Sex-related differences in the normal cardiac response to upright exercise

MICHAEL B. HIGGINbotham, M.B., KENNETH G. MORRIS, M.D., R. EDWARD COLEMAN, M.D., AND FREDERICK R. COBB, M.D.

ABSTRACT In previous studies from this laboratory, we found that approximately 30% of women with chest pain and normal coronary arteries demonstrated either a decrease in or a failure to increase radionuclide ejection fraction during exercise. To examine the hypothesis that this apparent abnormality in left ventricular function represents a physiologic difference between men and women, we prospectively studied central and peripheral cardiovascular responses to exercise in 31 age-matched healthy volunteers (16 women and 15 men). A combination of quantitative radionuclide angiography and expired-gas analysis was used to measure ejection fraction and relative changes in end-diastolic counts, stroke counts, count output, and arteriovenous oxygen difference during symptom-limited upright bicycle exercise. Normal male and female volunteers demonstrated comparable baseline left ventricular function and similar aerobic capacity, as determined by weight-adjusted peak oxygen consumption (22.1 ± 5.1 and 22.6 ± 4.3 ml/kg/min, respectively). However, their cardiac responses to exercise were significantly different. Ejection fraction increased from 0.62 ± 0.09 at rest to 0.77 ± 0.07 during exercise in men (p < .001), but was unchanged from 0.63 ± 0.09 at rest to 0.64 ± 0.10 during exercise in women. The ejection fraction increased by 5 points or more in 14 of 15 men, but in only seven of the 16 women. End-diastolic counts increased by 30% in women (p < .001), but was unchanged in men. Because decreases in ejection fraction were matched by increases in end-diastolic counts, relative increases in stroke counts and count output were the same for men and women. These data demonstrate a basic difference between men and women with respect to the mechanism by which they achieve a normal response of stroke volume to exercise; these differences must be taken into account when measurements of cardiac function during exercise stress are used for diagnostic purposes. Circulation 70, No. 3, 357-366, 1984.

IN EARLIER STUDIES from this laboratory we observed that the radionuclide ejection fraction either failed to increase or decreased during exercise in approximately 30% of women who presented for evaluation of chest pain and were found to have angiographically normal coronary arteries; similar responses were seen in only 10% of comparable men. The poor specificity of results of exercise radionuclide angiographic examination in women has also been noted by others. While these observations are consistent with the suggestion by several investigators that such patients may have abnormal cardiac function or myocardial perfusion, they may also indicate a fundamental difference in the cardiac responses of men and women to upright exercise; if the latter were true, one would also expect to see a difference between normal healthy men and women. Such a difference has not been described previously, and if present would be an important consideration in the correct interpretation of tests in which cardiac function is measured during upright exercise.

A prospective study was therefore undertaken to examine the effect of sex on the cardiovascular response to exercise. The study was designed specifically to examine populations of age-matched healthy male and female volunteers. Central and peripheral cardiovascular variables were measured noninvasively by a combination of radionuclide angiography and expired-gas analysis during staged symptom-limited upright bicycle exercise.

Methods

Subjects. Sixteen normal women from 32 to 68 years old (mean 52 ± 11 years) volunteered to participate in the study; none had a history of hypertension or were suspected of having...
heart disease. Three of these women were medical center staff who agreed to participate at the request of one of the investigators; each was sedentary and only two regularly exercised. The remaining 13 participants were identified after enrollment in a physical fitness program. They were starting the program with the expectation of improved general health and fitness, and with the intention of losing weight. No subject was extremely obese; weight ranged from 61 to 88 kg (mean 67 ± 11 kg). The two subjects who were exercising regularly before enrollment had been jogging.

Fifteen normal men from 31 to 67 years old (mean 46 ± 13 years) also volunteered for the study. Six were medical center staff, seven had enrolled in the training program described above, and two had been evaluated for atypical chest pain and results of treadmill testing and cardiac catheterization had been completely normal. All male subjects were sedentary and only three had been exercising regularly before the study. Body weight ranged from 76 to 122 kg (mean 91 ± 10 kg).

Once subjects had volunteered for the study, no further tests were performed for the purpose of selection; the study population thus represents a consecutive series of normal volunteers. Physical examinations were performed and electrocardiograms obtained in all subjects and results were normal. Although status of physical activity was not tested formally, the general condition of the normal volunteers appeared to be representative of the general sedentary middle-aged population.

