Autonomic Nervous System Responses to Exercise in Relation to Ventilatory Threshold

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We introduce our recent approach to study autonomic nervous system control of heart rate during exercise by means of heart rate variability (HRV) spectral analysis with special reference to its relationship to ventilatory threshold (Tvent). The rationale for the study was that HRV has been shown to reflect (cardiac) parasympathetic and sympathetic nervous system (PNS and SNS, respectively) activity, together with the underlying complexity of cerebral autonomic system in terms of fractal dimension (DF) of HRV time series. The experimental results showed that PNS was markedly reduced below Tvent, that the rate of change in sympathoadrenal activity indicators (plasma norepinephrine and epinephrine concentrations and SNS indicator) was enhanced above Tvent, and that these changes in PNS and SNS indicators were associated with the appearance of the low-dimensional (low DF) dynamics that might reflect less complex autonomic activity. These findings have been considered with respect to implication for clinical cardiology.

During incremental exercise, the minute ventilation (V̇E) begins to increase non-linearly with respect to oxygen uptake (V̇O₂) or work rate (WR) at a moderate exercise intensity, namely the ventilatory threshold (Tvent). This abrupt increase in V̇E was considered to be due to the abrupt onset of lactic acidosis and the resultant activation of blood bicarbonate buffering system.¹ ² ⁴

Since these early reports, many studies have cast doubt on the specific hypothesis that cellular dysxia, leading to metabolic acidosis, resulted in the occurrence of Tvent. The evidence has included the observations that blood lactate concentration (LA) rose significantly before Tvent,³ ⁴ that lactic acidosis induced by preliminary strenuous exercise failed to alter the pattern of ventilatory responses during subsequent incremental exercise,⁵ ⁶ that an alteration in blood acid-base status could not induce the concomitant change in Tvent,⁷ and that epinephrine infusion could change both LA and Tvent.⁸

In the review of Dempsey et al.,⁹ the 2 more direct counterevidences were provided. One was the report of Hagberg et al.¹⁰ in which they demonstrated a Tvent in patients with McArdle's disease despite their inability to develop lactic acidosis during exercise because of a lack of the enzyme, myophosphorylase. On the contrary, Dempsey et al.¹¹ reported that highly trained athletes could not hyperventilate in heavy exercise despite marked acidemia.

This evidence forced the original authors of the anaerobic threshold (AT) concept to modify the significance of Tvent and to incline more to gas exchange responses.¹² That is, they recently emphasized that an increase in carbon dioxide output (V̇CO₂) was always commensurate with an increase in H⁺ due to lactacidosis while Tvent was not always accompanied by this stimulus.¹³ However, such compromise may raise definite problems both methodologically and physiologically.

Methodologically speaking, it can be said that most noninvasive determinations of AT have been performed using parameters relating to V̇E response to exercise, not necessarily by what is called the "V-slope" method.¹⁴ Then the question arises; should we reinterpret all of the clinically presented results because these were not examined by the latter method? The answer to this question given by these authors was that AT determined by V̇E responses could be validated only for the subjects whose ventilatory control mechanisms responded "appropriately." However, considering that they regarded the appropriate responses as such that V̇E tracked the increase in V̇CO₂, this is circular logic.

To answer this question, therefore, a study on the physiologic mechanisms responsible for the onset of hyperventilation per se at Tvent is necessary.

Several factors other than lactacidosis were shown to affect V̇E during exercise at a moderate to high intensity. These included body temperature, catecholamines,¹⁵ ¹⁶ and more recently arterial concentration of potassium.¹⁷ All of these factors are listed in the recent review of Cunningham et al.¹⁸ to modulate feedback control of ventilation, and they are thought to be related to the sympathoadrenal activity.¹⁷

In this article, we introduce our recent approaches to autonomic nervous system control during exercise by means of heart rate variability (HRV; heartbeat intervals on beat-to-beat basis) spectral analysis with special reference to its relationship to Tvent. As the method was not for investigating the respiratory controller directly, the results of these studies could not delineate the detailed physiologic mechanisms responsible for Tvent. However, there was at least one potential implication of the results for clinical cardiology. This has been discussed in the last section.

