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Comparison of the Physiologic and Prognostic Implications of the Heart Rate versus the RR interval

Jeffrey J. Goldberger, MD, FHRS¹, Nils P. Johnson, MD², Haris Subacius, MA¹, Jason Ng, PhD¹, and Philip Greenland, MD³

¹Center for Cardiovascular Innovation and the Division of Cardiology, Feinberg School of Medicine, Northwestern University

²Division of Cardiology, Department of Medicine, Weatherhead PET Center For Preventing and Reversing Atherosclerosis, University of Texas Medical School and Memorial Hermann Hospital, Houston, Texas

³Department of Preventive Medicine, Feinberg School of Medicine, Northwestern University

Abstract

Background—The HR and RR interval are inversely related.

Objective—To determine which parameter better describes the autonomic changes that occur after exercise and which provides stronger prognostic significance.

Methods—Healthy volunteers (n=33) underwent sequential bicycle exercise tests with selective autonomic blockade during exercise to define the HR and RR interval changes in recovery due to parasympathetic effect, sympathetic effect, and sympathetic-parasympathetic interaction. The prognostic significance of resting HR and RR interval was assessed in a cohort study (n=33,781). The prognostic significance of exercise HR and RR interval and 1-minute HR and RR interval recovery was assessed in patients referred for exercise testing (n=2387).

Results—Parasympathetic effect on HR and RR interval both increased in recovery ($p<0.001$), while the sympathetic effect on HR declined ($p<0.001$) and the sympathetic effect on the RR interval paradoxically increased. Significant sympathetic-parasympathetic interaction was noted with the HR analysis but not with the RR interval. Resting HR and RR interval had similar prognostic implications by age and gender. While resting and exercise HR and RR interval had similar prognostic implications, 1-minute HR recovery was a multivariate predictor of mortality (HR 0.81; 95%CI 0.69–0.95), while 1-minute RR interval recovery was not.

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Address for Correspondence: Jeffrey J. Goldberger, M.D. Northwestern University Feinberg School of Medicine, Center for Cardiovascular Innovation, 251 East Huron, Feinberg Pavilion, Chicago, IL 60611, j-goldberger@northwestern.edu.

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Conclusions—Based on these findings, the HR (and its changes) are not necessarily interchangeable with the RR interval (and its changes) in either physiologic or prognostic studies. It is important to consider underlying physiologic constraints and identify wisely which parameter (or even other transformation of these parameters) is most suitable for a given analysis.

Keywords

heart rate; exercise; prognosis; nervous system; autonomic

INTRODUCTION

The prognostic significance of heart rate, whether measured at rest(1–6) or in the setting of exercise(7,8) is well established. The “heart rate” can be described as a true rate in beats per minute (HR) or as the RR interval in milliseconds. The RR interval and HR are hyperbolically related ($HR \times RR \text{ interval} = 60000$; see figure 1). Changes in these parameters are mediated in large part by the autonomic nervous system. The status of the autonomic input or “sympathovagal balance” that is reflected in either the HR or RR interval underlies the prognostic significance of these parameters. It has been shown that vagal nerve activity is linearly related to the RR interval.(9,10) We have also demonstrated that the RR interval is an excellent marker of sympathovagal balance.(11) Yet, much of the literature focusing on prognosis has evaluated HR rather than the RR interval. As the RR interval and heart rate are nonlinear transformations of each other, it is unclear whether HR or the RR interval is more suitable to characterize the “sympathovagal balance” and the associated prognostic significance of these variables. The aims of this study were: 1) to model the HR and RR interval changes after exercise in the setting of selective autonomic blockade to determine whether the RR interval better describes the autonomic changes that occur at this time and 2) to assess the prognostic significance of HR versus RR interval in absolute terms and as the one minute recovery after exercise.

METHODS

Physiology of HR versus RR interval during recovery from exercise

Participants—The physiologic comparison of HR to RR interval was assessed in a group of 33 healthy volunteers who were previously studied with selective autonomic blockade to determine autonomic effects on QT-RR dynamics after exercise.(12) Briefly, participants had normal physical examinations, ECGs, hematocrits, and serum electrolytes, were without cardiac complaints, and were not taking cardioactive medications. The study was approved by the Northwestern University Institutional Review Board and all participants provided written, informed consent.

Experimental Protocol—Volunteers underwent bicycle exercise testing on four separate days, each separated by at least 72 hours. On each day of testing, peripheral intravenous lines were inserted into the forearm for drug administration. Participants were attached to a cardiac monitor and a 12-lead ECG machine (Marquette Mac VU, Milwaukee, WI). Participants exercised on an electrically braked bicycle ergometer (SciFit Pro II, Tulsa, OK). Workload was maintained at 50W for 4 minutes, and then increased every 2 minutes as

tolerated in 25W increments to a maximum of 125W. The goal was to have all participants exercise comfortably for a total duration of 24 minutes achieving a HR of 120–130 beats per minute. HR was recorded prior to exercise, every minute during exercise, and every minute in recovery.

