Regulation of Stroke Volume during Submaximal and Maximal Upright Exercise in Normal Man

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SUMMARY. To characterize the hemodynamic factors that regulate stroke volume during upright exercise in normal man, 24 asymptomatic male volunteers were evaluated by simultaneous right heart catheterization, radionuclide angiography, and expired gas analysis during staged upright bicycle exercise to exhaustion. From rest to peak exercise, oxygen consumption increased from 0.33 to 2.55 liters/min (7.7-fold), cardiac index increased from 3.0 to 9.7 liters/min per m$^2$ (3.2-fold), and arteriovenous oxygen difference increased from 5.8 to 14.1 vol% (2.5-fold). The increase in cardiac index resulted from an increase in heart rate from 73 to 167 beats/min (2.5-fold), and an increase in left ventricular stroke volume index from 41 to 58 ml/m$^2$ (1.4-fold). During low levels of exercise, there was a linear increase in cardiac index due to an increase in both heart rate and stroke volume index; stroke volume index increased as a result of an increase in left ventricular filling pressure and end-diastolic volume index and, to a much smaller extent, a decrease in end-systolic volume index. During high levels of exercise, further increases in cardiac index resulted entirely from an increase in heart rate, since stroke volume index increased no further. Left ventricular end-diastolic volume index decreased despite a linear increase in pulmonary artery wedge pressure; stroke volume index was maintained by a further decrease in end-diastolic volume index. The degree to which stroke volume index increased during exercise in individuals correlated with the change in end-diastolic volume index ($r = 0.66$) but not with the change in end-systolic volume index ($r = 0.07$). Thus, the mechanism by which left ventricular stroke volume increases during upright exercise in man is dependent upon the changing relationship between heart rate, left ventricular filling, and left ventricular contractility. At low levels of exertion, an increase in left ventricular filling pressure and end-diastolic volume are important determinants of the stroke volume response through the Starling mechanism. At high levels of exertion, the exercise tachycardia is accompanied by a decrease in end-diastolic volume despite a progressive increase in filling pressure, so that stroke volume must be maintained by a decrease in end-systolic volume. (Circ Res 58: 281-291, 1986)
10 were in their 30's, and seven were 40–50 years old. All had sedentary occupations; nine subjects performed regular physical activity off the job in the form of jogging, and only three subjects jogged for at least 30 minutes every day. Subjects varied from 63–103 kg in weight and from 173–185 cm in height; body surface area ranged from 1.65–2.10 m². Hemoglobin ranged from 13.2–16.7 g/100 ml. No subject demonstrated any abnormality on the electrocardiogram or on physical examination.

All studies were performed under a research protocol approved by the Institutional Review Boards of both the Duke University and the Durham Veterans Administration Medical Centers.

Study Protocol

Participants initially reported to the cardiac catheterization laboratory at 8:00 AM in the postabsorptive state. Under local anesthesia, a 7-French balloon-tipped thermodilution Swan-Ganz catheter was introduced into the right pulmonary artery under fluoroscopic control, and an 18-gauge 2½” plastic cannula was introduced percutaneously into the left brachial artery. Subjects then were transferred to the exercise facility, where simultaneous hemodynamic, radionuclide, and gas exchange measurements were recorded at rest in the supine and sitting positions, and then at each work load achieved during upright bicycle exercise to exhaustion.

Exercise was performed on an isokinetic bicycle ergometer (Fitron, Lumex Inc.). Work load was commenced at 150 kilopond meters (kpm) per minute (25 watt) and was increased by 150 kpm per minute every 3 minutes until limited by exhaustion. For analysis, maximum exercise was taken to be the highest completed 3-minute exercise stage. During each stage of exercise, measurements were strictly timed so that arterial and mixed venous blood were sampled simultaneously with expired gas analysis, during the 3rd minute of each exercise stage. Equilibrium radionuclide angiograms were acquired during the 2nd and 3rd minute of each exercise stage. Pulmonary artery wedge pressure and thermodilution cardiac output measurements were recorded during the 2nd minute of each exercise stage. Pulmonary artery wedge pressure measurements were repeated at the end of the 3rd minute during at least one of the high work loads in each subject; none of the measurements made at 3 minutes exceeded those made at 2 minutes by more than 2 mm Hg.

Hemodynamic Measurements

All supine pressure measurements were related to a reference point at the mid axillary line, i.e., a level closely approximating the position of the right atrium. To ensure that an appropriate reference point was used for upright measurements, a small radioactive source was positioned on the chest wall opposite the center of the right atrium as indicated on the scintigraphic display on the gamma camera; pressure transducers were adjusted to this level. The position was often, but not always, opposite the 4th right intercostal space.

