Serial Exercise Radionuclide Angiography

Validation of Count-derived Changes in Cardiac Output and Quantitation of Maximal Exercise Ventricular Volume Change after Nitroglycerin and Propranolol in Normal Men

SHERMAN G. SORENSON, M.D., JAMES L. RITCHIE, M.D., JAMES H. CALDWELL, M.D., GLEN W. HAMILTON, M.D., AND J. WARD KENNEDY, M.D.

SUMMARY  R-wave-synchronous radionuclide angiography provides time-activity curve information that is assumed to be proportional to ventricular volumes. We performed serial 2-minute time-activity curves and simultaneous Fick cardiac outputs before and during graded, maximal, supine exercise in nine normal subjects; each subject exercised without drug intervention, after nitroglycerin and after intravenous propranolol. Imaging was performed using an R-wave-synchronized gamma camera-computer system, a high-sensitivity collimator and autologous 99mTc-labeled red blood cells. Fick cardiac output was determined from pulmonary and radial arterial blood samples and oxygen consumption. Changes in count-derived cardiac output, expressed as percent change from baseline, closely paralleled changes in Fick output at all levels of exercise for nondrug and nitroglycerin studies. After propranolol, agreement was maintained between both methods for low-to-moderate levels of exercise. Changes in count-defined end-diastolic volume, end-systolic volume and stroke volume agreed well with simultaneous heart rate, wedge pressure and Fick measurements and are in accord with known hemodynamic effects of exercise, nitroglycerin and propranolol. We conclude that radionuclide count data accurately reflect true hemodynamic change as determined by the Fick technique and may aid in defining the mechanisms of ventricular dysfunction in coronary and valvular heart disease, thereby providing a better understanding of the effects of interventions in these disorders.

INTEREST in cardiovascular response to exertion has expanded as physical exercise has assumed a greater role in the evaluation and treatment of patients with heart disease. Cardiovascular responses to exercise are complex and involve changes in myocardial contractility, ventricular volume, heart rate and arterial and venous tone. Although knowledge of changes in ventricular volumes is important in order to fully understand the cardiovascular responses to exercise in health and disease, these measurements have been difficult to perform because they require left ventricular angiography or the presence of surgically implanted epicardial markers.

The development of gated blood-pool radionuclide angiography has made possible noninvasive assessment of relative changes in ventricular volumes during rest and at various levels of upright or supine exercise. Specifically, radionuclide angiography assesses ventricular function and provides time-activity-curve-derived count information proportional to volume. Such volume-equivalent counts, which are relatively independent of geometry, may be used to quantitate change in ventricular volume and left ventricular ejection fraction during mild, moderate and severe exertion. Studies from this and other laboratories have shown a close correlation between the resting ejection fraction generated from time-activity curves and the resting ejection fraction determined by x-ray contrast left ventricular cineangiography. Although these studies indicate the validity of the count-volume proportionality assumptions upon which radionuclide angiography is based, recent experience with radionuclide angiography after pharmacologic or exercise interventions, which may alter ventricular volumes and contractility, emphasizes the need for simultaneous hemodynamic information in quantitating, interpreting and validating this technique.

Because count data provide a good measure of ejection fraction, the same data should provide an adequate measure of cardiac output if the total left ventricular count output is measured. Thus, to validate the technique and test the hypothesis that ventricular count output parallels cardiac output, we combined simultaneous radionuclide and Fick hemodynamic measurements to quantitate the direction and magnitude of change in ventricular volume, stroke volume and cardiac output during exercise, with and without commonly used cardiac drugs. We attempted to determine 1) whether count-based changes in cardiac output during exercise parallel hemodynamic changes as determined by the Fick technique; 2) what serial count-defined changes in end-diastolic volume, end-systolic volume, stroke volume and ejection fraction occur in normal men during exercise; and 3) how nitroglycerin and propranolol modify these count-defined changes.

Methods

Subject Selection and Prestudy Preparation

Nine normal healthy male volunteers (mean age 28
years, range 24–36 years) were studied. Normal cardiovascular function was confirmed by history, physical, chest x-ray, ECG and echocardiogram. The study protocol was approved by the University of Washington Human Subjects Committee and informed consent was obtained from each subject.

