Respiratory sinus arrhythmia, cardiac vagal control, and daily activity

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Grossman, P, F. H. Wilhelm, and M. Spoerle. Respiratory sinus arrhythmia, cardiac vagal control, and daily activity. *Am J Physiol Heart Circ Physiol* 287: H728–H734, 2004. First published January 29, 2004; 10.1152/ajpheart.00825.2003.—Ambulatory respiratory sinus arrhythmia (RSA) or high-frequency heart rate (HR) variability is frequently employed as an index of cardiac parasympathetic control and related to risk or severity of cardiovascular disease. However, laboratory studies indicate variations in physical activity and respiratory parameters of rate and tidal volume may confound estimation of vagal activity. Because little is known about these relations outside the laboratory, we examined ambulatory relations among RSA, respiration, physical activity, and HR during waking hours by employing a multichannel monitoring system. Forty healthy young-to-middle aged adults underwent daytime monitoring that included continuous registration of the ECG, respiration (inductance plethysmography), and accelerometry motion activity. Within-individual regression analyses were performed to examine minute-to-minute relations between RSA and respiration, HR, and indexes of physical activity (minute ventilation and motion). HR changes were assumed to be strongly related to within-individual variations of vagal tone. RSA adjusted for respiratory parameters and unadjusted RSA were compared for strength of prediction of other measures. Unadjusted RSA was related to respiratory parameters ($R = 0.80$) and moderately predicted minute-to-minute HR and activity variances (means = 56%, HR; 48%, minute ventilation; and 37%, motion). Adjusted RSA predicted significantly more HR and activity variance (means = 75%, 76%, and 57%, respectively) with narrower confidence intervals. We conclude that ambulatory RSA magnitude is associated with respiratory variations and physical activity. Adjustment for respiratory parameters substantially improves relations between RSA and significantly vagally mediated HR and physical activity. Concurrent monitoring of respiration and physical activity may enhance HR variability accuracy to predict autonomic control.

high-frequency heart rate variability; respiration; autonomic control; ambulatory monitoring; metabolic activity

RESPIRATORY SINUS ARRHYTHMIA (RSA), or high-frequency heart rate (HR) variability (HRV), is frequently employed as a measure of cardiac vagal tone under ambulatory conditions. Among both patients and healthy persons, ambulatory RSA measures are increasingly used to elucidate patterns of autonomic modulation of cardiovascular control and to index disease risk or severity (7, 10, 25, 33).

A number of human and animal studies confirm that HR changes during mild-to-moderate increase and decrease in physical activity are under parasympathetic control to a significant degree (5, 9, 11, 15, 23, 26, 34, 36, 40–42, 52). Therefore, fluctuations in daily physical activity, which are typically moderate in magnitude (e.g., walking at slow to moderate pace), should importantly reflect variations in cardiac parasym-pathetic tone. Disease-specific effects on range, frequency, and duration of physical activity may interact with and confound the assessment of individual differences in autonomic regulation; estimates of cardiac vagal activity may represent not only individual differences in constitutional parasympathetic control but also variations in daily activity pattern. Two laboratory studies have shown that variations in physical activity can influence HRV markers of cardiac vagal control, although these investigations provide somewhat contradictory results in terms of the direction of change and provide no direct quantification of variations in activity (3, 37). Thus far there has been no attempt to relate RSA to discrete variations in real-life, daily physical activity measured by motion or indexes of overall energy expenditure.

Another salient issue regarding RSA pertains to potential respiratory confounds when estimating cardiac vagal control. The simple magnitude of RSA is often assumed to be a valid index of cardiac parasympathetic control. However, a number of laboratory studies document that within-individual changes in respiratory parameters of rate and tidal volume (V_t) can seriously confound the association of RSA and cardiac vagal tone. Decreased V_t and increased breathing frequency (F_b), or respiration rate, can profoundly attenuate RSA under basal conditions in which cardiac vagal tone remains constant (8, 14–16). To date, however, we do not have information regarding how RSA is correlated with respiratory parameters under ambulatory real-life conditions or how RSA is associated with changes in cardiac vagal tone during daily activity.