Pulmonary and systemic pressures (systolic, diastolic, and electronically derived mean) were obtained with Hewlett-Packard pressure transducers and amplifiers, and were recorded continuously at a paper speed of 2.5 mm/sec. Values of mean pulmonary artery wedge pressure were taken at the average point in the respiratory cycle to average the effects of forced expiration and inspiration during exercise.

Blood samples taken during each exercise stage were chilled in an ice bath immediately after collection. The percent O₂ saturation of 3-ml arterial and mixed venous blood samples was measured on an Instruments Laboratories oximeter, calibrated with known dilutions of O₂-saturated blood. The O₂ content in the mixed venous and arterial blood samples was obtained for calculations of Fick cardiac output. Stroke volume was obtained by dividing Fick cardiac output by heart rate. Systemic and pulmonary vascular resistances (in dyn·sec·cm⁻⁵) were calculated by multiplying mean blood pressure (in mm Hg) by 80, and dividing by cardiac output. Cardiac output also was measured by thermodilution on a commercially available dedicated computer (Instruments Laboratories) at rest and during each exercise stage. Arterial lactate concentration was estimated by the standard technique of lactate oxidation and NAD⁺ reduction (Calbiochem-Behring rapid lactate kit).

Expired Gas Analysis

Expired gases were analyzed continuously both at rest and during exercise. The O₂ and CO₂ contents of the expired air were recorded continuously with Beckman OM-14 and LB-2 analyzers, respectively. Minute volume was recorded continuously with a Pneumoscan spirometer. Oxygen consumption (V̇O₂) was calculated at rest and during the last minute of each exercise stage from standard formulas after correction for temperature and barometric pressure. Peak VO₂ was used as an objective index of aerobic work performance or cardiovascular reserve.

To determine whether measurements of VO₂ during the 3rd minute of each exercise stage adequately represented steady state values, a separate study was performed in which five normal subjects performed graded maximum exercise using 6-minute exercise stages. Early (2–3 minute) and late (5–6 minute) measurements of VO₂ differed by only 3 ± 2%; the largest difference was 10% in one subject at peak exercise. The catheterization procedure did not appear to affect individual measurements of peak VO₂. Ten subjects underwent separate exercise tests without catheter placement within several weeks of the invasive study. In these subjects, whose peak VO₂ ranged from 23.0 to 50.0 ml/kg per min, no systematic difference was seen between the two studies, with mean VO₂ values of 33.7 ± 7.3 and 34.3 ± 7.3 ml/kg per min. Peak VO₂ differed by only 1.6 ± 1.8 ml/kg per min.

Radionuclide Angiography

After in vivo labeling of red blood cells with 30 mCi technetium-99m, gated equilibrium radionuclide studies were acquired, using a Searle LEM mobile γ camera with a high-sensitivity 30º slant hole collimator interfaced with an A² computer (Medico Data Systems). Gating was triggered by the R-wave of the electrocardiogram. All studies were acquired in the left anterior oblique projection that allowed optimum separation of left and right ventricles (approximately 40º); data acquisition time ranged from 1.5–2 minutes for each study. During the exercise studies, particular care was taken to minimize movement of the subject, to avoid firm gripping of the camera, and to maintain a constant work load throughout each radionuclide acquisition.

Using standard computer algorithms, we defined LV borders by a semiautomated edge-detection method; background was selected automatically by reference to the end-systolic frame, and ejection fraction (EF) was computed from the end-diastolic (ED) and end-systolic (ES) borders by a semiautomated edge-detection method; backg
counts, thus: \( EF = \frac{(ED \text{ counts} - \text{background}) - (ES \text{ counts} - \text{background}) + (ED \text{ counts} - \text{background})}{(ED \text{ counts} - \text{background})} \).

To minimize the influence of background and tissue attenuation on measurements of LV volume in this study, LV end-diastolic and end-systolic volumes were derived entirely from radionuclide ejection fraction and Fick stroke volume. Ejection fraction is affected little by the technical factors mentioned above, and is widely accepted as being the most accurate and reproducible measurement in quantitative radionuclide angiography (Gould, 1982). The decision to measure LV volumes in this manner was based on the fact that reported methods for radionuclide volume estimation have shown a standard error of approximately 30 ml when compared with contrast angiography (Dehmer et al., 1980; Links et al., 1982). This error constitutes approximately 25% of the normal end-diastolic volume and 50% of the normal end-systolic volume; in contrast, standard errors for estimations of ejection fraction have been of the order of 0.05, or 10% of the measurement (Dehmer et al., 1980). Although independent validation of measurements of LV volume during exercise is not possible, it seems highly likely that a technique employing Fick stroke volume and radionuclide ejection fraction would involve smaller errors than measurement of volumes by radionuclide techniques alone.

