Resting heart rate and cardiac autonomic tone during passive head-up tilt: a cross-sectional study in 569 subjects without cardiovascular diseases

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Research article

Keywords: autonomic nervous system, heart rate, heart rate variability, passive head-up tilt

Posted Date: November 4th, 2019

DOI: https://doi.org/10.21203/rs.2.16812/v1

Abstract

Background Resting heart rate (HR) and its variability (HRV) reflect cardiac sympathovagal balance that can stimulated by head-up tilting. HRV is significantly influenced by the level of HR, but how much HRV offers additional information about cardiac autonomic tone than HR alone remains unresolved. We examined the relation of resting HR with short term HRV during passive head-up tilt.Methods Hemodynamics of 569 subjects without medications with direct cardiovascular effects and known cardiovascular diseases were recorded using whole-body impedance cardiography, continuous radial pulse wave analysis and electrocardiography based HRV analysis in supine and upright positions. For statistical analyses the study population was divided into tertiles of resting heart rate according to sexes.Results Higher low frequency to high frequency ratio (LF/HF) of HRV (reflecting sympathovagal balance) was associated with higher HR in supine ($p<0.001$) and upright positions ($p=0.008$). The outcome was similar when the HRV analysis was based on HR instead of RR-intervals ($p<0.001$ supine, $p=0.012$ upright). The lowest HR tertile presented with higher supine to upright increase in LF/HF than the highest HR tertile (1.1 vs. 0.85, respectively, $p=0.037$).Conclusion Higher resting HR is related to higher LF/HF in supine and upright positions, reflecting higher cardiac sympathovagal balance. Lower resting HR is associated with lower resting LF/HF, but with a more pronounced increase in both HR and LF/HF during head-up tilt, suggesting greater change cardiac sympathovagal balance in response to upright posture.

Background

Heart rate variability (HRV) is associated with heart rate (HR), and this association is determined by cardiac autonomic nervous tone. Hence, higher sympathetic activity is related to higher HR and lower HRV [1-3]. Sympathetic tone can be easily stimulated by the change of body position from supine to upright [2, 4].

HRV has been widely studied and lower HRV is a risk factor for adverse cardiovascular outcomes [5] and a predictor of mortality of cardiac but also of other causes [6, 7]. Reduced HRV is also observed in psychic conditions such as mental stress and depression [8, 9]. Higher resting HR has been related with cardiovascular events and less favourable prognosis in healthy men and women [10, 11]. A recent meta-analysis concluded that resting HR is a predictor of cardiovascular and all-cause mortality in the general population independent of the classic cardiovascular risk factors [12]. The mechanisms of these relations are not well understood but an imbalance between vagal and sympathetic tone is a conceivable factor. Both HR and HRV represent the prevailing cardiac sympathovagal tone, and the association of reduced HRV with poor prognosis may be attributed to the concomitant level of HR [13-15].

The relation of HRV to HR is not only physiological but also mathematical, and the relation is not linear [3, 16]. HRV is usually calculated from consecutive RR-intervals reciprocal to HR measures. Therefore, when lower and higher initial HR levels are compared, a similar change in HR results in a greater change in RR-interval during lower HR. HRV is usually evaluated by the use of time or frequency domains, both of

which provide information about vagal and sympathetic tone [3]. From the frequency domain parameters the high frequency (HF) component represents vagal activation and the low frequency (LF) component predominantly represents the sympathetic component of HRV [2]. From the time domain parameters the square root of mean squared differences of normal to normal RR-intervals (RMSSD) mostly represents vagal tone while the standard deviation of normal to normal RR-intervals (SDNN) is an estimate of total HRV [3]. There are mathematical methods that can be applied to strengthen or weaken the dependence of HRV on HR [17].

Because HRV includes information of HR and its variation, it has not been ascertained which one of these factors (i.e. HR or HRV) relates HRV to poor prognosis [13, 18]. Furthermore, both HR and HRV are related with sex, and typically HR is lower but sympathovagal balance (LF/HF ratio) is higher among men [4, 19, 20]. In addition, the relation of higher resting HR with less favourable prognosis seems more pronounced among men than women in population based studies [10, 11, 19].

In this study we examined whether resting HR level predicts sympathovagal balance measured by HRV in time domain and frequency domain parameters during supine and upright position. The study population was without cardiovascular diseases and medications with direct cardiovascular influences. Because of the nonlinear relationship between RR-interval and HR, we tested the association of resting HR with HRV that was analysed from both HR and RR-intervals.

Methods

Subjects

This research is a part of DYNAMIC-study which is an on-going study focusing on non-invasive recording of hemodynamics from subjects with and without cardiovascular diseases (Clinicaltrialsregister.eu 2006-002065-39; Clinicaltrials.gov NCT01742702). The study has been approved by the ethics committee of the Tampere University Hospital and all study subjects gave informed consent. Volunteers for the research were recruited by announcements delivered in public organizations including Tampere University Hospital, Tampere University, Varala sports institute and occupational health care organizations. All study subjects were interviewed and examined by a physician who documented medical history and lifestyle habits. Smoking habits were determined as never smokers, previous smokers and current smokers and smoking in pack years was registered. Alcohol consumption was documented as weekly amounts of standard drinks (i.e. ~12 g alcohol). Physical activity was determined as number of exercise sessions (lasting at least 30 minutes) per week with at least moderate level of work load (for example brisk walking or jogging).

From the present study subjects with a history or cardiovascular disease, diabetes mellitus, kidney disease, heart rhythm other than sinus, alcohol or substance abuse, concurrent malignancy, or medications with direct effects on the cardiovascular system were excluded. Also subjects with

incomplete hemodynamic recordings (i.e. missing HR or HRV values) were excluded. Altogether 569 subjects (mean age 44.9, 95% confidence intervals of the mean (CI) (43.9, 45.9) years; 287 men) were included. The following stable medical conditions with adequate medications were included: asthma (medicated with inhaled corticosteroids, n=12), allergy (n=7), depression (n=29), dyslipidemia (n=13), dyspepsia (n=10), epilepsy (n=3), hypothyroidism (n=16), and rheumatoid arthritis or lupus (n=3). In total 74 females (26%) were on low dose hormone therapy, i.e. intrauterine device (44 subjects) or peroral combination therapy (30 subjects).

Laboratory tests

Blood sampling was conducted after overnight fasting. Concentrations of plasma sodium, potassium, glucose, creatinine, cystatin C, C-reactive protein, triglyceride, and total, high-density (HDL) and low-density lipoprotein (LDL) cholesterol were determined by Cobas Integra 700/800 (F. Hoffmann-LaRoche Ltd, Basel, Switzerland), or Cobas 6000, module c501 (Roche Diagnostics, Basel, Switzerland). Leukocyte count and hematocrit were determined by ADVIA 120 or 2120 analyzers (Bayer Health Care, Tarrytown, NY, USA). Estimated glomerular filtration rate was calculated using CKD-EPI creatinine-cystatin C equation [21].

Hemodynamic measurements

Trained research nurse carried out hemodynamic measurements in a quiet and temperature-controlled laboratory. The study subjects were guided to avoid caffeine products, smoking or heavy meals 4 hours prior to the investigation. Before proper measurements the subjects were resting supine about 10 minutes, during which period a tonometric sensor for pulse wave analysis was placed on left radial pulsation, brachial blood pressure cuff on right upper arm for blood pressure calibration, and electrodes of whole body impedance cardiography were placed on the body surface. The following hemodynamic variables were captured in a beat-to-beat fashion during 5 min periods in supine and passive upright position: HR (1/min), pulse wave velocity (PWV, m/s), systemic vascular resistance index (SVRI, systemic vascular resistance/body surface area, dyn*s/cm^5/m^2), cardiac index (cardiac output/body surface area, l/min/m^2) and radial blood pressure (mmHg).

