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Peak exercise oxygen uptake and left ventricular systolic and diastolic function and arterial mechanics in healthy young men

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Abstract Echocardiography can be used to estimate myocardial contractility by the assessment of the circumferential end-systolic stress-corrected left ventricular (LV) fractional shortening measured at midwall level (stress-corrected MWS). Whether stress-corrected MWS at rest predicts exercise peak oxygen uptake (peak $\dot{V}O_2$) is unknown. Also, it is not known whether the propagation rate of the early LV filling wave (E wave propagation rate, V_p), a new pre-load insensitive index of LV diastolic function, and echocardiographically assessed indices of arterial stiffness correlate to peak $\dot{V}O_2$. Accordingly, we performed echocardiographic studies and exercise tests with respiratory gas analysis in 15 young healthy male subjects (mean age 27 years, range 18–36). Neither stress-corrected-MWS ($r=0.20$, $P=NS$) nor ejection fraction ($r=-0.05$, $P=NS$) correlated significantly with peak $\dot{V}O_2$. Adjustment for age and resting heart rate had no effect on the results. In separate multiple regression models adjusting for standard covariates (age, LV size and heart rate), peak $\dot{V}O_2$ correlated with V_p ($\beta=0.98$, $P<0.01$), as well as with E/A ($\beta=0.85$, $P<0.01$), and with the isovolumic relaxation time (indicator of LV relaxation) ($\beta=-0.59$, $P<0.05$). Arterial stiffness indices showed no significant relation to peak $\dot{V}O_2$. We conclude that in young healthy male subjects, resting myocardial contractility and arterial stiffness are not significant correlates of peak $\dot{V}O_2$, whereas LV diastolic function, and in particular V_p , influences the variability of peak $\dot{V}O_2$.

Keywords Left ventricle · Function · Arterial stiffness · Exercise · Peak oxygen consumption

Introduction

Peak oxygen consumption (peak $\dot{V}O_2$) is a measure of exercise performance. While resting left ventricular (LV) ejection fraction (EF, the percentage of LV end-diastolic volume ejected in systole) does not predict peak $\dot{V}O_2$, an index of LV diastolic function, the ratio of early (E) to atrial contraction-dependent (A) transmitral waveform peak velocities (E/A), is related to peak $\dot{V}O_2$ (Vanoverschelde et al. 1993). However, EF is influenced by preload and afterload and is not a reliable indicator of LV myocardial contractility (de Simone et al. 1999). LV myocardial contractility can be assessed echocardiographically by means of circumferential LV midwall end-systolic stress-adjusted midwall fractional shortening (MWS), the stress-corrected MWS (de Simone et al. 1994). In addition, stress-corrected MWS is more closely related than EF to E/A (Palmieri et al. 1999a) and to LV early relaxation (Bella et al. 2001), measured by means of isovolumic relaxation time (IVRT). The E/A is a loading-dependent indicator of LV diastolic function which is only in part related to LV relaxation (Oh et al. 1997), whereas the relation of E wave propagation rate (V_p , the propagation rate of the early transmitral filling wave, a more load-independent index of LV diastolic dynamic) (Garcia et al. 2000) to peak $\dot{V}O_2$ has not been reported.

In addition, arterial mechanics have a role in determining exercise capability (Vaitkevicius et al. 1993; Yin et al. 1981). Arterial stiffness contributes to generate the blood pressure profile during LV ejection phase and is, therefore, a determinant of LV afterload (Stergiopoulos et al. 1999). The LV function and arterial mechanics are inter-related (Starling 1993). However, relationships of echocardiographic indices of arterial stiffness with peak $\dot{V}O_2$ have not been reported. Therefore, we assessed

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whether stress-corrected MWS, V_p and echocardiographic indices of arterial stiffness are correlates of peak $\dot{V}O_2$.

Methods

This study enrolled 15 healthy young male volunteers who trained for 60–90 min, two times per week (Table 1). All participants underwent echocardiography and, subsequently, exercise testing. Both evaluations were performed before noon on a single day while subjects were fasting. The study protocol was approved by the local ethics committee and each participant gave informed consent.