Measurement of ejection fraction by radionuclide angiography has been compared with contrast angiographic ejection fraction measurements in 27 males in our laboratory; linear regression analysis between radionuclide and contrast values demonstrated a correlation coefficient of 0.93 and a standard error of 0.047. Ejection fraction has been shown also to be a highly reproducible measurement both at rest and during exercise. In previous studies in our laboratory (Morris et al., 1983), ejection fraction measured on two occasions varied by approximately 0.03 both at rest and during exercise.

Left ventricular ejection time and peak ejection rate were derived from the volume curve of the radionuclide study using a method identical to that described by Magorien et al. (1983).

**Analysis**

Group data for each variable are expressed as mean ± SD. The significance of changes for the group between supine and upright rest, and between upright rest and peak exercise, was assessed by two-tailed paired \( t \)-tests.

The relationship between progressive changes in various cardiovascular parameters and changes in \( V_02 \) were expressed as both individual and group responses. For analysis of the group response, a polynomial regression analysis was performed on the data for each patient, beginning with the first power of \( V_02 \). An F-test was used to determine whether adding the next highest power of \( V_02 \) resulted in a significant reduction in the regression mean square. The regression equation that fit all the data points was determined by averaging the individual regression coefficients across all patients. Figures were constructed by plotting all data points; the regression line was constructed from the average regression coefficients.

**Results**

No serious complications resulted from these studies. Three cases of superficial thrombophlebitis resulted from the insertion of the Swan-Ganz catheter, but each case resolved with conservative therapy.

Table 1 illustrates mean values (±SD) and ranges for hemodynamic variables measured at rest in the supine and sitting positions, and during maximal upright bicycle exercise.

**Hemodynamics at Rest; Effects of Posture**

In the supine position, before sitting on the bicycle, all subjects were allowed to relax, and measurements were made when the heart rate was stable. Heart rate averaged 64 beats/min and exceeded 80 beats/min in only three of the 24 subjects. All subjects were normotensive, and values for all hemodynamic variables were within the accepted normal range (Table 1).

When the subjects assumed a sitting position on the bicycle, heart rate increased, diastolic blood pressure increased, pulmonary artery pressures decreased, and systemic and pulmonary vascular resistances increased. Left ventricular end-diastolic, end-systolic, and stroke volume indexes decreased, so that cardiac index decreased despite the small increase in heart rate. Arteriovenous \( O_2 \) difference increased to compensate for the decrease in cardiac index. Despite the decrease in LV filling as reflected by lower pulmonary pressures and LV volumes, no systematic differences were seen in ejection fractions between the supine (0.59) and upright (0.61) positions. Peak ejection rate and LV ejection time both decreased significantly from the supine to the upright position, consistent with reflex-mediated increases in contractility and heart rate.

**Exercise Performance and End-Points**

Group values for peak work load and \( V_02 \) are shown in Table 1. These data confirm the wide range of exercise performance to be expected from a heterogeneous population of normal subjects. Figure 1 confirms a linear increase in \( V_02 \) for each subject with increasing work load; the slightly more abrupt increase from rest to the initial stage of exercise resulted from additional work to overcome the inertia of the legs. As in other studies of untrained individuals (Mitchell et al., 1958), “true” maximum \( V_02 \) could not be confirmed in this study, since \( V_02 \) did not plateau at peak work loads. However, arterial lactate levels were consistent with the achievement of maximum or near-maximum levels of exertion; serum lactate exceeded 65 mg/dl in each subject, and was more than 90 mg/dl in 14 of the 24 subjects (Astrand, 1960).

**Hemodynamic Responses to Maximal Upright Bicycle Exercise**

The magnitude of changes in hemodynamic parameters from rest to peak exercise are shown in Table 1.

Maximum exercise hemodynamic data varied considerably between individual subjects. Peak heart rate varied from 136–190 beats/min; this variability was due primarily to age differences in the popula-
Hemodynamic Data at Rest and during Peak Exercise (Mean ± SD, and Range)