Minute-to-minute changes in HR over the day, largely due to fluctuations in physical exertion, may provide an independent index of cardiac vagal tone, which can be related to RSA or to measures derived from RSA that correct for simultaneous variations in F_b and/or V_t. Over the past half century, autonomic blockade studies have consistently indicated that exercise-induced HR changes <110 beats/min are highly correlated with changes in cardiac vagal activity degree (5, 9, 11, 15, 23, 26, 34, 36, 40–42, 52). With the use of multisignal ambulatory devices, assessments of naturalistic physical activity derived from accelerometry or minute ventilation (V_m) can be used to establish that daily variations in HR outside the laboratory are, indeed, tied to variations in activity, as well as to evaluate relations between physical activity and different RSA-based estimates of vagal tone.

In this investigation, we examined relations among RSA, respiration, and normal daily fluctuations in the physical activity among healthy young-to-middle-aged adults. We monitored one channel of the electrocardiogram (ECG), ventilation (via calibrated inductance plethysmography), and upper-torso

motion (via two-dimensional accelerometry). The major goal was to assess whether concurrent monitoring of respiration and physical activity are useful or necessary when estimating vagal tone by means of RSA.

The following questions were addressed. First, to what extent are minute-to-minute variations in RSA during daily activity related to respiratory parameters among healthy young-to-middle aged adults? Second, how are minute-to-minute changes in RSA related to primarily exertion-induced fluctuations in the HR (previously shown to be tightly related to variations in cardiac vagal tone within individuals)? Third, do adjustments for V_t and F_b improve RSA prediction of HR and physical activity measures during levels of exertion presumed to be associated with systematic changes in cardiac vagal control? Fourth, how strongly is RSA related to measures of metabolic/physical activity? Finally, are there gender differences in RSA and other measures in relation to physical activity?

METHODS

Subjects. Forty healthy young-to-middle-aged adult volunteers (mean age, 26.0 ± 6.3 yr SD, range $20\text{–}43$ yr; 20 female) participated in the study. The majority of subjects were university students, and all reported to be free of chronic or acute cardiovascular, respiratory, or other chronic disease. Subjects were informed that they would undergo 24-h monitoring of cardiovascular function, ventilation, and behavioral activity under conditions outlined below. The investigation was performed in accordance with the published recommendations of the Ethics Commission of the University of Freiburg, and all participants completed informed consent. Subjects were paid for participation.

Procedure. Subjects began sessions at approximately 9:00 AM on a weekday and were fitted with monitoring equipment and ECG electrodes. They first performed 800-ml volumetric calibration of inductance plethysmography bands used to determine volumetric coefficients for thoracic and abdominal respiratory bands. Participants then underwent a 2-h experimental session during which they performed a variety of standardized mental tasks. The tasks included a baseline, conversational speaking, a relaxation task, reading, an attentional task, a reaction time task, and mental arithmetic. These tasks and the evening attendance of a film provided standardized segments of registration relevant to related issues (unpublished observations).

Subjects were otherwise requested to resume their normal daily activities. Although monitoring was performed for 24 h, we only present data in this report from daytime and evening hours.

Measures. The following physiological signals were continuously registered via a multichannel ambulatory monitor (LifeShirt System; Vivometrics; Ventura, CA) and stored on flashcards: one channel of ECG (250 Hz), two channels of respiration via abdominal and thoracic inductance plethysmography bands (50 Hz); and one two-dimensional accelerometer at chest level (10 Hz). Respiratory, cardiac, and accelerometry measures were analyzed by the Vivologic analysis software (Vivometrics), a full disclosure analysis system allowing validation of all parameters. Respiratory parameters included F_b (breaths/min), V_t (ml), and V_m (l/min). Previous research has validated this method of ambulatory monitoring of respiratory timing and volumetric parameters (1, 35, 39, 47, 54). Motion activity was the sum of the two axes of the integrated accelerometer signal.

All registrations were manually screened for ECG arrhythmias, ectopic activity, and movement artifact in both the ECG and respiratory signals. Subjects with abnormal ECGs or excessive ectopic activity (>3% of all beats) were eliminated from analyses ($n = 4$).

Minutes with ectopic or other artifact in the remaining subjects were removed from all analyses.