One to four weeks before the study, each subject participated in a practice exercise session to familiarize himself with the exercise apparatus and level of exertion required, as well as to provide an estimate of maximal exercise duration. Using a specially designed bicycle ergometer/imaging table system (Quinton Instruments, Seattle, Washington), the subject pedaled in the supine position for 4-minute stages, beginning at 200 kilopond-meters/min (kpm) and increasing by 200 kpm each stage until he reached a symptom-limited maximum.

On the day of study, a 7F Swan-Ganz flow-directed balloon catheter was positioned in the pulmonary artery using pressure and electrocardiographic monitoring. A 20G, 1-inch Teflon catheter (Abbot Laboratories, North Chicago, Illinois) was placed percutaneously in the right radial artery, and an 18G, 1¼-inch, plastic intravenous catheter (Abbot Laboratories, North Chicago, Illinois) was placed in a superficial vein. Ten milliliters of venous blood were removed for labeling. Palmar arch patency was determined before and after radial artery catheter placement by double compression testing. Thirty millicuries of 99mTc-labeled red blood cells were injected via the peripheral venous catheter, and equilibration was allowed for 10 minutes.

Exercise Protocol

Nine subjects had two exercise tests, and eight of these nine subjects had three exercise tests, with at least 1 hour between tests for recovery. The reproducibility of hemodynamic measurements in normal men performing serial maximal exercise after rest intervals of 30–45 minutes has been shown. Excellent reproducibility for rest and exercise radionuclide angiography without intervention has also been reported. Nine subjects exercised without drug intervention and after nitroglycerin (0.6 mg sublingually). Eight subjects also exercised after propranolol (0.14 mg/kg i.v.). The sequence of testing was always control, postnitroglycerin and postpropranolol. Each exercise test consisted of 1) baseline data collection for 4 minutes (legs horizontal); 2) data collection during 4-minute exercise stages beginning at a work load of 200 kpm and increasing by 200 kpm each stage to a symptom-limited maximum; and 3) recovery data collection for three 2-minute periods (legs horizontal). For studies after drugs, nitroglycerin was administered upon completion of baseline data collection for that test, and exercise was begun after 3 minutes. For propranolol tests, propranolol HCl 0.14 mg/kg i.v. was administered over 5 minutes, and baseline and exercise testing then proceeded. There were no complications in any subject in this study.

Data Collection and Analysis

Imaging

Gated blood-pool imaging was performed after the injection of labeled red blood cells using a low-energy, high-sensitivity, parallel-hole collimator and an Ohio Nuclear Series 100 gamma scintillation camera interfaced with a dedicated computer system (Medical Data Systems, Ann Arbor, Michigan). Count and image acquisition occurred under electrocardiographic control such that corresponding 40-msec segments of each cardiac cycle were summed and stored in the computer core memory using the central half camera field of view on a 64 × 64 matrix using the Medical Data Systems MUGX program. The 45° left anterior oblique projection was used with repositioning for each exercise study; patients were allowed to sit between studies. Imaging was carried out such that serial measurements were made every 2 minutes throughout baseline, exercise and recovery periods. Images were processed for each time period by a manual, variable region-of-interest method. This method correlates well (r = 0.97) with a computer semiautomated variable region-of-interest method that more accurately quantitates ejection fraction and stroke counts. Using the manual method, an operator defined the maximal left ventricular end-diastolic image and a background region-of-interest arc 2–3 pixels removed from the left ventricular edge by light pen. Background-subtracted time-activity curves were generated and the end-systolic frame was identified as the frame with minimum left ventricular counts. A separate left ventricular end-systolic region of interest was then defined by light pen. Background-subtracted, composite time-activity curve data were used to obtain or derive end-diastolic counts (EDC), end-systolic counts (ESC), stroke counts (SC = EDC - ESC), ejection fraction and radionuclide cardiac output (RNCO = SC × HR, where HR is the number of cycles during a 2-minute collection period). End-diastolic and end-systolic counts and stroke counts for each time period were all heart-rate corrected by dividing by the number of cycles required for each image so that change in counts represented change in volume alone rather than increase in heart rate during collection periods.

