Radionuclide Measurement of Left Ventricular Volume: Comparison of Geometric and Counts-based Methods

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SUMMARY Radionuclide measurements of left ventricular volume were determined in 20 patients by geometric and nongeometric, counts-based techniques using data from first-pass and equilibrium blood pool scintigraphy. Two geometric analytic approaches were used: directly measured long and short axes and the area-length method. Each approach was applied to the single-plane right anterior oblique images obtained by the first-pass technique and to biplane data, using the right anterior oblique first-pass and left anterior oblique blood pool data together. For the nongeometric determinations, background-corrected left ventricular counts were related to blood counts. This ratio was converted to volume by means of a linear regression relationship with angiographic volumes.

All methods yielded high correlation coefficients ($r \geq 0.93$), but the standard errors of the estimates for the geometric techniques were high, and therefore the 95% confidence limits were wide. The use of biplane data improved the correlations, but area-length analysis of digitized data was no better than direct measurement of short axes from the analog images. The counts-based, nongeometric method provided the highest correlation and lowest standard error. These findings indicate that nongeometric left ventricular volume measurements using equilibrium blood pool scintigrams are the most accurate radionuclide technique. This approach also permits multiple determinations with a single dose of radiotracer.

RADIONUCLIDE ANGIOGRAPHY is an important clinical tool for the noninvasive evaluation of cardiac function and size. Although attention has been focused predominantly on measurements of left ventricular function, such as the ejection fraction, the ability to accurately quantitate ventricular size is a well-recognized goal. In early research and clinical studies, ventricular volumes were determined by applying the same measurements and geometric assumptions used in contrast ventriculography.1-4 More recently, radionuclide methods that use a nongeometric, counts-based technique have been proposed.5-7 Theoretical considerations favor this approach,4 but experience with it is limited. The present study was designed to evaluate simultaneously several geometric methods and a nongeometric, counts-based method in a group of patients to determine which is most accurate.

Methods

Patients

The study population consisted of 20 adult males who were in normal sinus rhythm and who underwent radionuclide angiography within 48 hours of cardiac catheterization. Subjects with irregular heart rhythms at the time of scintigraphy, excessive ventricular ectopy during contrast angiography, or significant differences in heart rate or arterial pressure between the two studies and those pretreated with nitroglycerin before angiography were excluded. The patients' medical regimens or clinical status were not altered between the tests.

Fifteen patients had coronary artery disease, including two with left ventricular aneurysms, five with segmental asynergy and eight with normal wall motion. The remaining five patients had valvular disease, including three with aortic regurgitation, one with aortic stenosis, and one with mitral regurgitation.

Left Ventricular Angiography

Cardiac catheterization was performed by the percutaneous femoral approach after 10 mg of oral diazepam premedication. Left ventriculography was performed before other contrast injections, with a #8F pigtail catheter, using Isoopaque 440 contrast. Single-plane, 30° right anterior oblique angiograms were obtained. Left ventricular end-diastolic and end-systolic outlines were drawn from the first fully opacified beat not preceded by a premature complex by an observer unaware of the radionuclide findings. The volumes were calculated by the area-length method using a standardized grid.8

Radionuclide Angiography

The radionuclide studies were performed with a single-crystal gamma scintillation camera (Ohio Nuclear Series 400) equipped with a medium-sensitivity, parallel-hole collimator. First-pass radionuclide angiography was performed in the 30° right anterior oblique projection after 20 mCi of technetium-99m sodium pertechnetate were injected.9 A Polaroid photograph was taken during the 3–5 seconds of the left ventricular phase of the first transit of activity. Data were also acquired in frame mode into a 64 × 64
pixel matrix on a dedicated nuclear medicine computer system (Gamma 11, Digital Equipment Corporation) and subsequently reformatted to create composite end-diastolic and end-systolic frames that included four to six cycles each. A picture was then taken of a calibrated reference grid.