For the whole body impedance cardiography measurement the CircMon^R-device (JR Medical Ltd., Tallinn, Estonia) and for pulse wave analysis the SphygmoCor pulse wave monitoring system (SpygmoCor PWMx, Atcor medical, Australia) was used. The measurement protocol is described in detail in our previous publications [22, 23] and it has been shown to be repeatable and reproducible [24, 25]. In addition, PWV values measured using impedance cardiography show good correlation with the tonometric method (r=0.82, bias 0.02 m/s, 95% CI 0.21 to 0.25) [26], cardiac output values measured using whole body impedance cardiography are congruent with the thermodilution method (bias 0.00

l/min, 95% CI -0.26 to 0.26) and the direct oxygen Fick method (bias -0.32 l/min, 95% CI -0.69 to 0.05) [27], and the correlation between stroke volume recordings using impedance cardiography and 3D-echocardiography has been shown to be good (r=0.781, bias 4.1 ml, 95% CI 2.2 to 10.4) [22].

Heart rate variability analysis

Beat-to-beat RR-intervals were captured from electrocardiogram recordings by the impedance cardiography device at 200 Hz sampling rate. Then HRV results were analyzed separately from both RR-intervals and HR by the use of Matlab-software (Natick, Massachusetts, USA). First, normal RR-intervals were recognized and an interval was considered ectopic or an artifact if it differed by more than 20 % from the previous ones. The artifact RR-intervals were processed by the cubic spline interpolation method [28].

The following HRV parameters were calculated from the measurements of 5 minutes in the supine and 5 minutes in the upright position: (1) time domain HRV parameters: mean of normal to normal RR (NN)-intervals, SDNN (standard deviation of NN-intervals) and RMSSD (square root of mean squared differences of NN-intervals), and (2) frequency domain parameters by the fast Fourier transformation method [3, 29]: power in low frequency range (LF, 0.04-0.15 Hz), power in high frequency range (HF, 0.15-0.40 Hz), LF to HR ratio (LF/HF) and total power.

As described above, the magnitude of HRV depends on the prevailing level of HR. Hence, we calculated the HRV parameters also based on the HR data in addition to the RR-interval data using mean of 60/RR-interval (i.e. HR) instead of pure RR-interval values in the calculations. Furthermore, to weaken the dependence of HRV on HR, the HRV power spectra (from RR-interval data) were divided by average RR-interval (avRRI) to the fourth power and these HRV values, total power, HF power, LF power and LF/HF ($TP/avRRI^4$, $HF/avRRI^4$, $LF/avRRI^4$, $LFHF/avRRI^4$, respectively) were included in the analyses [17].

Statistical analyses

IBM SPSS Statistics software (version 25, Armonk, New York, USA) was used for statistical analyses and p-values <0.05 were considered significant. Continuous data was reported as means and 95% CI if normally distributed, and as medians and interquartile range if asymmetrically distributed. For statistical analyses the study subjects were divided into three tertiles according to the mean resting HR, determined from the mean of the last 3 minutes during the 5 minutes of supine measurement. Because HR and HRV are significantly dependent on sex [4, 30], the tertiles were determined separately for men and women but for statistical power men and women were analyzed together.

Differences in study population demographics, hemodynamic measurements and laboratory values between the HR tertile groups were examined using analysis of variances (ANOVA). Tukeys HSD post hoc

test was performed for homogeneous and Tamhane's T2 post hoc test for nonhomogeneous variables. Natural logarithms of HRV parameters, C-reactive protein and fasting triglyceride concentrations were used in the statistical analyses to normalize their skewed distributions. The proportions of smoking habits (never, previous or current smoker) were compared using the χ^2 test.

The association of continuously measured HR with HRV during supine and upright positions was investigated using linear regression analysis (with natural logarithms of nonlinear HRV parameters). The other explanatory factors for linear regression analysis were selected as based on the comparisons between the tertile groups (ANOVA). We previously reported that blood pressure, cardiac index and SVRI are significantly related with the resting level of HR (in both supine and upright positions) [22]. Therefore, mean blood pressure from the hemodynamic variables was selected to the regression analyses rather than cardiac index and SVRI together. Linear regression model for supine and upright HR was calculated using RR-interval -related LF/HF ratio and then the analyses were repeated using LF/HR ratio divided by average RR-interval to the fourth power (to weaken the HR dependence) [17].

Results

Study population

The study subjects were divided into tertiles on the grounds of resting HR according to sexes, thus altogether 187 subjects were allocated to the lowest HR group (HR group 1), 190 subjects to the intermediate HR group (HR group 2) and 192 subjects to the highest HR group (HR group 3). From the traditional cardiovascular risk factors, body mass index and fasting plasma glucose were highest, and HDL cholesterol was lowest in the HR group 3 ($p<0.05$ for all, Table 1). In addition, fasting plasma triglycerides, C-reactive protein and cystatin C were highest in the HR group 3. The lifestyle habits amount of smoking, weekly alcohol consumption or physical activity did not differ between tertile groups ($p>0.05$ for all, Table 1). The study population demographics are presented in Table 1 and ranges of HR according to tertile groups in Table 2.

Determinants of blood pressure

Mean resting HR in the whole study population was 64/min (95% CI 63, 64) and there was a statistically significant difference in resting HR between sexes: resting HR among men was 63/min (95% CI 61, 64) and among women 65/min (95% CI 64, 66; $p<0.001$). Mean HR values according to the HR tertiles are depicted in Table 2 and Figure 1. Both systolic and diastolic radial blood pressures were lower in the HR group 1 when compared with HR group 3 (131/75 vs. 141/83 mmHg, respectively, $p<0.001$ for systolic and diastolic blood pressure, Table 2). Also cardiac index and PWV were lower in the HR group 1 in

comparison with other HR tertiles ($p<0.001$ for all comparisons), while SVRI was higher in the HR group 1 versus the HR tertiles 2 and 3 ($p<0.004$, for both comparisons, Table 2).

Resting heart rate and its variability analyzed using variance analysis

Median HRV values according to the HR tertile groups are presented in Table 3 and the outcomes of the statistical analyses in Figures 2 and 3. Mean logarithmic HRV values were first compared. Mean RR-interval was reciprocally shortened with increasing HR during supine and upright measurements ($p<0.001$ for all group comparisons, Figure 1). Also, SDNN and RMSSD were lower with increasing HR in the tertile groups both supine and upright ($p\leq0.005$ for all group comparisons, Figure 2).

From the frequency domain parameters, total power of variation decreased with increasing HR ($p\leq0.020$, for all group comparisons) and the differences remained similar during posture change from supine to upright ($p\leq0.034$, for all group comparisons, Figure 3A). Both parasympathetic and sympathetic tone related parameters (i.e. power in HF and LF range) were higher among the HR group 1 than in HR groups 2 and 3 ($p\leq0.004$ for all group comparisons, Figure 3B-C). The differences between the HR tertile groups were similar both supine and upright. The LF/HF ratio was lower in the HR group 1 when compared with HR group 3 during supine position ($p<0.001$ for group comparison, Figure 3D), while the differences between the HR tertiles were not statistically significant during upright position ($p=0.116$).

The change in LF power from supine to upright position was not significantly different between the groups ($p=0.155$), but the decrease in HF power was most marked in the HR group 1 and lowest in the HR group 3 (401 ms^2 in group 1, 202 ms^2 in group 2, 117 ms^2 in group 3, $p<0.001$ for all HR group comparisons). The posture change from supine to upright more increased the LF/HF in the HR group 1 than in the HR group 3 ($p=0.037$ for the difference). The supine to upright change in total power was not significantly different between the HR groups ($p=0.074$). The results of the HR tertiles in the analyses of HR based HRV parameters are presented in Supplemental Figures 1-2.

