

Frequency domain assessment of the coupling strength between ventricular repolarization duration and heart period during graded head-up tilt

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Abstract

We test the hypothesis that the degree of correlation between ventricular repolarization duration (VRD) and heart period (HP) carries information on cardiac autonomic regulation. The degree of correlation was assessed in the frequency domain using squared coherence function during an experimental protocol known to gradually induce a shift of sympathovagal balance toward sympathetic predominance (ie, graded head-up tilt). We observed a progressive decrease of squared coherence with tilt table inclination, thus confirming the working hypothesis. The VRD-HP uncoupling occurs in the high-frequency band, centered on the respiratory rate, thus suggesting that vagal withdrawal is responsible for the VRD-HP uncoupling.

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Introduction

When assessed on a beat-to-beat basis in stationary conditions, ventricular repolarization duration (VRD) and heart period (HP) exhibit rhythmical fluctuations in the low-frequency (LF) band (about 0.1 Hz in humans) and high-frequency (HF) band (at the respiratory rate).^{1–3} Despite the fact that the amplitude of these oscillations is dramatically different, which means that VRD fluctuations are 2 to 3 orders of magnitude smaller than that of HP oscillations, VRD and HP beat-to-beat series are significantly correlated both in the LF and HF bands.^{1,2} The high level of correlation is the result of the dependence of VRD on HP. This dependence is complex, and it includes a fast adaptation of the current VRD to the previous HP,^{4,5} long-term adaptations with time constant of about 1 to 2 minutes,^{5,6} and nonlinear phenomena such as the VRD-HP hysteresis⁶ and different responses to linearly increasing or decreasing HPs.⁷ The dynamic dependence of VRD on HP is usually studied in stationary conditions according to a model-based approach that linearizes VRD and HP dynamics under the

hypothesis of small variations around the mean value⁸ and describes VRD variations in terms of a linear combination of previous VRD changes, previous HP variations, and, eventually, influences of respiration, plus a noise term modeling influences capable of driving VRD independently of HP fluctuations.^{8–11} The exploitation of these modeling approaches allowed the quantification of the fraction of VRD variability driven by HP changes (ie, between 60% and 70% in healthy young subjects in a supine position).^{8,11}

In addition to the dependence of VRD on HP, VRD depends on factors independent of HP: for example, given the same HP, VRD depends on the state of autonomic nervous system.^{12–15} Although it is unclear how these factors affect VRD variability under stationary conditions, it was demonstrated that the fraction of power of VRD variability independent of HP variations cannot be dismissed: indeed, it ranges between 30% and 40% of the overall VRD variance in healthy subjects in a supine resting position.^{8,11} The presence of a portion of VRD variability independent of HP changes imposes a certain degree of uncorrelation between VRD and HP variabilities: correlation is high but significantly different from the value indicating perfect correlation (ie, 1). We hypothesize that the degree of correlation between VRD and HP variabilities might contain significant information about cardiac autonomic regulation.

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To test this hypothesis, we monitor the degree of correlation between VRD and HP series during an experimental protocol known to gradually modify cardiac autonomic control (ie, graded head-up tilt test). This experimental protocol is known to produce a shift of sympathovagal balance toward sympathetic predominance according to the tilt table inclination.^{16–19} The degree of linear association between VRD and HP series as a function of the frequency is assessed with a traditional linear approach based on the squared coherence function. Two methods for automatically computing VRD from the surface electrocardiogram were used²⁰: VRD was derived as the temporal difference between the R-wave peak and T-wave apex (RTa) or end (RTe).

