Cardiac Acceleration as a marker of Vagal Withdrawal in Heart Rate Control during Exercise in Humans

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Introduction

Exercise activates the sympathetic nervous system, increasing heart rate (HR), cardiac output and mean arterial pressure. Vagal withdrawal may also play a significant role in cardiac acceleration during exercise.1-3 Parasympathetic tone dominates the resting state4 and lowers the intrinsic HR of about 100 beats min-1 to the normal values of 70 to 80 beats min.-1 5 This phenomenon led to the hypothesis that the initial increment in HR during exercise could be due to reduced vagal tone at the onset, which increases the HR to 100 beats min.-1 Pharmacological studies have supported this hypothesis.1 Further increment in HR during exercise is brought about by sympathetic stimulation.2,4,6 Questions arise about the triggers for vagal withdrawal and sympathetic stimulation. One hypothesis is that vagal withdrawal is mediated by neural impulses from the cerebral cortex associated with the volitional component of exercise, also known as central command.2,6 Alternatively, sympathetic activation has been shown to be mediated by a reflex arising from cutaneous and muscle receptors.6,7 Thus, vagal withdrawal is assumed as being anticipatory feed forward, whereas sympathetic stimulation has been shown to be a feedback reflex.7

An important question in exercise physiology is whether the change from vagal modulation to sympathetic mediated cardiac acceleration can be detected from transients of HR response to exercise. If neural modulation changes in response to shifts from low intensity to high intensity exercise, the dynamics of HR response should represent the neural modulation of both vagus and sympathetic nerves. If vagal withdrawal is feed forward, it would result in a rapid increment in HR at the onset of exercise. Later on, reflex sympathetic stimulation would become dominant and HR would display slower dynamics owing to the reflex nature of the neuronal circuitry.

The purpose of this study was to find out if the effect of vagal withdrawal on exercise induced tachycardia in humans could be assessed using the difference in cardiac acceleration between graded steps of 50 and 100 Watts workload, respectively. This study identifies the degree of the time rate changes in heart rate in response to graded workload as a marker to differentiate the vagal withdrawal component from the sympathetic one during exercise.

Subjects and Methods

Fifteen healthy male subjects, mean age 27.1 years (SD ± 8.9), range 19 to 46 years, were recruited for this study. The mean body mass index (BMI) was 23.4 kg m-2 (SD ± 3.4). The subjects were staff and students of the Aga Khan University. None had any history of cardiopulmonary disease or was taking any medication. Informed consent was obtained before the study commenced. The study was performed according to the Declaration of Helsinki and was approved by the University Ethics Committee. Before exercise, all

subjects were given approximately 5 minutes rest on the bicycle to ensure that their HR had reached normal baseline values which were recorded.

Protocol

Subjects pedaled on a bicycle ergometer (Tunturi, Finland) for 2 minutes at 50 Watts (Step 1), then for another 2 minutes at 100 Watts (Step 2). A similar protocol has been used previously to evaluate vagal withdrawal.8 The level of exercise corresponded approximately to 35% (Step 1) and 70% (Step 2) of the subjects' maximum workload determined by a previous progressive exercise test. All subjects maintained a pedaling frequency of 50 to 60 revolutions per minute throughout the exercise test. During the test, HR was monitored by a three lead ECG (Cardiofax, Nihon Kohden, Japan) using bipolar electrodes. ECG based HR recordings were compared to Portapres (TNO, Holland) and Pulse oximeter (Ohmeda, USA) recordings. The comparison showed a similar pattern as reported in this study. Thus, all three different apparatuses can demonstrate a vagal withdrawal effect.

Analysis

HR was sampled consecutively every 10 seconds from the recordings for each subject to plot HR (mean ± SD) against time, from the point where the subject started exercising to the end of Step 2. Averaging R-R intervals of 4-5 cardiac cycles minimized respiratory and motion artifacts from the ECG recordings. Time constant (time required to produce 63% of the response) was calculated to compare the temporal characteristics of the dynamic HR response. Cardiac acceleration was calculated as the time rate of change in HR (the change in HR divided by the time in which the change took place). The degree of acceleration was compared between the two steps of exercise. If a similar degree of acceleration is observed in Step 1 and 2 workloads, it would characterize HR dynamics as a linear function, i.e., a constant rate of change in HR with respect to time. However, the vagal withdrawal response in exercise should result in non-linear HR dynamics, which will be experimentally established in this study.

A Student's paired t-test was used to analyze the data. All tests were two-tailed and the level of probability taken as significant was 5% ($p<0.05$).

Results

Dynamics of mean HR profile during two-step exercise

The relationship of mean HR with time is shown in Figure 1. In response to 50 Watt (Step 1) workload, HR increased from the baseline value of 80.3 ± 12.9 to 113.8 ± 13.6 beats min-1 (mean ± SD) with a time constant of 6.2 ± 3.9 seconds. Step 1 showed a rapid increase in HR during the first 10 seconds followed by a plateau. When the subjects continued cycling at 100 Watt workload following Step 1, HR increased from 113.8 ± 13.6 beats min-1 to a higher value of 145.1 ± 20.2 beats min-1 with a time constant of 40.8 ± 19.9 seconds. The difference in time constants between the two steps was significant ($p= 0.00001$) indicating faster dynamic response of HR in Step 1 as compared to Step 2. A point to note is that Step 2 lacks a plateau; there was a continuous rise in HR between 120 to 240 seconds. More than 70 percent of the HR changes in Step 1 occurred in the first 10 seconds, whereas only 23 percent of the changes in Step 2 occurred in the first 10 seconds.