Exercise protocols. All subjects reported to the exercise laboratory while in the postabsorptive state. After written informed consent was obtained, subjects exercised in the upright position on an isokinetic bicycle ergometer (Fitron, Lumex, Inc.) at a constant pedalling rate of 60 rpm.

After baseline measurements were obtained in resting subjects, they commenced exercise at a workload of 150 kilopond-meters (kpm)/min (25 W); every 3 min the workload was increased by the same amount. Exercise was continued until limited by fatigue and/or shortness of breath. During exercise the electrocardiogram was monitored continuously and standard limb leads and leads V_5 and V_6 were recorded at 1 min intervals. Blood pressure was measured by cuff manometry and was recorded at rest and at the end of each exercise stage.

Measurement of oxygen consumption and end points of exercise. Expired gases were analyzed continuously for calculation of oxygen consumption and production of carbon dioxide at rest and during progressive exercise. The oxygen content of expired air was measured with a Beckman OM-14 analyzer, and carbon dioxide content was measured with a Beckman LB-2 analyzer. Strip-chart recordings were made after instrument calibration, in subjects at rest, and during the last minute of each exercise stage. Minute volume was recorded continuously with a Pneumoscan spirometer. Maximum oxygen consumption was used as an objective index of aerobic work performance or cardiovascular reserve. The respiratory gas exchange ratio, or $V_{CO_2}/V_O_2$, was calculated for each exercise stage and was used as a measure of the extent of anaerobic metabolism, as described by Whipp et al. By making such measurements, it was possible to compare the two groups with respect to maximum aerobic capacity and degree of exercise effort or motivation.

Radionuclide angiography. The use of 3 min stages of exercise permitted acquisitions of data in subjects at rest, during at least two intermediate exercise stages, and at peak exercise. Radionuclide angiograms were acquired during the last 2 min of each exercise stage so that they corresponded with the other noninvasive measurements.

After labeling of red blood cells in vivo with 30 mCi technetium-99m, gated equilibrium radionuclide studies were performed with a Searle L.E.M. mobile gamma camera with a high-sensitivity 30 degree slant-hole collimator interfaced with an A^2 computer (Medical Data Systems). Gating was triggered by the R wave of the electrocardiogram. All images were acquired in the left anterior oblique projection that allowed best separation of left and right ventricles (approximately 40 degrees), and time of data acquisition ranged from 1.5 to 2 min for each study. During the exercise studies particular care was taken to minimize extraneous movement of the subject, to avoid firm gripping of the camera, and to maintain a constant workload.

Left ventricular ejection fraction was calculated with standard computer algorithms. Left ventricular borders were defined 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) counts, as follows:

$$\text{EF} = \frac{(\text{ED counts-background}) - (\text{ES counts-background})}{(\text{ED counts-background})}$$

where $\text{EDC}_0 = \text{back-corrected value}; \text{EDC}_1 = \text{value recorded at time } t; k = 0.693/\text{isotope half-life}.$

As shown in the Appendix, proportional changes in stroke counts and count output were derived from the measurements of end-diastolic counts, ejection fraction, and heart rate.

Proportional changes in arteriovenous oxygen difference from rest to exercise were measured indirectly from changes in count output and oxygen consumption ($V_O_2$). Thus, a measure of oxygen utilization, or “peripheral” cardiovascular function, was available in addition to the measures of “central” function made from radionuclide measurements alone.

The basic assumption necessary for use of these methods is that count data derived from a left ventricular region of interest, corrected for background activity, are proportional to left ventricular volume. This concept has been validated in studies from several different laboratories, and is the basis for measurement of ejection fraction. Absolute left ventricular volume was not calculated in the present study. The preceding calculations are dependent on the precision of measurements of ejection fraction and end-diastolic counts, which was tested by performing duplicate radionuclide studies in 30 subjects at rest; the variability between measurements was 0.02 ± 0.017 for ejection fraction and 7.7 ± 4.7% for end-diastolic counts. The noninvasive measurement of changes in cardiovascular function from rest to exercise was validated in a separate study involving eight healthy male volunteers. Radionuclide and expired-gas data were acquired as previously described; in addition, blood samples were taken from the pulmonary artery (via a Swan-Ganz catheter) and the brachial artery of each subject while at rest and during each exercise stage. Simultaneous direct and indirect measurements of changes in arteriovenous oxygen difference and cardiac output were compared.

