The Reproducibility of Radionuclide Angiographic Measurements of Left Ventricular Function in Normal Subjects at Rest and During Exercise

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SUMMARY In this investigation we determined the reproducibility of radionuclide measurements of left ventricular ejection fraction, end-diastolic volume, end-systolic volume, stroke volume, pulmonary transit time, pulmonary blood volume and cardiac output in 10 normal subjects. First-pass radionuclide angiograms were performed at rest and during upright, submaximal bicycle exercise on day 1 and day 3.

The resting heart rate for the group decreased from 79 ± 17 beats/min on day 1 to 71 ± 14 beats/min on day 3 (p < 0.01). This biologic variation probably contributed to the small but significant decreases in ejection fraction (62 ± 7 to 59 ± 7%, p < 0.05) and cardiac output (7.7 ± 1.9 to 6.6 ± 1.5 l/min, p < 0.02), and the increase in pulmonary transit time (5.8 ± 1.6 to 6.2 ± 1.3 seconds, p < 0.05) between day 1 and day 3. The mean variabilities in ejection fraction, cardiac output and pulmonary transit time were 4.0 ± 3.8%, 1.24 ± 1.23 l/min and 0.65 ± 0.64 second, respectively. No significant differences between studies were observed in resting end-diastolic volume, end-systolic volume and stroke volume. The mean variability in end-diastolic volume was 9.9 ± 5.1 ml.

Heart rate varied less during exercise to the same work load, and only pulmonary transit time and blood volume differed significantly between studies. During exercise the mean variabilities in ejection fraction, end-diastolic volume, cardiac output and pulmonary transit time were 3.2 ± 2.5%, 9.8 ± 6.2 ml, 1.59 ± 0.67 l/min and 0.25 ± 0.25 second, respectively. Radionuclide measurements of left ventricular function are highly reproducible if obtained under comparable hemodynamic conditions.

RADIONUCLIDE ANGIOCARDIOGRAPHY, a simple, noninvasive method for evaluating cardiac performance at rest and during exercise, is useful in a wide variety of clinical settings. Radionuclide measurements of left ventricular ejection fraction (EF), volumes and cardiac output (CO) correlate closely with those obtained by contrast ventriculography and dye-dilution techniques.1-7 Because sequential studies can be easily performed, radionuclide angiocardiography appears ideally suited for studying the natural course of heart disease and determining the effects of medical and surgical interventions. However, the reproducibility of radionuclide measurements at rest and during exercise has not been adequately assessed. This information is needed to differentiate random variation from a true physiologic change in hemodynamic measurements obtained by this new technique.

To assess the reproducibility of the radionuclide measurements, rest and exercise studies were performed 2 days apart in 10 normal subjects. The methods used to evaluate these studies were developed and validated at this institution.1,4,9 Each study was analyzed by two technicians, and the average of these two measurements on day 1 was compared with the average on day 3. These observations in normal subjects provide a frame of reference for the analysis of sequential radionuclide angiograms in patients with cardiac disorders.

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Methods

Study Design

The study group consisted of eight men and two women volunteers, ages 21-46 years (mean 31 years). All 10 subjects were asymptomatic and had normal physical examinations and 12-lead ECGs at rest. None had a history of cardiac disease.

Baseline blood pressure and heart rate were recorded after a 20-gauge polyethylene catheter had been placed in either the external jugular or antecubital vein. A 10-mCi dose of technetium-99m pertechnetate in a volume less than 1 ml was then rapidly administered with a brisk injection of 15 ml of normal saline. A multicrystal gamma camera (Baird-Atomic System Seventy-Seven) with a 1-inch, parallel-hole collimator positioned anterior to the precordium recorded counts at a 50-msec framing interval during the initial pass of the radionuclide through the central circulation. Upright exercise on an isokinetic bicycle ergometer (Fitron) was begun at a work load of 400 kilopond-meters (kpm)/min and increased by 200 kpm/min every 2 minutes until 85% of the age-predicted maximum heart rate was reached. Background counts over the precordium were next obtained for approximately 15 seconds, and a second 10-mCi bolus of technetium-99m pertechnetate was injected while exercise continued. The subject's chest was stabilized against the collimator during the exercise injection to prevent excessive motion. A single bipolar CM₅ electrocardiographic lead was continuously monitored by telemetry, and blood pressure was recorded at 1-minute intervals during exercise and the recovery period. Two days later each subject was again studied in the same manner at rest and during exercise to the identical work load achieved in the first study. All subjects completed both exercise periods without chest pain, electrocardiographic evidence of myocardial ischemia or significant arrhythmias.