Dynamic response of cardiac acceleration

The time rate of change in HR i.e. cardiac acceleration was used as another index for dissecting out vagal withdrawal from sympathetic effects on HR dynamics during exercise. At the initiation of Step 1, a rapid acceleration of HR was observed in the form of an overshoot response (Figure 2). Cardiac acceleration fluctuated around the baseline during the remainder of Step 1. In contrast to Step 1 a significantly small overshoot response of cardiac acceleration was observed during the Step 2 exercise challenge. The mean cardiac acceleration (± SEM) at 10 seconds in Step 1 and 130 seconds (i.e. 10 seconds in Step 2) was 2.40 ± 0.19 and 0.71 ± 0.12 beats min-1 sec-1, respectively. This difference was statistically significant ($p<0.0001$).

Discussion

The autonomic response to exercise has been well characterized. There is a general consensus that the parasympathetic tone is gradually withdrawn as workload increases, where as sympathetic activity increases once heart rate reaches 100 beats per minute.9 This would mean that the heart rate increase in Step 1 is due to the effect of vagal withdrawal. However, the heart rate increase in Step 2 results from augmented sympathetic activity in addition to the decreased parasympathetic activity. Thus, HR is modulated by vagal and sympathetic nerve activities to effect a transition to a higher value as quickly and smoothly as possible.10

The major pool of evidence supporting the loss of vagal tone at the onset of exercise is limited to either pharmacological studies1,8 or HR variability dynamics studies.3 However, both of these lines of evidence are indirect in nature. In pharmacological studies, the increment in HR after atropine administration is considered supportive of vagal withdrawal.1 In HR variability studies a decrease in high frequency peaks is believed to represent vagal withdrawal, although this has been associated with inconsistent results11 and its validity during exercise has also been questioned.12 Recently, microneurography has been used to study neuronal control of HR, however, the inferences are limited to the sympathetic autonomic system only.2 Thus, definite direct evidence regarding the modulation of cardiac parasympathetic tone at the onset of exercise is lacking. Therefore we have proposed a model in which cardiac acceleration can serve as a marker of vagal withdrawal activity.

Our protocol reveals the kinetics of neuronal control of HR by separating vagal modulation from sympathetic mediated cardiac acceleration. The first step (low workload 50 Watts exercise for 2 minutes) would reflect vagal modulation2,3 with minimal interference from sympathetic activity as evidenced by a pronounced cardiac acceleration during Step 1 exercise. The second step in our protocol involves cycling at 100 Watts (higher intensity exercise) immediately after the first step for 2 minutes. This step, in theory, represents sympathetic mediated cardiac acceleration with possible ongoing contribution from vagal withdrawal. Since sympathetic control of HR is via a reflex mechanism6,7, a reduced cardiac acceleration during Step 2 exercise indicates a reflex phenomenon. This confirms the 'temporal heterogeneity' of the mechanisms involved in the control of HR during exercise, as described by Magosso E et al.13

The new aspect of our study is the description of cardiac acceleration (time rate of change of HR), as a new marker of vagal withdrawal during steady state exercise. This parameter has been used to elucidate human HR dynamics during orthostatic stress in pregnant females.14 The initial rapid acceleration of HR seems to be due to vagal withdrawal. This

provides a very simple method to assess cardiac vagal activity. This analysis can easily be applied to HR dynamics of patients undergoing Exercise Tolerance Testing. As shown by Wennerblom et al.15, the time course of vagal withdrawal was delayed in patients with angina pectoris. This time course is brought back to normal by anti-anginal drugs. Thus, transients of vagal withdrawal could have significant prognostic value for angina patients.

There has been recent interest in the role of parasympathetic tone and vagal withdrawal in increments in HR. Vagal withdrawal has been shown to play an important precipitant of ischemia in patients with stable coronary artery disease16 and Syndrome X.17 In addition, patients with congestive heart failure have been demonstrated to have a reduced vagal tone, which improved significantly when these patients were treated with enalapril, digoxin and diuretics for four weeks.18 Thus attenuated parasympathetic tone and vagal withdrawal seem to play an important role in different cardiovascular pathologies. Of note is the fact that these abnormalities can be reversed to some extent by pharmacological interventions.15,18 In addition, exercise is known to enhance cardiac vagal tone at rest.19 Thus, there already are areas of focus for intervention and more research needs to be conducted to further elucidate the pathophysiology of cardiac autonomic dysfunction.

In view of our hypothesis and results, a model is proposed for the role of vagal withdrawal in exercise-induced tachycardia (Figure 3). Exercise anticipation generates a central command in the cerebral cortex that projects onto the vagal nucleus and inhibits it. Additionally, it maybe hypothesized that such an effect maybe reinforced by the pulmonary slow adapting receptors using the Hering-Breuer reflex as a peripheral off-switch mechanism. Thus both the central and peripheral off-switch mechanisms would decreases the release of acetylcholine at the sinoatrial node (SAN). Disinhibition of the SAN may be responsible for the initial rapid increment of HR in exercise.

In conclusion, large differences in HR acceleration in this study between Steps 1 and 2 indicate a change in the regulation of HR from Step 1 to Step 2 providing evidence for non-linear exercise dynamics. Therefore, it appears that the initial rapid component of increment in HR is due to vagal withdrawal. The change in HR due to vagal modulation is fast as opposed to the sympathetic drive-mediated increase in HR as evidenced by the different time constants. The difference in cardiac acceleration, as a new marker, between the two steps of exercise indicate vagal withdrawal as the frontline adaptive mechanism in the initial response to exercise induced tachycardia, followed secondarily by sympathetic drive.

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