Figures 1 and 2 summarize the results of the validation study in which proportional changes in arteriovenous oxygen difference and cardiac output from rest to exercise were compared with corresponding noninvasively determined estimates; the estimates correlated well (figure 1) with direct measurements of arteriovenous oxygen difference (r = .88) and cardiac output (r = .89). In figure 2, changes occurring with progressively more
PATHOPHYSIOLOGY AND NATURAL HISTORY–EXERCISE

strenuous exercise are shown for individual patients. Mean values obtained in the validation study were estimated accurately by noninvasive methods, which reproduces our findings in a previous validation study of patients with abnormal left ventricular function.15

Wall motion was assessed from a real-time endless-loop display of the unprocessed radionuclide data. The left anterior oblique view was divided into three segments — posterolateral, inferoapical, and septal — and each segment was judged normal or hypokinetic by consensus of at least two of the authors. Wall motion was analyzed without knowledge of the identity of the subject or the ejection fraction.

Statistical analysis. Cardiovascular variables in the two groups of subjects at rest and during peak exercise were compared with unpaired t tests. To compare the time course of changes in a certain variable, individual response curves were derived from linear regression analysis, and the slopes produced were compared with unpaired t tests.16 The significance of

FIGURE 1. Validation study. Proportional increases in Fick cardiac output (A) and directly measured arteriovenous oxygen difference (A-VO2, B) during exercise are plotted against the corresponding noninvasive estimates derived from radionuclide data in eight healthy male volunteers. The line of identity is shown.

FIGURE 2. Validation study. Invasive (direct) measurements of proportional changes in arteriovenous oxygen difference and cardiac output during progressive exercise are compared with noninvasive estimates of these variables. The heavy line represents mean data for the group.
changes in values from rest to maximal exercise was assessed by paired t tests. For each comparison, a p value of <.05 was considered indicative of significance.

Results

Exercise performance. All 31 normal volunteers exercised to exhaustion; none had chest pain or ST segment depression. Women achieved a lower maximal external workload (600 ± 77 kpm/min) than did men (740 ± 144 kpm/min), and this corresponded to a 27% lower total oxygen consumption (1.5 ± 0.3 vs 2.1 ± 0.6 liter/min). However, as shown in figure 3, women (group A) and men (group B) had the same level of aerobic capacity as measured by oxygen consumption indexed for body weight (22.6 ± 4.3 and 22.1 ± 5.1 ml/kg/min, respectively), suggesting that these groups did not differ greatly in terms of relative physical fitness. Men had a slightly lower oxygen consumption (expressed as ml/kg/min; figure 3) during intermediate exercise stages, as shown by a more gradually rising response curve compared with that for women (p = .002). However, when oxygen consumption was expressed in milliliters per minute, values for women were approximately 10% less than those for men at each intermediate workload.

The respiratory gas exchange ratio, an index of the degree of anaerobic metabolism, also is illustrated in figure 3. Maximum values were the same for women (1.16 ± 0.10) and men (1.14 ± 0.10). Each subject achieved a maximum ratio of at least 1.0, and values equal to or more than 1.1 were recorded for 11 of the 16 women and 11 of the 15 men. These findings suggest that exercise effort was similar for the two groups.

Central and peripheral cardiovascular responses to exercise. Heart rate and systolic blood pressure responses, as illustrated in figure 4, were comparable at rest and during exercise in the female and male subjects. Maximum values for heart rate were 156 ± 11 beats/min for women and 155 ± 17 beats/min for men; respective values for systolic blood pressure were 202 ± 25 and 216 ± 29 mm Hg. Although heart rate appeared to increase slightly more rapidly in women than in men, there was no significant difference between the response slopes.

Figure 5 illustrates the ejection fraction responses to graded upright bicycle exercise. In normal women and men, the mean resting ejection fraction and the distribution of individual resting measurements were similar. The ejection fraction responses during submaximal exercise also were similar (for example, at 300 kpm/min ejection fraction was 0.71 ± 0.11 for women and 0.71 ± 0.08 for men); however, at maximum exercise there was an almost uniform decrease in ejection fraction in women, while in men it either remained
PATHOPHYSIOLOGY AND NATURAL HISTORY—EXERCISE

**FIGURE 5.** Ejection fraction responses during exercise in which the workload was increased every 3 min. Progressive individual data are shown for the two study groups. Mean submaximal and maximal group data are plotted on the right, and are compared as in figures 3 and 4.