The initial test was performed without autonomic blockade. Blood samples for determination of plasma epinephrine and norepinephrine levels were taken one minute prior to the end of exercise and at 5 and 10 minutes of recovery. At the second through fourth sessions, the identical exercise protocol was performed as on the first day but with selective autonomic blockade(13) administered during exercise. At sessions two and three, one of the following two drugs was administered (in random order for each subject):

- a. intravenous atropine (0.04 mg/kg) in divided doses (0.01 mg/kg every 30 seconds) to achieve complete parasympathetic blockade (PB). Atropine was administered between minutes 16 and 18 of exercise.
- b. intravenous propranolol (0.2 mg/kg) given at 1 mg/min to achieve complete β -adrenergic sympathetic blockade (SB). Propranolol was administered at 1 mg/min so that administration was completed by the 18th minute of exercise.

At session four, propranolol and atropine were both administered as in sessions two and three to achieve complete double blockade. The propranolol was initiated so that administration was completed by the 16th minute of exercise at which time the atropine was given over the next two minutes.

Data Analysis—From the HR data obtained at peak exercise and the following 10 minutes of recovery from each of the four exercise studies, the RR interval was calculated. The HR and RR interval were then both used for linear modeling of the autonomic effects in the post-exercise recovery period. In the setting of complete double blockade, the HR and RR interval (HR_0 , RR_0) changes are predominantly nonautonomic (though there may be a small alpha adrenergic component). The general model for HR and RR interval recovery after exercise includes this nonautonomic component, the effect of withdrawal of sympathoexcitation, the effect of parasympathetic reactivation, and a sympathetic-parasympathetic interaction component. For each individual, each component was defined based on the data obtained from all four studies as follows:

1. the parasympathetic effect on the HR (HR_p) and RR interval (RR_p) is the difference in HR or RR interval in the setting of double blockade (HR_0 , RR_0) and in the setting of β -adrenergic sympathetic blockade (HR_{SB} , RR_{SB}), with the magnitude of the effect defined by the absolute value of the difference.

$$HR_p = HR_{SB} - HR_0 \text{ or } RR_p = RR_{SB} - RR_0$$

note that these will have opposite sign)

2. the sympathetic effect on the HR (HR_s) and RR interval (RR_s) is the difference in HR or RR interval in the setting of double blockade (HR_0 , RR_0) and in the setting of parasympathetic blockade (HR_{PB} , RR_{PB}), with the magnitude of the effect defined by the absolute value of the difference.

$$HR_s = HR_{PB} - HR_0 \text{ or } RR_s = RR_{PB} - RR_0$$

(note that these will have opposite sign)

3. the magnitude of the sympathetic-parasympathetic interaction on the HR (HR_{SPI}) and RR interval (RR_{SPI}) is reflected in the difference between the baseline HR (HR_{Base}) and RR interval (RR_{Base}) and the sum of the nonautonomic component, the sympathetic effect, and the parasympathetic effect (that is, everything not accounted for by one of these mechanisms)

$$HR_{SPI} = HR_{Base} - (HR_0 + HR_s + HR_p)$$

$$RR_{SPI} = RR_{Base} - (RR_0 + RR_s + RR_p)$$

Statistics—Data are expressed as mean $\pm$ standard error. Sympathetic effect (HR_s and RR_s), parasympathetic effect (HR_p and RR_p), and sympathetic-parasympathetic interaction (HR_{SPI} and RR_{SPI}) were modeled using repeated measures methodology with repeated HR and RR interval measurements during peak exercise and 10 minutes of recovery as the within-subject variable. Eleven measurements of each effect for each subject were examined for evidence that sympathetic-parasympathetic interaction effects are different from zero. Likelihood ratio test comparing two nested models—ones with and without the fixed effects of the recovery minute in the model—was used to test for changes in the magnitude of the sympathetic-parasympathetic interaction effects during recovery.

Prognostic significance of resting heart rate versus RR interval

Participants—Between November 1967 and January 1973, the Chicago Heart Association Detection Project in Industry screened 39,573 women and men. A total of 5792 participants were excluded as previously described.⁽⁵⁾ Details on the standardized methods used in the Chicago Heart Association field examination have been described.⁽¹⁴⁾ The prognostic significance of resting heart rate with a mean follow-up of 22 years was previously reported.⁽⁵⁾ The present analysis includes the same population with a mean follow-up of 29 years.

Statistics—The heart rate data were transformed to RR intervals. Cox proportional hazards regression models were used to calculate relative risks of death associated with a difference of 12 beats per minute (approximately one standard deviation) in heart rate or a difference of 127 msec (approximately one standard deviation) in RR interval for women and men stratified by age.