Cardiac parameters included HR (in beats/min) and RSA (in ms). RSA was quantified in the time domain using the peak-valley algorithm to estimate amplitude of RSA (15, 18). This method has been previously validated as almost perfectly correlated with spectral analysis estimations (18). To briefly describe the procedure, concurrent respiratory and instantaneous R-R interval (derived from the ECG) are measured. Because R-R interval shortening typically is associated with inspiration and lengthening with expiration, the inspiratory phase of a breath is used as a window for determining the shortest R-R interval, and expiratory phase is used as a window for determining the longest R-R interval. Additional adjustments for window length are also calculated on the basis of known phase shifts related to F_b, and the algorithm assures that scores above zero for any breath require R-R shortening during the inspiratory window and lengthening during the expiratory window. Peak-to-valley R-R interval difference scores are then calculated on a breath-by-breath basis and averaged over time. Simulation studies indicate that this estimation procedure is robust against nonstationary trends within the human physiological range of HR (13).

Because earlier validation of this method was made under laboratory conditions, we compared standard spectral analysis and time-domain peak-valley estimates for a subset of 10 subjects during daytime and nighttime registrations. Forty 5-min periods were randomly selected for each subject, and correlation coefficients were determined both within and across subjects. Details regarding the spectral analysis can be found in previous reports (20). Within-subject correlations varied between 0.96 and 0.99, with a mean of 0.97 between the two quantification procedures (all P values $<10^{-13}$). The between-subject correlation coefficient was 0.96 ($N = 10$; $P = 0.00001$). These findings confirm earlier laboratory results of essential equivalence between quantifications. We chose to employ the peak valley quantification rather than the spectral measure for the following reasons: *1*) it is faster and easier to calculate; *2*) it determines quantification of breath-by-breath RSA based on real respiratory frequency and not on a respiratory frequency band that may not accurately reflect RSA when breathing is either faster or slower than the predetermined bandwidth (typically $0.15\text{–}0.5$ Hz or $9\text{–}30$ counts/min); and *3*) because RSA is quantified on a breath-by-breath basis, more precise and separate adjustments can be made for respiratory parameters of frequency and volume than with spectral analysis.

Statistical analyses. Individual regression analyses for each subject were performed for all major questions. This means that, on average, 840 observations (i.e., minutes) were initially employed for each of the 40 subjects. However, when relations between HR and RSA measures are examined, regression analyses employed only minutes during which HR was <110 beats/min, which is the primary range of cardiac parasympathetic control (5, 9, 15, 23, 26, 34, 40–42). All individual R values presented in this article were highly significant (P values $< 10^{-4}$).

Linear multiple regression analyses were performed to examine relations between the natural logarithm of RSA (transformed to normalize the distribution and to provide to spectral power equivalents) and respiratory parameters of F_b and tidal volume. Visual inspection of the individual regression plots confirmed that respiratory-RSA relations were linear for every subject. On the other hand, RSA relations to HR and to physical activity measures (V_m and motion analyzed separately) were consistently exponential on inspection. Therefore, nonlinear exponential growth regression analyses were employed by using the quasi-Newton estimation procedure.

In further analyses, we employed a measure of RSA adjusted for respiration by dividing untransformed RSA by V_t. Used in previous research (12, 15, 32, 45, 51, 53), this parameter is the transfer function, or gain, of RSA in milliseconds per milliliter of tidal volume change. As with the uncorrected RSA analyses, we calculated individual-subject regressions of this RSA transfer function (RSA_{TF}) in

relation to minute-to-minute HR, V_m, and accelerometer activity. Visual inspection of regression plots also confirmed that the same exponential growth model could be used as mentioned above for each of these sets of analyses and for all subjects. Furthermore, we examined whether additionally entering F_b into the regressions would improve prediction of the criterion variables of HR and activity measures when using RSA_{TF} as predictor.

Separate analyses were performed for relations between RSA measures and the two indexes of physical activity: V_m and motion. V_m has been demonstrated to be a reliable index of overall metabolic activity under ambulatory conditions, which largely reflects changes in the net sum of muscular work (18). We also employed paired t-tests to determine whether adjusted RSA_{TF} provided improved prediction of HR and physical activity to that of unadjusted RSA.