Because each exercise period was 24 minutes or less and serial count analysis of samples in three subjects showed no significant decline in activity for that period of time in a given test, no correction for decay was made. Percent changes in each measured variable from baseline were calculated as

\[
\text{observed counts} - \frac{\text{baseline counts}}{\text{baseline counts}} \times 100
\]

Fick Data

Expired air was collected in neoprene bags with a low-resistance valve (Systems Research Lab, Dayton, Ohio) and 4-cm internal diameter tubing. Collections were performed for 3 minutes during resting baseline
and the last 2 minutes of each 4-minute exercise stage. Oxygen consumption was calculated with a Beckman paramagnetic analyzer and spirometrically determined volumes were corrected to dry standard temperature and pressure. Oxygen contents of pulmonary and radial arterial samples were obtained using the LEX-O2-CON system (Lexington Instruments, Waltham, Massachusetts) on duplicate samples drawn during baseline bag collection and on single samples drawn over 20 seconds during the middle period of bag collections for each exercise stage. In one subject, an arterial line could not be placed for technical reasons, so a single arterial sample was used for subsequent arteriovenous difference calculations, correcting for hematocrit change during exercise. Heart rate derived from the ECG, arterial pressure and pulmonary artery pressure were recorded at 1-minute intervals and pulmonary artery wedge pressures were recorded at 2-minute intervals by means of an Electronics for Medicine VR6 recorder. Cardiac output for each stage was calculated by the direct Fick technique. Changes were calculated as percent change from baseline.

**Statistical Analysis**

We used the paired t test for statistical comparison of measurements made after a single intervention, where each patient served as his own control. For sequential studies over time, we used two-factor analysis of variance with repeated measures on one factor and Dunnett's t test. Based on the restrictions of this method of analysis, comparisons were made on seven subjects who exercised through the twentieth minute of exercise (stage V). Two subjects who exercised through the sixteenth minute of exercise (stage IV) were excluded from statistical analysis but are included in graphic presentations.

**Results**

Each subject exercised the same duration for baseline, postnitroglycerin and postpropranolol studies. The mean duration of symptom-limited exercise was 19.6 minutes (peak work load 1000 kpm): two subjects exercised for 16 minutes (800 kpm), six subjects exercised for 20 minutes (1000 kpm), and one subject exercised for 24 minutes (1200 kpm). Symptomatically, subjects complained of greater dyspnea and diaphoresis at peak exercise after propranolol than for baseline or postnitroglycerin studies.

**Fick and Hemodynamic Data**

Mean heart rate, radial artery pressure, pulmonary capillary pressure and Fick method data are presented in table 1 for baseline, postnitroglycerin and postpropranolol studies. The mean heart rate increased from 65 to 155 beats/min after nitroglycerin and from 63 to 128 beats/min after propranolol. The resting heart rate before nitroglycerin was greater than baseline (p < 0.05), suggesting incomplete return to baseline. Heart rates after nitroglycerin were significantly greater than at baseline, (p < 0.05), demonstrating near-maximal β blockade at the dosage level of 0.14 mg/kg of intravenous propranolol. Mean arterial pressure response to exercise did not differ for any of the three tests, but paired t testing showed lower resting pressures before nitroglycerin administration (for the second test) and after propranolol. Mean pulmonary capillary wedge pressure increased from 9 to 13 mm Hg without drug, from 11 to 14 mm Hg after nitroglycerin and from 11 to 29 mm Hg after propranolol. Although an anticipated fall in wedge pressure after nitroglycerin was prevented by leg elevation, wedge pressures were lower than baseline during stages I and II. At maximum exercise after nitroglycerin, wedge pressure did not differ from control peak wedge pressure. Wedge pressures after propranolol were significantly greater than control wedge pressures during stages III (22 vs 11 mm Hg), IV (25 vs 14 mm Hg) and V (29 vs 13 mm Hg) (p < 0.05). Resting oxygen consumption was less than resting baseline (p < 0.05) after propranolol, but no difference was evident at any level of exercise for either nitroglycerin or propranolol studies. Arteriovenous oxygen (AVO2) differences were similar for baseline and postnitroglycerin studies. After propranolol, however, AVO2 differences were much greater than baseline study AVO2 differences for stages II, III, IV and V (p < 0.05). Exercise cardiac output and stroke volume did not differ for the three studies. However, postpropranolol cardiac outputs were uniformly lower than control cardiac outputs at all levels (p = 0.1). Resting cardiac output for the second (nitroglycerin) study before nitroglycerin administration was less than control, as was resting cardiac output after propranolol.