Experimental protocol and data analysis

Experimental protocol

We studied 15 healthy nonsmoking humans (age, from 24 to 54 years; median, 28 years; 9 men and 6 women). A detailed medical history and examination excluded the evidence of any disease. The subjects did not take any medication and consume any caffeine or alcohol-containing beverages in the 24 hours before the recording. Informed consent was required from all subjects before taking part in the study. Subjects were on the tilt table supported by 2 belts at the level of the thigh and waist, respectively, and with both the feet touching the footrest of the tilt table. During the protocol, the subjects breathed spontaneously but were not allowed to talk. The study adheres to the principles of the Declaration of Helsinki for medical research involving human subjects. The human research and ethical review boards of the L. Sacco Hospital and the Department of Clinical Sciences approved the protocol.

Electrocardiogram (Biosignal Conditioning Device, Marazza, Monza, Italy) from lead II was recorded at rest (REST) and during head-up tilt (T). Electrocardiogram was sampled at 1000 Hz using an A/D board (National Instruments, Austin, TX) plugged in a personal computer. After 7 minutes at REST, the subjects underwent a 10 minute session of T, with table angles randomly chosen within the set {15,30,45,60,75,90} (T15, T30, T45, T60, T75, T90). Each T session was always preceded by a REST session and followed by 8 minutes of recovery. All subjects were able to complete the overall protocol without experiencing any sign of presyncope. The duration of the phases was never varied.

Variability series extraction

Electrocardiogram traces were preprocessed according to Porta et al²⁰ to limit noise and cancel baseline wandering. Heart period was computed as the temporal distance between 2 consecutive R peaks (R-R interval). The R-wave peak was detected using a derivative threshold algorithm, and its occurrence was fixed using parabolic interpolation. The T-wave apex was searched in a predefined temporal window, the duration of which depended on the preceding R-R interval. The T-wave apex was located using parabolic

interpolation.²⁰ The T-wave end was located according to a threshold on the first derivative set as a fraction (ie, 30%) of the absolute maximal first derivative value computed on the T-wave downslope.²⁰ Ventricular repolarization duration was computed as RTa and RTe intervals. The i -th RTa or RTe intervals followed the i -th R-R interval, thus directly linking the current RT interval to the preceding R-R duration. All the R-wave peak detections were carefully checked to avoid erroneous identifications or missed beats. R-R and RT series were not corrected or filtered except in correspondence of isolated premature ventricular contractions, which, in the study population, were very few. In this case, cubic spline interpolation technique was applied over the R-R and RT values that were directly influenced by the occurrence of the premature ventricular contraction. The series length ranged from 220 to 260 beats and was kept constant while varying the experimental condition in the same subject. After calculating the R-R, RTa, and RTe mean (μ_{R-R} , μ_{RTa} , and μ_{RTe}), the R-R, RTa, and RTe series were linearly detrended before any further analysis. R-R, RTa, and RTe variance (σ^2_{R-R} , σ^2_{RTa} , and σ^2_{RTe}) were calculated from detrended series.

Spectral analysis of variability series

Spectral analysis was performed via a parametric approach exploiting an autoregressive (AR) model.²¹ Briefly, the AR model describes the beat-to-beat series in the time domain as a linear combination of p past samples weighted by the coefficients a_i 's plus a zero mean white noise. The Levinson-Durbin recursive algorithm was used to estimate directly from the data the coefficients of the AR model and the variance of the white noise. The number of coefficients p was chosen according to the Akaike figure of merit. According to the maximum entropy spectral estimation approach,²² power spectral density was computed from the AR coefficients and from the variance of the white noise. The power spectral density was factorized into terms, referred to as *spectral components*, the sum of which provides the entire power spectral density.²³ A spectral component was labeled as LF if its central frequency was between 0.04 and 0.15 Hz, whereas it was classified as HF if its central frequency was between 0.15 and 0.5 Hz.²⁴ The *LF and HF powers* were defined as the sum of the powers of all LF and HF spectral components, respectively. They were expressed in absolute units (in milliseconds squared) and labeled as LF_{R-R} , HF_{R-R} , LF_{RTa} , HF_{RTa} , LF_{RTe} , and HF_{RTe} .