Heart rate variation with the approach to weaken the heart rate dependence

HRV parameters analyzed with the approach to weaken the HR dependence (HRV divided by average RR-interval to the fourth power) were all associated with the resting HR tertiles. All of the measured frequency domain HRV parameters (TP/$avRRI^4$, HF/$avRRI^4$, LF/$avRRI^4$, LFHF/$avRRI^4$) were lowest within the HR tertile 1 and highest within the HR tertile 3, both supine and upright ($p < 0.001$ for all ANOVA tests and post hoc tests, respectively, Figure 4).

Heart rate and heart rate variation in linear regression analyses

The relation of resting and upright HR and HRV was studied in a stepwise linear regression model where the HRV variables (R-R interval related LF/HF and HR relation weakened LFHF/avRRI^4) and the statistically significant confounding factors mentioned above were selected as independent variables (i.e. age, PWV, mean blood pressure, sex, BMI, C-reactive protein, triglycerides, HDL cholesterol, fasting plasma glucose and cystatin C). The coefficients of the linear regression analyses are presented in the Supplemental Tables 1-4.

Resting HR was positively related with LF/HF ($p<0.001$ for LF/HF, coefficient Beta for LF/HF 0.299, $R^2=0.237$ for the model, Supplemental Table 1). Also upright HR was positively related with LF/HF ($p<0.001$ for LF/HF, coefficient Beta for LF/HF 0.342, $R^2=0.252$ for the model, Supplemental Table 2).

Both supine and upright HR were positively related with the LF/HF ratio also in analyses where the dependence on HR was weakened with the LFHF/avRRI^4 approach ($p<0.001$, coefficient Beta for LFHF/avRRI^4 0.697, $R^2=0.582$ for the model in the supine position, Supplemental Table 3; $p<0.001$, coefficient Beta for LFHF/avRRI^4 0.690 and $R^2=0.570$ for the model in the upright position, Supplemental Table 4).

Discussion

In the present study we showed that lower resting HR predicts greater increase in sympathovagal balance (i.e. LF/HF) during the change from supine to upright posture. In addition, both supine LF and HF power, calculated from RR-intervals, were negatively associated with resting HR level indicating more active autonomic nervous control of HR in subjects with lower resting HR. Even when the dependency of HRV on average HR was weakened by the use of a mathematical method, statistically significant relation with HRV and HR was detected. These findings suggest that lower resting HR is an indicator of more active autonomic nervous system and that HRV is not only a derivative of HR.

On the grounds of the previous studies both HR and HRV are indicators of sympathovagal tone [1, 31], and both are also predictors of cardiovascular diseases such as coronary disease [6, 7, 10], heart failure [11, 32-34] and even mortality [7, 12, 19, 35]. In addition, while the mathematical association of HR with HRV is obvious, their physical relation during stimulation of autonomic nervous tone is not fully understood [13, 14, 36]. In the present study the relation of HRV with HR was studied in 569 subjects without medications with direct cardiovascular effects or diagnosed cardiovascular diseases during supine and upright position.

There are controversial studies of the relation of HR with HRV [1, 13, 14, 16, 18]. The mathematical relation of these two variables is clear, but whether HRV does more represent the level of sympathetic tone than HR alone it is not finally settled. However, our results suggest that low resting HR is associated with decreased LF/HF, e.g. lower sympathetic and higher vagal tonus, independent from the method of calculation. Sacha et al. have presented a method for the strengthening and weakening of the HRV dependence of the average HR [17]. Within the present study, the HRV values with the mathematical HR

dependency weakening approach were still clearly related to the resting HR in supine and upright positions. Consequently, HRV was strongly related with resting HR level regardless of the HRV calculation method.

High resting HR and decreased HRV are associated with poor cardiovascular health and mortality [5-7, 10-12, 19]. The present study population consisted of rather healthy subjects without cardiovascular diseases and population was divided into tertiles according to the resting HR within each sex. This approach reduced possible differences in the distribution of such cardiovascular risk factors that are significantly influenced by sex. However, subjects with the highest HR also presented with other markers of less favorable prognosis, i.e. decreased HRV (total power) and HDL cholesterol levels, increased triglyceride, fasting plasma glucose, C-reactive protein levels, and higher body mass index (Table 1). In addition, higher resting HR was related with higher blood pressure and pulse wave velocity (Table 2).

Heart rate variability measurements based on RR-interval

Within the present study population resting HR was inversely related with both sympathetic component (LF power) and vagal component (HF power and RMSSD) of HRV, and the relation with sympathovagal balance (LF/HF) was positive regardless of body position. These findings support the view that lower resting HR is an indicator of increased vagal tone [37, 38] and decreased sympathetic tone.

During posture change from supine to upright vagal tone (HF power) decreased significantly independent from the resting HR level. This finding is consistent with two previous studies where HRV was recorded from 22 and 12 healthy subjects, respectively, during head-up tilt [2, 39]. Moreover, SDNN and total power, which represent of total autonomic tone, were negatively related with resting HR during supine and upright recordings, the findings of which are congruent with previous studies [13]. In our study there was no statistically significant change in sympathetic tone (LF power) during posture change from supine to upright in any of the HR groups. Hence, the change in the autonomic tone in response to head-up tilt seems to be more mediated by an alteration in vagal than the sympathetic tone regardless of the resting HR level. Not only during resting position but also during head-up tilt, subjects with lower HR were characterized by more reactive autonomic nervous tone.

Previously Tsuji et al. studied the relation of HRV with cardiovascular events in 2501 patients with a mean age 53 years. They found that reduced LF, HF and total power were significantly related with increased risk for cardiovascular events when the other risk factor were taken into consideration ($p<0.05$) [35]. In the present study, lower supine LF/HF ratio and the greater change in this variable in response to upright posture may hence reflect better cardiovascular health in the subjects with lower HR.

Information provided by heart rate variability measurements based on heart rate

In addition to common RR-interval based HRV determinations, we also calculated the HRV parameters from the prevailing HR instead of RR-interval values to strengthen the knowledge of the relation between HR and HRV. In the HR based HRV analysis, resting HR was related with lower LF power (sympathetic

tone) but HF power (vagal tone) did not differ between the resting HR tertiles during supine position (Supplemental Figure 2). During the head-up tilt a similar decrease in HF power (vagal tone) was detected in all HR groups, but LF power increased more in the lowest HR group when compared with the higher HR groups. Thus, during the upright position the HRV differences almost disappeared within the HR tertiles. The HR based HRV evaluation may more represent cardiac sympathetic influences than the RR-interval based approach. As far as we know, there are no previously published results of the HR based HRV measurements.

The different HRV measurement methods generated opposite results about the association of resting HR with HRV. This can be explained by the negative mathematical relation between HR and RR-interval. In the RR-interval based HRV analyses, the evaluated vagal tone significantly differed between the HR groups (Figure 1C), but in the HR based HRV analyses there were no differences in vagal tone between the HR groups.

Importantly, regardless of the HRV measurement method (RR-interval based or HR based), lower resting HR was related to a lower supine LF/HF ratio, and a more pronounced change in this variable during head-up tilt, indicating a greater change in the sympathovagal balance in response to upright posture.

Study limitations

It is known that age has effect on autonomic tone [4, 39-41]. Lipsitz et al. compared HRV changes during head-up tilt in healthy young (18-35) and older subjects (71-94 years). They reported the loss of autonomic influences on HR regulation as a function of age [39]. The same result was observed in a larger study by Barantke et al., where HRV remained unchanged during postural tilt in older subjects (58-88 years) without cardiac diseases [41]. In the present study, the mean age was same within the resting HR tertiles (Table 1) and only 22 subjects (8%) were over 60 years of age (range 18-72). All of the study subjects were included in the analyses, and the possibility remains that the effect of age on HRV was not totally eliminated even though age was included as one of the confounding factors in the regression analyses. Also sex has marked effect on autonomous tone and reduced HRV has been observed male subjects [4, 20, 30]. The sex-specific HR tertiles were constructed in order to avoid powerful confounding of sex on the results.