Data Processing

The radionuclide angiocardiograms were analyzed with computer software initially developed in this laboratory and now incorporated into the Baird-Atomic System Seventy-Seven. The acquired data is first corrected for field nonuniformity and dead time. In addition, the exercise studies are also corrected for preexisting background counts in each crystal from the initial resting study.

Each study is next displayed serially on an oscilloscope, with each image representing 20 summed 50-msec frames. Using a magnetic pen and a zone grid corresponding to the detector's 294 crystals, the technician selects a preliminary left ventricular region of interest. An indicator-dilution curve is then generated for this region, and the end-systolic and end-diastolic frames (50 msec) are identified for four to eight cardiac cycles when the bolus is maximal within the left ventricle. All the end-systolic frames are added and displayed in analog mode as an average end-systolic image; similarly, all the end-diastolic images are added. By subtracting the end-systolic image from the end-diastolic image, which includes counts from other structures within the chest, a relatively pure left ventricular image is identified, because the left ventricle is the only area in the entire field that loses counts during systole. A second left ventricular indicator-dilution curve is then generated for this new region of interest. The computer continues this process in an iterative fashion until constant end-systolic and end-diastolic frames are defined for each beat. Summation of the beats from this curve constructs a representative cardiac cycle by using the identified end-systolic and end-diastolic frames to retain the appropriate phasic relationship of data from each 50-msec accumulation interval in the entire cardiac cycle. This process results in a left ventricular curve from an area reproducibly and objectively outlined by a computer algorithm.

The second step in data processing is the removal of background counts from the left ventricular data. These counts arise from adjacent structures, such as the left atrium, pulmonary veins, aorta and coronary blood pools, as well as from radiation scatter into the region of the left ventricle. Subtraction of these background counts is necessary for accurate determination of left ventricular EF. Further, the linear relationship between counts and left ventricular volume demands data from which all background counts have been excluded.

The technique of background subtraction used in this study first defines the spatial distribution of counts that coincides in time with the appearance of the tracer bolus in the left atrium but before entry of tracer into the left ventricle. This image of background counts is multiplied by a derived intensity factor that describes the average change in counts in the structures outside the left ventricle.

The left ventricular EF is determined from the background-corrected representative cardiac cycle: [(end-diastolic counts - end-systolic counts)/(end-diastolic counts)] × 100. A computer program outlines the end-diastolic and end-systolic perimeters at the 21% isocount contour of the end-diastolic image. Previous imaging of elliptical phantoms filled with 5 mCi of technetium-99m pertechnetate in water showed that the 21% count level corresponds most closely to the phantom border. The aortic valve plane is identified from dynamic images and by isolation of the zone demarcating alternate count increases and decreases during diastole and systole. Left ventricular end-diastolic volume (EDV) is calculated by the length-area method of Dodge and associates for an ellipsoid of revolution modified for the single anterior plane projection: 0.85 A²/L, where A is the area obtained by planimetry and L is the longest length measured with a sonic digitizing device (Graph-Pen) coupled to a PDP 11/45 computer. Regional wall motion is assessed by inspecting both dynamic and static images of the representative cycle (fig. 1). Stroke volume (SV), end-systolic volume (ESV) and CO are derived from the measured EF, EDV and HR by the following equations:
used for other concurrent clinical studies. The interobserver variability in EF, EDV and PTT was calculated as the mean ± SD of the absolute differences in these paired determinations. Linear regression equations and correlation coefficients were also derived by the least-squares method.

The mean ± SD of the absolute differences in the averaged measurements from day 1 to day 3 represented the interstudy variability. The results were further analyzed for possible significant changes from day 1 to day 3 by the t test for paired measurements.

