Does fitness level modulate the cardiovascular hemodynamic response to exercise?

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IT HAS BEEN TRADITIONALLY accepted that stroke volume (SV) plateaus during submaximal aerobic exercise and that the increase in cardiac output (CO) from submaximal to maximal exercise is due solely to the increase in heart rate (HR) (2). However, recent studies have shown that endurance-trained athletes do not demonstrate a plateau in SV during exercise (6, 7, 30), and thus SV, CO, and oxygen consumption are greater at peak exercise, compared with those values in less fit subjects. It has been hypothesized that endurance-trained subjects are better able to use the Frank-Starling mechanism during incremental exercise (6, 7).

Levine et al. (12) demonstrated that Starling curves are shifted upward and to the left at rest in endurance-trained athletes compared with nonathletes. Specifically, at the same pulmonary artery wedge pressure (PAWP), athletes had elevated SV compared with controls, whereas at the same SV, PAWP was lower in the athletes. Levine et al. hypothesized that chronic intense exercise produces a volume overload, increasing ventricular compliance and shifting the Starling curve. Noninvasive studies suggest that diastolic filling is better in trained subjects during exercise (6, 7, 13, 18). Cross-sectional studies examining left ventricular (LV) function with Doppler echocardiography (6, 18) have shown that peak exercise LV filling rate is increased in trained athletes. Similarly, exercise training increases peak exercise filling rate, which is believed to be an important adaptation to allow for an increase in exercise SV (13). It remains unknown whether the greater LV filling rate and thus greater end-diastolic volume (EDV) and SV during exercise in trained subjects are secondary to increases in cardiac filling pressure, or alternatively, greater ventricular compliance.

Grouped data indicate that PAWP and right atrial pressure (RAP) increase with exercise in normal humans (9, 19); however, these studies have not examined whether fitness modulates the cardiovascular hemodynamic response to exercise. Bevegard et al. (4) remarked that athletes had both a higher SV and PAWP during submaximal exercise, compared with nonathletes. However, interpretation of these findings is difficult because the data were evaluated at the same exercise HR (170 beats/min), and therefore it is unknown whether this intensity represents either the same relative or absolute workload between groups.

In this study, we examined the effect of fitness level [maximal oxygen consumption (VO2max)] on the cardiovascular hemodynamic response to incremental exercise in healthy male subjects. We hypothesized that subjects with higher levels of aerobic fitness would have better diastolic function during exercise, and therefore lower LV filling pressures at the same workload, or, alternatively, that they would have increased SV at the same LV filling pressure.

METHODOLOGY

Research Design

This study reports data from a larger project that also examined pulmonary gas exchange and intrapulmonary shunt,
and descriptive cardiovascular data have been reported previously (23). Institutional ethics review board approval was obtained, and all participants provided written, informed consent to participate. Three experimental sessions were completed during a 3-wk period in the following order: a graded exercise test to determine ventilatory threshold and VO$_2$ max, a practice session to familiarize the subject with the protocol, and the experimental day.

Subjects

Eight physically active healthy male subjects participated in this investigation (Table 1). A ninth subject had been excluded due to a lack of good-quality exercise echocardiograms. Before analysis, subjects were classified into either LO (VO$_2$ max < 55 ml·kg$^{-1}$·min$^{-1}$) or HI (VO$_2$ max > 55 ml·kg$^{-1}$·min$^{-1}$) group based on VO$_2$ max score indexed to body weight.

Experimental Trial

Protocol. Each subject was instrumented with a radial artery catheter (20-gauge Angiocath, Becton-Dickson, Sandy, UT) and a Swan-Ganz catheter (Edwards Lifesciences; Irvine, CA). After placement of the catheters, subjects rested quietly for 10 min before data collection. Each subject was then positioned on the cycle ergometer (model 740E ergometer, Siemens Malvern, PA), and resting upright data were collected. Subsequently, a discontinuous exercise protocol staged according to power output was conducted in the following order: workload I, 75 W; workload II, 150 W; workload III, ventilatory threshold; workload IV, 25 W above ventilatory threshold; and workload V, 90% of VO$_2$ max. Five-minute rest periods were given between workloads. Additional workloads were also conducted with the application of lower body positive pressure to determine how acute increases in pulmonary vascular pressures affect pulmonary gas exchange (results not reported). For workloads below 90% of VO$_2$ max, data collection began after the first 2 min of each 5-min workload. At 90% VO$_2$ max, data collection began once the target oxygen consumption was reached (typically 90 s); the workload usually lasted ~3 min before the subject became fatigued.