Assessment of the strength of VRD-HP coupling

The assessment of the strength of the VRD-HP relation was estimated via the squared coherence function measuring the degree of a linear correlation between VRD and R-R series as a function of the frequency. The squared coherence function is assessed as

$$K_{VRD-R-R}^2(f) = \frac{[C_{VRD-R-R}(f)]^2}{S_{VRD}(f) \cdot S_{R-R}(f)} \quad (1)$$

where $|C_{VRD-R-R}|^2$ is the squared cross-spectrum modulus between VRD and R-R series, and S_{VRD} and S_{R-R} are

the power spectra of VRD and R-R series. $K^2_{\text{VRD-R-R}}$ ranges from 0 to 1, respectively, indicating a perfect uncorrelation and a full correlation. The calculation of $C_{\text{VRD-R-R}}$ requires a bivariate approach instead of the monivariate one required by spectral analysis. We chose a parametric approach based on bivariate AR model²⁵ to estimate $C_{\text{VRD-R-R}}$, S_{VRD} , and $S_{\text{R-R}}$. The model order was fixed to 10, and the coefficients of the bivariate AR model were identified using least-squares approach.^{26,27} $K^2_{\text{VRD-R-R}}$ was sampled in correspondence of the weighted average of the central frequencies of the LF and HF components found in the R-R series, where the weights were the powers of the components. The parameters $K^2_{\text{VRD-R-R(LF)}}$ and $K^2_{\text{VRD-R-R(HF)}}$ were assessed with both VRD = RTa and VRD = RTe.

Statistical analysis

To check whether parameters changed with respect to those found at REST, a 1-way repeated-measures analysis of variance or the Friedman repeated-measures analysis of variance on ranks when appropriate was applied (Dunn test). Linear regression analysis of any extracted parameter on tilt angles was carried out. Pearson product moment correlation coefficient, r , was calculated. A P value less than .05 was considered significant.

Results

The mean of R-R, RTa, and RTe ($\mu_{\text{R-R}}$, μ_{RTa} , and μ_{RTe}) significantly decreased with respect to REST when tilt table inclination was larger or equal to 45°, 30°, and 30°, respectively (Fig. 1A, C, E). Whereas the R-R variance, $\sigma^2_{\text{R-R}}$, significantly decreased (Fig. 1B), the RTa and RTe variances, σ^2_{RTa} and σ^2_{RTe} , significantly increased (Fig. 1D, F). The significant decrease of $\sigma^2_{\text{R-R}}$ occurred when tilt table inclination was larger or equal to 60°, whereas the increase of σ^2_{RTa} and σ^2_{RTe} was significant during T75 and T90.

The R-R power in the LF band, $\text{LF}_{\text{R-R}}$, remained constant with tilt table angles (Fig. 2A). Similar trend was observed in the case of the RTa and RTe powers in the HF band (ie, HF_{RTa} and HF_{RTe} ; Fig. 2D, F). Whereas the R-R power in the HF band, $\text{HF}_{\text{R-R}}$, decreased when tilt table angles were larger or equal to 30° (Fig. 2B), the RTa and RTe powers in the LF band (ie, LF_{RTa} and LF_{RTe} ; Fig. 2C, E) increased when tilt table inclinations were larger or equal to 45° and 30°, respectively.

Fig. 3 shows an example of R-R and RTa series and the associated squared coherence function $K^2_{\text{RTa-R-R}}$ at REST (Fig. 3A-C) and during T90 (Fig. 3D-F). Both $K^2_{\text{RTa-R-R(LF)}}$ and $K^2_{\text{RTa-R-R(HF)}}$ decrease during T90, but the decrease of $K^2_{\text{RTa-R-R(HF)}}$ is more evident.