**Fick and Radionuclide Comparison**

**Cardiac Output Correlation**

Changes in Fick-derived cardiac output and stroke volume expressed as percent change from baseline are presented in table 2 with corresponding count-based changes in ventricular volumes, cardiac output and ejection fraction. Comparison of raw data, i.e., Fick output in liters/minute vs count-derived output in counts/minute is complicated by differences in each subject in attenuation, scatter, radioisotope dosage and timing of study. These factors result in count-volume relationships that are linear for a given subject but discordant when comparisons are made between subjects. Therefore, for these reasons and because counts are a relative rather than an absolute manifestation of volume change, comparison of Fick with radionuclide data is best made using percent

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*Because data for this subject did not differ from 1000 to 1200 kpm, mean analysis is presented through stage V (20 minutes, 1000 kpm) only.*
Table 1. Hemodynamic Response in Normal Men to Maximal Supine Exercise after Nitroglycerin and Propranolol

<table>
<thead>
<tr>
<th>Stage</th>
<th>Rest</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
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<tbody>
<tr>
<td>KPM</td>
<td>0</td>
<td>200</td>
<td>400</td>
<td>600</td>
<td>800</td>
<td>1000</td>
</tr>
<tr>
<td>Time (minutes)</td>
<td>n</td>
<td>9</td>
<td>4</td>
<td>8</td>
<td>12</td>
<td>16</td>
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<tr>
<td>Heart rate (beats/min)</td>
<td>B</td>
<td>65 ± 3</td>
<td>93 ± 6</td>
<td>105 ± 5</td>
<td>122 ± 7</td>
<td>135 ± 4</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>B</td>
<td>89 ± 4</td>
<td>97 ± 4</td>
<td>98 ± 4</td>
<td>102 ± 5</td>
<td>108 ± 5</td>
</tr>
<tr>
<td>Mean pulmonary wedge pressure (mm Hg)</td>
<td>B</td>
<td>9 ± 1</td>
<td>15 ± 1</td>
<td>13 ± 2</td>
<td>11 ± 2</td>
<td>14 ± 3</td>
</tr>
<tr>
<td>Mean O2 consumption (l/min/m2)</td>
<td>B</td>
<td>185 ± 12</td>
<td>441 ± 11</td>
<td>603 ± 13</td>
<td>792 ± 17</td>
<td>1006 ± 21</td>
</tr>
<tr>
<td>Arteriovenous O2 difference (ml/l)</td>
<td>B</td>
<td>55 ± 3</td>
<td>78 ± 4</td>
<td>89 ± 2</td>
<td>100 ± 4</td>
<td>112 ± 4</td>
</tr>
<tr>
<td>Fick cardiac output (l/min)</td>
<td>B</td>
<td>7.1 ± 0.6</td>
<td>11.3 ± 0.7</td>
<td>13.5 ± 0.5</td>
<td>15.9 ± 0.5</td>
<td>18.0 ± 0.6</td>
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<tr>
<td>Stroke volume (ml/min)</td>
<td>B</td>
<td>109 ± 8</td>
<td>119 ± 6</td>
<td>131 ± 8</td>
<td>137 ± 5</td>
<td>131 ± 8</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.

*Difference compared with baseline significant at p < 0.05 by paired t test (rest) and Dunnett's t test (exercise).

Abbreviations: B = baseline; N = after nitroglycerin 0.6 mg sublingually; P = after propranolol 0.14 mg/kg i.v.; KPM = kilopond-meters/min.