Cardiorespiratory measures. Expired gases were analyzed with a commercially available metabolic cart (ParvoMedics, TrueMAX, Salt Lake City, UT), and heart rate was recorded by ECG. Arterial blood samples (2–3 ml) were drawn from the radial artery catheter, and mixed venous samples (2–3 ml) were drawn from the distal port of the Swan-Ganz catheter; arterial and mixed venous oxygen saturation were corrected for temperature (measured with the Swan-Ganz catheter) and pH. CO was calculated from the Fick equation. Systemic arterial blood pressure was measured from a pressure transducer attached to the radial arterial catheter, and mean pulmonary arterial pressure (PAP), PAWP, and right atrial pressure (RAP) were obtained from the Swan-Ganz catheter. The pressure transducers were set at the level of the right atrium; the position was monitored continually. Mean pressures over at least three respiratory cycles during the latter 2 min of each workload are reported.

Calculations. Systemic mean systolic pressure was calculated as diastolic pressure plus ½ pulse pressure (14) and was assumed to be equivalent to end-systolic pressure (ESP). LV stroke work (SW) was calculated as the difference between ESP and PAWP, multiplied by SV, and it is reported in millimeters of mercury per liter. Pericardial pressure was estimated from RAP (26), and LV transmural filling pressure (TMFP) was then calculated as the difference between mean PAWP and RAP (3). The difference between mean arterial pressure minus RAP, divided by CO, was taken as total peripheral resistance; and PAP – PAWP/CO was used to calculate pulmonary vascular resistance. LV end-diastolic volume (EDV) was estimated from Fick SV and two-dimensional echocardiographic short-axis fractional area change (22), obtained during exercise using a commercially available instrument (model Sonos 5500, Hewlett-Packard, Andover, MA). All images were acquired and subsequently analyzed at least in triplicate by the same experienced sonographer, who was naive as to the hypothesis of the study. Within-subject coefficient of variation for fractional area change averaged 7.5% at rest and 8.7% during exercise and was similar between groups. Aortic saline contrast echocardiography was also conducted at each workload (results not reported).

Statistical analysis. For each dependent variable, three planned comparisons (rest, 150 W, and peak exercise) were made between the two groups using an unpaired Student’s t-test. An absolute submaximal workload (150 W) was used to allow comparison between subjects at a similar metabolic rate and CO; however, it is important to note that this workload resulted in a different relative intensity between groups. Peak exercise represents a similar relative intensity between subjects (90% VO$_2$ max), and it was the highest sustainable workload. A Bonferroni correction factor was applied to maintain the familywise error rate at 0.05. For all inferential analyses, the probability of type I error was set at 0.05.

RESULTS

Subject characteristics are reported in Table 1. No between-group differences in body surface area were found; therefore, absolute CO and SV values are reported.

Individual and group values are illustrated in Figs. 1 and 2 and reported in Table 2. No between-group differences in cardiovascular or hemodynamic data were observed at rest.

With the increasing metabolic demand of exercise, all subjects increased their CO, SV, and SW (Fig. 1). At 150 W, CO, SV, and SW were similar between groups. With further increases in exercise intensity the two groups demonstrated qualitatively divergent SV and SW responses. From submaximal to peak exercise, all LO subjects showed a plateau or

Table 1. Characteristic data of subjects with low and high aerobic fitness

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>LO (n = 5)</th>
<th>HI (n = 5)</th>
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<tbody>
<tr>
<td>Age, yr</td>
<td>29.7 ± 2.0 (26–33)</td>
<td>29.6 ± 2.1 (25–37)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>179 ± 1 (178–180)</td>
<td>182 ± 2 (179–188)</td>
</tr>
<tr>
<td>Mass, kg</td>
<td>83.9 ± 3.8 (77.2–90.6)</td>
<td>75.9 ± 1.8 (68.8–79.0)</td>
</tr>
<tr>
<td>Body surface area, m$^2$</td>
<td>2.0 ± 0.0 (2.0–2.1)</td>
<td>2.0 ± 0.0 (1.9–2.1)</td>
</tr>
<tr>
<td>VO$_2$ max, l/min</td>
<td>3.6 ± 0.4 (3.05–4.3)</td>
<td>4.6 ± 0.2* (4.4–5.1)</td>
</tr>
<tr>
<td>Relative VO$_2$ max, ml·kg$^{-1}$·min$^{-1}$</td>
<td>43.3 ± 3.4 (36.4–47.8)</td>
<td>60.2 ± 1.4* (56.1–63.9)</td>
</tr>
</tbody>
</table>

Values are data presented as means ± SE and with range in parentheses; n, no. of subjects LO, low aerobic fitness; HI, high aerobic fitness; VO$_2$ max, maximal VO$_2$. *P < 0.05 vs. LO.
A decrease in SV (and SW) such that the increase in CO was entirely due to HR. In contrast, in all HI subjects, the highest values for SV and SW were observed at peak exercise. At their respective peak levels of exercise, SV, SW, and CO were significantly greater in HI than in LO subjects.