Finally, we examined the effects of activity level on RSA measures by determining quintiles of V_m for each subject, based on equal number of minutes (i.e., each quintile represented 20% of total minutes). Repeated-measures analyses of variance of RSA were then performed across those quintiles with all subjects combined ($n = 40$).

RESULTS

RSA-respiration relations. Multiple regression analyses of RSA as criterion variable and respiratory measures (F_b and V_t) as predictors confirmed that RSA magnitude was significantly associated with respiratory parameters during daily life. Figure 1 displays a histogram of the individual multiple regression coefficient (R) values across subjects, and Fig. 2 is a regression plot from a typical subject. The average amount of variance accounted for by respiratory parameters was 0.64 (±0.09 SD; 95% CI = 0.58–0.69; average $R = 0.80$).

RSA-HR relations. To determine that minute-to-minute variations in HR below 110 beats/min were primarily due to metabolic demands, V_m was related within subjects to alterations in HR: the average R across subjects was 0.74, and the average amount of shared variance was 0.55 (±0.13 SD; 95% CI = 0.52–0.59). This indicated that HR fluctuations were likely to have reflected changes in vagal control (23, 26, 40, 42).

We next computed nonlinear regression analyses for the prediction of minute-to-minute HR using as separate predictors *1*) raw, unadjusted RSA, and *2*) RSA_{TF}, adjusted for V_t. Histograms of individual R values for each set of analyses are

presented in Fig. 3, and Fig. 4 is a typical scatterplot of one subject. When unadjusted RSA was the predictor, the mean variation in HR accounted for was 0.56 (±0.18 SD; 95% CI, 0.51–0.62; $R = 0.75$). When RSA_{TF} was the predictor, the mean variance accounted for increased to 0.75 (±0.13 SD; 95% CI, 0.71–0.79; $R = 0.87$). Inclusion of F_b as a second predictor in the RSA_{TF} regression analyses did not improve estimation, indicating that additional correction for F_b was unnecessary once RSA was normalized for V_t. A paired t-test comparing the shared variance between HR and the two RSA measures indicated that RSA_{TF} predicted significantly more of the minute-to-minute HR variation than unadjusted RSA [$t(39) = 14.33$, $P < 10^{-16}$].

Additionally, the range of HR variation accounted for was much greater in the unadjusted RSA analyses (see Fig. 3). For example, 53% of subjects had <60% of their HR variation accounted for by RSA, whereas only 8% of subjects when RSA_{TF} was employed as the predictor. Given that minute-to-minute variations in HR predominantly reflected parasympathetic control, these results suggest that adjusted RSA is a better index of cardiac vagal tone than raw RSA during ambulatory monitoring.

RSA-physical activity relations. V_m was employed as the primary marker of overall metabolic activity. When RSA_{TF}

Fig. 2. Multiple regression prediction of RSA during daily activity using F_b and V_t for a typical subject. $R = 0.83$.

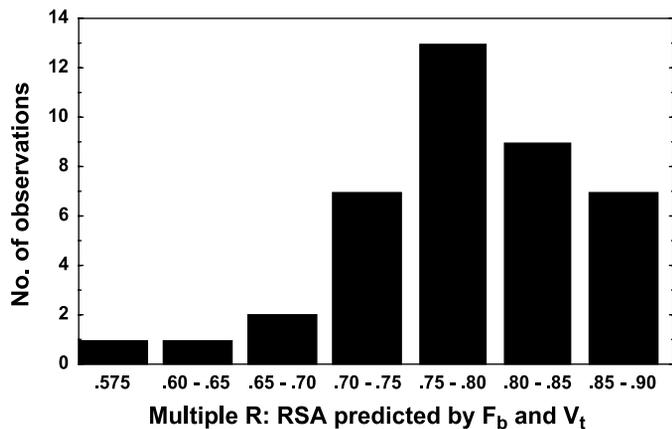Predictor equation = 9.8 + (-.84 F_b) + (-.10 V_t)