Table 2. Hemodynamic and Count Response to Maximal Supine Exercise in Normal Men

<table>
<thead>
<tr>
<th>Stage</th>
<th>Rest</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
</tr>
</thead>
<tbody>
<tr>
<td>KPM</td>
<td>0</td>
<td>200</td>
<td>400</td>
<td>600</td>
<td>800</td>
<td>1000</td>
</tr>
<tr>
<td>Time (minutes)</td>
<td>n</td>
<td>9</td>
<td>4</td>
<td>8</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>End-diastolic count volume (% change)</td>
<td>B</td>
<td>0</td>
<td>3 ± 4</td>
<td>5 ± 3</td>
<td>5 ± 4</td>
<td>5 ± 4</td>
</tr>
<tr>
<td>End-systolic count volume (% change)</td>
<td>B</td>
<td>0</td>
<td>-8 ± 6</td>
<td>-9 ± 6</td>
<td>-5 ± 7</td>
<td>1 ± 6</td>
</tr>
<tr>
<td>Stroke count volume (% change)</td>
<td>B</td>
<td>0</td>
<td>7 ± 5</td>
<td>12 ± 5</td>
<td>16 ± 6</td>
<td>17 ± 4</td>
</tr>
<tr>
<td>Fick stroke volume (% change)</td>
<td>B</td>
<td>0</td>
<td>10 ± 8</td>
<td>24 ± 11</td>
<td>29 ± 9</td>
<td>24 ± 10</td>
</tr>
<tr>
<td>Count output (% change)</td>
<td>B</td>
<td>0</td>
<td>53 ± 7</td>
<td>83 ± 9</td>
<td>121 ± 13</td>
<td>156 ± 15</td>
</tr>
<tr>
<td>Fick output (% change)</td>
<td>B</td>
<td>0</td>
<td>56 ± 13</td>
<td>93 ± 11</td>
<td>149 ± 14</td>
<td>180 ± 27</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>B</td>
<td>0.74 ± 0.02</td>
<td>0.77 ± 0.03</td>
<td>0.79 ± 0.02</td>
<td>0.81 ± 0.02</td>
<td>0.82 ± 0.02</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.

Abbreviations: B = baseline; N = after nitroglycerin 0.6 mg sublingually; P = after propranolol 0.14 mg/kg i.v.; KPM = kilopond-meters/min.
change from baseline for each method. Figure 1 shows changes in Fick cardiac output and radionuclide count output with increasing work load over time in nine subjects exercising without drug intervention. There is no difference between Fick output and radionuclide count-derived output at any level of exercise. Figure 2 compares cardiac outputs by each method in nine subjects exercising after 0.6 mg of sublingual nitroglycerin. As with the control study, there is no difference between either method at any level of exercise. After propranolol, 0.14 mg/kg i.v., comparison of cardiac output by both methods (fig. 3) shows good agreement until stage IV, where divergence occurs. By stage V the difference is significant (p < 0.01). The reasons for discordance at peak exercise are unclear but may relate to nonlinearity of the Fick output resulting from error in resting output determination or from error in the count method due to lower counts, secondary to slower heart rates and delay because propranolol tests were performed last.

Volume Response to Exercise

Control

Figure 4 shows the relationships between count-derived end-diastolic volume, end-systolic volume and stroke volume in nine subjects exercising to a symptom-limited maximum. Because baseline and recovery data were collected with legs horizontal and all exercise data with legs up, the effect of leg elevation must be considered. We studied the effect of leg elevation in a subset of 18 patients with normal global left ventricular function (ejection fraction > 0.55) by gated equilibrium radionuclide angiography, comparing ventricular count volumes and stroke count volumes with legs in both positions but without exercise or drug intervention (unpublished data). In this group, mean end-diastolic count volume (± SEM) increased by 6 ± 2% (p < 0.05) with leg elevation. End-
systolic count volume increased 9 ± 3% (p < 0.05), stroke volume and heart rate were unchanged and ejection fraction fell by 5 ± 2% (p < 0.05). The reproducibility of serial, 1-minute, gated-image end-diastolic counts (r = 0.99) and end-systolic counts (r = 0.94) is excellent.

In figure 4, end-diastolic volume increased by 3% with leg elevation and mild exercise and then gradually increased a further 4% over the course of remaining exercise, an amount equal to that with leg elevation only. End-systolic count volume, however, decreased incrementally with time and increased work load. Stroke count volume (end-diastolic minus end-systolic counts) increased gradually by 22% at maximum exercise. Changes for each variable over time were statistically significant (p < 0.01). During recovery, with feet removed from the pedals, end-diastolic volume, end-systolic volume and stroke volume declined.