Echocardiography

The LV structure and function were evaluated according to a standard protocol (Palmieri et al. 1999b) using a General Electric VIVID 7 echocardiographic machine (Horten, Norway, software version 1.1.5/1004) equipped with a multifrequency matrix probe 1.5–4 MHz (model M3S), a digital storage system and videotape recorder. Two-dimensionally guided M-mode tracings were used to measure LV structure, if they were correctly oriented anatomically. Alternatively, linear measurements of LV structure from two-dimensional parasternal long-axis views were used (Schiller et al. 1989).

The LV measurements were averaged from two to five cardiac cycles from views in which LV internal dimension was maximized following recommendation of the American Society of Echocardiography (Sahn et al. 1978). End-diastolic LV dimensions were used to calculate LV mass by a formula that yields values which are highly correlated to LV weight determined by autopsy (Devereux et al. 1986). Also, procedures followed for assessment of LV structure and function are known to be highly reliable (Palmieri et al. 1999b). All measurements were made by a single reader (V.P.), blinded to the subject's name and clinical information.

Haemodynamics and vascular compliance

Echocardiographic stroke volume was assessed by Doppler, as the product of the time–velocity integral of the aortic flow at the aortic annulus and the aortic annulus area (Devereux et al. 1997). Cardiac

output was stroke volume \times heart rate, and stroke index was stroke volume/body surface area. Total arterial compliance was assessed as the ratio of brachial pulse pressure/Doppler stroke index (Palmieri et al. 2003). The arterial compliance of the descending aorta was assessed by sampling blood flow using Doppler echocardiography at the transition from thoracic to abdominal aortic segment:

$$\frac{\text{Diastolic flow Time Velocity Integral}}{\text{Systolic flow Time Velocity Integral}}$$

with the assumption that the higher the diastolic flow compared to that in systole, the higher the contribution of the aortic elasticity to forward blood flow (Shimamoto et al. 1996).

LV systolic chamber function and myocardial contractility

The EF, LV MWS and the circumferential end-systolic stress were computed using echocardiographic data (de Simone et al. 1994). The EF was:

$$100 \times \frac{\text{End Diastolic Volume} - \text{End Systolic Volume}}{\text{End Diastolic Volume}}$$

LV volumes were calculated from LV linear measurements (Teichholz et al. 1976). The EF represents global LV chamber systolic function if ventricular wall motion is uniform. However, because ejection-phase indices of LV performance depend on afterload, measurement of myocardial afterload is helpful to determine whether LV function reflects myocardial contractile performance. A noninvasive measure of myocardial afterload is the circumferential end-systolic stress, measured using the end-systolic LV measurement and simultaneous cuff blood pressure (Gaasch et al. 1989):

$$\text{Systolic BP} \times \left(\frac{\text{LVID}_s}{2} \right)^2 \times \left\{ \frac{\left[1 + \frac{\left(\frac{\text{LVID}_s + \text{PWT}_s}{2} \right)^2}{\left(\frac{\text{LVID}_s}{2} + \frac{\text{PWT}_s}{2} \right)^2} \right]}{\left(\frac{\text{LVID}_s}{2} + \text{PWT}_s \right)^2 - \left(\frac{\text{LVID}_s}{2} \right)^2} \right\}$$

where LVID_s is LV internal systolic diameter, and PWT_s is the LV posterior wall thickness in systole. Ejection-phase indices of LV function are negatively related to circumferential end-systolic stress in both normotensive and hypertensive subjects (de Simone et al. 1994). Because the majority of the myocardial fibres at the mid LV cavity are oriented circumferentially, LV shortening was also

Table 1 Anthropometric, haemodynamic, left ventricular (LV) and exercise capacity characteristics of subjects. Data are means (SD) (range). *E/A* Ratio of the peak velocities of E and A waveforms; *EF* ejection fraction; *EDT* E deceleration time; *IVRT* isovolumic relaxation time; *peak $\dot{V}O_2$* peak exercise oxygen uptake; *stress-corrected MWS* circumferential end-systolic stress-adjusted midwall fractional shortening; *V_p* E wave propagation rate