<table>
<thead>
<tr>
<th></th>
<th>Supine</th>
<th>Upright</th>
<th>P (Sup vs. Upr)</th>
<th>Peak exercise</th>
<th>P (Upr Rest vs. Ex)</th>
</tr>
</thead>
<tbody>
<tr>
<td>W (kg/m)</td>
<td></td>
<td></td>
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<tr>
<td>VO₂ (liters/min)</td>
<td>0.31 ± 0.06</td>
<td>0.33 ± 0.06</td>
<td>0.142</td>
<td>963 ± 146</td>
<td>&lt;0.001</td>
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<tr>
<td>(0.20-0.45)</td>
<td>(0.25-0.49)</td>
<td></td>
<td>(750-1200)</td>
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<tr>
<td>HR (beats/min)</td>
<td>64 ± 12</td>
<td>73 ± 12</td>
<td>0.007</td>
<td>167 ± 16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(48-90)</td>
<td>(51-92)</td>
<td></td>
<td>(136-190)</td>
<td></td>
<td></td>
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<tr>
<td>SAPs (mm Hg)</td>
<td>130 ± 14</td>
<td>136 ± 12</td>
<td>0.153</td>
<td>220 ± 24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(110-160)</td>
<td>(115-160)</td>
<td></td>
<td>(160-270)</td>
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<tr>
<td>SAPd (mm Hg)</td>
<td>71 ± 6</td>
<td>74 ± 6</td>
<td>0.001</td>
<td>94 ± 8</td>
<td>&lt;0.001</td>
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<tr>
<td>(60-85)</td>
<td>(70-95)</td>
<td></td>
<td>(85-115)</td>
<td></td>
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<tr>
<td>TSVR (dyne-sec-cm⁻³)</td>
<td>1148 ± 290</td>
<td>1466 ± 260</td>
<td>&lt;0.001</td>
<td>585 ± 101</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(648-1900)</td>
<td>(976-1837)</td>
<td></td>
<td>(384-758)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAPs (mm Hg)</td>
<td>20 ± 4</td>
<td>15 ± 4</td>
<td>&lt;0.001</td>
<td>34 ± 6</td>
<td>&lt;0.001</td>
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<tr>
<td>(15-31)</td>
<td>(7-22)</td>
<td></td>
<td>(26-45)</td>
<td></td>
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<tr>
<td>PAPd (mm Hg)</td>
<td>9 ± 2</td>
<td>7 ± 3</td>
<td>0.001</td>
<td>17 ± 6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(6-14)</td>
<td>(2-11)</td>
<td></td>
<td>(7-35)</td>
<td></td>
<td></td>
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<tr>
<td>TPVR (dyne-sec-cm⁻³)</td>
<td>65 ± 31</td>
<td>103 ± 43</td>
<td>&lt;0.001</td>
<td>67 ± 22</td>
<td>&lt;0.001</td>
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<td>(13-140)</td>
<td>(27-191)</td>
<td></td>
<td>(36-112)</td>
<td></td>
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<tr>
<td>PAWPm (mm Hg)</td>
<td>9 ± 3</td>
<td>3 ± 2</td>
<td>&lt;0.001</td>
<td>10 ± 3</td>
<td>&lt;0.001</td>
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<tr>
<td>(4-12)</td>
<td>(5-15)</td>
<td></td>
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<tr>
<td>CI (liters/min per m²)</td>
<td>3.6 ± 0.8</td>
<td>3.0 ± 0.6</td>
<td>0.005</td>
<td>9.7 ± 1.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(2.5-5.4)</td>
<td>(1.9-4.1)</td>
<td></td>
<td>(7.5-12.4)</td>
<td></td>
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<tr>
<td>SVI (ml/m²)</td>
<td>57 ± 14</td>
<td>41 ± 9</td>
<td>&lt;0.001</td>
<td>58 ± 8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(38-77)</td>
<td>(24-58)</td>
<td></td>
<td>(47-76)</td>
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<tr>
<td>LVEDVI (ml/m³)</td>
<td>97 ± 25</td>
<td>68 ± 18</td>
<td>&lt;0.001</td>
<td>77 ± 13</td>
<td>0.011</td>
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<tr>
<td>(68-147)</td>
<td>(32-96)</td>
<td></td>
<td>(46-106)</td>
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<tr>
<td>LVESEI (ml/m³)</td>
<td>41 ± 6</td>
<td>28 ± 5</td>
<td>&lt;0.001</td>
<td>19 ± 10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(27-54)</td>
<td>(8-50)</td>
<td></td>
<td>(4-44)</td>
<td></td>
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<tr>
<td>LVEF</td>
<td>0.59 ± 0.06</td>
<td>0.61 ± 0.09</td>
<td>0.641</td>
<td>0.76 ± 0.10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(0.50-0.75)</td>
<td>(0.45-0.78)</td>
<td></td>
<td>(0.53-0.90)</td>
<td></td>
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</tr>
<tr>
<td>PER (EDV/sec)</td>
<td>-2.85 ± 0.49</td>
<td>-3.49 ± 0.88</td>
<td>&lt;0.001</td>
<td>-6.76 ± 1.25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(-3.49-2.10)</td>
<td>(-6.20-2.61)</td>
<td></td>
<td>(-11.10-5.22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVET (sec)</td>
<td>0.36 ± 0.04</td>
<td>0.32 ± 0.04</td>
<td>&lt;0.001</td>
<td>0.19 ± 0.02</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(0.30-0.47)</td>
<td>(0.26-0.39)</td>
<td></td>
<td>(0.13-0.23)</td>
<td></td>
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</tr>
<tr>
<td>Ao₂ (vol%)</td>
<td>20.6 ± 14</td>
<td>20.8 ± 14</td>
<td>0.702</td>
<td>21.2 ± 1.7</td>
<td>0.824</td>
</tr>
<tr>
<td>(18.4-23.3)</td>
<td>(18.6-23.5)</td>
<td></td>
<td>(18.7-23.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CovO₂ (vol%)</td>
<td>16.2 ± 1.3</td>
<td>15.0 ± 1.3</td>
<td>&lt;0.001</td>
<td>7.1 ± 0.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(14.1-19.1)</td>
<td>(12.6-16.9)</td>
<td></td>
<td>(12.6-16.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A-Vo₂ (vol%)</td>
<td>4.4 ± 0.7</td>
<td>5.8 ± 0.9</td>
<td>0.001</td>
<td>14.1 ± 1.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(3.8-5.0)</td>
<td>(3.5-7.2)</td>
<td></td>
<td>(10.4-17.5)</td>
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</tr>
</tbody>
</table>