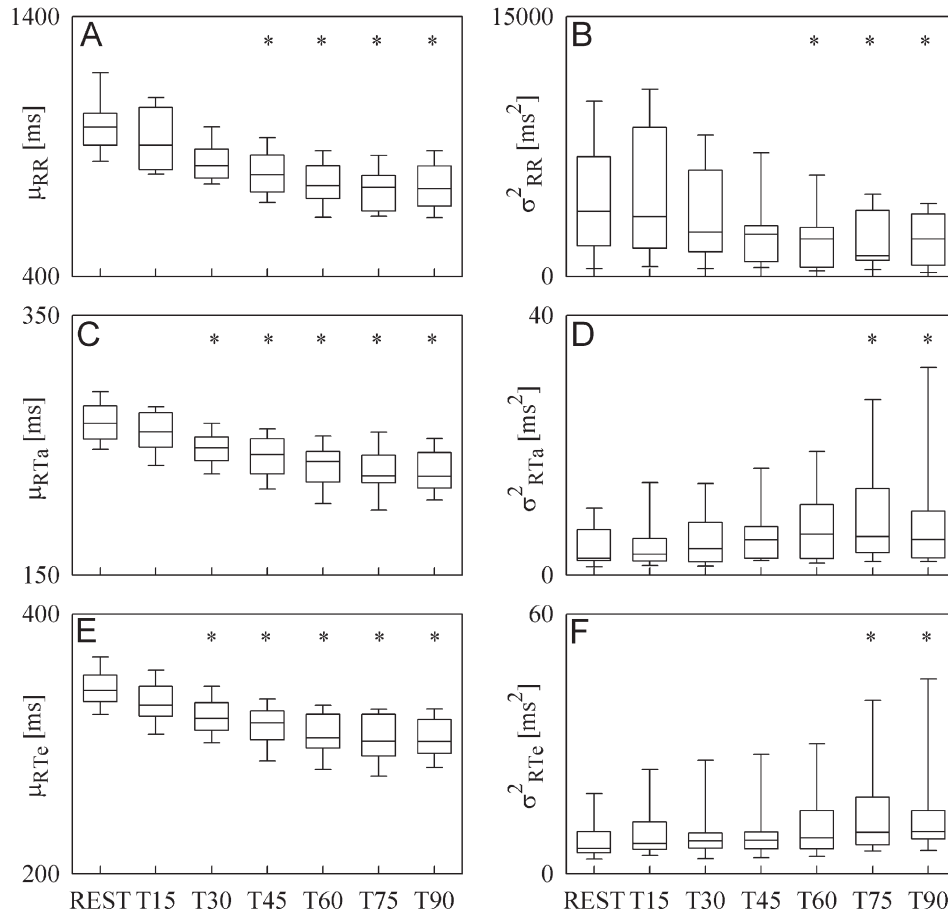


Fig. 1. Box-and-whisker plots report the 10th, 25th, 50th, 75th, and 90th percentiles of $\mu_{\text{R-R}}$ (A), $\sigma^2_{\text{R-R}}$ (B), μ_{RTa} (C), σ^2_{RTa} (D), μ_{RTe} (E), and σ^2_{RTe} (F) as a function of the tilt table angle. * $P < .05$ vs REST.