Prognostic significance of exercise HR versus RR interval and heart rate recovery versus RR interval recovery

Patients—The prognostic comparison of HR and RR interval recovery was performed in a cohort of patients referred to our nuclear stress cardiology laboratory for a treadmill exercise stress study with SPECT perfusion imaging. The prognostic significance of early and late heart rate recovery has been previously reported.⁽¹⁵⁾ Briefly, patients age ≥ 18 years who underwent stress testing between August 1998 and December 2003 (to ensure availability of archived and decipherable digitized ECG waveforms) and available ECG tracings at peak exercise and at 1 minute into recovery were included.

Data Analysis—Standard demographic and clinical information as well as Bruce protocol treadmill exercise data were collected, as previously reported.(16) The HR and RR at peak exercise and 1 minute into recovery were recorded and determined HR and RR recovery. All-cause mortality was determined from the Social Security Administration Death Master File.(17) Length of survival was computed as the number of days between the treadmill exercise stress test and the date of death or the end of December 2010, whichever came first. All of the patients had at least 7 years of follow-up.

Statistics—Statistical tests were performed using R version 2.13 (R Foundation for Statistical Computing, Vienna, Austria) with missing data (6% of 6 affected variables) imputed by the MI (“multiple imputation”) package version 0.09–14 for multivariable models only. All applicable tests were two-tailed and $p < 0.05$ was considered statistically significant. Univariate Cox proportional hazards models explored all variables for subsequent multivariable model building. Schoenfeld residuals tested the assumption of proportional hazards and found no significant deviations. Plots of beta coefficients from univariate Cox proportional hazards models were visually examined by quartile of each continuous variable for departures from linearity. Three variables (body mass index, resting heart rate, and 1-minute RR recovery) appeared visually to have a J-shaped effect. Of these three, only 1-minute RR recovery showed significance of either term in a 2-variable Cox proportional hazards model, confirmed by significant improvement in its nested model after adding the squared term ($\chi^2=6.45$, $p=0.011$). Therefore, each variable and its square were entered simultaneously in univariate and multivariable models.

Nested multivariable Cox proportional hazards models included all variables apart from peak HR and 1-minute RR and HR recovery for the baseline model. For comparing the added prognostic value of peak HR versus RR interval, two nested Cox models were compared to the baseline model, each adding just one of these two variables.

As a separate analysis comparing the added prognostic value of 1-minute HR versus RR interval recovery, two nested Cox models were compared to the baseline model, each adding just one of these two variables. Given the high correlation between peak HR and 1-minute HR recovery (Pearson $r^2=0.77$, $p<0.001$), peak HR was excluded. The nested Cox proportional hazards models provided a baseline χ^2 and the new χ^2 after adding a variable. Changes in χ^2 (the χ^2) for the number of added variables (df=1 for peak HR or RR, 1-minute HR recovery; df=2 for 1-minute RR recovery and its square) were compared using the χ^2 distribution, which is one-tailed.

RESULTS

Physiology of HR versus RR interval during recovery from exercise

There were 19 males and 14 females with a mean age of 54 ± 7 years. Peak exercise HRs were 135 ± 2 (baseline), 150 ± 2 (atropine), 96 ± 3 (propranolol), and 105 ± 2 bpm (double blockade). Peak exercise RR intervals were 450 ± 8 (baseline), 402 ± 5 (atropine), 628 ± 15 (propranolol), and 575 ± 9 msec (double blockade). Figure 2 shows the HR and RR interval recovery for each of the four conditions.

The parasympathetic effect on HR and RR interval recovery is shown in Figures 3A and 3B. Both HR_p and RR_p showed significant deviation from zero ($p<0.001$) with increasing magnitude in recovery relative to their peak exercise values. This is consistent with the expected rapid parasympathetic reactivation following the end of exercise. Figure 3C demonstrates the increase in both HR_p and RR_p magnitude as HR_0 and HR_{SB} both decrease over time.

The sympathetic effect on HR and RR interval recovery is shown in Figures 3D and 3E.

HR_s showed the expected positive deviation from zero ($p<0.001$) and decrease in the magnitude of the deviation with time in recovery. However, RR_s had a negative deviation from zero, but the magnitude of the deviation paradoxically increased with time in recovery. The origin of the discordance between the directional changes in HR_s and RR_s can be seen in the plots of Figure 3F. HR_s decreases as both HR_0 and HR_{PB} decrease, but because HR_0 is on a steep part of the curve there is a proportionally larger change in RR_0 than in RR_{PB} . Thus, the RR_s ($RR_{PB}-RR_0$) increases in magnitude. In addition, both epinephrine and norepinephrine plasma levels showed a decline in recovery (Exercise, 5 minute and 10 minute recovery values for epinephrine 88 ± 8 , 57 ± 5 , and 47 ± 4 pg/ml and for norepinephrine 1478 ± 440 , 945 ± 176 , and 739 ± 126 pg/ml), confirming that the decreasing magnitude of HR_s is a better reflection of sympathetic effect than the increasing magnitude of RR_s .

