (22)  |
| Women           | 337   | 294    | 334     | 40     | 88    | 426  |
| (20)            | (20)  | (21)   | (6.6)   | (19)   | (21)  |
| Men−women       | −18†  | −19†   | −17†    | 2NS    | −11†  |
|                 |       |        |         |        | 5†    |
|                 |       |        |         |        | −16†  |

*Parameter estimates (in milliseconds) are all rate adjusted, with rate-adjusted QTpeak interval being a common reference.
†p < .001.
NS = non-significant for gender differences.

Subscripts “epi” and “endo” refer to epicardial and endocardial, respectively; RTepi rate-adjusted QTpeak time; APDgrad = (APDendo − APDepi); Te-Tp, Tend-Tpeak interval; APDgrad, APD of the last region repolarized.

The data, listed above for left lateral wall, were closely similar for other regions and showed that APDs were 16 to 19 milliseconds shorter and rate-adjusted QT was 11 milliseconds shorter in men than in women (P < .001), but sex differences in transmural RT gradients were minimal. Tend-Tpeak interval was rate invariant. Shorter APDs and earlier onset of RTepi in men during repolarization initial half-period are the primary determinant of sex differences in QT interval. More localized rather than transmural RT gradients remain a plausible mechanism for cardiovulnerability in women.

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