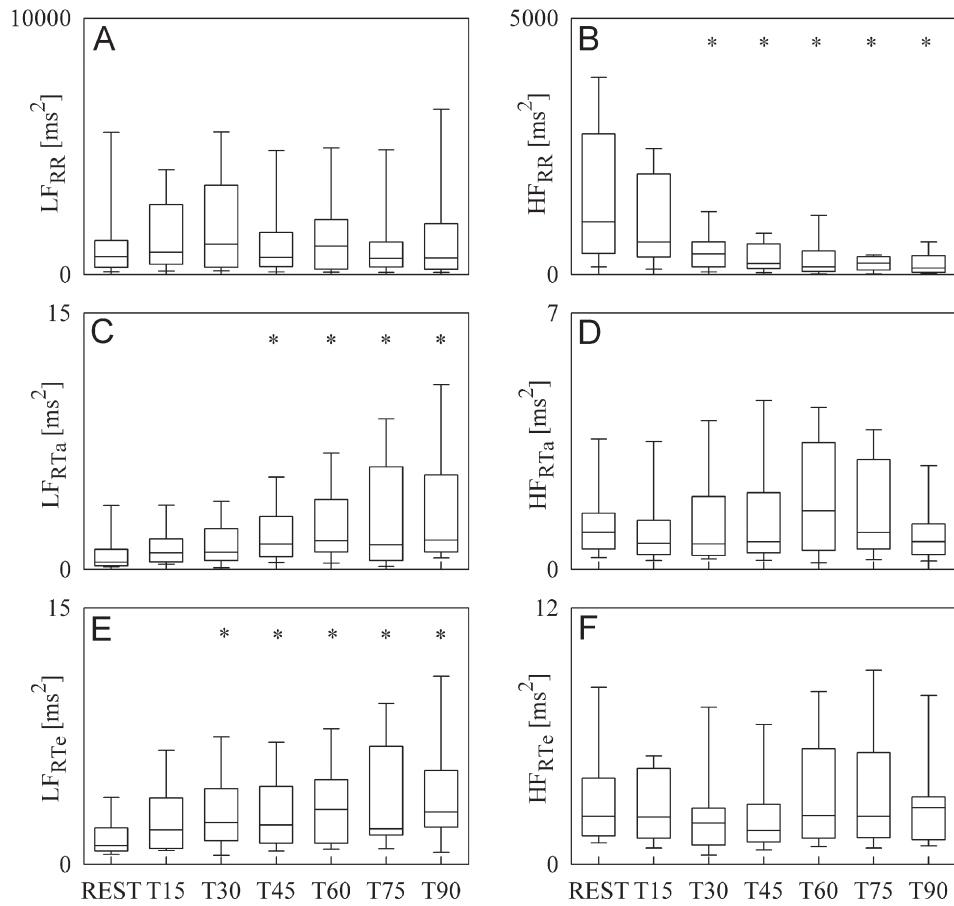


Fig. 2. Box-and-whisker plots report the 10th, 25th, 50th, 75th, and 90th percentiles of LF_{R-R} (A), HF_{R-R} (B), LF_{RTa} (C), HF_{RTa} (D), LF_{RTc} (E), and HF_{RTc} (F) as a function of the tilt table angle. * $P < .05$ vs REST.

Fig. 4 shows the course of a squared coherence in LF and HF bands as a function of tilt table inclination. The squared coherence assessed in the LF band (ie, $K^2_{RTa-R-R}[LF]$ and

$K^2_{RTc-R-R}[LF]$; Fig. 4A, C) did not vary with tilt table angles. On the contrary, the squared coherence in the HF band (ie, $K^2_{RTa-R-R}[HF]$ and $K^2_{RTc-R-R}[HF]$; Fig. 4B, D)