The previously demonstrated negative correlation between the change in ejection fraction from rest to exercise and resting ejection fraction and age were also found in the present study. Linear regression analyses in which change in ejection fraction was related to resting ejection fraction and to age yielded r values of −.46 and −.40, respectively. These overall relationships applied in both the female and male groups (change in ejection fraction vs resting ejection fraction r = −.67 for men, −.34 for women; change in ejection fraction vs age r = −.38 for men, −.17 for women), and therefore did not affect the intergroup comparisons. Changes in ejection fraction did not correlate with peak $V_{O_2}$ (r = −.03) or the ratio of respiratory gas exchange (r = −.17), confirming that differences in ejection fraction were unrelated to physical fitness and were not an artifact caused by variable exercise effort during the test.

Proportional increases in end-diastolic counts are shown in figure 6. There were clear differences in stroke volume between normal male and female volunteers. In women, end-diastolic counts increased at low exercise levels by 20% to 30%, and this increase was maintained at maximum exercise (p < .001). In men, there was an early increase of approximately 10%, but no net change at maximal exercise. The overall response curves and maximal values for end-diastolic counts were clearly different for the two groups (p < .001). Despite differences between cardiac volume responses in men and women, changes in stroke counts were similar, increasing to a plateau during the early stages of exercise (figure 6); stroke counts increased 33% in women and 23% in men at peak exercise.

Count output increased progressively in each group and responses in normal male and female subjects were very similar (figure 6); count output increased approximately 2.5-fold and the relationship between the ratio of exercise to resting count output and workload was essentially the same in each group. Peripheral utilization of $O_2$, expressed as the relative change from rest to peak exercise, appeared comparable in the normal men and women. The ratio of exercise to resting arteriovenous $O_2$ difference increased progressively to a maximum of 2.33 ± 0.45 in women and 2.34 ± 0.51 in men.
Wall motion analysis showed no asynergy induced by exercise in any subject, despite the global decrease in function in many women.

Cardiovascular variables also were expressed in relation to percent maximum $V_{O_2}$ to correct for the possible effect of variations in peak $V_{O_2}$ between subjects. When the results were analyzed as described earlier, the findings were unchanged; women and men remained significantly different with respect to ejection fraction ($p = .0006$) and the ratio of exercise to resting end-diastolic counts ($p = .0002$), but not with respect to this ratio for stroke counts ($p = .20$) or count output ($p = .87$).

**Discussion**

Our results confirm that normal middle-aged men and women achieve increases in stroke volume during upright exercise by different mechanisms. In men, a 23% increase in stroke counts resulted from an increase in ejection fraction with little or no change in end-diastolic counts, while in women a similar increase in stroke counts (33%) was achieved through an increase in end-diastolic counts without an increase in ejection fraction from rest to maximal exercise. These differences were demonstrated in normal sedentary male and female volunteers who were unselected and well-matched for age, resting left ventricular function, heart rate, and blood pressure. The absence of a relationship between the change in ejection fraction and such exercise variables as maximum $V_{O_2}$ and respiratory gas exchange ratio further supports the conclusion that the observed differences were related to sex rather than to variations in physical condition or motivation to exercise.

**Comparison with previous studies.** Although there have been numerous studies describing the changes in heart rate, stroke volume, cardiac output, and arteriovenous $O_2$ difference that accompany exercise in normal subjects, few have examined changes in cardiac volume and ejection fraction in healthy female and male volunteers. The demonstration in the present study of a physiologic difference in the ejection fraction response to exercise in normal men and women is consistent with preliminary observations in our laboratory and in others. Previous reports from our laboratory showed that approximately 30% of women with chest pain and angiographically proven normal coronary arteries either failed to increase or decreased their ejection fraction, compared with only 10% of comparable men. Greenberg et al. also confirmed the poor specificity of the ejection fraction response to exercise in the diagnosis of coronary artery disease in women. In their study, five of 11 normal women (three of five asymptomatic volunteers and two of six with normal coronary arteries) failed to increase their ejection fraction by 0.05, a level found by many investigators to distinguish accurately between normality and abnormality in men. 

