Relationship between arterial stiffness and heart rate recovery in apparently healthy adults

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Introduction: Arterial stiffness and heart rate recovery (HRR) following exercise testing have emerged as variables holding significant prognostic value in a number of populations. The purpose of the present study is to examine the relationship between arterial stiffness and HRR in a group of apparently healthy subjects.

Methods: Two hundred and nine apparently healthy subjects underwent maximal exercise testing. Heart rate at one and two minutes post exercise was subtracted from maximal heart rate during the exercise test to produce two measures of heart rate recovery. Aortic wave velocity, in meters per second, was obtained via a new magnetic resonance technique.

Results: Pearson Product Moment Correlation analysis revealed a significant correlation between aortic wave velocity and heart rate recovery. Stepwise linear regression analysis revealed that age, maximal aerobic capacity, heart rate recovery at one minute, and diastolic blood pressure were all significant predictors of aortic wave velocity ($r = 0.63$, $r^2 = 0.40$, $p < 0.001$).

Conclusions: The results of the present study indicate that heart rate recovery is significantly correlated with a measure of large artery stiffness and adds predictive value to other clinical variables. This analysis provides further evidence that assessment of heart rate recovery should be considered in subjects undergoing exercise testing in clinical practice.

Keywords: exercise testing, oxygen consumption, aortic wave velocity

Introduction

The clinical value of exercise testing in the apparently healthy and a number of patient populations is well established (Gibbons et al 1997, 2002; Myers et al 2002; Spin et al 2002). Maximal oxygen consumption (VO_{2max}) is by far the most frequently assessed outcome of exercise testing, although many other measures have demonstrated clinical value. One such variable is the decline in heart rate following maximal exercise testing.

Several studies indicate that an abnormally prolonged heart rate recovery (HRR) following aerobic exercise may indicate the presence of coronary artery disease (Diaz et al 2001; Lipinski et al 2004) and endothelial dysfunction (Huang et al 2004). Even among apparently healthy subjects, HRR is reportedly an indicator of aerobic fitness and cardiovascular health (Cardus et al 1967; Kostis et al 1982; Darr et al 1988). Possible mechanisms and major factors influencing variations in HRR have been studied by several groups (Arai et al 1989; Imai et al 1994; Pierpont et al 2000). Accrued evidence from these studies suggests that the rate at which parasympathetic tone increases following the cessation of exercise appears to heavily influence the time course of HRR.

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In recent years, noninvasive measures of central arterial stiffness have also been shown to significantly predict cardiovascular dysfunction. Specifically, a number of investigations have found that decreased aortic compliance (increased stiffness) predicts cardiovascular events and mortality (Blacher, Asmar, et al 1999; Blacher, Guerin, et al 1999; Asmar et al 2001; Laurent et al 2001; Boutouyrie et al 2002; Cruickshank et al 2002; Safar et al 2002). Most previous work investigating the prognostic significance of arterial stiffness has been carried out in groups with underlying physiologic abnormalities such as hypertension, diabetes, or renal disease, which are all risk factors for cardiovascular disease.

Several investigators have reported a significant relationship between VO_{2max} and arterial stiffness (Vaitkevicius et al 1993; Rerkpattanapipat et al 2002; Bonapace et al 2003). The relationship between arterial stiffness and HRR has, however, not been investigated. Therefore, the primary objective of the present study is to examine the relationship between aortic wave velocity (AWV), a measure of large artery stiffness, and HRR in a group of apparently healthy individuals. A secondary goal is to determine if HRR adds additional value to other previously established variables in predicting AWV.

Methods

Subject characteristics

Two hundred and nine subjects (111 male/98 female), recruited from the general population in the metro-Richmond area, were included in this study. The primary thrust of the investigation was to examine the relationship between our new measure of aortic stiffness and both resting and exercise variables of interest. The mean age of the group was 48.4 (± 14.7) years. Inclusion criteria consisted of the ability to successfully put forth a near-maximal to maximal effort during exercise testing without an abnormal hemodynamic/electrocardiograph (ECG) response. Exclusion criteria included: history of myocardial infarction, angina or stroke, evidence of coronary heart disease, peripheral arterial disease or diabetes, pregnancy, age < 21 years, and magnetic resonance imaging contraindications (eg, ferromagnetic implants, claustrophobia). Written informed consent was obtained from all subjects prior to testing. Approval from the Institutional Review Board at Virginia Commonwealth University was obtained before study initiation.

Data collection

Body mass index (BMI) in kilograms per meters squared was calculated and recorded for each subject on the day of maximal exercise testing. Resting heart rate and blood pressure were additionally recorded prior to exercise testing in the seated position. Resting blood pressure values reported in the present investigation are the average of five separate recordings for each subject.

Ventilatory expired gas analysis was obtained using a metabolic cart (Vmax Spectra29, SensorMedics, Inc, Yorba Linda, CA, USA). The oxygen and carbon dioxide sensors were calibrated using gases with known oxygen, nitrogen, and carbon dioxide concentrations prior to each exercise test. The flow sensor was also calibrated before each test using a three-liter syringe.