Abbreviations: W = work load; VO₂ = oxygen consumption; HR = heart rate; SAPs, SAPd and PAWPm = systemic blood pressure (systolic, diastolic, and mean); TSVR = total systemic vascular resistance; PAPs, PAPd and PAWPm = pulmonary arterial pressure (systolic, diastolic and mean); TPVR = total pulmonary vascular resistance; CI = cardiac index, SVI = stroke volume index; LVEF = left ventricular ejection fraction; PER = peak ejection rate; LVET = left ventricular ejection time; LVEDVI = left ventricular end-diastolic volume index; LVESEI = left ventricular end-systolic volume index; Ao₂ = systemic arterial oxygen content; CovO₂ = pulmonary arterial oxygen content; A-Vo₂ = arteriovenous oxygen difference.
Changes in vascular resistance during upright exercise differed considerably for the systemic and pulmonary circulations. Total systemic vascular resistance decreased dramatically from 1446 to 585 dyne × sec × cm⁻²; the value at peak exercise was much lower than the supine value at rest. In contrast, there was a small decline in calculated pulmonary vascular resistance from 103 to 67 dyne × sec × cm⁻², with the exercise value equaling the rest supine value.

**Pattern of Hemodynamic Responses to Progressive Upright Exercise**

To examine cardiovascular mechanisms during progressive exercise independent of individual differences in maximal aerobic capacity, each variable was considered as a function of VO₂ normalized to its peak value.

**Heart Rate**

Heart rate increased progressively with increasing levels of work in each subject and increased linearly in relation to VO₂.
Systemic Arterial Pressure

Systolic arterial pressure increased linearly with increasing \( \text{VO}_2 \) (Fig. 2). In contrast, diastolic blood pressure did not increase until subjects had exercised to approximately 50% of peak \( \text{VO}_2 \), resulting in a second order polynomial curve fit. Mean arterial pressure increased linearly due to the predominant effect of changes in systolic pressure. Systemic vascular resistance declined exponentially.

Pulmonary Arterial Pressure

As shown in Figure 3, the pattern of changes in pulmonary arterial pressure during progressive upright exercise was different from that seen in the systemic circulation. Systolic pulmonary arterial pressure increased more rapidly during initial stages of exercise than during the later stages; this response was best described by a curvilinear function. Diastolic pulmonary artery pressure increased in a slightly curvilinear fashion. A small curvilinear decline in pulmonary vascular resistance was seen during progressive exercise.

Pulmonary Artery Wedge Pressure

Pulmonary artery wedge pressure increased linearly during progressive upright exercise (Fig. 4). Curves for pulmonary artery diastolic pressure and mean pulmonary artery wedge pressure had similar slopes, but the wedge pressure was approximately 3 mm Hg less than the diastolic pressure at low levels of exercise and 5 mm Hg less at higher levels.

Cardiac Output

Figure 5 illustrates a linear relationship between cardiac index and \( \text{VO}_2 \) during progressive upright exercise. The linear relationship between these two parameters is comparable to previous studies (Rowell, 1974; Clausen, 1976; Astrand and Rodahl, 1977) and provides validation of the Fick cardiac output measurements. To validate Fick measurements of cardiac output further, cardiac output was measured also by the thermodilution technique immediately before the Fick measurements, during each stage of exercise. Measurements of cardiac index by the two independent techniques were highly correlated \((r = 0.95)\) with a standard error of 0.96 liter/min per m\(^2\). Values were distributed evenly about the line of identity except for outputs greater than 9 liters/min per m\(^2\), where thermodilution values exceeded Fick; overestimation of cardiac output at high flow rates is a common observation with indicator dilution techniques (Reeves et al., 1961; Hanson and Tabaikin, 1964).