Many medications, especially beta blockers, have direct effect on HR and other hemodynamic variables and also on HRV [42, 43]. In the present study subjects with cardiovascular medications were all excluded. However, not only cardiovascular medications but also for example antidepressants have effects on HRV [44] and also mental illnesses have been associated with reduced HRV [8, 9]. The present study included subjects who were medicated with antidepressants but all were in the stable phase of the disease. In addition to posture, breathing frequency is associated with HRV via autonomous activity [4]. In the present study the respiratory frequency during hemodynamic measurements was not included in the analyses.

Conclusions

In the present investigation the relation of resting HR and its short term variability during supine and upright position was studied in 569 subjects. Resting HR was significantly associated with HRV regardless of the HRV determination method. Higher resting HR was related with higher LF/HF in both supine and upright position, but in addition lower resting HR anticipated a more pronounced increase in sympathovagal balance during head-up tilt. These findings suggest that even though HRV is a mathematical derivative of HR (or RR-interval) and they are both markers of autonomic nervous activity, HRV is not only a substitute for HR. Nevertheless, on the grounds of resting HR level it is possible to estimate autonomic nervous system activity and function.

Abbreviations

avRRI^4, average RR-interval to the fourth power; CI, confidence interval; eGFR, estimated glomerular filtration rate; HF, high frequency component; HDL, high-density lipoprotein; HR, heart rate; HRV, heart rate variability; LDL, low-density lipoprotein; LF, low frequency component; LF/HF, low to high frequency ratio; PWV, pulse wave velocity; RMSSD, square root of mean squared differences of normal to normal RR-intervals; SDNN, standard deviation of normal to normal RR-intervals; SVRI, systemic vascular resistance index

Declarations

Ethics approval and consent to participate

The Ethics Committee of the Tampere University Hospital has approved this study and all subjects gave informed consent prior to participation as stipulated in declaration of Helsinki (reference number R06086M). This study is a part of DYNAMIC-study which has been registered to database of clinical trials (ClinicalTrials.gov, ID: NCT01742702).

Consent for publication

Not applicable

Availability of data and materials

The data been used during the present study is not publicly available as our clinical database contains several indirect identifiers and the informed consent obtained does not allow publication of individual patient data. However, the datasets are available from the corresponding author on reasonable request.

Competing interests

The authors have no conflicts of interest to disclose.

Funding

The study was supported by Competitive State Research Financing of the Expert Responsibility Area of Tampere University Hospital, Finnish Cultural Foundation, Finnish Foundation for Cardiovascular Research, Sigrid Jusélius Foundation, Paavo Nurmi Foundation, Aarne Koskelo Foundation, Finnish Medical Foundation, and Orion-Farmos Research Foundation. The funding was granted on the basis of applications that contained the study design. The sources of funding were not in any way involved in the collection, analysis, and interpretation of data, or in the writing the manuscript.

Author contributions

JK and IP designed the study, analysed and interpreted the data, and drafted the first version of the manuscript. MU and JV contributed to data interpretation. JK, AT, AJT, PK and IP contributed to data collection and experiments. AT, AJT, PK, JV, MK and JM contributed to critical revision of the manuscript. All authors read and approved the final manuscript.

Acknowledgements

The authors thank Paula Erkkilä, RN, Reeta Kulmala, RN, Pirjo Järventausta, RN, and Mirja Ikonen, RN, for invaluable technical assistance.

References

1. Grassi G, Vailati S, Bertinieri G, Seravalle G, Stella ML, Dell'Oro R, Mancia G: Heart rate as marker of sympathetic activity. *J Hypertens* 1998, 16(11):1635-1639.
2. Montano N, Ruscone TG, Porta A, Lombardi F, Pagani M, Malliani A: Power spectrum analysis of heart rate variability to assess the changes in sympathovagal balance during graded orthostatic tilt. *Circulation* 1994, 90(4):1826-1831.
3. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Circulation* 1996, 93(5):1043-1065.
4. Stolarz K, Staessen JA, Kuznetsova T, Tikhonoff V, State D, Babeanu S, Casiglia E, Fagard RH, Kawecka-Jaszcz K, Nikitin Y: Host and environmental determinants of heart rate and heart rate variability in four European populations. *J Hypertens* 2003, 21(3):525-535.
5. Thayer JF, Yamamoto SS, Brosschot JF: The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. *Int J Cardiol* 2010, 141(2):122-131.
6. Buccelletti E, Gilardi E, Scaini E, Galiuto L, Persiani R, Biondi A, Basile F, Silveri NG: Heart rate variability and myocardial infarction: systematic literature review and metanalysis. *Eur Rev Med Pharmacol Sci* 2009, 13(4):299-307.
7. Dekker JM, Crow RS, Folsom AR, Hannan PJ, Liao D, Swenne CA, Schouten EG: Low heart rate variability in a 2-minute rhythm strip predicts risk of coronary heart disease and mortality from

several causes: the ARIC Study. Atherosclerosis Risk In Communities. *Circulation* 2000, 102(11):1239-1244.

8. Kemp AH, Quintana DS: The relationship between mental and physical health: insights from the study of heart rate variability. *Int J Psychophysiol* 2013, 89(3):288-296.
9. Sgoifo A, Carnevali L, Alfonso Mde L, Amore M: Autonomic dysfunction and heart rate variability in depression. *Stress* 2015, 18(3):343-352.
10. Cooney MT, Vartiainen E, Laatikainen T, Juolevi A, Dudina A, Graham IM: Elevated resting heart rate is an independent risk factor for cardiovascular disease in healthy men and women. *Am Heart J* 2010, 159(4):612-619 e613.
11. Nanchen D, Leening MJ, Locatelli I, Cornuz J, Kors JA, Heeringa J, Deckers JW, Hofman A, Franco OH, Stricker BH *et al*: Resting heart rate and the risk of heart failure in healthy adults: the Rotterdam Study. *Circ Heart Fail* 2013, 6(3):403-410.
12. Zhang D, Shen X, Qi X: Resting heart rate and all-cause and cardiovascular mortality in the general population: a meta-analysis. *CMAJ* 2016, 188(3):E53-63.
13. Monfredi O, Lyashkov AE, Johnsen AB, Inada S, Schneider H, Wang R, Nirmalan M, Wisloff U, Maltsev VA, Lakatta EG *et al*: Biophysical characterization of the underappreciated and important relationship between heart rate variability and heart rate. *Hypertension* 2014, 64(6):1334-1343.
14. Stauss HM: Heart rate variability: just a surrogate for mean heart rate? *Hypertension* 2014, 64(6):1184-1186.
15. Sacha J, Barabach S, Statkiewicz-Barabach G, Sacha K, Muller A, Piskorski J, Barthel P, Schmidt G: How to select patients who will not benefit from ICD therapy by using heart rate and its variability? *Int J Cardiol* 2013, 168(2):1655-1658.
16. Sacha J, Pluta W: Different methods of heart rate variability analysis reveal different correlations of heart rate variability spectrum with average heart rate. *J Electrocardiol* 2005, 38(1):47-53.
17. Sacha J, Barabach S, Statkiewicz-Barabach G, Sacha K, Muller A, Piskorski J, Barthel P, Schmidt G: How to strengthen or weaken the HRV dependence on heart rate--description of the method and its perspectives. *Int J Cardiol* 2013, 168(2):1660-1663.
18. Sacha J: Interaction between heart rate and heart rate variability. *Ann Noninvasive Electrocardiol* 2014, 19(3):207-216.
19. Kannel WB, Kannel C, Paffenbarger RS, Jr., Cupples LA: Heart rate and cardiovascular mortality: the Framingham Study. *Am Heart J* 1987, 113(6):1489-1494.
20. Huikuri HV, Pikkujamsa SM, Airaksinen KE, Ikaheimo MJ, Rantala AO, Kauma H, Lilja M, Kesaniemi YA: Sex-related differences in autonomic modulation of heart rate in middle-aged subjects. *Circulation* 1996, 94(2):122-125.
21. Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, Kusek JW, Manzi J, Van Lente F, Zhang YL *et al*: Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med* 2012, 367(1):20-29.