Figures 3G and 3H show the results for the sympathetic-parasympathetic interaction terms. Estimates of the HR_{SPI} by minute of recovery ranged from -6.2 ± 2.4 to -16.7 ± 2.2 bpm ($p<0.014$, table 1). The negative sign of the interaction indicates that heart rate during the baseline stage was 6 to 17 beats lower than what would have been predicted by the magnitudes of the parasympathetic and sympathetic effects alone—an antagonistic effect of the interaction. The likelihood ratio test showed significant improvement in model fit to the data when the magnitude of the HR_{SPI} was allowed to vary by minute of recovery ($p<0.001$). This finding indicated significant changes in the magnitude of HR_{SPI} with time during recovery and suggested that the effect cannot be modeled as a single average across all recovery. HR_{SPI} magnitude increased by 7.3 ± 1.8 bpm from the beginning to the first minute in recovery ($p<0.001$) and an additional 2.7 ± 1.3 bpm ($p=0.043$) from minute one to minute two. There were no further changes in HR_{SPI} during the remaining minutes of recovery (table 2). Significant deviation of RR_{SPI} from zero was not detected (table 2) during the first 10 minutes of recovery ($p>0.11$).

Prognostic significance of resting heart rate versus RR interval

The cohort included 33,781 participants, ages 18–74 years with 56% males (Table 3). Mean resting heart rate in each group ranged from 74.9–79.5 bpm. The resting HR was a significant predictor of mortality in males aged 18–39 and 40–59 years and in females aged 40–59 years, and not in the other groups. The resting RR interval was a significant predictor in the same groups with the same magnitude of effect (but in the opposite direction due to the inverse relationship of HR and RR interval).

Prognostic significance of exercise HR versus RR interval and heart rate recovery versus RR interval recovery

The cohort included 2,387 patients, in whom mean age was 55 ± 12 years and 57% were male. As expected, typical risk factors were significant univariate predictors. After a mean follow-up of 9.9 ± 1.5 years, 10% of the cohort had died. Both 1-minute HR and RR recovery were significantly lower among those who died (17 ± 9 bpm and 58 [38–85] ms, respectively) than among the survivors (23 ± 9 bpm and 64 [46–86] ms, respectively). Adding peak HR or RR improved the baseline multivariable model a similar amount (for peak HR, $\chi^2=11.6$, $p=0.001$, $df=1$; for peak RR, $\chi^2=10.4$, $p=0.001$, $df=1$).

Figure 4 shows a Kaplan-Meier survival curve by quartile of 1-minute HR and RR recovery, demonstrating worse survival in the lowest quartile of HR and RR interval recovery. Table 4 shows only the significant variables in the baseline and nested multivariable Cox proportional hazards models. While both 1-minute HR and RR interval recovery are significant univariate predictors of survival, only 1-minute HR recovery significantly improved the baseline multivariable model ($\chi^2=6.63$, $p=0.010$, $df=1$), while 1-minute RR interval recovery did not ($\chi^2=3.00$, $p=0.22$, $df=2$).

DISCUSSION

The present study demonstrated that the HR (and its changes) are not necessarily interchangeable with the RR interval (and its changes) in either physiologic or prognostic studies. For example, when using a linear model, only changes in HR, and not RR interval, in the post-exercise recovery period provided qualitatively correct physiologic description of the sympathetic changes during this time. Physiologic modeling using the RR interval led to the nonsensical conclusion that sympathetic effect increases in the post-exercise recovery period. Further, the prognostic significance of resting HR or peak exercise HR was equivalent to the prognostic significance of resting RR interval or minimum exercise RR interval. Importantly, the one minute HR recovery was a multivariate predictor of prognosis, while the one minute RR interval recovery was not. Based on these findings, it is important to consider underlying physiologic constraints and, when possible, calibration to a gold standard or known physiology, in choosing which parameter (or even other transformations of these parameters) is most suitable for a given analysis. Importantly, potentially misleading information can be obtained with an incorrect choice. These data support the need for careful assessment of the proper transformation of HR to be used in analyses incorporating this variable.

Qualitative changes in autonomic tone that occur after the cessation of exercise – namely, withdrawal of sympathoexcitation and parasympathetic reactivation – affect both the HR and RR interval. Based on the mathematical relationship between HR and RR interval, there is no reason *a priori* to identify either of these variables (or other mathematical transformations of these variables) as more closely tied to physiologic changes in the autonomic effects on the sinus node nor to prognosis. When study data are confined to the relatively linear portions of the curve (figure 1), the HR and RR interval may be interchangeable for analyses that are linear; nonlinear analyses of these variables may not be equivalent even when operating on the linear portion of the curve. Importantly, when linear

or nonlinear transformations of the HR (or RR interval) are performed, the transformed HR (or RR interval) parameter may not reflect the same physiology as the transformed RR interval (or HR) parameter.