Fig. 1. Histogram of individual multiple regression coefficients (R values) in which respiratory sinus arrythmia (RSA) was jointly predicted by breathing frequency (F_b) and tidal volume (V_t). Each observation represents one subject across all minutes of the waking day.
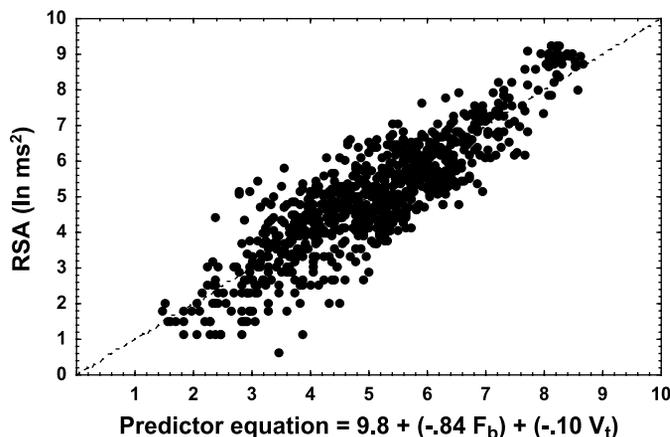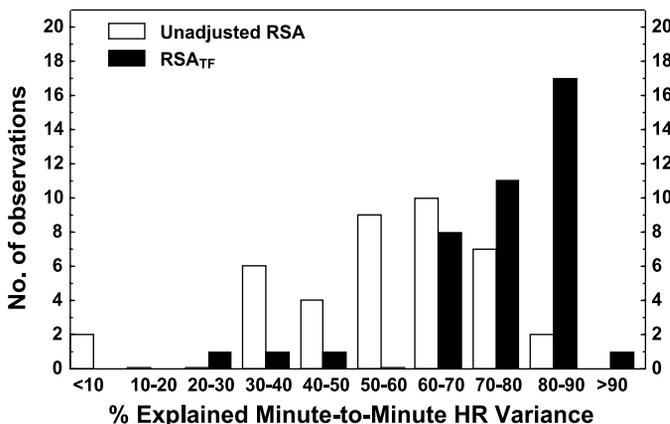

Fig. 3. Histogram of minute-to-minute heart rate (HR) variance predicted by each RSA measure. Individual observations represent the regression results of a single subject. RSA_{TF}, RSA transfer function.
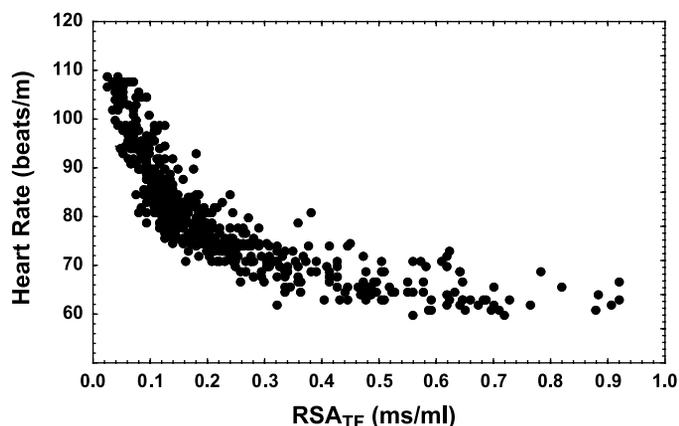
Fig. 4. Relationship of HR and RSA_{TF} during daily activity for a typical subject.

was used as the predictor, the mean variance accounted for over 40 subjects was 0.76 (± 0.08 SD; 95% CI = 0.74–0.79; average $R = 0.87$). When unadjusted RSA was used, shared variance was 0.48 (± 0.20 SD; 95% CI = 0.42–0.55; $R = 0.68$; see Fig. 5). As with the HR analyses, a paired t-test revealed that RSA_{TF} predicted significantly more of the V_m variance across subjects [$t(39) = 12.55$; $P < 10^{-14}$]. Additional inclusion of F_b into the regression analyses did not improve the prediction.

When these analyses were repeated by replacing accelerometry data as the index of metabolic activity, similar highly significant differences were found [$t(39) = 11.22$; $P < 10^{-13}$], although the explained variance was less for both measures (mean explained variance: 0.57 $\pm$ 0.13 SD for RSA_{TF}; 0.37 $\pm$ 0.16 for unadjusted RSA).