**HRV Parameters to Evaluate Autonomic Control of Heart**

The study of HRV has evolved with time series spectral analysis. In the frequency domain, human HRV spectra have displayed 2 or more major harmonic components.¹⁹ One is at frequency >0.15 Hz, mediated solely by changing levels of parasympathetic nervous system (PNS) activity.²⁰ ²¹ The other components are usually seen at or below 0.1 Hz and are coherent with blood pressure variability.²² It has been demonstrated that the latter components at frequencies <0.15 Hz might be associated with both sympathetic nervous system (SNS) and PNS activities.²³ ²⁴

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There are components in the HRV signal other than those taken to indicate PNS and SNS activities. HRV also consists of a nonharmonic component characterized by its broadband spectrum. This broad-band noise has been suggested to be “fractal” in nature, and can be characterized by the fractal dimension (Df) which in some sense is indicative of the complexity of a given time series. We have recently developed a technique, coarse graining spectral analysis (CGSA), that permits simultaneous evaluation of the harmonic components related to PNS and SNS activities, as well as computation of Dr of nonharmonic components.

The rationale to use this method has been detailed by Yamamoto and Hughson. Briefly, the method was based on the fact that the fractal nonharmonic component retains its power after it is cross-correlated with its rescaled version, whereas, the harmonic component does not. A standard FFT method was used to estimate auto-power spectra of the original HRV time series (Sxx) and cross-power spectra between the original and rescaled (coarse grained) time series (Sxxc). Sxx was shown to represent harmonic plus nonharmonic (fractal) components, whereas, Sxxc represented the nonharmonic (fractal) component. Thus, we subtracted Sxxc from Sxx to obtain the harmonic component.

From the harmonic component, the integrated power in 0.05 to 0.15 Hz (P1) and 0.15 to 1.0 Hz (P2) was calculated. PNS and SNS activities were evaluated by high frequency power (Pf) and ratio of low to high frequency power (Pf/Pois) respectively. PNS indicator was normalized to total HRV power with consideration for the effect of change in magnitude of respiratory sinus arrhythmia.

The nonharmonic (fractal) component in the HRV spectrum has been reported to have power-law characteristics, as expressed by $P \propto f^{b}$ in log frequency (f) vs log power plots where b is the spectral exponent. Therefore, the fractal component was plotted in a log frequency vs log power plane with $b$ estimated as the slope of the linear regression of this plot. From the value of $b$, Dr was calculated as $Df = 2/(b-1)$ for $1 < b \leq 3$. For $b > 3$ and $0 \leq b < 1$, Dr was taken as 1 and infinity ($\infty$), respectively.

The value of Dr or $b$ can have the following physiologic meanings. The brain consists of a number of (nonlinear) oscillators and the interactions among them generate very complex dynamics. Dr is thought to be the physical reflection of the number of these oscillators. For example, the dimensionality of human cerebral activity, evaluated by correlation dimension (the lower limit of Dr) of an electroencephalographic (EEG) recording, has been reported to be $8 \approx \sim 20$ in the awake, eye-opened, but quiet state. A high-dimensional system is also called “information rich,” and this makes redundant processing of external stimuli possible. Considering the fact that there are projections that could transmit the cerebral activity to the autonomic centers, it is not surprising to see high Dr ($b$ close to unity) in the resting human HRV with high level of PNS activity.

Babloyantz and Destexhe, in the first report for the existence of low dimensional dynamics in the field of human physiology, demonstrated that the correlation dimension of EEG during epileptic seizure had a low mean value of 2.05. As to the implication of this finding, they speculated that the agent producing the seizure tended to drive the brain activity toward a stable periodic motion. In such states, information processing would be impossible and recovery would be extremely difficult. However, to process reflex activities, the brain remains on a chaotic attractor, albeit one of very low dimensionality. In an analogous way, we have recently shown that the increase of defensive SNS responses to orthostatic challenges and exercise was associated with Dr of HRV close to 2.0 ($b \sim 1.0$), suggesting that Dr of HRV was indicative of a functional state of the autonomic centers. The reduction in Dr has also been observed in various physiologic and pathologic situations, including susceptibility to syncope induced by orthostatic challenges and aging, and electrical instability of the heart.