Left Ventricular Volumes

Progressive changes in LV stroke volume index, end-diastolic volume index, and end-systolic volume index are illustrated in Figure 6, with each parameter shown on the same scale.

Stroke volume index increased initially, reached a plateau at approximately 50% of peak \( \text{VO}_2 \), and tended to decrease slightly at peak exercise. End-diastolic volume index increased uniformly.
during the initial exercise levels, reached its peak value at approximately 40% of maximum \( V_{O_2} \), and then remained unchanged or decreased as peak exercise was approached. End-diastolic volume index tended to decrease in 17 of the 24 subjects during the last exercise stage, compared with a slight increase in the remaining seven subjects.

End-systolic volume index decreased linearly, though by a small extent, during progressive upright exercise.

**Systolic Left Ventricular Performance**

Systolic LV performance, as measured by the ejection phase indices, ejection fraction, peak ejection rate, and LV ejection time, increased progressively during upright bicycle exercise (Fig. 7). Ejection fraction increased more rapidly during the early stages of exercise, while changes in peak ejection rate and ejection time were linear throughout exercise.

**Effect of Age**

To determine whether the variability in age among subjects could have influenced the cardiovascular mechanisms described in this study, multiple linear regression analyses were performed to determine the relationship between age and cardiovascular variables at rest and during peak exercise. No significant age relationship was seen for any hemodynamic measurement at rest. Significant relationships \((r = 0.41)\) were seen between age and some variables at peak exercise: \( V_{O_2} \) ml/m\(^3\) \((r = -0.43)\), heart rate \((r = -0.63)\), systemic vascular resistance \((r = 0.59)\), pulmonary vascular resistance \((r = 0.42)\) cardiac index \((r = -0.54)\), and LV ejection time \((r = 0.42)\). However, no correlation was seen between age and stroke volume index, end-diastolic volume index, end-systolic volume index, ejection fraction, peak ejection rate, or pulmonary artery wedge pressure during exercise. Thus, whereas, in our study, age did affect peak heart rate, cardiac index, and \( O_2 \) consumption, it had no significant effect on the LV pressure, volume, and contractility responses to exercise, and as such was unlikely to have affected the major findings of this study.

It may be of interest to note that the magnitude of decline in end-diastolic volume, from its highest value during submaximal exercise to that at peak exercise, was related inversely to age \((r = -0.47; P = 0.03)\). Since this measure of the apparent decrease in cardiac compliance during peak exercise was greater in younger subjects, our findings do not
support a significant decline in left ventricular dia-
stolic function over the studied age range.

Discussion

Left ventricular stroke output is regulated by three
factors, i.e., diastolic stretch or filling of the left
ventricle, the contractile state of the myocardium,
and systolic wall tension or afterload stress (Sarnoff
and Mitchell, 1961; Brutsaert and Sonnenblick,
1973; Nixon et al., 1982). During exercise, afterload
stress increases so that increases in stroke volume
may be achieved only from increases in left ventricu-
lar filling and/or contractility. Our study illustrates
the complex interaction between the pulmonary and
systemic circulations that exists during exercise, and
demystifies that increases in both left ventricular
filling and contractility are important determinants
of stroke volume in humans during upright exercise.

During low levels of exercise, the linear increase
in cardiac output resulted from increases in both
heart rate and stroke volume. The increase in left
ventricular stroke volume resulted mainly from an
increase in left ventricular filling, as reflected by
an increase in left ventricular end-diastolic volume and
an increase in pulmonary artery wedge pressure,
and, to a smaller extent, from a decrease in end-
systolic volume that resulted from enhanced left
ventricular contractility. The initial response of the
right ventricle to the stimulus of exercise was seen
as a sharp increase in systolic pulmonary artery
pressure. Mean pulmonary artery pressure increased
almost proportionately with cardiac output, so that
calculated total pulmonary vascular resistance de-
creased only slightly. Thus, the pulmonary vascula-
ture appeared to act as a fixed conduit, with little
ability to control blood flow or pressure to the left
side of the heart. In contrast, systemic vascular
resistance decreased markedly during exercise. This
major difference between the pulmonary and sys-

temic circulations is consistent with earlier studies
of the pulmonary circulation (Harris and Heath,
1977).