After Nitroglycerin
The volume responses for these nine normal subjects exercising to a symptom-limited maximum after the administration of 0.6 mg of nitroglycerin sublingually are shown in figure 5. End-diastolic count volume initially fell by 9% despite leg elevation, but increased to the same degree as during the nondrug study at maximum exercise. These changes correspond with significantly lower pulmonary capillary wedge pressures early but not late in exercise. End-systolic count volume initially fell to a greater degree than end-diastolic volume. The slope of the decrease from stage I to stage V, however, is identical to that of the nondrug study. Stroke count volume is initially unchanged, but by the end of stage V has increased by 25%, an amount equal to the increase in the nondrug study (22%). Because cardiac output was the same at all levels of exercise, the loss of stroke volume increase at lower levels was compensated for by a significantly greater heart rate (p < 0.05; table 1) after nitroglycerin for low but not peak levels of exercise. Changes in end-diastolic volume, end-systolic volume and stroke volume over time were significant (p < 0.01). During recovery, end-systolic volume declined little, but end-diastolic volume fell to a greater degree than during the baseline study.

**FIGURE 4.** Left ventricular volume changes during exercise and recovery in nine untreated normal men. EDV = count-defined end-diastolic volume; ESV = count-defined end-systolic volume; SV = count-defined stroke volume; KPM = kilopond-meters/min.

**FIGURE 5.** Left ventricular volume changes during exercise and recovery in nine normal men after nitroglycerin 0.6 mg sublingually. EDV = count-defined end-diastolic volume; ESV = count-defined end-systolic volume; SV = count-defined stroke volume; KPM = kilopond-meters/min.
After Propranolol

In figure 6, responses of count-determined end-diastolic volume, end-systolic volume and stroke volume after propranolol 0.14 mg/kg i.v. differ markedly from responses shown in figures 1 and 2. End-diastolic volume initially increased by 13% and then remained unchanged. Simultaneous pulmonary wedge pressures were significantly higher for propranolol studies at higher levels of exercise. End-systolic volume, in contrast to nondrug and nitroglycerin studies, increased, plateaued and did not decline until maximal work loads were approached. At higher work loads, a mild decline in end-systolic volume is apparent. Increase in stroke volume occurred promptly with leg elevation, remained unchanged through exercise and did not differ from baseline (table 2). Changes in each variable over time were significant ($p < 0.01$). During recovery, end-diastolic volume changed little, end-systolic volume decreased and stroke volume declined minimally.

Ejection Fraction Response to Exercise

Mean ejection fraction responses for control, post-nitroglycerin and postpropranolol exercise studies are shown in figure 7. The postnitroglycerin exercise ejection fraction tended to be greater than the control ejection fraction (not significant) and the postpropranolol exercise ejection fraction response was slightly less than during the control study ($p < 0.05$). These nearly similar ejection fraction responses belie the marked differences in ventricular volumes from which they are derived (figs. 4–6).

Discussion

Gated equilibrium radionuclide angiography offers several advantages as a method of exercise study, for it quantitates changes in volume, is relatively independent of geometry and is not limited by invasive methods or factors restricting exercise level or duration. While methods to determine ejection fraction at rest and during exercise have been established, count-derived estimates of left ventricular output and stroke volume have been less well established. This study comparing simultaneous hemodynamic and radionuclide information during graded, maximal, supine exercise testing has shown good agreement between

![Figure 6. Left ventricular volume changes during exercise and recovery in eight normal men after propranolol HCl 0.14 mg/kg i.v. EDV = count-defined end-diastolic volume; ESV = count-defined end-systolic volume; SV = count-defined stroke volume; KPM = kilopond-meters/min.](image)