Repeated-measures analysis of variance across quintiles of physical activity (V_m) employing RSA and RSA_{TF} separately as dependent variables revealed highly significant effects of activity level for both RSA measure (P values $< 10^{-16}$ with Greenhouse-Geisser correction; see Fig. 6). From highest to lowest quintiles of activity, RSA_{TF} manifested a 5.5-fold change, unadjusted RSA two natural logarithm units change.

These findings, therefore, indicate that both RSA quantifications are highly responsive to changes in metabolic activity. However, within individuals, the adjusted RSA measure was superior to unadjusted RSA in predicting activity in the primary range in which cardiac parasympathetic influences were dominant.

Gender differences. Repeated-measures ANOVA values were used to examine gender differences across the activity quintiles for all variables. The only significant differences found were for the two RSA measures (see Fig. 7). A gender by activity interaction effect indicated that women showed progressively greater RSA and RSA_{TF} than men as activity decreased [$F(2.1, 80.4) = 3.5$, and $F(1.4, 54.7) = 3.59$, respectively, with Huynh-Feldt corrections; P values < 0.05].

DISCUSSION

We review the major findings of this study. First, ambulatory data recorded during daily life among healthy individuals confirmed laboratory findings showing within-individual relations between RSA magnitude and F_b and V_t (8, 14–16). Second, unadjusted RSA was a moderately good predictor of

minute-to-minute variations in HR that can be assumed to primarily reflect cardiac parasympathetic control (23, 26, 40, 42). Third, when RSA was adjusted for V_t, this measure was more strongly related to minute-to-minute HR change and presumably to change in cardiac vagal tone. Fourth, this relation was not improved by statistically controlling for F_b. Fifth, normal variations in physical activity exerted large effects upon each measure of RSA. Sixth, within individuals, RSA_{TF} was most highly sensitive to changes in activity. Finally, women manifested greater RSA than men at lower, but not at higher, levels of physical activity.

The within-individual association between respiratory parameters and RSA has long been a contentious issue with regard to the accuracy of RSA as an index of cardiac vagal tone (15). For at least four decades it has been known that voluntary alteration of respiratory parameters can profoundly influence RSA magnitude; slowing and deepening of breathing will amplify RSA magnitude among healthy adults, whereas faster, more shallow breathing may all but eliminate RSA (15). Several pharmacological studies (8, 15, 16, 30) have additionally documented that these respiratory-mediated changes in RSA are not related to variations in cardiac vagal tone and, hence, that V_t and F_b can greatly confound estimation of cardiac vagal tone.