Characteristic	Measurement
Age (years)	27 (5) (18–36)
Body mass index (kg m^{-2})	23.9 (2.2) (19.9–28.3)
Body surface area (m^2)	1.89 (0.16) (1.65–2.25)
Systolic blood pressure (mmHg)	124 (8) (108–142)
Diastolic blood pressure (mmHg)	80 (7) (64–89)
Heart rate (beats min^{-1})	60 (8) (51–75)
LV mass index (g m^{-2})	91 (16) (71–123)
Stroke index (ml m^{-2})	42 (6) (34–52)
EF (%)	57 (4) (51–65)
Stress-corrected MWS (%)	112 (5) (105–119)
Stroke index (ml m^{-2})	42 (6) (34–52)
Pulse pressure/stroke index ($\text{mmHg m}^{-2}/\text{ml}$)	1.07 (0.18) (0.81–1.35)
Descending aorta compliance index	0.32 (0.08) (0.19–0.50)
<i>E/A</i>	1.7 (0.4) (1.07–2.5)
<i>EDT</i> (ms)	167 (35) (110–230)
<i>IVRT</i> (ms)	73 (13) (60–100)
V_p (cm s^{-1})	56 (5) (48–63)
Delta % systolic blood pressure during exercise	49 (13) (22–78)
Delta % diastolic blood pressure during exercise	–16 (17) (–39 to +25)
Delta % heart rate during exercise	192 (36) (147–269)
Peak $\dot{V}O_2$ ($\text{ml kg}^{-1} \text{min}^{-1}$)	53 (8) (37–65)

assessed at the midwall (Shimizu et al. 1991) and compared to MWS predicted for measured circumferential end-systolic stress calculated using an equation developed in a reference population (de Simone et al. 1994). The ratio per cent of observed over predicted MWS was termed stress-corrected MWS and indicates stress-corrected myocardial contractility (de Simone et al. 1994). This approach allows assessment of myocardial contractility because myocardial shortening and stress are on the same axis.

LV diastolic dynamics

All parameters of diastolic function were measured off-line by an in-house non-commercial multi-media system (EchoReviewSystem). The LV filling was evaluated by pulsed Doppler, placing the sample volume in the centre of the tips of the mitral leaflets, with the cursor beam perpendicular to the mitral plane in the apical four-chamber view. Peak E and A waveform velocities were measured starting from the E–A waveform with highest E wave. The E deceleration time (EDT), and indicator of LV passive relaxation, was calculated as the time from E peak to the point identified by the tangent to the E waveform descending shoulder on the baseline. The V_p was assessed by colour M-mode, with cursor-beam placed through the left ventricle perpendicular to the mitral annulus. The aliasing velocity limit of the colour Doppler scale was set at $\pm 55 \text{ cm s}^{-1}$, shifting the colour baseline toward the LV apex to see low flow velocities. The sweep rate was at 100 cm s^{-1} , while the subject was asked to hold his breath. The V_p was identified by a standard method previously described (Garcia et al. 1998). The IVRT was assessed in apical five-chamber view by continuous Doppler, using colour Doppler guide to identify the inflow–outflow interface in the LV output tract. The IVRT, indicating the early LV relaxation phase, was measured as the time from the end of aortic flow to the beginning of the E wave while the subject was invited to hold the breath.

Exercise

Exercise was a multistage treadmill protocol with 2-min step increments until exhaustion (modified Bruce protocol). Respiratory gas analysis was recorded on metabolic chart (Benchmark Exercise Test System, Morgan, Bologna, Italy). The $\dot{V}O_2$, carbon dioxide production and minute ventilation were measured as moving averages of eight breaths. During each stage of exercise, 12-lead ECG, heart rate and blood pressure were recorded. All subjects were encouraged to exercise until exhaustion, and had a peak respiratory exchange ratio > 1.1 . Maximal exercise capability was

defined by the peak $\dot{V}O_2$, expressed as the average of the last minute of exercise.

Statistical analysis

Data in tables are means with standard deviations and ranges in parentheses. All continuous variables were log-transformed before the use of parametric tests. Bivariate Pearson correlation was used to evaluate relationships of peak $\dot{V}O_2$ to LV systolic and diastolic function, arterial function, exercise blood pressure and heart rate. Separate and alternative multiple regression analyses were used to assess relations of peak $\dot{V}O_2$ to indices of LV systolic function, arterial compliance and exercise blood pressure controlling for resting heart rate and age, potentially expressing duration and level of physical training, as well as to evaluate relations of peak $\dot{V}O_2$ to LV diastolic function controlling for age, resting heart rate and LV diastolic diameter. $P < 0.05$ indicated statistical significance.