![Figure 7. Ejection fraction changes during exercise and recovery without drug, after nitroglycerin and after propranolol in normal men. The shaded areas represent one standard deviation derived from the nondrug study. KPM = kilopond-meters/min.](image)
both methods for measuring change in cardiac output. Changes in cardiac output assessed by radionuclide counts parallel the direction and magnitude of changes measured by the Fick method. Such agreement, in conjunction with ejection fraction, correlates with studies,1-4 validates the count-volume proportionality assumptions upon which blood-pool imaging is based. Hemodynamic responses to submaximal supine exercise in normal men and women assessed by Fick techniques have been reported.14-16 and our hemodynamic data are in accord with these studies. Ekelund and Holmgren have combined these studies and reported on the results in 36 untrained young men and 14 untrained young women.17 For submaximal exercise, oxygen consumption increased linearly with cardiac output. The AVO2 difference increased hyperbolically in relation to oxygen consumption (or work load), rising from 25 to 125 vol/l. Our Fick data for graded maximum exercise demonstrated similar linear O2 consumption-cardiac output and hyperbolic O2 consumption-AVO2 difference relationships. Bruce et al.18 showed a plateau in O2 consumption and heart rate after 1-2 minutes of exercise at a new level. Our data collection for each method allowed a 2-minute period with each change in work load to permit this phenomenon to occur. Figures 1, 2, and 3 compare changes in cardiac output for both methods without drug intervention, after nitroglycerin and after propranolol, respectively. The cardiac output throughout exercise assessed by Fick studies is very similar without drug or after nitroglycerin or propranolol, although the mechanisms of maintaining cardiac output for each is different. After nitroglycerin, preload is markedly reduced and adjustments in output are primarily rate dependent. After propranolol, however, rates are slower, filling is greater and increases in stroke volume assume more importance in increasing output.20-24 Despite these divergent mechanisms, agreement between count and Fick methods persisted. The reasons for discordant responses between both methods after propranolol at peak exercise are unclear but do not relate to methods of left ventricular or background region-of-interest selection. Possible causes may relate to the non-linearity of the Fick curve, which increased abnormally at peak exercise, or to lower count rates due to propranolol-reduced heart rates and propranolol studies being performed last.

Changes in stroke volume during exercise have been more controversial than cardiac output, due to dependence of change in stroke volume on preload, contractility, afterload and body position. Ekelund and Holmgren17 also summarized changes in stroke volume in the same 36 men and 14 women undergoing submaximal supine exercise. Stroke volume increased, decreased or was unchanged upon transition from rest to exercise. Mean stroke volume increased 13% with transition to exercise and then tended to remain unchanged with increasing but submaximal work loads. Using dog models, other investigators have shown an increase in stroke volume at maximal exercise.19-20 Our Fick stroke volume data are in general accord with these studies. Mean stroke volume increased 18% with initial pedaling and increased further to 30% at midexercise and tended to plateau subsequently. The greater percent change compared with that reported by Ekelund and Holmgren may be partly explained by increasing preload with leg elevation and propranolol.

This study also describes the application of gated radionuclide angiography to the serial quantitation of adaptive changes in count-defined ventricular volumes that occur with graded, maximal, supine exercise in normal subjects with and without drug intervention. Previous investigations of the response of ventricular volume to exercise have been limited to studies in animals, which have shown conflicting results, and a few isolated studies in men. Recent animal studies by Erikson et al.,19 Horwitz et al.20 and Vatner et al.,21 however, have resolved the controversy generated by the fixed heart rate heart-lung model used by Starling22 and the submaximal exercise studies from Rushmer and co-workers.23, 24 The later studies have shown that heart rate increase at low-to-moderate levels of exercise is the usual means of cardiac output increase. At maximal exercise, however, end-diastolic dimensions increase and stroke volume is augmented by the Frank-Starling mechanism. Similar volume changes are operative at low levels of exercise if heart rate is held constant. Using high doses of propranolol, these investigators have also shown an increase in end-diastolic dimension over untreated control, abolition of end-systolic dimension decrease and impaired performance.20, 21 Our data in normal men performing maximal supine exercise are in agreement with these animal studies. Without drug intervention, we have shown an increase in end-diastolic volume with leg elevation that remains constant throughout exercise, a progressive decrease in end-systolic volume and an associated increased in stroke volume and ejection fraction. While our nondrug studies do not show an end-diastolic volume increase at peak exercise (over that observed with leg elevation alone), these findings are in accord with the observation in running untethered dogs that end-diastolic dimension at maximal exercise did not exceed supine resting dimensions.21 Our nitroglycerin studies, however, are relevant in that end-diastolic volume increased, after an initial decline, to a degree equal to the small increase occurring in the nondrug study at maximal exertion (fig. 5). It is likely that impedance falls to minimal values during maximal exercise in normal subjects and that nitroglycerin would, therefore, have little effect at these levels of exertion. End-systolic volume, after an initial acute fall after nitroglycerin, decreased during exercise at a rate equal to that in the nondrug study. After nitroglycerin, initial cardiac output increases were due to heart rate alone, but at peak exercise were due to Frank-Starling and chronotropic mechanisms. Responses after propranolol for this study are also consistent with the findings of Horwitz et al.20 and Vatner et al.21 In our study, end-diastolic volume after propranolol increased to a greater degree than during the nondrug study early in exercise but was not greater
at maximal exercise. End-systolic volume increased initially, but to a lesser degree than end-diastolic volume, and remained unchanged throughout exercise. At maximal exercise (fig. 6), end-systolic volume may have decreased slightly. It appears that after propranolol, stroke volume is initially augmented solely by the unmasking and facilitation of the Frank-Starling mechanism secondary to reduction in heart rate. Inotropic effects were apparently prevented at least until maximum exercise was achieved at the dose of propranolol used in this investigation.