No statistically significant between-group difference was observed in RAP, either at rest or at any point during exercise. At 150 W (submaximal exercise) PAWP and correspondingly TMFP were lower in HI subjects, and both were similarly lower at peak exercise. As illustrated in Fig. 3, HI subjects had greater peak values of SV and SW despite lower values of TMFP and PAWP.

Peripheral vascular resistance was not different between groups at rest and during submaximal exercise, but at peak exercise, resistance was lower in HI subjects (Table 2). No significant between-group differences were found in ESP at rest or during exercise. Mean pulmonary artery pressure was not different at rest or during submaximal exercise (P = 0.33), whereas at peak exercise there was a trend (P = 0.06) for PAP to be higher in LO subjects.

Estimated EDV was not different between groups at rest or during submaximal exercise (see Fig. 4); however, EDV was significantly greater in HI subjects at peak exercise. Indexes of LV end-diastolic compliance (EDV/PAWP and EDV/TMFP) were significantly higher (i.e., better) during both submaximal and peak exercise in HI subjects.

DISCUSSION

Cardiovascular Responses to Acute Exercise

We found that subjects with greater aerobic fitness demonstrated better diastolic function and compliance compared with...
Fig. 2. Cardiac filling pressure responses during upright rest and graded exercise. A: individual responses. B: subjects grouped into LO and HI. Values are means ± SE.

Table 2. Mean (± SE) Data at rest and during exercise in subjects with low and high aerobic fitness

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Submaximal Exercise</th>
<th>Peak Exercise</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>LO (ml/kg/min)</td>
<td>HI (ml/kg/min)</td>
<td>LO (ml/kg/min)</td>
</tr>
<tr>
<td>Power output</td>
<td>11.3 ± 1.6</td>
<td>14.4 ± 2.0</td>
<td>150 ± 0</td>
</tr>
<tr>
<td>Minute ventilation, l/min</td>
<td>74 ± 10</td>
<td>65 ± 5</td>
<td>150 ± 9</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>138 ± 3</td>
<td>141 ± 3</td>
<td>182 ± 3</td>
</tr>
<tr>
<td>End-systolic pressure, mmHg</td>
<td>16.7 ± 1.1</td>
<td>17.2 ± 1.5</td>
<td>6.1 ± 0.1</td>
</tr>
<tr>
<td>Peripheral vascular resistance, mmHg l⁻¹min⁻¹</td>
<td>13.9 ± 0.6</td>
<td>12.1 ± 0.7</td>
<td>22.2 ± 2.3</td>
</tr>
<tr>
<td>Pulmonary artery pressure, mmHg</td>
<td>0.93 ± 0.23</td>
<td>0.83 ± 0.15</td>
<td>0.47 ± 0.08</td>
</tr>
</tbody>
</table>

Values are means ± SE. *P < 0.05 vs. LO.
their less fit counterparts, because left heart filling pressures were consistently lower during exercise, whereas SV and EDV were either the same (submaximal exercise) or greater (peak exercise). Levine and colleagues reported that both younger (12) and older (1) endurance-trained athletes had greater resting diastolic compliance during cardiac volume loading (rapid infusion of saline) and unloading (lower body negative pressure). Our results extend these findings by demonstrating that individuals with a high VO$_2$ max have enhanced diastolic function and compliance during submaximal and peak exercise compared with subjects with a lower VO$_2$ max. Accordingly, individuals with the greatest diastolic compliance also had the highest peak SV and CO, and therefore our findings support noninvasive exercise studies that postulated that the enhanced exercise SV in endurance-trained athletes was due to favorable changes in diastolic function (6, 7, 13, 18, 29, 30). Moreover, our results suggest that the greater transmitral filling rate observed in fitter subjects during exercise (6, 7, 13, 18) is due to improved LV compliance, as opposed to greater LV filling pressure. Earlier investigations of exercising subjects with right heart catheterization (9, 19) may have overlooked the effect of fitness on diastolic function and LV filling pressure, because only aggregate responses were examined.

The mechanisms for the enhanced exercise SV and diastolic function were not examined in this study, but they may be related to remodeling of the myocardium and pericardium and to enhanced diastolic relaxation. As the LV contracts below its equilibrium volume, the resulting elastic recoil has been proposed to cause a negative pressure in early diastole, increasing the transmitral filling gradient (25). Indeed increased contractility has been shown to augment ventricular suction in dogs (10, 16, 17, 25) and humans (27). Hori et al. (10) proposed that contraction below the equilibrium volume may be important during exercise, because ventricular suction would limit the rise in left atrial pressure needed to maintain filling. Cheng et al. (5) found that reducing early diastolic pressure was the primary mechanism to increase filling rate in the exercising dog. In the present study, the lower exercise values of TMFP and PAWP in HI may be related to greater LV suction; however, this cannot be confirmed without obtaining LV pressure during the entire cardiac cycle. Chronic exercise has been shown to cause favorable adaptations in myocardial function, including enhanced calcium reuptake and longitudinal myocyte growth (for a review see Ref. 15), that improve diastolic relaxation and compliance, and we would suggest that these myocardial changes are the likely explanation for the lower LV filling pressures during exercise in our fitter subjects.