---

**FIGURE 6.** Cardiovascular responses to progressive exercise. Proportional changes from rest to exercise (Ex/R) are shown for end-diastolic counts (EDC), stroke counts (SC), count output (CO), and arteriovenous $O_2$ difference (A-VO$_2$). Data are displayed as in the previous figures.
In a recent study, Rodeheffer et al. examined the cardiac responses in groups of 15 female and 46 male normal volunteers carefully selected to include only subjects with a very low likelihood of coronary artery disease; this study was mainly concerned with describing age-related differences, but also demonstrated a possible sex difference in the ejection fraction response to exercise. Ejection fraction failed to increase by 0.05 in five of 15 women (33%) compared with only seven of 46 men (15%). The fact that these differences are not as marked as those seen in the previous study may be explained by the high proportion of men in whom findings were atypical in the previous study, and by the possibility that the screening procedures used (which included stress thallium scintigraphy in all subjects over 40 years of age) may have excluded some normal women with atypical responses.

Peak \( \dot{V}_\text{O}_2 \) for both the male and female volunteers in the present study was considerably lower than that described in most of the published literature, both when values were corrected and uncorrected for body weight. This difference becomes more understandable when the characteristics of the study populations are considered. With few exceptions, previous studies have described very well conditioned subjects, whereas the present study involved sedentary subjects, many of whom were enrolling in an exercise training program. Our results do not differ greatly from those described by DeBusk et al., who studied a group of "moderately fit" middle-aged men being entered into a study of the effects of bed rest and training. The initial maximal \( \dot{V}_\text{O}_2 \) at a heart rate of 170 ± 3 beats/min in these men was 25.4 ± 6.2 ml/kg/min, compared with a value of 22.1 ± 5.1 ml/kg/min in our male subjects. The discrepancy between peak \( \dot{V}_\text{O}_2 \) levels in the present study and those in the large study of Hosack and Bruce may be partially explained by the well-described 6% to 11% difference in peak \( \dot{V}_\text{O}_2 \) in subjects performing bicycle and those performing treadmill exercise.

Further contribution to the low values for \( \dot{V}_\text{O}_2 \) found in the present study was made by the fact that many of our participants almost certainly did not attain truly maximal \( \dot{V}_\text{O}_2 \) despite symptom-limited exercise; this is shown by the absence of a plateau in the \( \dot{V}_\text{O}_2 \) response and by maximum heart rate of 156 ± 11 and 155 ± 17 beats/min in women and men, respectively. It should be emphasized that the purpose of the present study was not to characterize maximum \( \dot{V}_\text{O}_2 \) in middle-aged subjects, but to obtain several measurements of central and peripheral cardiovascular function during exercise. For the comparison between the sexes to be valid at maximal exercise, it was not necessary that the subjects achieve maximal \( \dot{V}_\text{O}_2 \); but only that male and female subjects achieve equivalent levels of peak exercise in relation to maximal \( \dot{V}_\text{O}_2 \). There is strong evidence that this was achieved; maximal values for respiratory gas exchange ratio were greater than 1.0 in all subjects and greater than 1.1 in 11 of 16 women and 11 of 15 men. Thus, the differences in cardiovascular variables observed in the present study at peak exercise were observed during closely matched levels of stress. Furthermore, differences were seen at submaximal levels of exercise expressed as absolute workload or percent of maximal \( \dot{V}_\text{O}_2 \).

Although peak \( \dot{V}_\text{O}_2 \) expressed in liters per minute was 27% lower in women than in men, in contrast to what has been reported in several previous studies, weight-corrected values were not greater in men. This may be explained partially by the fact that average weight of the male subjects (91 ± 10 kg) was considerably higher than that of the females (67 ± 11 kg). The weight difference between the sexes was exaggerated by the fact that three of the males were obese, weighing over 100 kg. Also, previous studies described male and female populations well matched for level of physical activity either by careful selection or by the use of large numbers of subjects. Sex-related differences would be expected to be less apparent in sedentary middle-aged populations in whom there is wide variability in aerobic capacity.