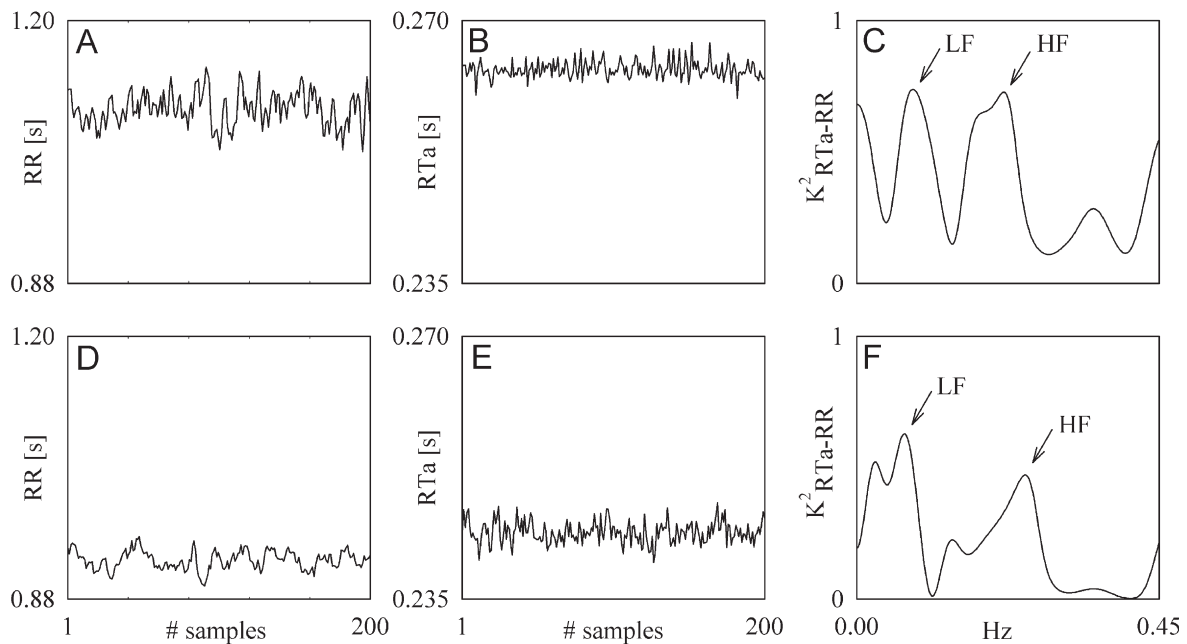


Fig. 3. Representative example of R-R and RTa beat-to-beat series at REST (A, B) and during T90 (D, E). The associated squared coherence function is shown in panels (C) and (F), respectively. The decrease of $K^2_{RTa-R-R}(HF)$ induced by T90 is apparent, whereas that of $K^2_{RTa-R-R}(LF)$ is marginal.

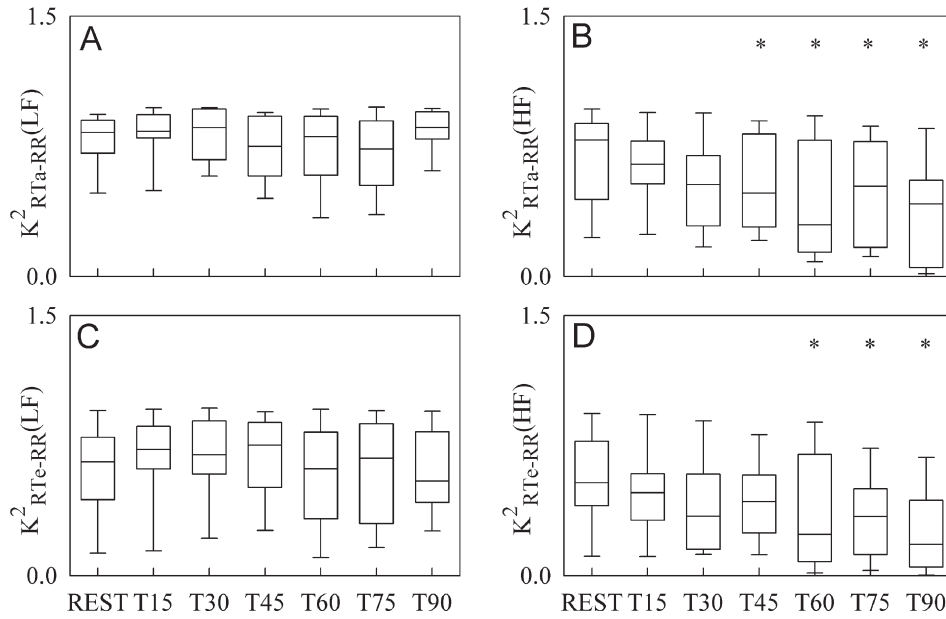


Fig. 4. Box-and-whisker plots report the 10th, 25th, 50th, 75th, and 90th percentiles of $K^2_{RTa-R-R}(LF)$ (A), $K^2_{RTa-R-R}(HF)$ (B), $K^2_{RTe-R-R}(LF)$ (C), and $K^2_{RTe-R-R}(HF)$ (D) as a function of the tilt table angle. * $P < .05$ vs REST.

significantly decreased when tilt table angles were larger or equal to 45° and 60° , respectively.

