Assessing Baroreflex sensitivity in aerobically trained athletes: Comparison of sequence analysis and cardiovascular system identification (CSI).

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A. Statement of study rationale and purpose

Endurance exercise training results in a variety of adaptations in cardiovascular function, the most notable of which is a decreased heart rate at rest. [1] This has been postulated to be due to increased vagal tone in athletes.[2,3] However, the vagus outflow tract is not easily measurable and several surrogate markers of vagal tone have been studied to test this theory. One such measurement is heart rate variability (RR intervals). In endurance trained athletes heart rate variability has been demonstrated to be increased, suggesting that exercise may play a role as an useful adjunct to drug therapy in lessening the derangement's of autonomic balance found in many cardiovascular diseases.[4] Further studies of the autonomic nervous system in athletes where prior work has demonstrated perturbations of the usual autonomic control will enable further understanding of the physiology and pathophysiology of both normals and diseased states which include a broad spectrum of illnesses from MI, CHF, to diabetes which hopefully will lead to better treatments in these conditions. Preliminary work in the autonomic lab has shown an increased incidence of syncope and rate of positive tilt table tests in endurance trained athletes suggesting that the adaptations in autonomic control seen in these athletes may also lead to alterations or an override of the usual heart rate baroreflex (HRB) which regulates HR/BP control under a variety of stimuli. It is unclear if this reflex is due to a reduction in baroreflex. responsiveness or if other mechanical relationships such as increased limb compliance, eccentric ventricular hypertrophy, or an increase in plasma volume may attenuate baroreflex responsiveness.[5] This investigation is proposed to further our understanding of syncope in athletes and in particular baroreflex sensitivity in endurance trained athletes.

Heart Rate baroreflex has been studied using a variety of measurements including blood pressure drop from the supine to standing position, carotid neck suction in which pressure is applied to the carotid baroreceptor and subsequent measurements in HR/BP are followed, phenylephrine injection in which BP is pharacologically manipulated and changes in HR are observed in an open feedback loop, and lower body negative pressure (LBNP) has been applied where the HR response to LBNP is subsequently measured. Studies using these measurements have furthered our understanding of baroreflex sensitivity (BRS) however they also use means that are not physiologic to interrogate what is usually a closed system in order to observe BRS. A direct method of analysizing heart rate and blood pressure in spontaneous beat-to-beat sequences has been suggested as a measure of BRS.[6] This model is based on the idea that baroreceptors not only control abrupt changes in pressure but are continuously activated around a set point for a certain individual, allowing continuous monitoring of baroreflex gain.[7] This beat-to-beat sequence model allows studies to be completed on an intact system. However, in this model the effect of lung volume on heart rate, also known to be regulated by the autonomic nervous system, is not taking into account. A system in which measurements can be obtained under intact closed-loop systems allowing data acquisition including HR, BP and instantaneous lung volume (11LV) in addition to feedforward and feedback prediction of changes between these variables provides a better model of the intact cardiovascular system. Cohen et al have developed such a model and have been able to demonstrate changes in the autonomic nervous system and BRS in physiologic states at rest, from supine to standing, with pharmacologic blockade and they most recently have demonstrated subtle degrees of diabetic autonomic neuropathy that other measure of BRS have failed to identify.[8,9,10] In this study we aim to examine the baroreflex sensitivity in endurance trained athletes which we hypothesis to be altered from controls. The two models of BRS which we intend to compare are the beat-to-beat sequence model detailed in Baber et al as

well as the closed loop model proposed by Cohen et al.[6,8]

B. Study Design and Statistical Analysis

This study will entail measurements of HR baroreflex in a study group that is being recruited for the Neurally-Mediated Syncope in Athletes Protocol in which 225 subjects will be screened to obtain a sample size of 180 endurance trained athletes with 180 age matched controls. Subjects are to include men and women of various ethnic backgrounds. The study design requires 2 visits. The first visit will allow the participant to sign a consent form, complete a questionnaire on their medical history, and level of fitness. During this initial visit, participants will complete a graded exercise test with assessment of maximal oxygen consumption (V02max) (See Study Procedures Q. Subjects will be divided into endurance trained athletes and age matched controls based on their exercise history and V02max. (See study subjects). After acceptance into the study and graded exercise test participants will be asked to return for baseline autonomic testing including heart rate, blood pressure, and instantaneous lung volume monitoring at rest in the supine position in a quiet room. Participants will be instructed to avoid caffeinated and alcoholic beverages and refrain from exercise on the morning of the testing. Measurements will be made between the hours of 10am and 4pm and 2-4 hours after the last meal.