Most previous studies in fit subjects have shown that stroke volume increases by approximately 50% during upright exercise. However, it is well known that exercise stroke volume is higher in trained populations. The increase in stroke counts of 30% seen in the present study is considerably less than the above-mentioned values, but is not inconsistent with the 30% increase described by Ekblom et al. in studies performed in subjects before exercise training. Our demonstration of a gradual increase in stroke counts during early workloads, with the plateau at approximately 50% of maximum, is similar to observations on stroke volume made in several other studies.

Stroke volume was measured as a proportional change in stroke counts from rest to exercise in our study so that we were unable to compare absolute values for maximum exercise in men and women. Most previous investigators have observed greater values for stroke volume in men than in women both at rest and during maximal exercise. The demonstration of a comparable relative increase in stroke counts with exercise is consistent with these findings.

Cardiac output, measured as count output in our
study, increased approximately 2.5-fold in the present study; this is low when compared with results of previous studies, but compatible with the lower values for \( V_0 \) obtained.

Our study confirmed a previously described linear increase in arteriovenous \( O_2 \) difference to a maximum of 2½-fold in normal subjects.\(^{24,30}\) Arteriovenous \( O_2 \) difference has been shown to be higher in men as a result of their higher hemoglobin content.\(^{19}\) However, consistent with the findings in our study, this difference has been observed in subjects both at rest and during exercise, leading to the conclusion that proportional increases do not differ between the sexes.\(^{19,24,30}\)

**Mechanism of the different cardiac responses in men and women.** While our data confirm that the ejection fraction decreases during upright exercise in a large proportion of normal women, the mechanism of this response is unclear and cannot be explained by the findings in this study. One possible explanation is that variations in the ejection fraction, which is not a specific index of left ventricular contractility, represent the normal response of the left ventricle to different loading conditions in women and men during exercise. This possibility is supported by the observation in hemodynamic studies that a decrease in stroke volume follows an increase in arterial blood pressure (a major component of afterload) or a reduction in left ventricular filling pressure (preload), as expected from the Starling principle.\(^{34,35}\) Recently, Peter and Jones\(^{36}\) demonstrated that isometric exercise results in a decrease in radionuclide ejection fraction, in association with an increase in blood pressure. Since blood pressure increased a little more rapidly in women than in men in the present study, it is possible that this relatively rapid increase in afterload could be an important determinant of the ejection fraction response. However, the presence of this mechanism is not supported by results of studies in experimental animals,\(^{37}\) which have demonstrated that acute increases in afterload result in only very transient subendocardial ischemia and brief rather than sustained alterations in ventricular performance. Furthermore, failure of the ejection fraction to increase in the present study was not associated with a greater elevation in systolic blood pressure at peak exercise.

A further possible explanation for the different ejection fraction responses in men and women is related to the observation that in women, left ventricular end-diastolic counts increased by 20% to 30% during exercise, whereas no change was observed in men. The increase in chamber size in women would be expected to increase wall tension to a greater extent than in men, assuming that changes in wall thickness were similar. This increase may have caused an increase in afterload with a resultant decrease in fiber shortening. It is unlikely that the ejection fraction decreased because of inadequate left ventricular filling (preload), since end-diastolic counts increased to a greater extent during exercise in women than in men.

Previous observations by Foster et al.\(^{38}\) and Barnard et al.\(^{39}\) that the ejection fraction may decrease during sudden strenuous exercise even in healthy young men suggested to us that the apparently abnormal ejection fraction response in women may in some way be related to the rapidity of the exercise protocol or to physical deconditioning; we considered the possibility that in previous studies\(^{1,2}\) increasing the workload at 1 min intervals may have represented sudden strenuous exercise in deconditioned women. However, the use of a gradual (3 min) protocol did not abolish the tendency for the ejection fraction to decrease in women. Further evidence that the decrease in ejection fraction was unrelated to exercise conditioning was the lack of correlation between exercise performance and the ejection fraction change: the ejection fraction decreased in many women despite an exercise capacity equal to that of men.

A further possibility to be considered is that middle-aged women have a relatively reduced ability to increase left ventricular contractility in response to exercise stress compared with men of a similar age. Decreases in ejection fraction were accompanied by increases in end-diastolic counts, which is consistent with a compensatory increase in cardiac size that would be required to maintain stroke volume despite reduced systolic function. Although this cannot be proven, it raises the possibility that female sex may have an influence on the contractile reserve of the left ventricle. While a decrease in ejection fraction is also consistent with myocardial ischemia, it seems unlikely that a large proportion of healthy female volunteers would experience myocardial ischemia during exercise.