22. Koskela JK, Tahvanainen A, Haring A, Tikkakoski AJ, Ilveskoski E, Viitala J, Leskinen MH, Lehtimaki T, Kahonen MA, Koobi T *et al*: Association of resting heart rate with cardiovascular function: a cross-sectional study in 522 Finnish subjects. *BMC Cardiovasc Disord* 2013, 13:102.
23. Tikkakoski AJ, Tahvanainen AM, Leskinen MH, Koskela JK, Haring A, Viitala J, Kahonen MA, Koobi T, Niemela O, Mustonen JT *et al*: Hemodynamic alterations in hypertensive patients at rest and during passive head-up tilt. *J Hypertens* 2013, 31(5):906-915.
24. Tahvanainen A, Koskela J, Tikkakoski A, Lahtela J, Leskinen M, Kahonen M, Nieminen T, Koobi T, Mustonen J, Porsti I: Analysis of cardiovascular responses to passive head-up tilt using continuous pulse wave analysis and impedance cardiography. *Scand J Clin Lab Invest* 2009, 69(1):128-137.
25. Tahvanainen AM, Tikkakoski AJ, Leskinen MH, Nordhausen K, Kahonen M, Koobi T, Mustonen JT, Porsti IH: Supine and upright haemodynamic effects of sublingual nitroglycerin and inhaled salbutamol: a double-blind, placebo-controlled, randomized study. *J Hypertens* 2012, 30(2):297-306.
26. Wilenius M, Tikkakoski AJ, Tahvanainen AM, Haring A, Koskela J, Huhtala H, Kahonen M, Koobi T, Mustonen JT, Porsti IH: Central wave reflection is associated with peripheral arterial resistance in addition to arterial stiffness in subjects without antihypertensive medication. *BMC Cardiovasc Disord* 2016, 16:131.
27. Koobi T, Kaukinen S, Ahola T, Turjanmaa VM: Non-invasive measurement of cardiac output: whole-body impedance cardiography in simultaneous comparison with thermodilution and direct oxygen Fick methods. *Intensive Care Med* 1997, 23(11):1132-1137.
28. Peltola MA: Role of editing of R-R intervals in the analysis of heart rate variability. *Front Physiol* 2012, 3:148.
29. Bergland G: A guided tour of the fast Fourier transform. *IEEE Spectrum* 1969:41-52.
30. Koenig J, Thayer JF: Sex differences in healthy human heart rate variability: A meta-analysis. *Neurosci Biobehav Rev* 2016, 64:288-310.
31. Malik M, Camm AJ: Components of heart rate variability–what they really mean and what we really measure. *Am J Cardiol* 1993, 72(11):821-822.
32. Nolan J, Batin PD, Andrews R, Lindsay SJ, Brooksby P, Mullen M, Baig W, Flapan AD, Cowley A, Prescott RJ *et al*: Prospective study of heart rate variability and mortality in chronic heart failure: results of the United Kingdom heart failure evaluation and assessment of risk trial (UK-heart). *Circulation* 1998, 98(15):1510-1516.
33. Chattipakorn N, Incharoen T, Kanlop N, Chattipakorn S: Heart rate variability in myocardial infarction and heart failure. *Int J Cardiol* 2007, 120(3):289-296.
34. Adamson PB, Smith AL, Abraham WT, Kleckner KJ, Stadler RW, Shih A, Rhodes MM: Continuous autonomic assessment in patients with symptomatic heart failure: prognostic value of heart rate variability measured by an implanted cardiac resynchronization device. *Circulation* 2004, 110(16):2389-2394.
35. Tsuji H, Larson MG, Venditti FJ, Jr., Manders ES, Evans JC, Feldman CL, Levy D: Impact of reduced heart rate variability on risk for cardiac events. The Framingham Heart Study. *Circulation* 1996,

94(11):2850-2855.

36. Sacha J, Pluta W: Alterations of an average heart rate change heart rate variability due to mathematical reasons. *Int J Cardiol* 2008, 128(3):444-447.
37. Parati G, Saul JP, Di Rienzo M, Mancia G: Spectral analysis of blood pressure and heart rate variability in evaluating cardiovascular regulation. A critical appraisal. *Hypertension* 1995, 25(6):1276-1286.
38. Malliani A, Pagani M, Lombardi F, Cerutti S: Cardiovascular neural regulation explored in the frequency domain. *Circulation* 1991, 84(2):482-492.
39. Lipsitz LA, Mietus J, Moody GB, Goldberger AL: Spectral characteristics of heart rate variability before and during postural tilt. Relations to aging and risk of syncope. *Circulation* 1990, 81(6):1803-1810.
40. Tsuji H, Venditti FJ, Jr., Manders ES, Evans JC, Larson MG, Feldman CL, Levy D: Determinants of heart rate variability. *J Am Coll Cardiol* 1996, 28(6):1539-1546.
41. Barantke M, Krauss T, Ortak J, Lieb W, Reppel M, Burgdorf C, Pramstaller PP, Schunkert H, Bonnemeier H: Effects of gender and aging on differential autonomic responses to orthostatic maneuvers. *J Cardiovasc Electrophysiol* 2008, 19(12):1296-1303.
42. Jandackova VK, Scholes S, Britton A, Steptoe A: Are Changes in Heart Rate Variability in Middle-Aged and Older People Normative or Caused by Pathological Conditions? Findings From a Large Population-Based Longitudinal Cohort Study. *J Am Heart Assoc* 2016, 5(2).
43. Sandrone G, Mortara A, Torzillo D, La Rovere MT, Malliani A, Lombardi F: Effects of beta blockers (atenolol or metoprolol) on heart rate variability after acute myocardial infarction. *Am J Cardiol* 1994, 74(4):340-345.
44. Huang WL, Liao SC, Kuo TB, Chang LR, Chen TT, Chen IM, Yang CC: The Effects of Antidepressants and Quetiapine on Heart Rate Variability. *Pharmacopsychiatry* 2016, 49(5):191-198.

Tables

Table 1. Study population demographics and laboratory values in the heart rate tertiles according to sexes.