Results of correlation analysis of all the parameters vs tilt table angles are shown in Table 1. All the considered parameters were linearly related with tilt table angles, with notable exceptions of LF_{R-R} , HF_{RTa} , HF_{RTe} , $K^2_{RTa-R-R}(LF)$, and $K^2_{RTe-R-R}(LF)$. Correlation of μ_{R-R} , μ_{RTa} , μ_{RTe} , σ^2_{R-R} , and HF_{R-R} on tilt table inclinations was negative and highly significant (ie, $P < .001$). On the contrary, correlation of σ^2_{RTa} and σ^2_{RTe} with tilt table angles was positive and weaker ($r = 0.25$ and $r = 0.2$, respectively; $P < .05$). Correlation of the power of RTa and RTe series on the magnitude of gravitational stimulus gained importance when it was assessed in the LF band: $r = 0.33$ and $r = 0.3$ in the

case of LF_{RTa} and LF_{RTe} , respectively ($P < .01$). The series of RTe and RTa became progressively uncoupled to R-R series in the HF band: indeed, $r = -0.36$ and $r = -0.30$ in the case of $K^2_{RTa-R-R}(HF)$ and $K^2_{RTe-R-R}(HF)$, respectively ($P < .01$). The slopes of the regression lines of $K^2_{RTa-R-R}(HF)$ and $K^2_{RTe-R-R}(HF)$ on tilt table angles were not significantly different. When parameters derived from RTa and RTe variabilities were significantly linearly related with tilt table angles, the magnitude of the correlation (ie, r^2) derived from indexes extracted from RTa series was larger than that derived from the RTe one.

Discussion

A significant fraction of VRD variability is driven by HP changes due to the relation between VRD and HP.^{2,4,5,8,11,28,29} However, both autonomic nervous system influences determining changes of VRD independently of HP¹²⁻¹⁵ and respiratory-related artifacts, which likely to affect more importantly VRD measurement than the HP one,²⁰ generate a certain amount of VRD variability unrelated to HP variations. The presence of a quote of VRD variability independent of HP changes limits VRD-HP correlation by inducing a certain degree of uncoupling between VRD and HP series.^{1,2,8}

The present study demonstrates that the degree of linear correlation between VRD and HP carries information about cardiac autonomic regulation. Indeed, it progressively changes during an experimental protocol capable to produce a gradual modification of cardiac autonomic control.

The observed progressive uncoupling is not surprising and can be related to the progressive dissociation between HP and VRD regulations with the magnitude of the gravitational stimulus (ie, the tilt table inclination). This progressive dissociation appears clearly at the level of

Table 1
Correlation analysis of all extracted parameters vs tilt table angles

	<i>r</i>	<i>P</i>	
μ_{R-R}	-0.684	8.40×10^{-16}	Yes
σ^2_{R-R}	-0.331	5.62×10^{-4}	Yes
μ_{RTa}	-0.615	2.87×10^{-12}	Yes
σ^2_{RTa}	0.249	1.11×10^{-2}	Yes
μ_{RTe}	-0.647	9.16×10^{-14}	Yes
σ^2_{RTe}	0.2	4.10×10^{-2}	Yes
LF_{R-R}	0.012	0.90	No
HF_{R-R}	-0.528	7.12×10^{-9}	Yes
LF_{RTa}	0.326	1.94×10^{-4}	Yes
HF_{RTa}	0.027	0.785	No
LF_{RTe}	0.297	2.08×10^{-3}	Yes
HF_{RTe}	0.067	0.497	No
$K^2_{RTa-R-R}(LF)$	-0.055	0.58	No
$K^2_{RTa-R-R}(HF)$	-0.362	1.46×10^{-4}	Yes
$K^2_{RTe-R-R}(LF)$	-0.082	0.42	No
$K^2_{RTe-R-R}(HF)$	-0.30	1.93×10^{-3}	Yes