C. Data Analysis

Baroreflex sensitivity (BRS) is a measure of the autonomic nervous system and baroreceptor responsiveness to a stimulus (e.g. change in blood pressure) that results in a modulation in heart rate. In this study, we will analysis the HR baroreflex using two methods. The first is the sequence method described by Baber et al in which spontaneous beat-to-beat changes in heart rate are measured as a function of the beat-to-beat changes in blood pressure. [6] Analysis of the fluctuations in the physiological signals using FFT Fourier transform will transform this data to its power spectrum in the frequency and time domains. The second method of measuring BRS will utilize a system identification of closed-loop cardiovascular control (CSI) described by Cohen et al. This method, described in detail in ref 9, mathematically analyzes the beat-to-beat fluctuations in noninvasively measured heart rate signals (derived from the surface EKG), arterial blood pressure (ABP), and instantaneous lung volumes (JILV) to characterize quantitatively the physiological mechanisms responsible for the coupling between these variables. The transfer relations, presented as impulse response functions, will be characterized by amplitude, area, and time. Statistical comparisons between the group (control vs. endurance trained athletes) averages of all peak amplitudes will be made with the paired t test.

Power analysis done with a sample size of 180 should provide enough power to detect a difference in the change of BRS. CSI has been used to evaluate BRS in diabetics and normals with the smallest difference detected being a 30% difference in BRS (requiring 150 people to power). The difference in BRS between an individual lying and standing is 50% (requiring 30 people to power). No direct comparison between controls and athletes have been made using the CSI model as a measure of BRS.

D. Study Procedures

a. Data acquisition

After the subjects have remained at rest for 20 minutes, data acquisition will begin and will include continuous EKG, blood pressure (BP), and lung volume (ILV) monitoring. Continuous BP monitoring will be obtained by the noninvasive finger-cuff method to provide beat-to-beat estimates of arterial blood pressure. This method has been shown to accurately follow changes in arterial pressure.[11] Instantaneous lung volume will be measured with a two belt chest-abdomen inductance plethysmograph. During data acquisition subjects will be instructed to breathe on cue according to a randomly spaced sequence of auditory tones. The interbreath times range from 1 to 15s with a mean of 5s to avoid

discomfort. This random breathing technique provides broadband respiratory activity while preserving normal ventilation.[9] Subjects will be given 2 minutes prior to data acquisition to adjust to the random breathing pattern. Subjects will be allowed to control the depth and shape of each breath to preserve comfortable ventilation. Twelve minutes of data acquisition will be obtained. Total study participation time for the second visit will be approximately one hour.

b. V02 max test

The subject is either seated on a cycle ergometer or stands on the belt of a treadmill with electrodes and blood pressure equipment secured. A disposable mouthpiece is used to enable the subject to breathe room air and while capturing all expired air. Following a warm-up a ramp protocol is begun with incremental increases in resistance. The test is terminated following the subjects exertion level with cutoffs for HR and BPmax. Total time of test: 20 min. The signals are then converted by a microprocessor to calculate V02max.

E. Study Drugs

There are no study drugs used in this protocol.

F. Medical Devices

There are no medical devices used in this protocol.

G. Study Questionnaire

Study subjects will be asked about their general medical history including a history of heart problems, arrhythmia, syncope, presyncope, medication and supplement/steroid usage and any prior hospitalizations.

H. Study Subjects

Healthy male and female subjects between the ages of 18-40 who are nonsmokers, not taking any drugs, consume no more than 300 mg/day of caffeine, with a body mass index between 19 and 25 kg/m2 and a stable body weight (<2.5 kg gain or loss during the 6 months before the study) will be recruited for this study. This criteria will minimize the confounding influence of disease, drugs, caffeine, obesity, weight change and erratic dietary habits on autonomic function. Participants who engage in aerobic activity (running, cycling, swimming) and who achieve a V02max of >55 mg/kg per min will be classified as endurance trained. Age matched controls who meet the above criteria for tobacco usage, drug, caffeine intake, BMI, and stable body weight who do not participate in any regular exercise program in the past year and who achieve a V02max. <40 mg/kg per min will be classified as untrained.

I. Recruitment of Subjects

Subjects will be recruited from the Syncope in Highly Trained Athletes protocol. This protocol has been advertised on posted fliers at runners clubs, fitness centers and other athletic organizations. Controls will be recruited through Columbia Presbyterian Staff, Columbia University Students and friends.

J. Confidentiality of Study Data

The data obtained from this study will only identify a patient with a numeric identification code. Data files will be stored on the clinical research server with password protection for access.

K. Potential Conflict of Interest

There are no potential conflicts of interest with this protocol.

L. Location of the Study

Irving Center for Clinical Research: Autonomic Function Laboratory
Principal Investigator: Daniel Bloomfield, MD,
V02 max testing will take place in:
PH 9: Exercise Laboratory for the Division of Circulatory Physiology

M. Potential Risks

Risks of Exercise Testing: The potential risks that exist with exercise testing in the general population include hypo/hypertension, syncope, dysrhythmias, and in rare cases MI, stroke, or death. These risks are uncommon even in an older population with heart disease. The risks of exercise testing we expect to be minimal among endurance trained athletes and controls without prior history of complications to exercise. Emergency equipment and a physician with trained personnel will be present should any event arise.

N. Alternatives

The alternative is not to participate.

O. Compensation to Subjects

Subjects who desire their results, such as V02 max, BMI, EKG, physical exam, autonomic profile will be given their individual results, otherwise no compensation is provided.

P. Cost to Subjects

Costs only include time of involvement for 2 visits.

Q. Minors

This study does not involve the participation of minors

R. Radiation or Radioactive Substances

This study does not use radiation or radioactive Substances.

S. References

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