Fig. 3. Left ventricular performance during upright rest, submaximal (150 W), and peak exercise in LO and HI subjects. Values are means ± SE. *150 W: pulmonary wedge pressure and transmural pressure significantly lower than LO, P < 0.05. #Peak exercise: stroke volume, stroke work, pulmonary wedge pressure, and transmural pressure significantly different from LO, P < 0.05.
submaximal to peak exercise (despite increases in both PAWP and TMP) indicates that changes in myocardial mechanics, independent of the pericardium, constrained filling during incremental exercise in LO subjects. It is not clear what limited LV filling in HI subjects at peak exercise. RAP and PAWP increased equally at high exercise intensities in HI subjects, which suggests a pericardial limitation to filling (11). Studies with athletic animals have demonstrated that, when the pericardium is removed, peak EDV, SV and V\textsubscript{O\textsubscript{2}}\text{max} are increased (8, 24). It is possible that a similar pericardial constraint limits EDV and SV during high-intensity exercise in HI subjects. A limitation of the present study is that exercise was not performed at or above V\textsubscript{O\textsubscript{2}}\text{max}, making inferences regarding cardiovascular function at true peak aerobic intensity difficult. Notwithstanding this limitation, it is evident that HI subjects were better able to use the Frank-Starling mechanism to increase SV during incremental exercise.

Study Limitations

As pointed out previously (28), measuring central pressures during exercise is made difficult by the large swings in pleural pressure during intense exercise. Similar to previous studies, our pressures are reported relative to atmospheric pressure, without consideration of intrathoracic pressure. Rowell et al. (21) stated that intrathoracic pressure becomes more negative with increases in tidal volume and breathing frequency during exercise, whereas Reeves and Taylor (20) acknowledged that, when averaged over several respiratory cycles, mean intrathoracic pressure is near zero and little changed from resting values in the healthy lung. It is important to note that changes in intra-thoracic pressure do not affect TMFP (PAWP – RAP). Furthermore, during submaximal exercise LO subjects had slightly higher minute ventilation, potentially reducing intrathoracic pressure; however, TMFP and PAWP were instead found to be greater in this group. Thus we suggest that our central hemodynamic findings are not an artifact of ventilation.

The cross-sectional design of our study limits the application of our results. Whereas the HI subjects were all competitive athletes (cyclists or triathletes) who performed more consistent and intense aerobic exercise compared with the LO group, we cannot rule out the effect of genetics on V\textsubscript{O\textsubscript{2}}\text{max} and cardiac function. In addition, the small sample size limits detection of small between-group differences (i.e., type II error). Surprisingly, we did not observe any between-group differences in cardiovascular function at rest. This may be explained by the small sample size or the lack of a true “resting state” (due to the invasiveness of the study).

This study examined the effect of fitness level on the cardiac hemodynamic response to exercise in healthy male subjects. Subjects with greater aerobic fitness demonstrated better diastolic function and compliance compared with their less fit counterparts, because left heart filling pressures were consistently lower during exercise, whereas SV and EDV were either the same (submaximal) or elevated (peak exercise). In addition, the limitations to peak stroke volume appear to be different between LO and HI subjects: in LO, intrinsic myocardial factors seem to be important and, in HI, extrinsic myocardial factors (e.g., the pericardium) limit LV filling.

**Limitations to SV**

Data from the present study allow for discussion regarding limitations to exercise SV. LO subjects failed to increase SV with incremental exercise despite increases in PAWP, which is similar to the grouped response reported by Higginbotham et al. (9) in a sample of relatively unfit subjects (mean V\textsubscript{O\textsubscript{2}}\text{max} = 30 ml·kg\textsuperscript{-1}·min\textsuperscript{-1}). Higginbotham et al. concluded that the reduction in SV with graded exercise was due to an inadequate time for filling because of exercise-induced tachycardia. However, in our study, HR was similar between LO and HI subjects at peak exercise, and SV was significantly greater in HI subjects. We did not measure diastolic time, but the similarity of the HRs suggests that tachycardia and the shortening of diastole is unlikely to explain the divergent SV response. Janicki (11) proposed that when pericardial constraint is present, SV and EDV plateau with increases in PAWP because of a parallel increase in pericardial pressure (as estimated by RAP). We would propose that the reduction in SV in LO from
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REFERENCES