		Heart rate tertiles according to sexes							
		1		2		3		All	
		n=187		n=190		n=192		n=569	
Age (years)		44.2	(42.4, 46.0)	45.6	(44.0, 47.2)	44.9	(43.3, 46.5)	44.9	(43.9, 45.9)
Sex	Male	93	(50 %)	98	(52 %)	96	(50 %)	287	(50 %)
	Female	94	(50 %)	92	(48 %)	96	(50 %)	282	(50 %)
Body mass index (kg/m^2)		26.0	(25.5, 26.6)	26.6	(26.0, 27.2)	27.6*	(26.9, 28.3)	26.7	(26.4, 27.1)
Smoking	Never	99	(53 %)	113	(59 %)	119	(62 %)	331	(58 %)
	Previous	59	(32 %)	57	(30 %)	49	(26 %)	165	(29 %)
	Present	28	(15 %)	20	(11 %)	24	(13 %)	72	(13 %)
Smoking (pack years)		4.3	(2.3, 6.3)	4.6	(2.6, 6.7)	7.7	(5.1, 10.3)	5.6	(4.3, 6.9)
Physical exercise (times per week)		3.3	(3.0, 3.6)	3.0	(2.7, 3.2)	3.1	(2.9, 3.3)	3.1	(3.0, 3.2)
Alcohol (doses per week)		4.2	(3.3, 5.1)	4.2	(3.5, 5.0)	4.9	(4.0, 5.7)	4.4	(4.0, 4.9)
Hematocrit		0.42	(0.42, 0.42)	0.42	(0.42, 0.42)	0.42	(0.41, 0.43)	0.42	(0.42, 0.42)
C reactive protein (mg/l)		1.1	(1.1, 1.4)	1.7	(1.2, 2.0)	2.2*	(1.6, 2.7)	1.7	(1.4, 1.9)
Potassium (mmol/l)		3.8	(3.8, 3.8)	3.9	(3.8, 3.9)	3.8	(3.8, 3.8)	3.8	(3.8, 3.8)
Sodium (mmol/l)		140	(140, 141)	140	(140, 141)	140	(140, 141)	140	(140, 140)
Creatinine (µmol/l)		77	(74, 78)	73	(72, 75)	72	(71, 74)	74	(73, 75)
Cystatin C (mg/l)		0.83	(0.80, 0.84)	0.83	(0.82, 0.86)	0.86*	(0.84, 0.88)	0.84	(0.82, 0.86)
eGFR (ml/min/1.73m^2)		99	(97, 101)	99	(96, 101)	98	(96, 100)	99	(97, 100)
Fasting plasma									
Glucose (mmol/l)		5.4	(5.3, 5.4)	5.4	(5.3, 5.5)	5.5*	(5.4, 5.6)	5.4	(5.4, 5.5)
Total cholesterol (mmol/l)		5.1	(5.0, 5.2)	5.1	(5.0, 5.3)	5.2	(5.0, 5.3)	5.2	(5.1, 5.2)
Triglycerides (mmol/l)		1.1	(1.0, 1.2)	1.2*	(1.1, 1.3)	1.5*†	(1.3, 1.7)	1.3	(1.2, 1.3)
HDL cholesterol (mmol/l)		1.7	(1.7, 1.8)	1.6*	(1.5, 1.6)	1.5*	(1.4, 1.5)	1.6	(1.5, 1.6)
LDL cholesterol (mmol/l)		3.0	(2.8, 3.0)	3.0	(3.0, 3.2)	3.1	(2.9, 3.2)	3.0	(3.0, 3.1)

Values are counts (percent) and means (confidence intervals). Statistics: *p<0.05 vs tertile 1, †p<0.05 vs tertile 2; analysis of variance, Tukey HSD/Tamhane's T2 post hoc test. Natural logarithms of C reactive protein and fasting triglyceride concentrations were used in statistical analyses to normalize their distributions.
Abbreviations: eGFR, estimated glomerular filtration rate by CKD-EPI cystatin C and creatinine equation; HDL, high density lipoprotein; LDL, low density lipoprotein.

Table 2. Supine hemodynamic parameters in the heart rate tertiles according to sexes.

	Heart rate tertiles according to sexes							
	1		2		3		All	
te (1/min)	54	(53, 55)	62*	(62, 63)	74*†	(73, 75)	64	(63, 64)
te range (1/min)								
ɔmen	45-58		59-67		67-103		45-103	
ɛn	41-58		59-67		67-99		41-99	
blood pressure (mmHg)	131	(128, 134)	135	(132, 137)	141*†	(138, 144)	136	(134, 137)
blood pressure	75	(73, 77)	80*	(78, 82)	83*†	(81, 85)	79	(78, 81)
ıve velocity (m/s)	7.9	(7.6, 8.1)	8.6*	(8.3, 8.9)	8.9*	(8.6, 9.2)	8.5	(8.3, 8.6)
index (ml/min/m^2)	2.6	(2.5, 2.7)	2.9*	(2.9, 3.0)	3.2*†	(3.2, 3.3)	2.9	(2.9, 3.0)
; vascular resistance (m^5/m^2)	2828	(2733, 2923)	2633*	(2555, 2710)	2496*†	(2416, 2575)	2651	(2601, 2700)

Values are means (confidence intervals) of three minutes continuous measures. Statistics: *p<0.05 vs tertile 1, †p<0.05 vs tertile 2; analysis of variance, Tukey HSD/Tamhane’s T2 post hoc test.

Table 3. Heart rate variability values according to resting heart rate tertiles during five minutes measurement at supine and upright position.

	Heart rate tertiles according to sexes							
	1		2		3		All	
Supine								
Mean RR-interval (ms)	1081	(1045, 1152)	962	(933, 990	824	(774, 863)	962	(863, 1045)
SDNN (ms)	38	(29, 51)	32	(24, 44)	25	(17, 34)	31	(22, 43)
RMSSD (ms)	42	(30, 59)	32	(23, 44)	21	(15, 31)	31	(21, 46)
Power in low frequency range (ms^2)	484	(264, 982)	441	(207, 939)	246	(132, 480)	379	(191, 799)
Power in high frequency range (ms^2)	550	(276, 1059)	323	(163, 709)	168	(68, 428)	330	(146, 745)
Low- to high-frequency ratio	0.92	(0.50, 1.69)	1.38	(0.73, 2.38)	1.65	(0.77, 2.98)	1.29	(0.65, 2.31)
Total power (ms^2)	1300	(657, 2165)	873	(463, 1663)	485	(266, 916)	800	(416, 1597)
Upright								
Mean RR-interval (ms)	916	(842, 1003)	820	(781, 853)	716	(667, 759)	809	(733, 886)
SDNN (ms)	31	(24, 41)	26	(19, 34)	20	(14, 29)	26	(19, 36)
RMSSD (ms)	26	(19, 35)	19	(15, 25)	14	(10, 20)	19	(14, 27)
Power in low frequency range (ms^2)	439	(204, 871)	302	(143, 746)	203	(90, 480)	310	(146, 722)
Power in high frequency range (ms^2)	149	(78, 353)	96	(42, 204)	51	(23, 143)	96	(40, 238)
Low- to high-frequency ratio	2.90	(1.23, 6.08)	3.48	(1.76, 5.91)	3.82	(1.83, 6.76)	3.32	(1.66, 6.46)
Total power (ms^2)	730	(384, 1406)	470	(239, 1035)	332	(147, 727)	492	(239, 1058)

Values are medians (interquartile range). Abbreviations: SDNN, standard deviation of all normal RR intervals; RMSSD, the root mean square of differences between adjacent normal RR intervals.