Previous studies of ventricular volume response in man have been limited in number by technical considerations. Braunwald et al. using low-level exercise (in patients who had undergone atrial septal defect repair or mitral valve replacement) with a two-dimensional, metallic-clip method, showed a reduction of end-diastolic and end-systolic measurements. Gorlin et al. reported unchanged end-diastolic volumes and decreased end-systolic volumes in 20 patients with a variety of cardiac disorders assessed by an earlier, less well standardized thermodilution method during mild exercise. Using contrast ventricular angiography, Sharma et al. studied patients at rest and immediately after bicycle-exercise-induced angina or 6 minutes of supine exercise and showed a decline or no change in end-diastolic volume and a fall in end-systolic volume in normal subjects or patients without angina. Patients with angina increased both end-diastolic and end-systolic volumes during exercise. Caldwell et al. found similar changes in maximal exercise with a three-dimensional, metallic-clip method in patients who had undergone aorto-coronary bypass surgery. Echocardiography has been applied to evaluate left ventricular volume change during submaximal and maximal exercise. Echocardiographic assessment of exercise dimension change after propranolol has revealed increases in end-diastolic and end-systolic dimensions compared with control; these findings are similar to ours.

We and others have reported on the application of radionuclide angiography to quantitate serial volume changes after hemodynamic intervention. Studies applying radionuclide angiography to exercise, however, have emphasized a reduction in ejection fraction as being indicative of coronary artery disease or left ventricular dysfunction. Nonetheless, the ejection fraction is modified by the complex interplay of heart rate, myocardial contractility, preload and afterload, and the mechanisms of change in ejection fraction for differing hemodynamic states have not been clearly defined. This study defines some of these changes in normal men treated acutely with nitroglycerin and propranolol and confirms the findings of previous studies in man. We observed mild differences in ejection fraction response to exercise after drug intervention that belie significant differences in preload, ventricular shortening and ventricular volume determinations from which the ejection fraction is derived. Caution should be exercised in applying the acute β blockage changes in ejection fraction that we observed in normal men after intravenous propranolol to patients with coronary artery disease and chronic β blockade, where mechanisms may differ. Studies of the effect of propranolol on resting ejection fraction assessed by radioisotope methods in coronary artery disease patients have reported no change or a fall in ejection fraction after increasing doses of propranolol. In patients with coronary artery disease, propranolol appears to improve exercise ejection fraction response as assessed by exercise gated radionuclide angiography. Our data show blunted ejection fraction response throughout supine exercise in normal men after intravenous propranolol.

In summary, this study validates the assumption that radionuclide count data closely reflect cardiac chamber volumes by showing parallel changes with the Fick cardiac output during exercise. Further, these relationships appear to be valid for nitroglycerin-treated and untreated subjects. At moderate levels of exercise after propranolol, the correlation remains valid. Although our results apply only to normal subjects, this study supports the feasibility of applying radionuclide angiography to the noninvasive quantitation of changes in ventricular volumes during exercise to define mechanisms of ventricular dysfunction in coronary and valvular heart disease more accurately, thereby providing a better understanding of the natural history of these disorders and the effect of interventions.

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Serial exercise radionuclide angiography. Validation of count-derived changes in cardiac output and quantitation of maximal exercise ventricular volume change after nitroglycerin and propranolol in normal men.
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