Results

The EF was not related to peak $\dot{V}O_2$ (Table 2), as confirmed by a subsequent partial correlation controlling for circumferential end-systolic stress (partial $r = -0.08$). Similarly, the stress-corrected MWS did not show a significant relation to peak $\dot{V}O_2$ ($r = 0.20$, $P = 0.4$). After accounting for age and resting heart rate, relations of EF and stress-corrected MWS to peak $\dot{V}O_2$ remained non-significant. The peak $\dot{V}O_2$ did not show significant relations to LV diastolic and systolic diameters. The LV mass index as well as stroke volume showed no statistically significant relation to peak $\dot{V}O_2$.

Peak $\dot{V}O_2$ was related to the exercise percentage increment of systolic blood pressure ($r = 0.53$, $P < 0.05$), but not to the exercise percentage increase in diastolic blood pressure or heart rate ($r = 0.06$, $r = 0.1$ respectively). Peak $\dot{V}O_2$ did not show a relationship to peak exercise systolic ($r = 0.31$) and diastolic ($r = -0.16$) blood pressure, or peak heart rate ($r = 0.13$). After adjustment for age and heart rate, the correlation of exercise percentage increment of systolic blood pressure with peak $\dot{V}O_2$ was confirmed (beta = 0.78, $P < 0.05$).

Table 2 Correlations of peak $\dot{V}O_2$ to LV structure and function and arterial stiffness. Data are Pearson's r bivariate correlation coefficient and beta values indicating the standardized adjusted coefficient of correlation obtained by multiple regression analysis

	Dependent variable: peak $\dot{V}O_2$	Bivariate correlations r	Standardized coefficient of correlation beta
			Adjusted for age and resting heart rate
EF		-0.05	-0.04
Stress-corrected MWS		0.20	0.22
LV diastolic diameter		-0.04	
LV systolic diameter		0.004	
LV mass index		-0.26	-0.26
Stroke volume at rest		0.03	0.05
Pulse pressure/stroke index		-0.15	-0.14
Descending aorta compliance index		0.07	0.15
			Adjusted for age, resting heart rate and LV diastolic diameter
E/A		0.52*	0.85**
EDT		0.18	0.28
IVRT		-0.45	-0.59*
V_p		0.83**	0.98**

* $P < 0.05$, ** $P < 0.01$

The peak $\dot{V}O_2$ showed no statistically significant relations to the pulse pressure/stroke index and the descending aorta compliance index (Table 2). Adjustment for mean blood pressure, a potential confounding factor, did not impact on results (data not shown).

In contrast, peak $\dot{V}O_2$ showed a positive relationship with V_p (Table 2). The peak $\dot{V}O_2$ also showed a relation to the E/A. The relation of peak $\dot{V}O_2$ to E/A was due to the relation between peak E wave velocity and peak $\dot{V}O_2$ ($r=0.71$, $P=0.01$), whereas peak A wave velocity bore no correlation to peak $\dot{V}O_2$. Peak E wave was not significantly related to LV diastolic diameter. Relations of indicators of early and passive LV relaxation, IVRT and EDT, to peak $\dot{V}O_2$, did not reach the statistical significance. In multivariate analyses adjusting for age, LV diastolic diameter (index of LV pre-load) and heart rate, relations of E/A and V_p to peak $\dot{V}O_2$ were confirmed. The relation of V_p to peak $\dot{V}O_2$ remained (beta=0.76, $P<0.01$) in a multivariate model controlling for age, heart rate, LV mass and circumferential end-systolic stress.

In a multiple regression analysis controlling for age, resting heart rate and stress-corrected MWS, peak $\dot{V}O_2$ was related to V_p (beta=0.96, $P<0.01$, $R^2=0.77$). In a subsequent model including E/A for V_p and using the same set of covariates, E/A showed an independent relation to peak $\dot{V}O_2$ (beta=0.80, $P<0.05$, $R^2=0.40$). In another multiple regression model including IVRT as a parameter of diastolic function, and age, resting heart rate and stress-corrected MWS as covariates, longer IVRT did not show a significant relation to peak $\dot{V}O_2$ (beta=-0.46, $R^2=0.24$). Similarly, when EDT was considered as a LV diastolic function parameter, EDT did not show an independent relation to peak $\dot{V}O_2$ (beta=0.19, $R^2=0.11$). In a multivariate model, peak $\dot{V}O_2$ was related to V_p (beta=0.90, $P<0.01$, $R^2=0.81$) independently of age, resting heart rate, stress-corrected MWS and IVRT.