**Clinical implications.** The finding of a uniform increase in ejection fraction during exercise in asymptomatic men appears to confirm that a decrease in left ventricular ejection fraction is highly specific for the diagnosis of cardiac disease in male patients. It should be remembered, however, that the specificity of a test is influenced strongly by the patient population in which it is employed. This point has been emphasized recently by Rozanski et al.,\(^{40}\) who noted that the specificity of radionuclide angiography decreased markedly at their institution over a 5 year period during which
the study population dramatically changed through the selection of patients with a higher pretest probability of disease and the exclusion of many patients from cardiac catheterization. For this reason, ejection fraction responses may be less uniform in men presenting for investigation of chest pain than in normal male volunteers.

Berger et al. concluded, from a study of patients with chest pain and normal coronary arteries, that failure of the ejection fraction to increase by 0.05 indicated "abnormal left ventricular reserve"; these investigators did not test an asymptomatic control group. While our results do not exclude the possibility that ischemia is responsible for failure of the ejection fraction to increase in some women with chest pain and normal coronary arteries, the demonstration of a similar response in a large population of healthy women, who had a very low probability of developing myocardial ischemia, implies that failure of the ejection fraction to increase is nonspecific and cannot be interpreted as an indication of ischemia or myocardial dysfunction in women.

We thank Ms. Margaret Wilson and Ms. Cindy Baker for their technical support, Dr. Kerry Lee for his assistance with analysis, Medical Media Production Service at the VA Medical Center for preparation of the illustrations, and Cathie Collins for her excellent work in preparing the manuscript.

References

33. Rodeheffer RJ, Gerstenbith G, Becker LC, Fleg JL, Weisfeldt ML, Lakatta EG: Exercise cardiac output is maintained with ad-
HIGGINBOTHAM et al.

Appendix
The following equations were used to calculate relative changes in end-diastolic counts, stroke counts, count output, and arteriovenous O₂ difference from rest to exercise.

\[
\frac{\text{Ex/R EDC}}{\text{EDC}} = \frac{\text{EDC}_{\text{EX}}}{\text{EDC}_{\text{R}}}
\]

\[
\frac{\text{Ex/R SC}}{\text{SC}} = \frac{\text{SC}_{\text{EX}}}{\text{SC}_{\text{R}}} = \frac{\text{EDC}_{\text{EX}} \times \text{EF}_{\text{EX}}}{\text{EDC}_{\text{R}} \times \text{EF}_{\text{R}}}
\]

\[
\frac{\text{Ex/R CO}}{\text{CO}} = \frac{\text{CO}_{\text{EX}}}{\text{CO}_{\text{R}}} = \frac{\text{SC}_{\text{EX}} \times \text{HR}_{\text{EX}}}{\text{SC}_{\text{R}} \times \text{HR}_{\text{R}}}
\]

\[
\frac{\text{Ex/R A-VO₂}}{\text{A-VO₂}} = \frac{\text{A-VO₂}_{\text{EX}}}{\text{A-VO₂}_{\text{R}}} = \frac{\text{CO}_{\text{EX}} \times \text{VO₂}_{\text{EX}}}{\text{CO}_{\text{R}} \times \text{VO₂}_{\text{R}}}
\]

\[
\frac{\text{Ex/R } \dot{\text{VO₂}}}{\text{R/EX CO}} = \frac{\dot{\text{VO₂}}_{\text{EX}}}{\dot{\text{VO₂}}_{\text{R}}} = \frac{\text{R/EX CO}}{\text{R/EX CO}}
\]

where Ex = exercise; R = rest; EDC = end-diastolic counts; SC = stroke counts; CO = count output; A-VO₂ = arteriovenous O₂ difference. Ex/R represents the ratio of the exercise to the resting value, and thus expresses the proportional change from rest to exercise.
Sex-related differences in the normal cardiac response to upright exercise.
M B Higginbotham, K G Morris, R E Coleman and F R Cobb

Circulation. 1984;70:357-366
doi: 10.1161/01.CIR.70.3.357

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1984 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/70/3/357

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/