The issue is, however, complex and requires serious consideration. In the laboratory, it may often be possible to have subjects pace their breathing when assessing vagal tone by means of RSA to control for potential respiratory confounds. However, in uncontrolled daily life, this is unfeasible. Additionally, respiratory variations in daily life may not only directly influence RSA magnitude but may also sometimes actually covary with cardiac vagal tone and energy expenditure. Hence, during exercise, respiration characteristically becomes more rapid as vagal control decreases (19). Therefore, part of the RSA diminution may be due to respiratory influences and part to actual decreases in vagal tone. To statistically adjust RSA for F_b may bring about an underestimation of exercise-induced vagal change; on the other hand, ignoring respiratory parameters may produce an overestimation of vagal inhibition. Thus adjusting for F_b may bias vagal tone estimation in a direction opposite to the bias of not controlling for respiratory parameters at all.
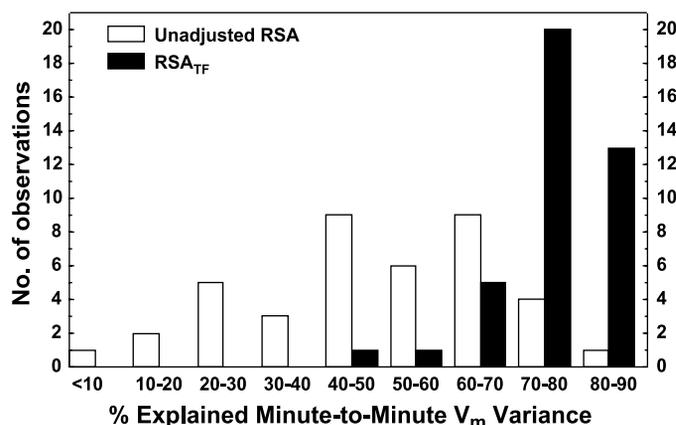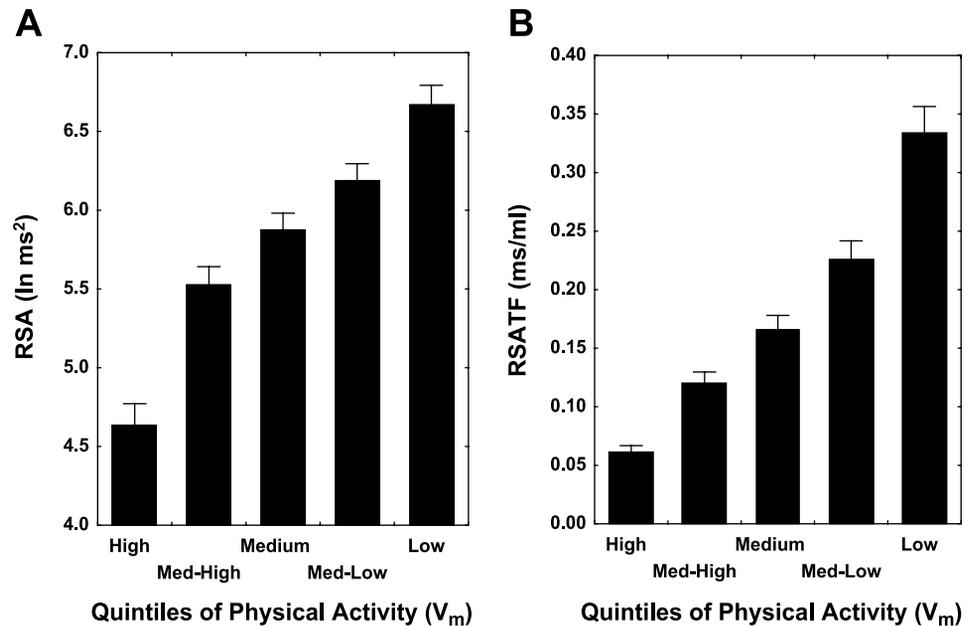

Fig. 5. Histogram of minute-to-minute minute ventilation (V_m) variance in activity accounted for by each RSA measure. Each observation represents a single subject.

Fig. 6. RSA and RSA$_{TF}$ as a function of quintile of physical activity (V_m). Each quintile represents one-fifth of total minutes at varying ranges of V_m. A: unadjusted RSA; B: RSA$_{TF}$.

We, therefore, employed RSA$_{TF}$ (RSA/V_t) as a RSA measure adjusted for respiration. First, this measure had been successfully employed in previous research and has provided supplementary information to unadjusted RSA in clinical and nonclinical studies of vagal control (12, 15, 24, 27–29, 32, 38, 44, 45, 48, 51, 53). Second, under steady-state conditions, RSA magnitude is directly related to V_t, and V_t and F_b are rather strongly reciprocally related, so that controlling RSA for one respiratory variable is likely to control it for the other (19). Third, with increasing metabolic demand, this inverse relation between F_b and V_t changes to a more positive one characterized by increasing volume and increasing rate (19). Finally, by employing the gain of RSA in relation to V_t, smaller values of RSA$_{TF}$ are likely to be obtained as the relation between RSA magnitude and V_t moves from the positive steady-state direct relationship during rest to an inverse one during elevated metabolic activity; thus as exercise intensity increases, V_t increases but RSA magnitude is reduced.

Our assumption that minute-to-minute HR variation was, in fact, vagally mediated to a significant degree was supported by 1) the within-subject association between minute-to-minute HR and V_m (as measure of physical activity; average $R = 0.74$), and 2) the substantial body of literature indicating that HR change during submaximal physical exertion and recovery is closely associated with variations in cardiac vagal activity (5, 9, 11, 15, 23, 26, 34, 36, 40–42, 52).

In comparison with unadjusted RSA, RSA$_{TF}$ indeed showed superior prediction of minute-to-minute variations in HR. Findings were even more marked when the two RSA measures were employed to predict physical activity. These results, therefore, support a substantial augmentation in prediction of cardiac vagal control when respiratory parameters are taken into account.