From a mathematical perspective, the fact that HR and RR interval are not interchangeable is expected. Assuming that a linear model of either HR or RR interval is a valid physiologic construct for the autonomic changes in the post-exercise period, performing the nonlinear transformation to the other variable will necessarily change this (the differences in the reciprocals of a variable is not equal to the reciprocal of the differences). While the mathematics cannot predict whether HR or RR interval (or some other transformation of these variables) would best fit the model, once one variable is identified the other will likely not be effective in the same model. Interestingly, in the limited range of the resting HR or the peak exercise HR, both have similar prognostic value. Once again, this is expected. In the limited HR range of 50–80 bpm (figure 1), there is a highly linear relationship of the HR and RR interval with an $R^2=0.985$. Thus, in this heart rate range the HR and RR interval can be considered to be linearly related and their prognostic significance should be equivalent. Similarly, in the limited HR range of 100–150 bpm, there is a highly linear relationship of the HR and RR interval with an $R^2=0.989$, but with a very different slope than at the slower heart rates. When performing even simple manipulations of the HR, i.e. subtraction to calculate the heart rate recovery, the nonlinear relationship of HR and RR interval can create havoc.

It has long been appreciated that there are sympathetic-parasympathetic interactions on the heart, such that the combined effect of any level of sympathetic and parasympathetic stimulation is not merely the sum of the independent effects of each. Accentuated antagonism(18) refers to the larger response that is observed with parasympathetic stimulation in the setting of sympathetic stimulation. This phenomenon was described with respect to the heart rate. In the present study, a larger effect on the HR was observed in the absence of any blockade (i.e. the opportunity to display a sympathetic-parasympathetic interaction) than was observed in the setting of β -adrenergic blockade where this interaction is blocked, consistent with the previously described physiology of accentuated antagonism. This physiology was not apparent in the RR interval analysis.

Clinical use of various transformations of the HR and RR interval is most commonly known in the setting of rate correction of the QT interval. The most widely used rate correction divides the QT interval by the square root of the RR interval (Bazett's (19) formula), but others incorporate division by the cube root of the RR interval (Fridericia)(20) or even linear formulas of the RR interval (Framingham)(21) or HR(22,23). The use of these divergent transformations of the RR interval to describe the identical physiology of the rate dependence of the QT interval underscores the empiric nature of choosing a transformation that best describes the observed physiology. Interestingly, when compared to each other, the linear formula with HR was found to be the best choice (23).

In other applications, both heart rate and RR interval have been used and widely accepted. It is unusual for a physiologic based reason to be cited for the choice of one over the other. This likely reflects a tacit understanding that they are equivalent. However, their

mathematical relationship to each other does not provide license to use them interchangeably in all applications. For example, while time domain measures of heart rate variability are uniformly reported based on RR interval variability in msec, the frequency domain parameters are mostly reported based on RR interval variability but are sometimes reported in bpm² reflecting actual HR variability. It is interesting to consider that the methodology for calculation of heart rate variability involves the measurement of the beat by beat RR intervals. It was surely natural then to use this as the primary variable for calculation of heart rate variability, rather than first performing the nonlinear transformation to convert the RR intervals to instantaneous HRs. Heart rate variability calculations are based upon the beat by beat changes, i.e. calculation of the root mean square of successive differences in the RR interval. Indeed, evaluation of the amplitude spectra of modeled data using intervals or their reciprocal does show some qualitative and quantitative differences(24). Further work will need to address this question.

Limitations

There is no gold standard for the parasympathetic, sympathetic, and interaction effects on the sinus node. Thus, the present findings only provide qualitative confirmation that analyses of heart rate may differ from those with the RR interval when assessing autonomic effects on the sinus node. This study cannot identify which variable is best; in particular there may be situations where they are equivalent, where one is superior to the other, or where a different transformation of these variables is required. Thus, it is important to consider which variable (HR, RR interval, or other transformations of these variables) is most proper for the analysis.

Conclusion

There is a clear mathematically defined hyperbolic relationship between the HR and RR interval. Over limited ranges of HR, this relationship is even piecewise linear. While these relationships have enabled the use of either variable in clinical studies, this practice is erroneous. This needs to be considered in the design and analysis of studies incorporating the heart rate or mathematical manipulations of this variable.