**Autonomic Response and Ventilatory Threshold**

In an earlier study, we observed the HRV responses to constant load exercise with intensity set relative to Vvent. Eight subjects completed six 17-min submaximal exercise tests and one resting measurement in the sitting position. During submaximal tests, WR was increased for the initial 3 min in a ramp fashion until it reached constant WRs of 20 W, or 30%, 60%, 90%, 100%, and 110% of the predetermined Vvent while ventilatory profile, alveolar gas exchange, and HRV were measured continuously. From the HRV data, PNS and SNS indicators were calculated.

The results showed the PNS indicator to decrease dramatically compared with rest when the subjects exercised. It continued to decrease until the intensity reached 60% Vvent. The SNS indicator, on the contrary, was statistically unchanged up to 100% Vvent, while it increased significantly at 110% Vvent.

We have recently studied these autonomic nervous system responses to exercise for more detail by adopting a ramp work protocol and by observing catecholamines and Dr ($b$) responses.

Briefly, 6 healthy male volunteers performed incremental exercise test on an electrically braked cycle ergometer, consisting of a 5-min warm-up period at 50 W, followed by WR increment in a ramp fashion until exhaustion. The rate of increase in WR was 2.0 W·min$^{-1}$. This very slow ramp protocol allowed us to observe quasi-steady-state responses of HRV analyzed for successive 10-min periods of data. The steady-state nature of heart rate response was particularly important for HRV spectral analysis. Arterialized venous blood was sampled every 5 min from an indwelling catheter in a superficial vein on the heated dorsum of the hand for the analyses of LA, plasma norepinephrine (NE), and epinephrine (E) concentrations.

Overall responses of the physiologic variables are shown in Figures 1 through 3. As was suggested by Wasserman et al, the rate of change in LA during the very slow ramp exercise was so small that VCO$_2$ increased almost linearly in relation to exercise intensity (Fig 1). Thus, the determination of Vvent of V-slope method was impossible for all subjects. Nevertheless, the profile of end-tidal O$_2$ (PetO$_2$) and CO$_2$ (PetCO$_2$, Fig 1) pressures showed clear evidence of the onset of hyperventilation (Vvent) at moderate exercise intensity. Such a reduction in PetCO$_2$ at Vvent is to be expected for these very slow ramps because so-called “isocapnic buffering” is an anomaly of the specific 15
In Figures 1 through 3, all variables have been shown as ensemble averages for 6 subjects in relation to the Tvent determined by the PetO₂ and PetCO₂ profiles. The statistical comparison of regression slopes below and above Tvent showed that only PetCO₂ in Figure 1 changed systematically at Tvent.

Figure 2 shows the responses of LA, NE, and E. Each of LA, NE, and E increased gradually with an increase in exercise intensity, with an apparently greater increase in concentration as intensity exceeded Tvent. A threshold-like response of the blood catecholamine concentrations was suggested in the recent study of Mazzeo and Marshall. However, the recent study of Savard et al suggested that efflux of catecholamines from exercising leg muscles increases progressively with greater exercise intensity.

The responses of HRV-related variables are summarized in Figure 3. In agreement with the results of our earlier study, PNS indicator decreased as WR increased, reaching very low values at Tvent. The SNS indicator increased gradually over WR below Tvent. At WR greater than Tvent, it increased more steeply with a significant (p<0.05) change in the slopes. More interestingly, the mean value for β reached 2.04 (corresponding to DF of 1.92) at Tvent with the higher values (lower DF) thereafter. A similar finding was obtained for the heart rate responses to the graded levels of orthostatic stress indicating that the fractal component of HRV had low dimensional, less complex dynamics.

In summary, our recent results concerning autonomic nervous system responses during exercise in relation to W-min⁻¹ protocol. In Figures 1 through 3, all variables have been shown as ensemble averages for 6 subjects in relation to the Tvent determined by the PetO₂ and PetCO₂ profiles. The statistical comparison of regression slopes below and above Tvent showed that only PetCO₂ in Figure 1 changed systematically at Tvent.