During high levels of exercise, cardiac output con-
tinued to increase linearly, primarily as a result of a
continued linear increase in heart rate, since there
was no further increase in stroke volume. Increased
right ventricular contractility was reflected as an
increase in systolic pulmonary artery pressure, with-
out a change in pulmonary vascular resistance. Pul-
monary artery wedge pressure continued to increase
throughout exercise, but was not accompanied by
Further increases in end-diastolic volume. In fact, end-diastolic volume decreased during the final stages of exercise, suggesting a decrease in left ventricular compliance. It is possible that the apparent decrease in compliance resulted from the decrease in diastolic filling time as heart rate increased from 73 to 167 beats/min (Kjellberg et al., 1949). Total duration of diastole declined from 502 to 717 msec, despite a significant decrease in left ventricular ejection time, and the decrease in end-diastolic volume seen at peak exercise was greatest in younger subjects, who had higher exercise heart rates. Stroke volume was maintained by a reduction in left ventricular end-systolic volume, presumably the result of further increases in contractility.

The importance of the Frank-Starling mechanism, i.e., an increase in fiber length due to increased chamber filling, in enhancing left ventricular stroke volume during exercise in man has been widely disputed (Rushmer, 1959; Chapman et al., 1969). Although it is now generally agreed that stroke volume increases during upright exercise (Rowell, 1974; Clausen, 1976; Astrand and Rodahl, 1977), the observation that this increase is small compared with the increase in heart rate has been used to support the argument that the Starling mechanism is relatively unimportant in humans (Rushmer, 1959). However, the findings of the present study suggest that the Starling mechanism is of major importance for both maintaining and increasing stroke volume during exercise. First, it has been observed that in the resting state, an increase in heart rate by pacing is accompanied by a decrease in left ventricular end-diastolic diameter and stroke volume, so that cardiac index does not change (Harrison et al., 1963; Sonnenblick et al., 1965; Braunwald et al., 1967; Vatner et al., 1972); thus the increase in left ventricular filling during exercise prevents the reduction in left ventricular end-diastolic volume and stroke volume that would otherwise result from an increase in heart rate. Second, increased filling caused an actual increase in end-diastolic volume which accounted for 50% of the total increase in stroke volume from rest to peak exercise.

Robinson et al. (1966) performed a unique experiment to examine the factors that determine the stroke volume response to exercise in humans. In six men with minimal cardiac disease, right atrial pressure and cardiac output (measured by dye dilution) were recorded during exercise, before and after acute augmentation of blood volume. This study showed that a marked increase in right atrial pressure was accompanied by an increase in cardiac output at rest, but not during exercise. The authors concluded that cardiac filling did not impose a limitation of stroke volume, and that the limitation of stroke volume may be due to one of three factors: (1) limited ability of the right ventricle to deliver blood to the left side of the heart, (2) pericardial limitation of left ventricular filling, or (3) limitation of left ventricular filling due to shortened diastole at high heart rates. The observation in the present study that left ventricular end-diastolic volume decreased at peak exercise, despite a continued increase in pulmonary artery pressure and pulmonary artery wedge pressure, suggests that stroke volume was more likely to be limited by diastolic filling than by a limitation of right ventricular ejection. Furthermore, the observation that left ventricular end-diastolic volume in the supine position was larger than at peak exercise argues against the pericardium as the limiting factor to filling. Our study thus supports the hypothesis that stroke volume, which declined slightly at peak exercise, is limited by the effects of tachycardia on left ventricular filling.

The results of the present study differ considerably from those obtained in dogs (Vatner et al., 1972; Horwitz et al., 1972) or in man during supine exercise (Harrison et al., 1963; Sonnenblick et al., 1965; Braunwald et al., 1967), Harrison et al. (1963), Sonnenblick et al. (1965), and Braunwald et al. (1967) noted a decrease in end-diastolic diameter, a decrease in end-systolic diameter, and no change in stroke volume during low levels of supine exercise in humans. Increases in cardiac output were due solely to changes in heart rate. Left ventricular volume and pressure changes in dogs during progressive exercise were studied by Vatner et al. (1972) and Horwitz et al. (1972), and have been reviewed recently by Vatner and Pagani (1976); these investigators found that left ventricular end-diastolic diameter did not change during submaximal exercise, but increased markedly during severe levels of exertion.

It is important to note that there were marked similarities between the studies of dogs and supine man, but that the pattern of response was completely different from the results obtained in our study in man exercising in the upright position. These marked postural and species differences probably reflect the importance of baseline (pre-exercise) heart rate and filling conditions. As pointed out by Vatner and Pagani (1976), if heart rate changes greatly during exercise (as in dogs, or in humans with a low resting heart rate), stroke volume will tend to increase by only a small amount. Similarly, if filling of the left ventricle is optimal before exercise commences (as in the supine position), left ventricular end-diastolic volume and stroke volume will tend to change little. In contrast, small increases in heart rate from, for example, the higher value seen in upright as opposed to the supine position, or relatively poor initial left ventricular filling (as in the upright position) will enhance the stroke volume response to exercise. The relationship between heart rate and stroke volume changes has been illustrated further by the observation that exercise in dogs (Vatner et al., 1972) and in supine man (Harrison et al., 1963; Sonnenblick et al., 1965; Braunwald et al., 1967) with the heart rate held constant by pacing was accompanied by marked increases in left ven-
tricular end-diastolic diameter and stroke volume, in contrast to the uncontrolled exercise state.