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Abbreviations

ECG	electrocardiogram
HR	heart rate
PB	parasympathetic blockade
SB	sympathetic blockade

SPI sympathetic-parasympathetic interaction

REFERENCES

1. Seccareccia F, Pannozzo F, Dima F, Minoprio A, Menditto A, Lo Noce C, Giampaoli S. Malattie Cardiovascolari Aterosclerotiche Istituto Superiore di Sanita Project. Heart rate as a predictor of mortality: the MATISS project. *Am J Public Health*. 2001; 91:1258–1263. [PubMed: 11499115]
2. Kannel WB, Kannel C, Paffenbarger RS Jr, Cupples LA. Heart rate and cardiovascular mortality: the Framingham Study. *Am Heart J*. 1987; 113:1489–1494. [PubMed: 3591616]
3. Palatini P, Casiglia E, Julius S, Pessina AC. High heart rate: a risk factor for cardiovascular death in elderly men. *Arch Intern Med*. 1999; 159:585–592. [PubMed: 10090115]
4. Thomas F, Bean K, Provost JC, Guize L, Benetos A. Combined effects of heart rate and pulse pressure on cardiovascular mortality according to age. *J Hypertens*. 2001; 19:863–869. [PubMed: 11393668]
5. Greenland P, Daviglius ML, Dyer AR, Liu K, Huang C, Goldberger J, Stamler J. Resting heart rate is a risk factor for cardiovascular and noncardiovascular mortality: the Chicago Heart Association Detection Project in Industry. *Am J Epidemiol*. 1999; 149:853–862. [PubMed: 10221322]
6. Fox K, Borer JS, Camm AJ, Danchin N, Ferrari R, Lopez Sendon JL, Steg PG, Tardif JC, Tavazzi L, Tendera M. for the Heart Rate Working Group. Resting heart rate in cardiovascular disease. *J Am Coll Cardiol*. 2007; 50:823–830. [PubMed: 17719466]
7. Lauer MS, Okin PM, Larson MG, Evans JC, Levy D. Impaired heart rate response to graded exercise. Prognostic implications of chronotropic incompetence in the Framingham Heart Study. *Circulation*. 1996; 93:1520–1526. [PubMed: 8608620]
8. Jouven X, Empana JP, Schwartz PJ, Desnos M, Courbon D, Ducimetiere P. Heart-rate profile during exercise as a predictor of sudden death. *N Engl J Med*. 2005; 352:1951–1958. [PubMed: 15888695]
9. Katona PG, Poitras JW, Barnett GO, Terry BS. Cardiac vagal efferent activity and heart period in the carotid sinus reflex. *Am J Physiol*. 1970; 218:1030–1037. [PubMed: 5435400]
10. Kollai M, Jokkel G, Bonyhay I, Tomcsanyi J, Naszlady A. Relation between tonic sympathetic and vagal control of human sinus node function. *J Auton Nerv Syst*. 1994; 46:273–280. [PubMed: 8014377]
11. Goldberger JJ. Sympathovagal balance: how should we measure it? *Am J Physiol*. 1999; 276:H1273–H1280. [PubMed: 10199852]
12. Sundaram S, Carnethon M, Polito K, Kadish AH, Goldberger JJ. Autonomic effects on QT-RR interval dynamics after exercise. *Am J Physiol Heart Circ Physiol*. 2008; 294:H490–H497. [PubMed: 17993603]
13. Jose AD, Taylor RR. Autonomic blockade by propranolol and atropine to study intrinsic myocardial function in man. *J Clin Invest*. 1969; 48:2019–2031. [PubMed: 5398888]
14. Stamler J, Dyer AR, Shekelle RB, Neaton J, Stamler R. Relationship of baseline major risk factors to coronary and all-cause mortality and to longevity: findings from long-term follow-up of Chicago cohorts. *Cardiology*. 1993; 82:191–222. [PubMed: 8324780]
15. Johnson NP, Goldberger JJ. Prognostic value of late heart rate recovery after treadmill exercise. *Am J Cardiol*. 2012; 110:45–49. [PubMed: 22463837]
16. Johnson NP, Holly TA, Goldberger JJ. QT dynamics early after exercise as a predictor of mortality. *Heart Rhythm*. 2010; 7:1077–1084. [PubMed: 20478405]
17. Cowper DC, Kubal JD, Maynard C, Hynes DM. A primer and comparative review of major US mortality databases. *Ann Epidemiol*. 2002; 12:462–468. [PubMed: 12377423]
18. Levy MN. Sympathetic-parasympathetic interactions in the heart. *Circ Res*. 1971; 29:437–445. [PubMed: 4330524]
19. Bazett H. An analysis of time relations of electrocardiogram. *Heart*. 1920; 7:353–370.
20. Fridericia L. Die Systolendauer im Elektrokardiogramm bei normalen Menchan und bei Herzdranken. *Acta Med Scand*. 1920; 53:469–486.