Figures

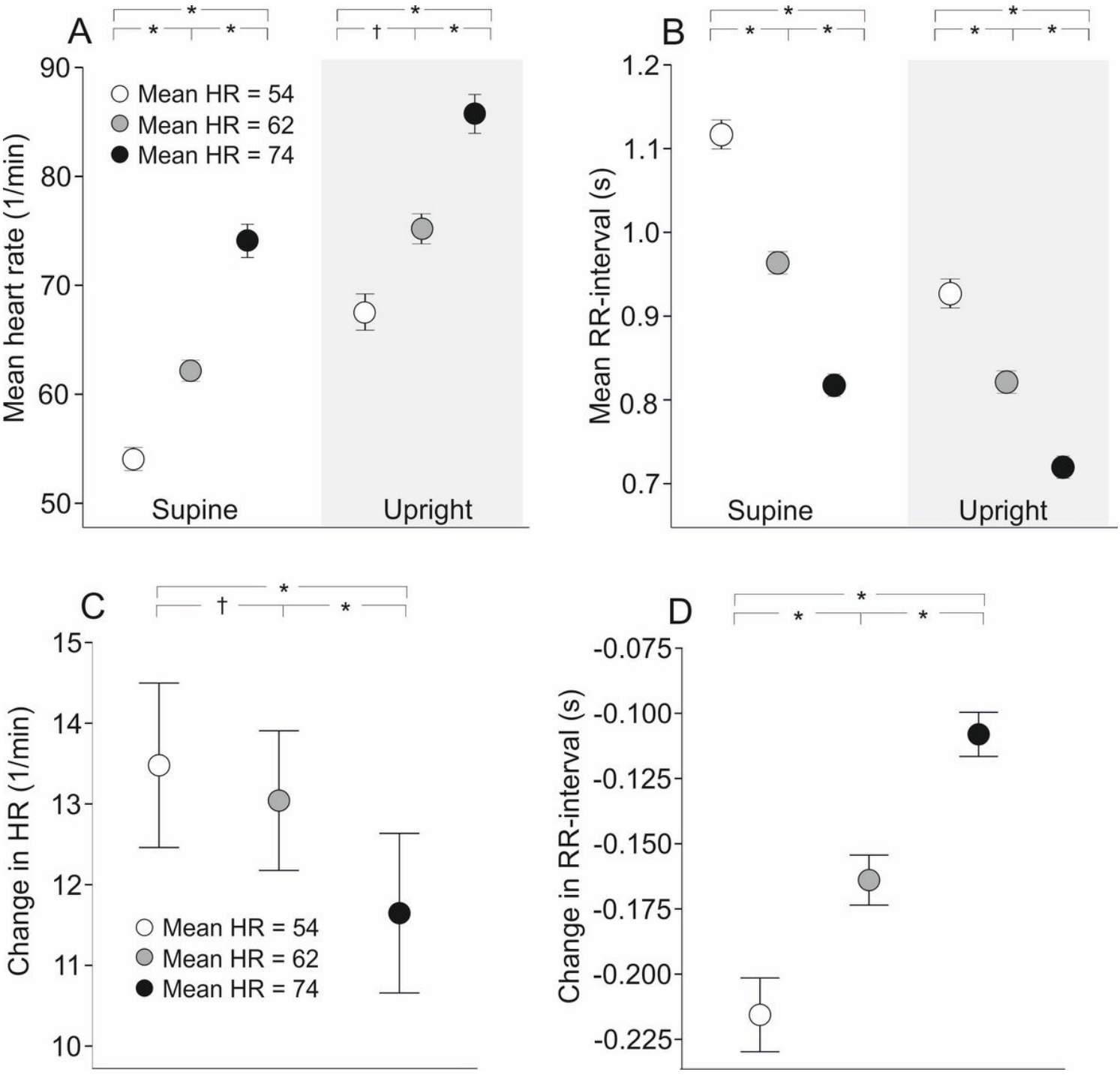

Figure 1

Supine and upright heart rate (A), RR-interval (B), and the change in heart rate (C) and RR-interval (D) during passive head-up tilt according to the resting heart (HR) tertiles. Mean (symbol), 95% confidence intervals of the mean (whiskers); n=569, *p<0.001, †p<0.05, analysis of variance with Tukey's HSD post hoc test.

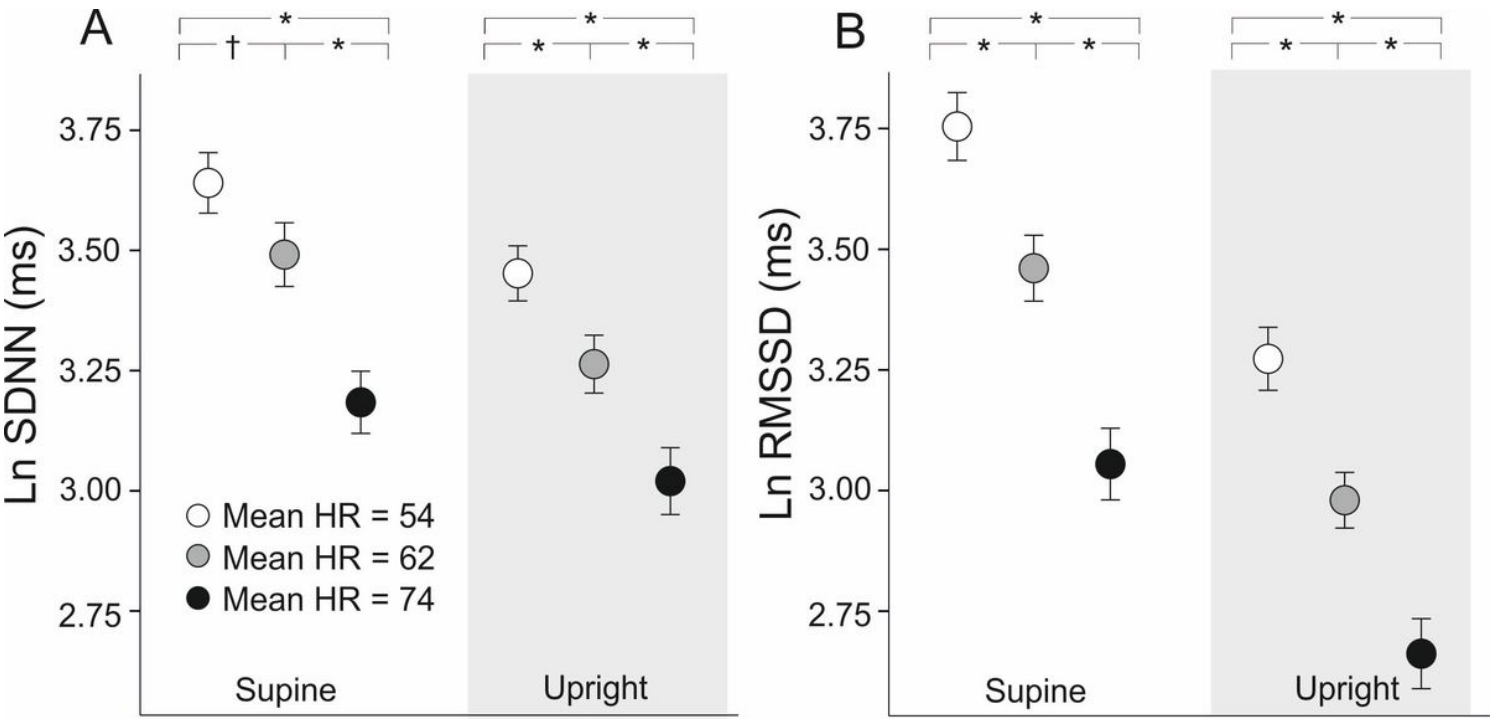

Figure 2

Natural logarithm (Ln) of supine and upright standard deviation of normal to normal RR-intervals (SDNN) (A), and square root of mean squared differences of normal to normal RR-intervals (RMSSD) (B) according to the resting heart rate (HR) tertiles; n=569, *p<0.001, †p<0.05, analysis of variance with Tukey's HSD post hoc test.