Results

Interobserver Variability

When the same radionuclide angiocardiograms were independently analyzed by two technicians, the 20 paired determinations for EF, EDV and PTT correlated well (fig. 2). The interobserver variability in EF was 2.0 ± 1.5% at rest and 2.1 ± 1.0% during exercise. The largest absolute difference between two EF

Analysis of Data

Each radionuclide angiocardiogram was randomly assigned to any two of five technicians. No technician was allowed to know the results obtained by another or to record his own results for later reference. Each technician independently provided measurements of the EF, EDV and PTT that he considered most accurate for processing by a method identical to that of the EF, EDV and PTT that he considered most accurate for processing by a method identical to that

\[ \text{SV (ml)} = \text{EDV (ml)} \times \text{EF} \]

\[ \text{ESV (ml)} = \text{EDV (ml)} - \text{SV (ml)} \]

\[ \text{CO (l/min)} = \text{SV (ml)} \times \text{HR (beats/min)} \]

Time-activity curves are generated over the pulmonary artery and left atrium, and the pulmonary transit time (PTT) in seconds is defined as left atrial

\[ \text{MTT} = \text{pulmonary arterial MTT} \]

where MTT is the mean transit time of the curves from each chamber. The pulmonary blood volume (PBV) is calculated by multiplying the CO and the mean PTT. This estimate assumes even mixing of tracer in the PBV and a mean pulmonary blood flow equal to systemic CO.

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TABLE 1. Hemodynamic Measurements at Rest

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<th>EDV (ml)</th>
<th>SV (ml)</th>
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<th>CO (l/min)</th>
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Abbreviations: EF = ejection fraction; EDV = end-diastolic volume; SV = stroke volume; ESV = end-systolic volume; CO = cardiac output; PTT = pulmonary transit time; PBV = pulmonary blood volume.

determinations was 5%. The interobserver variability in EDV was 7.5 ± 4.7 ml at rest and 7.9 ± 5.7 ml during exercise. No absolute difference in EDV greater than 19 ml occurred. The interobserver variability in PTT was 0.35 ± 0.39 second at rest and 0.37 ± 0.48 second during exercise.

Variability Between Studies

Radionuclide measurements of left ventricular function on day 1 and day 3 are listed for the 10 normal subjects at rest in table 1 and during exercise in table 2; mean values are summarized in table 3. Changes in these measurements from day 1 to day 3 are plotted at rest and during submaximal exercise in figures 3–6.

The mean resting HR was significantly faster on day 1 than on day 3 (79 ± 17 vs 71 ± 14 beats/min, p < 0.01). A significant difference was also observed between the two resting studies in EF (62 ± 7 vs 59 ± 7%, p < 0.05), CO (7.7 ± 1.9 vs 6.6 ± 1.5 l/min, p < 0.02) and PTT (5.8 ± 1.6 vs 6.2 ± 1.3 seconds, p < 0.05). No significant difference between studies occurred in EDV, ESV, SV or PBV.

The variability in resting EF was 4.0 ± 3.8%. Four subjects had a decrease in EF of 5% or more from day 1 to day 3, and in three, the HR decreased by at least 14 beats/min. The largest change occurred in subject 8, whose initial resting EF was 70% at a HR of 98 beats/min, which decreased to 57% at a HR of 72 beats/min during the subsequent study. The correlation coefficient between resting EF and HR was 0.73. The volume measurements were influenced less by

FIGURE 3. Variability in ejection fraction between studies. The regression equation (y), correlation coefficient (r), mean variability (D) and probability of significant difference (p) from day 1 to day 3 are given at rest and during exercise. Lines of identity are drawn.
HR, EDV varied 9.9 ± 5.1 ml between studies, and the largest difference was only 24 ml. Because SV did not change significantly from day 1 to day 3, the decrease in CO reflected the decrease in HR. The variability in CO was 1.24 ± 1.23 l/min, and the largest difference (3.9 l/min) again occurred in subject 8, whose HR decreased by 26 beats/min from day 1 to day 3.

Less variation in HR occurred during exercise to the same work load, and no significant difference occurred in any radionuclide measurements except PTT and PBV from day 1 to day 3. The variability in EF between studies was 3.2 ± 2.5% and in EDV 9.8 ± 6.2 ml. The largest difference in EF was 8% in subject 9, who had the highest EF during exercise. No change in EDV greater than 25 ml was noted from day 1 to day 3. The variation in CO during exercise was also small (1.59 ± 0.67 l/min). The largest difference (2.3 l/min)
FIGURE 4. Variability in end-diastolic volume between studies.

FIGURE 5. Variability in cardiac output between studies.

FIGURE 6. Variability in pulmonary transit time between studies.

occurred in subject 5, a former Olympic swimmer who had the highest CO during exercise.

Despite the significant difference in PTT during exercise from day 1 to day 3, the variability between studies was only $0.25 \pm 0.25$ second. Individual variations in PBV tended to be large, reflecting in part the derived nature of its measurement.