21. Sagie A, Larson MG, Goldberg RJ, Bengtson JR, Levy D. An improved method for adjusting the QT interval for heart rate (the Framingham Heart Study). *Am J Cardiol.* 1992; 70:797–801. [PubMed: 1519533]
22. Hodges M, Salerno D, Erlien D. Bazett's QT correction reviewed-Evidence that a linear QT correction for heart is better. *J Am Coll Cardiol.* 1983; 12:694.
23. Luo S, Michler K, Johnston P, Macfarlane PW. A comparison of commonly used QT correction formulae: the effect of heart rate on the QTc of normal ECGs. *J Electrocardiol.* 2004; (37 Suppl): 81–90. [PubMed: 15534815]
24. Berger RD, Akselrod S, Gordon D, Cohen RJ. An efficient algorithm for spectral analysis of heart rate variability. *IEEE Trans Biomed Eng.* 1986; 33:900–904. [PubMed: 3759126]

Clinical Perspectives

The heart rate is a basic vital sign that provides important physiologic and prognostic information because of its direct and easily measurable modulation by autonomic inputs to the heart, specifically the sinus node. Because it is easily measured, it has become a widely applied tool. While it is typically reported in beats/min, the heart rate is also often used in its reciprocal form – the RR interval – such as in Bazett's formula for rate correction of the QT interval. While there is a mathematical formula that defines their relationship, the reciprocal nature of these variables does not allow them to be substituted for each other in all situations. For example, the difference in reciprocals of two values is not equal to the reciprocal of the difference in these two values. This manuscript explores several situations - in some, simple substitution of these two different ways of expressing the heart rate does not materially affect the results and in others it does. It is therefore important when using either one of these parameters to ensure that a physiologically appropriate form of the variable is used in the analysis and to cautiously consider the possibility of misleading results due to use of the wrong form of the variable. This is challenging as gold standards do not exist for the physiology modeled by the heart rate. Qualitative analysis and clinical interpretation of the results is therefore mandatory to ensure their validity.

Figure 1.

Plot of the mathematical relationship between the RR interval and heart rate with superimposed linear regression analyses on the curve for heart rates of 50–80 bpm and 100–150 bpm. Over each of those heart rate ranges, there is an excellent fit of the curve but with a much steeper slope at the lower heart rates.

Figure 2.

Plots of heart rate (A) or RR interval (B) in normal subjects in the recovery period after multiple sessions of bicycle exercise at baseline and after selective autonomic blockade.

Figure 3.

Plots of the parasympathetic effect, sympathetic effect, and sympathetic parasympathetic interaction on heart rate and RR interval.

A. Plot of the parasympathetic effect on heart rate (HR_p) - defined by the difference of the heart rate after β -adrenergic sympathetic blockade (HR_{SB}) and double autonomic blockade (HR_o). In recovery, the magnitude of the parasympathetic effect on heart rate increases.

B. Plot of the parasympathetic effect on the RR interval (RR_p) - defined by the difference of the RR interval after β -adrenergic sympathetic blockade (RR_{SB}) and double autonomic

blockade (RR_0). In recovery, the magnitude of the parasympathetic effect on the RR interval increases.

C. Plots of the mathematical relationship between the RR interval and heart rate with the superimposed values for HR_{SB} and HR_0 at three time points of recovery. Both HR_{SB} and HR_0 decrease over time in recovery. Based on their relative location on the curve, as the HR_p increases, so does the RR_p .

D. Plot of the sympathetic effect on heart rate (HR_s) - defined by the difference (HR_s) of the heart rate after parasympathetic blockade (HR_{PB}) and double autonomic blockade (HR_0). In recovery, the magnitude of the sympathetic effect on heart rate decreases.

E. Plot of the sympathetic effect on the RR interval (RR_s) - defined by the difference (RR_s) of the RR interval after parasympathetic blockade (RR_{PB}) and double autonomic blockade (RR_0). In recovery, the magnitude of the sympathetic effect on the RR interval paradoxically increases.

F. Plots of the mathematical relationship between the RR interval and heart rate with the superimposed values for HR_{PB} and HR_0 at three time points of recovery. Both HR_{PB} and HR_0 decrease over time in recovery. Based on their relative location on the curve, specifically HR_0 being on a steeper part of the curve, as the HR_s decreases, the RR_s actually increases.

G. Plot of the sympathetic parasympathetic interaction on heart rate (HR_{SPI}). In recovery there is an increasing magnitude of sympathetic parasympathetic interaction on the heart rate.

H. Plot of the sympathetic parasympathetic interaction on the RR interval (RR_{SPI}). In recovery there is no significant sympathetic parasympathetic interaction on the RR interval.

Figure 4.

Kaplan-Meier curves by 1-minute HR and RR recovery. (A). All-cause survival differs among quartiles of 1-minute HR recovery. The quartile with the lowest HR recovery has the worst survival. (B). All-cause survival differs among quartiles of 1-minute RR recovery computed as RR 1 min-RR peak. Therefore the quartile with the worst survival has the lowest RR recovery.