Nevertheless, it is important to mention several caveats regarding RSA and our other index of cardiac vagal tone. First, with the examination of our own criterion measure of vagal tone in this investigation, i.e., HR at low to moderate levels of activity, human sympathetic responses to dynamic exercise (muscle sympathetic nerve activity, norepinephrine, and epinephrine) begin to increase when HR approaches the level at which vagal withdrawal is nearly complete (5, 23, 42), indicating that modest levels of sympathetic activity are still present at lower intensities of exertion. Individual differences in physical conditioning may also have impact on the parasympathetic and sympathetic influences on HR at submaximal levels of exertion, although blockade studies suggest similar relations among healthy subjects whether they report regular exercise or not (e.g., 5, 23). Additionally, it would have been useful to concurrently examine beat-to-beat blood-pressure changes during variations in RSA and physical activity. However, we were concerned that the intrusiveness of currently available blood pressure monitors might distort the natural relationships between RSA and activity that we were primarily interested to characterize.

Other research has shown that RSA, itself, can be influenced by variations in β-adrenergic stimulation (16, 22, 49), and this relation may be further complicated by effects of interactions of the two autonomic branches upon cardiac chronotropic activity, such as accentuated antagonism (31, 50). Recent
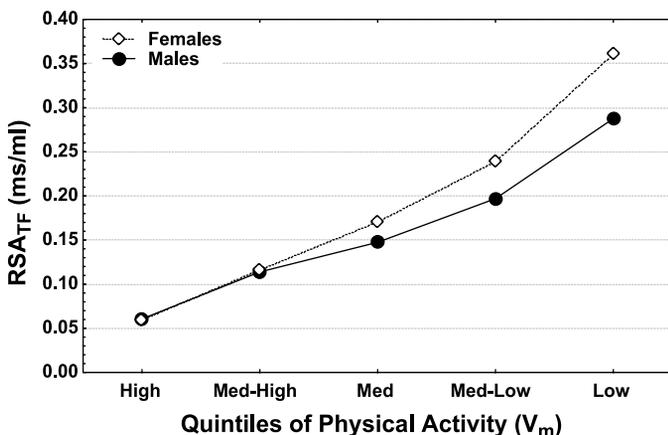

Fig. 7. RSA$_{TF}$ in relation to gender and quintile of physical activity (V_m).

studies have also suggested that cardiac vagal tone and RSA may actually dissociate under specific conditions related to alterations of ventilatory control (21, 43). Consequently, much care must be taken when employing any RSA measure as an index of cardiac vagal tone; although under many conditions, RSA, if prudently assessed, may still largely reflect parasympathetic activity (e.g., 4, 6, 15, 17, 22).

The powerful association between RSA measures and activity parameters during waking hours indicates that ambulatory monitoring of RSA, in particular, and HRV, in general, are likely to be strongly affected by group or individual differences in frequency, duration, and extent of daily physical activity. The large, lawful differences in RSA related to physical activity found in this investigation highlight a major difficulty in assessing autonomic control without concurrent assessment of physical activity. These findings may have major significance for clinical studies in which the extent of disease can profoundly influence both autonomic regulation and patterns of physical activity. Therefore, it seems important to consider concurrent monitoring of V_m or motion activity when assessing RSA or other HRV measures outside the clinic. Interestingly, other studies have examined very low-frequency components of HRV by experimentally comparing active and sedentary schedules. Investigations have found that increased variation of activity over periods of minutes or hours enhances, rather than attenuates, very-low frequency and ultra-low frequency components (2, 3, 37, 46). These results may simply reflect the fact that variation in physical activity produces variation in HR and that fluctuations of physical activity may often importantly influence these very slow components of HRV during daily life. On the other hand, the progressive attenuation of RSA with increasing levels of physical exertion probably largely represents the direct consequence of cardiac vagal withdrawal. In conclusion, these findings highlight the importance of concurrent monitoring of respiratory and physical activity when measuring HRV estimates of cardiac vagal tone. Inclusion of these measures is likely to provide improved accuracy of estimating HRV, valuable information regarding the context in which monitoring takes place, and new indexes of real-life autonomic regulation and responsiveness in health and disease.

DISCLOSURES

P. Grossman and F. H. Wilhelm are both consultants to VivoMetrics (Ventura, CA).

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