The quantitative changes in central and peripheral cardiovascular variables seen in the present study were consistent with other studies of normal subjects, as summarized in well-referenced reviews (Rowell, 1974; Clausen, 1976; Astrand and Rodahl, 1977). Exercise performance as assessed by peak O$_2$ consumption was somewhat less in our study (2.55 ± 3.1 liters/min or 30.4 ± 6.2 ml/kg per min) than has been described in many studies of healthy male volunteers (Mitchell et al., 1958; Saltin and Astrand, 1967); however, many of these studies have involved well-trained individuals who would be expected to have a higher aerobic capacity than our untrained population. In recent studies of sedentary individuals, Martin et al. (1983) and DeBusk et al. (1983) reported peak levels of O$_2$ consumption similar to those seen in our subjects. A near-maximum level of exertion was confirmed in our study by the high plasma lactate levels obtained.

Our findings confirm previous observations of a linear increase in heart rate, an increase in blood pressure, and a decrease in systemic vascular resistance during exercise (Bevegard et al., 1960; Astrand et al., 1964; Robinson et al., 1966; Epstein et al., 1967; Julius et al., 1967; Ekblom et al., 1968; Thadani and Parker, 1978). An increase in stroke volume during the first half of exercise, followed by a plateau, is also consistent with these studies. The small decline in stroke volume at peak exercise in our study has not been a consistent finding, but has been noted by other investigators (Keul et al., 1981). Maximum values for stroke volume index and cardiac index in our study were very similar to values obtained by Hossack and Bruce (1980), who observed that indirect estimates of cardiac index increased from 2.6 to 9.6 liters/min per m$^2$ (compared with our values of 3.0 and 9.7 liters/min per m$^2$) and stroke volume index from 37 to 56 ml/m$^2$ (compared with our values of 41 and 58 ml/m$^2$) during treadmill exercise to a maximum O$_2$ consumption of 38 ml/kg per min. Our findings of a small increase in end-diastolic volume index during upright bicycle exercise is consistent with previous noninvasive studies (Rerych et al., 1978; Crawford et al., 1979; Sorensen et al., 1980; Higginbotham et al., 1983). Maximum values of arteriovenous O$_2$ difference in the present study 14.1 ± 1.8 vol% are slightly lower than previously reported (Astrand et al., 1964), perhaps reflecting differences in physical conditioning or technical differences between previously derived values and the direct measurements used in the present study.

Few previous studies have measured pulmonary artery and pulmonary artery wedge pressures during upright exercise in humans (Bevegard et al., 1960; Granath et al., 1964; Julius et al., 1967; Messin et al., 1970; Thadani and Parker, 1978), and even fewer of these have examined asymptomatic normal volunteers (Granath et al., 1964; Messin et al., 1970).

The findings in our study are consistent with these previous reports.

In summary, the pressure and volume responses of the left ventricle to progressive upright exercise in humans differ considerably from those previously measured in exercising dogs and in man exercising in the supine position. During low levels of upright exercise, stroke volume increases primarily as a consequence of an increase in left ventricular filling pressure and end-diastolic volume (Starling mechanism) with a small contribution from a decreased end-systolic volume. During high levels of exercise, left ventricular end-diastolic volume does not increase, despite a further increase in filling pressure; on the contrary, end-diastolic volume decreases, possibly as a result of reduced diastolic filling at high heart rates. Stroke volume at high levels of exercise is maintained through a progressive decrease in end-systolic volume.

We gratefully acknowledge James Stanfield, NMT, Debbie Repass, NMT, Jean Wilson, RN, and Jane Watkinson, RN, for technical assistance; the Medical Media Production Service of the Durham Veterans Administration Medical Center for the illustrations; and Cathie Collins for preparation of the manuscript.

This study was supported by Grant HL-17670 from the National Heart, Lung, and Blood Institute, by the Geriatric Research, Education, and Clinical Center (GRECC), and by General Medical Research Funds from the Veterans Administration.

Dr. Higginbotham was supported by a grant from the American Heart Association, North Carolina Affiliate.

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Received February 25, 1985; accepted for publication August 29, 1985.

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INDEX TERMS: Exercise • Hemodynamics • Stroke volume
Regulation of stroke volume during submaximal and maximal upright exercise in normal man.

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doi: 10.1161/01.RES.58.2.281

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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