Discussion

In this investigation we determined the intrinsic variability of radionuclide measurements of left ventricular function at rest and during exercise. Normal subjects were selected so that changes in clinical status would not contribute to any differences in measurements between studies. The results provide a frame of reference for interpreting serial studies in patients with cardiac disease.

The interobserver variability in the analysis of the same radionuclide angiogram was very small, indicating that significant error was not introduced by having different technicians perform the data processing. The comparison was limited to EF, EDV and PTT, because all other radionuclide measurements were derived from these three measurements and HR. Because technicians with various levels of experience were randomly involved in the data processing, no systematic bias was introduced by having the same technician always analyze the first or second study.

The interobserver variability in EF was $2.1 \pm 1.0\%$ at rest. In contrast, Cohn et al. reported an average difference of $5\%$ using contrast ventriculography. The radionuclide method of determining EF is free from geometric constraints and consequently does not depend upon volume analysis. The interobserver variability in EDV was only $7.5 \pm 4.7$ ml, a value considerably better than that reported in studies using contrast ventriculography. Because the end-diastolic perimeter and aortic valve plane are derived by automated techniques with radionuclide angiography, the potential human error introduced by drawing the angiographic silhouettes by hand, especially when the cine resolution is not optimal, is circumvented. The relatively low interobserver variability in deriving radionuclide measurements of left ventricular function permits sequential studies to be processed by different technicians.

Several factors besides methodologic errors inherent in the technique may contribute to changes in radionuclide measurements on sequential assessment. These include interobserver differences, alterations in clinical status and biologic variations. The interobserver variability is small, and its effect was further reduced in this study by averaging the values from the two technicians. By studying only normal subjects, the possibility of a change in clinical status was excluded. However, the group did have a significant decrease in resting HR from day 1 to day 3. This biologic variability was probably related to greater familiarity with the procedure at the second study. HR fluctuated less during exercise when the subjects achieved the same work load on both occasions.

The three measurements that were most influenced by HR in this study were EF, CO and PTT; volume measurements were less affected by variations in HR. No significant difference between studies occurred in EDV, ESV and SV at rest and during exercise. In the three subjects in whom the resting HR decreased more than 13 beats/min from day 1 to day 3, the EF also decreased $5\%$ or more. In subjects whose resting HR changed by less than 9 beats/min between the studies, the absolute difference in EF was $5\%$ or less. These findings indicate that changes in EF from one study to another may reflect different hemodynamic states as well as different clinical conditions. Consequently, HR must be considered when comparing the effect of medical or surgical interventions on EF.
The variability in EF between studies was 4.0 ± 3.8% at rest and 3.2 ± 2.5% during exercise. Therefore, at 95% confidence levels, repeat EF determinations should not vary by more than 8% at rest and 5% during exercise in normal subjects. A difference in EDV of at least 20 ml between studies would be required for the change to be considered meaningful. A similar variability in EF of 4.4 ± 3.6% was reported by Marshall and associates\textsuperscript{13} in 20 patients with cardiac disease who had three resting radionuclide angiocardiograms separated by an average of 4.3 days. Although no systematic difference in HR and blood pressure occurred between studies in their investigation, subtle changes in physiologic status may have contributed to the occasional large variations in EF in individual patients.

The results of this investigation compare favorably with those of studies of the reproducibility of measurements made by contrast ventriculography. McAnulty et al.\textsuperscript{14} showed variabilities between studies in EF and EDV of 4 ± 10% and 4.9 ± 19.1 ml, respectively, in 14 patients who had contrast ventriculograms performed on successive days. Cohn et al.\textsuperscript{11} reported that the variability in these measurements depended upon the time separating the two studies. In 10 patients who had a repeat contrast ventriculogram within 90 minutes of the initial one, the average difference in EF was 4%, but when the interval between the studies was greater than 24 hours (2–4 days), the average difference in five patients was 13%. Patients exhibiting large variations in EF between the two studies also had wide fluctuations in HR, blood pressure or degree of asynery.

Radionuclide angiocardiography can be used to assess left ventricular function serially with a low intrinsic variability, and different technicians can perform the data processing of sequential studies without introducing substantial or systematic error. Therefore, this noninvasive technique should be ideal for following the natural course of heart disease and evaluating the effects of medical and surgical interventions. However, biologic variabilities such as HR and blood pressure may directly influence EF, CO and PTT measurements, and sequential studies should be obtained under comparable hemodynamic conditions whenever possible.

References
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