Table 1

Mixed effects estimates of the Sympathetic-Parasympathetic Interaction (SPI) by minute in recovery and outcome

Minute in Recovery	HR _{SPI}			RR _{SPI}		
	Estimate	SE	p-value	Estimate	SE	p-value
0	-6.182	2.385	0.014	-6.307	9.850	0.527
1	-13.447	2.694	<0.001	-3.882	14.241	0.787
2	-16.107	2.362	<0.001	6.153	15.336	0.691
3	-16.453	2.288	<0.001	8.271	15.761	0.603
4	-16.673	2.410	<0.001	11.793	18.184	0.521
5	-16.671	2.225	<0.001	15.257	16.356	0.358
6	-14.973	2.269	<0.001	11.013	16.201	0.502
7	-16.273	2.333	<0.001	23.197	15.539	0.145
8	-14.703	2.280	<0.001	10.363	15.753	0.515
9	-16.394	2.308	<0.001	28.567	17.678	0.116
10	-14.515	2.415	<0.001	16.586	17.968	0.363

Table 2

Estimates of HR_{SPI} and RR_{SPI} changes by minute (R0 to R3)

Recovery Minutes	HR_{SPI}			RR_{SPI}		
	Estimate	SE	p-value	Estimate	SE	p-value
R0-R1	7.265	1.804	<0.001	-2.425	10.421	0.818
R1-R2	2.660	1.260	0.043	-10.035	8.477	0.246
R2-R3	0.346	0.659	0.603	-2.118	5.427	0.699

Rx - recovery at x minutes after cessation of exercise

Table 3

Hazard ratios for a one SD change in heart rate (HR) or RR Interval for coronary heart disease mortality in the Chicago Heart Association Study (mean follow-up 29 years)

Sex	Age (years)	N	Variable	Hazard ratio (95% CI)	p
Male	18–39	9706	HR	1.318 (1.187–1.463)	<0.0001
			RR	0.749 (0.667–0.841)	<0.0001
	40–59	7760	HR	1.225 (1.184–1.319)	<0.0001
			RR	0.797 (0.752–0.845)	<0.0001
	60–74	1321	HR	0.995 (0.899–1.102)	0.93
			RR	1.022 (0.928–1.125)	0.66
Female	18–39	6928	HR	0.976 (0.741–1.285)	0.86
			RR	1.019 (0.762–1.364)	0.90
	40–59	6915	HR	1.240 (1.148–1.340)	<0.0001
			RR	0.807 (0.743–0.877)	<0.0001
	60–74	1151	HR	1.124 (0.989–1.276)	0.07
			RR	0.885 (0.778–1.008)	0.06

Table 4

Nested multivariable Cox models comparing HR versus RR recovery at 1 minute

Variable	Baseline model		Added HR recovery		Added RR recovery	
	Hazard ratio (95% CI)	p	Hazard ratio (95% CI)	p	Hazard ratio (95% CI)	p
Age (per 10 years)	1.67 (1.45–1.93)	<0.001	1.62 (1.41–1.87)	<0.001	1.67 (1.45–1.92)	<0.001
Diabetes	1.96 (1.43–2.71)	<0.001	1.92 (1.39–2.65)	<0.001	1.95 (1.42–2.69)	<0.001
Prior PCI or CABG	1.54 (1.07–2.23)	0.021	1.49 (1.03–2.15)	0.032	1.50 (1.04–2.17)	0.032
Beta-blocker medications	1.36 (0.99–1.87)	0.06	1.37 (1.00–1.89)	0.05	1.40 (1.02–1.93)	0.040
Diuretic medications	1.41 (1.01–1.97)	0.046	1.40 (1.00–1.96)	0.047	1.41 (1.01–1.97)	0.044
Exercise time (per minute)	0.90 (0.85–0.95)	<0.001	0.90 (0.85–0.95)	<0.001	0.90 (0.85–0.95)	<0.001
Double product (per 1,000 mmHg/minute)	0.93 (0.90–0.95)	<0.001	0.94 (0.91–0.96)	<0.001	0.93 (0.90–0.95)	<0.001
Ejection fraction (%)	0.97 (0.96–0.99)	<0.001	0.97 (0.96–0.99)	<0.001	0.97 (0.96–0.99)	<0.001
1 minute HR recovery (per 10 bpm)	N/A		0.81 (0.69–0.95)	0.010	N/A	
1 minute RR recovery (per 100 ms)	N/A		N/A		0.66 (0.30–1.44)*	0.30

* linear term hazard ratio shown, squared term 1.06 (95%CI 0.68–1.64) p=0.81

bpm=beats per minute

CABG=coronary artery bypass grafting

CI=confidence interval

HR=heart rate

ms=milliseconds

N/A=not applicable

PCI=percutaneous coronary intervention