P indicates probability of the type I error; yes, the variable is significantly related with tilt angles, with $P < .05$; no, not significantly related with tilt angles.

variances: indeed, whereas HP variance progressively decreased with tilt table angles,^{16,17,19,30} the VRD variability gradually increased. The dissociation between HP and VRD regulations is evident even when the variance is decomposed in the LF and HF bands. In the LF band, the HP power was unrelated to the tilt table angles, whereas the VRD power progressively increased. In the HF band, the HP power decreased as a function of tilt table angles, whereas the VRD power remained constant. Data suggest that VRD variability can be used to infer cardiac sympathetic control,^{31–34} especially when the sympathetic drive is high (ie, at the highest tilt table inclination)³⁵ and when assessed in the LF band (the relation of LF power with tilt table angles is stronger than that of the variance). Conversely, the absolute amount of HP variability, especially when assessed in the HF band, is mainly related to vagal modulation³⁶ being progressively reduced during a graded head-up tilt protocol.^{16,17,19,30} The stability of LF power of the HP variability with tilt table inclination can be explained in terms of the involvement of baroreflex in buffering arterial pressure changes.^{16,37} Baroreflex control does not affect VRD changes; thus, LF power of VRD variability can increase with tilt table angles. The steadiness of HF power of the VRD variability with tilt table inclination suggests that this index has no relation with autonomic nervous system² and that it is related to respiratory-related artifacts, such as cardiac axis movements, capable of rhythmically distorting the T-wave morphology.²⁰

The present study demonstrates that uncorrelation between VRD and HP variabilities is related to the uncoupling between HF oscillations present on both VRD and HP variability series. Indeed, the degree of correlation between LF oscillations remained constant. Because graded head-up tilt induces an increase of sympathetic tone and a vagal withdrawal proportional to the tilt table angles, we suggest that vagal withdrawal, more than sympathetic activation, is responsible for the observed uncoupling. This finding implies that LF oscillations of VRD variability preserved a more significant dependence on HP changes than did HF oscillations.

We observe that when the VRD variability parameters were assessed from RTa series, the strength of the linear relation with tilt table angles was stronger (ie, r^2 was larger) than that obtained from RTe series. This finding might be explained in terms of the effects of broad band noise, known to affect more importantly RTe measurement than the RTa one²⁰ and responsible for limiting the dependence of any RT measure on R-R interval.

Cardiac axis is affected by body position, thus possibly diminishing the amplitude of the T wave with tilt table angles. As a result, part of the gradual uncoupling between R-R and RTa measures could be explained in terms of a reduction of the signal-to-noise ratio due to the gradual decrease of T-wave amplitude with tilt table inclination. However, because this artifact affects more importantly RTa than RTe measures, we should find that the slope of the regression line of $K^2_{RTa-R-R}$ on tilt table angle is steeper than that of $K^2_{RTe-R-R}$. Because we did not find a significant

difference between the slopes, we suggest that the progressive uncoupling between RTa or RTe and R-R cannot be solely explained in terms of cardiac axis modification with body position, and a major involvement of the autonomic nervous system is likely. Future studies should address specifically the issue of the relation between T-wave amplitude and levels of VRD variability. The use of the vector magnitude instead of single lead might be helpful in maximizing signal-to-noise ratio and keeping under control influences of the body position and noise on RTa and RTe measurements.

Conclusions

The degree of correlation between VRD and HP beat-to-beat variabilities provides information about cardiac autonomic regulation and seems to be more related to the vagal withdrawal than sympathetic activation observed during head-up tilt. We conclude that indexes monitoring the VRD-HP coupling should be monitored in addition to more traditional VRD variability markers when inferring cardiac control directed to ventricles.

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