Discussion

We examined the relationships of myocardial systolic and diastolic function and arterial stiffness to peak $\dot{V}O_2$ in a group of 15 healthy young male subjects. The first new finding of our study was that peak $\dot{V}O_2$ showed no significant correlation with resting stress-corrected MWS, an index of myocardial contractility. We also confirmed that at rest LV chamber systolic function, measured as EF, showed no significant relation to peak $\dot{V}O_2$ (Di Bello et al. 1995; Dubach et al. 1997; Leung et al. 1997). Peak $\dot{V}O_2$ is related to peak cardiac output (Di Bello et al. 1996; Schulman et al. 1996). In a group of mildly hypertensive and normotensive subjects, stress-corrected MWS was lower in hypertensive than in normotensive subjects both at baseline and during exercise despite an approximately similar peak $\dot{V}O_2$ reached by the two groups (Palatini et al. 2001).

We found a strong correlation between V_p , a measure of efficiency of LV diastolic function not previously used in similar studies, and peak $\dot{V}O_2$. Moreover, V_p was more strongly related than E/A, IVRT and EDT to peak $\dot{V}O_2$; the relation of V_p to peak $\dot{V}O_2$ was independent of age, heart rate, LV loading-condition, myocardial contractility and IVRT. Although the relation between LV diastolic function and peak $\dot{V}O_2$ was expected (Di Bello et al. 1996; Vanoverschelde et al. 1993), we demonstrated that LV haemodynamic conditions and LV relaxation account only in part for the relation between the V_p and peak $\dot{V}O_2$. It appeared that the atrio-ventricular pressure gradient (determining the E peak velocity) and the intra-ventricular flow propagation rate (measured by means of V_p) at the beginning of the diastolic interval are important correlates of peak $\dot{V}O_2$. In addition, 81% of the variability of peak $\dot{V}O_2$ was explained by a multivariate model including V_p , whereas the multivariate model including E/A for V_p explained only 40% of the variability of peak $\dot{V}O_2$. Given the fact that the increase in cardiac output during exercise is in large part achieved by increasing heart rate (Wyns et al. 1982), and that, in elite athletes, greater venous return appears to contribute to maintaining LV end-diastolic volume at a constant level despite increase in heart rate and shortening of diastolic interval during exercise (Di Bello et al. 1995), the data suggest that better LV diastolic properties quantified at rest may predict a better adaptation of the pump performance during exercise with favourable direct impact on peak $\dot{V}O_2$ (Clausen et al. 1976; Vanoverschelde et al. 1993).

We also evaluated the relations of echocardiographic indices of arterial stiffness at rest with peak $\dot{V}O_2$, and found no significant relations of peak $\dot{V}O_2$ to the pulse pressure/stroke index or to an index of compliance of the descending aorta. However, the relations were in the direction of higher peak $\dot{V}O_2$ associated with lower arterial stiffness, independent of covariates. During exercise, systolic blood pressure increased only by an average of 49%, whereas heart rate increased by a mean of 192%. Increments in systolic blood pressure correlated with peak $\dot{V}O_2$, suggesting that in normal young subjects exercise-induced increase in systolic blood pressure, to which arterial stiffness may contribute, may represent the capability of the left ventricle to generate stroke work rather than a factor limiting LV ejection phase. However, the relations of arterial stiffness and exercise capability may change in case of increased arterial stiffness, as seen in hypertensive subjects, and in the elderly.

Conclusions

In normal young men, peak $\dot{V}O_2$ is not related to echocardiographically estimated parameters of LV chamber and myocardial systolic function at rest. Conversely, LV diastolic dynamic at rest correlated with peak $\dot{V}O_2$, independent of myocardial contractility,

heart rate and preload. In addition, echocardiographic indices of arterial stiffness did not show a significant relationship with peak $\dot{V}O_2$.

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