Physician-supervised maximal exercise tests were conducted using a modified Balke treadmill exercise protocol. Monitoring consisted of continuous 12-lead electrocardiography, blood pressure measurements at regular intervals during the exercise test, heart rate recordings at every stage via the electrocardiogram, and rating of perceived exertion (Borg 6–20 scale). Subjects were encouraged to exercise to muscular fatigue. Test termination criteria followed American Heart Association guidelines (Gibbons et al 1997). Monitoring of heart rate and blood pressure persisted in the standing position at least five minutes into the recovery phase following exercise testing.

Exercise test data calculations

The percentage of age-predicted maximum heart rate achieved during exercise was determined by dividing maximal exercise heart rate by (220 minus age) and multiplying that value by 100. Heart rate recovery at one (HRR_1) and two minutes (HRR_2) was the difference between heart rate at maximal exercise and heart rate at one and two minutes into recovery, respectively, and was expressed in beats per minute. Oxygen consumption (in L/min and $mL \cdot kg^{-1} \cdot min^{-1}$) was collected throughout the exercise test. VO_{2max} was defined as the final 20-second averaged value during the last stage of the exercise test.

Measurement of aortic wave velocity

All magnetic resonance examinations were performed on a 1.5 T whole-body MR unit (Vision, Siemens Medical Solutions, Erlangen, Germany). Subjects were positioned supine on a standard spine array receiver coil and centered

in the magnet using the xiphisternum as an anatomical landmark. Electrocardiogram gating was used to synchronize magnetic resonance acquisitions to the early systolic portion of the cardiac cycle. After acquiring transaxial and sagittal scout images of the thoracic aorta, cardiac-triggered aortic wave velocity (AWV) measurements were performed as described previously (Itskovich et al 2001). The strategy of the measurement is to simultaneously record the initial systolic flow velocity waveforms at two sites within the descending thoracic aorta, separated by a known distance (84 mm). Since the flow propagation rate is finite, a distinct delay can be discerned between the two velocity waveforms. The separation distance divided by this observed delay time yields the AWV.

After each AWV measurement, magnetic resonance data analysis was performed offline, by downloading the raw data to a laptop PC. Using customized software based on Matlab Version 6.5 (The MathWorks Inc, Natick, MA, USA), various processing steps, including complex fast Fourier transform with zero-filling, flow image construction, and automated AWV calculation could be completed within approximately 30 s of data acquisition. The mean of five individual measurements was used to compute an overall AWV for each subject.

Our group has recently conducted a test-retest reliability analysis of the AWV measurement technique in a group of 10 apparently healthy individuals. The intraclass correlation coefficient for the two AWV values was 0.97, $p < 0.001$. The standard error of measurement with 95% confidence intervals for AWV was ±0.18 m/s. Based on these results, we are highly confident in the reliability of our single AWV measurement.

Statistical analysis

Mean and standard deviation were calculated for baseline and exercise testing variables as well as AWV. All continuous variables underwent logarithmic transformation in an attempt to improve linear relationships and homoskedacity. Pearson Product Moment Correlation was used to examine the relationship between both resting and exercise test variables and AWV. Stepwise linear regression analysis was performed to assess the ability of resting and exercise variables to predict AWV. Entry and removal values for the regression analysis were 0.05 and 0.10, respectively. A statistical software program was used for all analyses (SPSS 12.0 for Windows, Chicago, IL, USA).

Table 1 Mean and standard deviation values of key study variables

	Mean	Standard deviation
Body mass index (kg/m^2)	24.8	±4.3
Resting blood pressure (systolic/diastolic in mmHg)	122.9/72.9	± 13.3/7.9
Resting heart rate (beats per minute)	64.6	± 11.3
Peak heart rate (beats per minute)	173.6	± 17.2
Percentage of age predicted maximal heart rate achieved[a] (%)	101.3	±7.9
Aortic wave velocity (m/s)	5.8	± 1.9
VO_{2max} ($mLO_2 \cdot kg^{-1} \cdot min^{-1}$)	39.2	± 11.9
HRR_2 (beats per minute)	53.6	± 13.1
HRR_1 (beats per minute)	28.9	± 11.3

[a] Calculation: peak exercise heart rate *divided by* (220 *minus* age) *times* 100.
Abbreviations: HRR, heart rate recovery; VO_{2max}, maximal oxygen consumption.

Results

None of the 209 subjects were diagnosed with any cardiovascular or pulmonary conditions and were therefore considered healthy. Furthermore, none of the subjects were taking a beta-blocking agent or any other medication which would alter the heart rate response to exercise. With respect to the maximal exercise test, no subject included in this analysis demonstrated ST segment changes during exercise suggestive of cardiac ischemia; all demonstrated a normal hemodynamic and ECG response to the maximal exercise test. The mean and standard deviation for baseline, exercise testing and AWV variables collected for this study are listed in Table 1. As illustrated by the mean values, the group participating in this study was generally normotensive and had both a normal bodyweight and aerobic capacity.