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In summary, our recent results concerning autonomic nervous system responses during exercise in relation to
Tvent showed that PNS withdrew almost completely below Tvent, that the rate of changes in sympathoadrenal activity indicators was enhanced above Tvent, and that these changes in PNS and SNS indicators were associated with the appearance of the low-dimensional dynamics that might reflect less complex autonomic activity.

DISCUSSION

Seeking the mechanisms responsible for Tvent is considered to be important not only physiologically, but also methodologically. Proper interpretation of the accumulated results for estimation of the so-called "AT" by noninvasive ventilatory responses to exercise is required. Within this context, our results showed a possible link between autonomic nervous system status and Tvent, although a delineation of the central and the peripheral controller scheme for the hyperventilation was beyond the scope of these studies. In addition, these results could have at least one potential implication for clinical cardiology.

The concept of AT was originally developed by Wasserman and McIlroy for evaluating cardiac performance of cardiac patients. Later, several investigators supported this concept indirectly by showing that the patients with the lower maximal cardiac performance and the higher NYHA classifications of function had the lower Tvent. However, this does not necessarily mean that the lower Tvent in these patients has been caused by their impaired cardiac performances via the mechanisms originally proposed, i.e., lactacidemia due to decreased oxygen transport. Indeed, Coyle et al. reported that well-trained ischemic heart disease patients could show similar LA responses during graded exercise as well as similar endurance capacity to age-matched trained runners despite the reduced $V_{O2\ max}$ and maximal cardiac output of the patients. This observation suggested oxidative capacity of the skeletal muscle as a possible determinants of LA response during exercise. Indeed, the recent review by Connell et al. has convincingly shown that lactate efflux and muscle redox potential are interactive functions of muscle enzyme concentrations and substrate availability. Neither changes in lactate efflux, nor in redox indicators such as lactate to pyruvate ratio, as suggested by Wasserman et al., can indicate intracellular dysoxia. Thus, if one examined the relationship between lactacidemia and Tvent, the lower Tvent in cardiac patients might merely reflect their physical inactivity due to the disease per se, not the impaired cardiac function.

It should be emphasized that the spectral analysis of HRV evaluated the activity of cardiac autonomic nerves innervating the sinoatrial node. The cardiac parasympathetic tone affects electrical stability of the heart. Electrical stimulation of the vagus nerves has been shown to increase ventricular fibrillation threshold and decrease the incidence of spontaneous ventricular fibrillation during myocardial ischemia, while bilateral vagotomy or atropine has been shown to increase arrhythmia formation. Recently, Billman and Hoskins, using HRV spectral analysis in dogs with healed anterior myocardial infarctions, reported that the dogs susceptible to ventricular fibrillation by a coronary occlusion during submaximal exercise had lower PNS indicators than the resistant.

On the other hand, sympathetic neural activity also increases the ventricular vulnerability to fibrillation. In anesthetized dogs, stellate ganglion stimulation decreased the ventricular fibrillation threshold by about 60%. The same type of response was also observed for extrasystole threshold. It is of note that this effect has been shown to be evident especially without PNS activity. In our results, Tvent was accompanied by the enhancement of SNS with the simultaneous withdrawal of PNS almost completely. Taken together, these data suggested that changes in cardiac autonomic profile at Tvent might increase susceptibility to a cardiac electrical instability.

Furthermore, Skinner et al. recently published their preliminary observations on the dimensionality of HRV and arrhythmogenesis in a cardiac patient wearing a Holter monitor at the time of his death. They stated the correlation dimension decreased to an integer dimension approximating 1.0 prior to the onset of lethal arrhythmogenesis and that a fractal process in the heartbeat generator provided protection from arrhythmogenesis. Considering that Dr (β) of HRV decreased (increased) gradually to 1.0 (to 3.0) above Tvent in our study, indicating loss of complexity, the exercise intensity above Tvent could lead to increased risk of cardiac vulnerability. The relationship between the change in cardiac autonomic nervous system status and a possible cardiac vulnerability during moderate exercise remains to be investigated clinically as well as experimentally in future research.

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