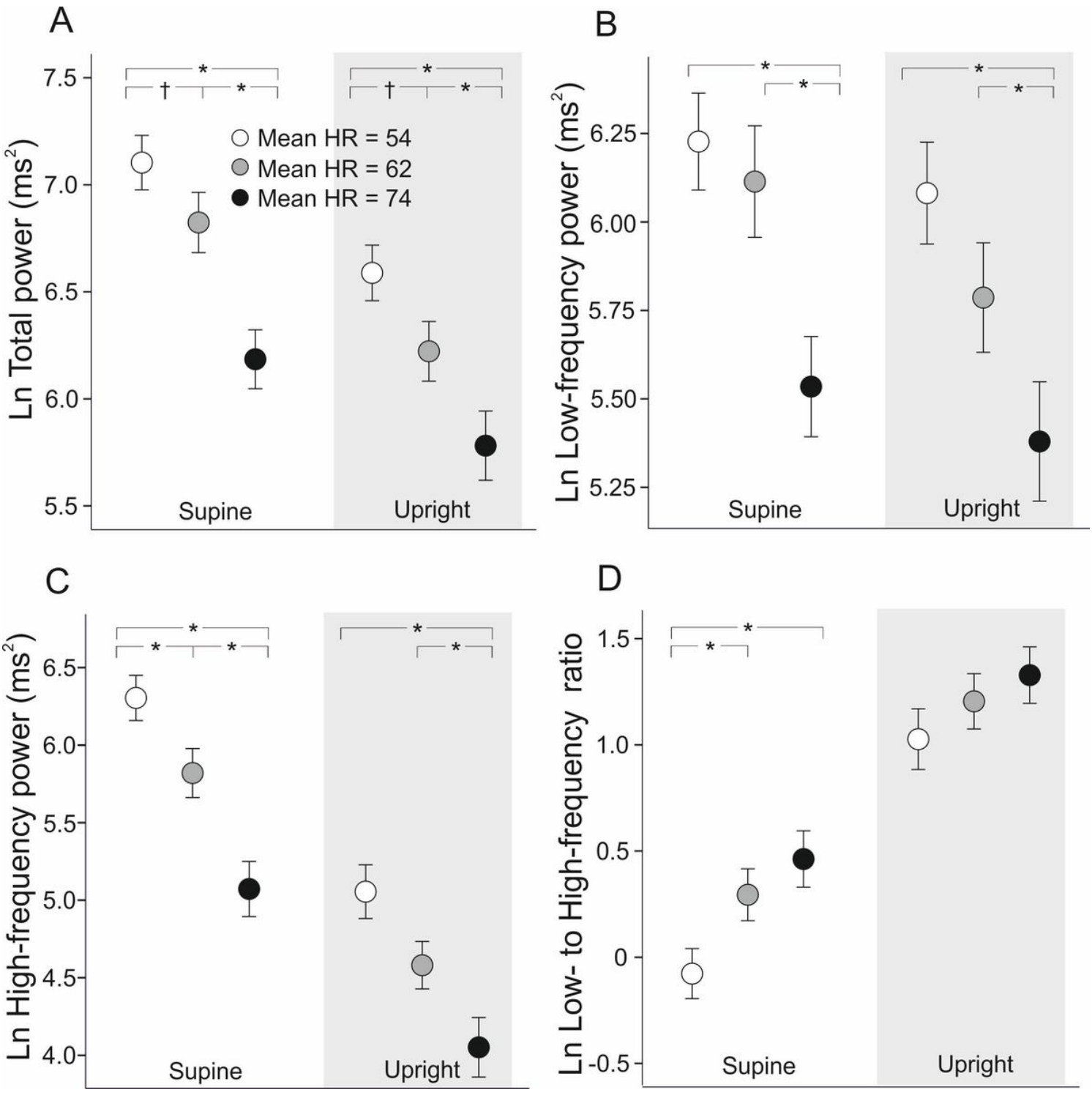

Figure 3

Heart rate variability calculated from RR-intervals: natural logarithm (Ln) of supine and upright total power (A), low frequency power (B), high frequency power (C), and low to high frequency power ratio (D) according to the resting heart rate (HR) tertiles; n=569, †p<0.05, *p<0.001, analysis of variance with Tukey's HSD post hoc test.

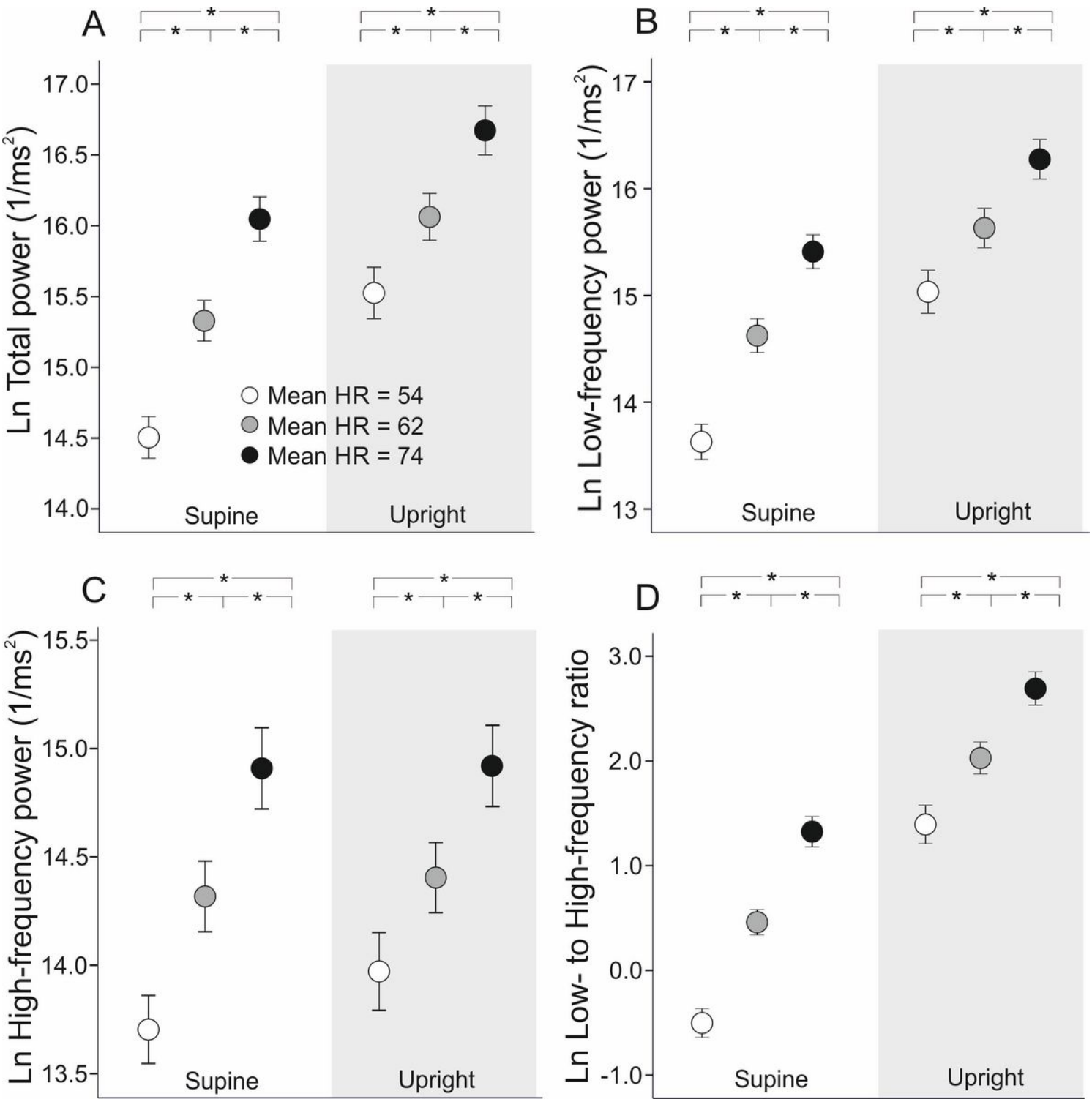

Figure 4

Heart rate dependence on heart rate variability weakened by dividing heart rate parameters by average RR-intervals to the fourth power [17]: natural logarithm (Ln) of supine and upright total power (A), low frequency power (B), high frequency power (C), and low to high frequency power ratio (D) according to the resting heart rate (HR) tertiles; n=569, *p<0.001, analysis of variance with Tukey's HSD post hoc test.

Supplementary Files

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