Table 2 Pearson Product Moment Correlation between resting and exercise variables and aortic wave velocity after logarithmic transformation

Variables	AWV
Age	–0.54[a]
Body mass index	0.11
Systolic blood pressure	0.36[a]
Diastolic blood pressure	0.33[a]
Resting heart rate	0.22[a]
VO_{2max}	–0.51[a]
HRR_1	–0.28[a]
HRR_2	–0.32[a]

[a] $p < 0.001$
Abbreviations: AWV, aortic wave velocity; HRR, heart rate recovery; VO_{2max}, maximal oxygen consumption.

Table 3 Stepwise linear regression analysis for aortic wave velocity

Independent variables	r	r^2	p-value
Step 1: Log(Age)	0.53	0.28	< 0.001
Step 2: Log(VO_{2max})	0.61	0.37	< 0.001
Step 3: Log(HRR_1)	0.62	0.39	0.03
Step 4: Log(diastolic blood pressure)	0.63	0.40	0.04

Formula: Log(AWV) = 0.21 + 0.31Log(age) – 0.29Log(VO_{2max}) – 0.10Log(HRR_1) + 0.33Log(diastolic blood pressure).
Abbreviations: AWV, aortic wave velocity; HRR, heart rate recovery; VO_{2max}, maximal oxygen consumption.

Pearson Product Moment Correlation revealed that, with the exception of BMI, all other variables were significantly correlated with AWV (Table 2).

Stepwise linear regression analysis revealed that the logarithmic transformation of age, VO_{2max}, HRR_1, and diastolic blood pressure were all significant predictors of Log(AWV) (Table 3). These four independent variables accounted for 40% of AWV variability ($r = 0.63$, $r^2 = 0.40$, $p < 0.001$). Sex and the logarithmic transformation of systolic blood pressure, HRR_2, BMI, and resting heart rate did not contribute any additional predictive value and were removed from the regression.

Discussion

The mean percentage of age-predicted maximal heart rate and insignificant variance (<8%) suggest maximal effort was achieved. The mean BMI and VO_{2max} values listed in Table 1 also suggest that the study group was within normal ranges of weight, blood pressure, and aerobic fitness.

The correlations between AWV and age, blood pressure, and VO_{2max} were expected, as these findings have been previously reported albeit using other techniques to assess arterial compliance (Vaitkevicius et al 1993; Dart et al 2001; Mackey et al 2002; Bonapace et al 2003). The relationship between AWV and HRR, however, has not been previously reported. The persistence of a significant association between HRR and AWV in the linear regression analysis may suggest that they are physiologically linked. The fact that combining HRR with age, and diastolic blood pressure and VO_{2max}, and so providing a better picture of cardiovascular health with respect to arterial stiffness, illustrates the importance of utilizing a greater amount of exercise test data when assessing one's health status. It should be stressed that, while the relationship between HRR and AWV was significant, the strength of this correlation was not profoundly robust. Heart rate recovery should therefore be viewed as another piece of the puzzle in reflecting an individual's cardiovascular health as opposed to a stand-alone diagnostic variable.

Increased aortic stiffness is associated with a cascade of deleterious physiological effects, which may progress in a cyclical pattern. Impaired vessel distention during cardiac systole increases cardiac afterload and the risk of left ventricular hypertrophy (Nussbacher et al 1999). The increased demand placed upon the heart by noncompliant vessels is likely to be a primary reason for the association between arterial stiffness and cardiovascular risk (Benetos et al 2000; Blacher et al 2000). Intervening upon elevated large vessel stiffness before chronic effects can take hold would clearly be advantageous. Based upon the results of the present study, aerobic fitness, a modifiable variable through chronic exercise, is related to the degree of arterial stiffness an individual possesses. It may therefore be reasonable to hypothesize that improvements in aerobic fitness may lead to improved arterial compliance and therefore a reduced risk for cardiovascular disease.

The subjects in the present study were all apparently healthy with no indications of cardiovascular disease. As such, these results should not be extrapolated to populations with signs/symptoms or a confirmed diagnosis of cardiovascular disease, as the relationship between arterial stiffness and HRR may differ. Furthermore, an optimal threshold value for arterial stiffness, by any measurement technique, has presently not been established. We were therefore unable to compare the differences in the variables collected in this study based upon an arterial stiffness threshold. Future research should also be directed toward such comparisons when such an arterial stiffness threshold value is established.

Exercise testing continues to be a valuable clinical assessment technique in both apparently healthy individuals and those diagnosed with cardiovascular disease. The results of the present study further support the diagnostic validity of exercise testing and suggest the clinical assessment of additional exercise variables, such as HRR, may help to better define an individuals level of cardiovascular health.

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