After in vivo red cell labeling,11 equilibrium blood pool scintigraphy was then performed with minor modifications of published methods.12 The left anterior oblique projection that provided the best separation between the right and left ventricles (usually 45°), with an additional 10° caudal angulation was used. Eleven 64 × 64 pixel frames were obtained over the initial 55% of the cardiac cycle (the equivalent of 20 frames per RR cycle). Acquisition was continued for 10 minutes, providing 200,000–400,000 counts per frame. A 4-ml blood sample was drawn midway through the acquisition period, and soon after the completion of the blood pool scintigram, it was placed 18 inches from the camera head and counted for 2 minutes.

Radionuclide Determination of Volume: Geometric Methods

Table 1 is a summary of the two geometric methods. Both methods were applied to right anterior oblique ventricular outlines from the first-pass study for the single-plane analyses and to the first-pass right anterior oblique and equilibrium left anterior oblique findings together for the biplane analyses.

Method 1, described by Sullivan et al.,1 used a direct measurement of the long and short axes from the Polaroid pictures taken during the left ventricular phase of the first transit. These were assumed to reflect the end-diastolic silhouette of the ventricle. End-diastolic volume was calculated from the major and minor axes by the method of Greene et al.13 End-systolic volume was calculated from this end-diastolic volume and the first-pass ejection fraction, which was obtained from the time-activity curve in the standard manner.10 In method 2, biplane volumes from the directly measured axes were determined by using an additional minor axis from the left anterior oblique positioning picture.

For method 3, area-length analysis was used with the computer-generated end-diastolic and end-systolic composite images from the first-pass right anterior oblique radionuclide angiograms. Biplane volumes were then determined by the area-length technique to calculate a second minor axis from the end-diastolic and end-systolic frames of the left anterior oblique equilibrium study (method 4). The reference grid was used to determine the dimensions of the digitized display matrix.

Radionuclide Determination of Volume: Counts-based Method

The fifth method of volume analysis was a modification of the nongeometric, counts-based techniques described by Dehmer et al.7 and Slutsky et al.8 In this approach, the left ventricular activity was related to blood activity to provide a measurement of volume, which was then converted to milliliters by regression analysis with contrast angiography. The background-corrected left ventricular activity in the end-diastolic and end-systolic frames (\(A_{LV/frame}\) in counts) was determined using manually defined end-diastolic and end-systolic regions of interest and an inferoposterior paraventricular region for background determination. Left ventricular activity per minute of counting (\(A_{LV/min}\) in counts/min) was then determined by dividing \(A_{LV/frame}\) by the number of acquired cycles (C) and frame duration (T-frame minutes):

\[
A_{LV/min} (\text{counts/min}) = \frac{A_{LV/frame}}{C \times T_{\text{frame}}} \quad (1)
\]

Nuclear counts per milliliter of blood were then determined by counting a 4-ml blood sample drawn midway through scintigraphy at a distance of 18 inches from the collimator and correcting for background activity in the field. Blood activity (\(A_{\text{blood-cor}}\) in counts/min) at the time of scintigraphy was then back-calculated from the blood activity at the time of counting (\(A_{\text{blood}}\)), knowing the transpired time (T) and the decay rate of technetium-99m:

\[
A_{\text{blood-cor}} (\text{counts/min}) = A_{\text{blood}} \times e^{-0.001925T} \quad (2)
\]

Finally, a ratio of left ventricular activity to blood activity was determined that is theoretically proportional to ventricular volume:

\[
\text{Ratio (nuclear units)} = \frac{A_{LV/min}}{A_{\text{blood-cor}}} \quad (3)
\]

Data Analysis

The end-diastolic and end-systolic volumes, as well as both taken together, were correlated with the contrast angiographic volume using linear regression analysis. The correlation coefficients, standard errors of the estimate, and 95% confidence limits for the

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Abbreviations: RAO = right anterior oblique; LAO = left anterior oblique; ESV = end-systolic volume; EDV = end-diastolic volume; EF = ejection fraction.
points were determined. The statistical significance of differences in correlation coefficients was examined by standard methods, and the significance of the differences in the standard errors was examined by Bartlett's test for comparison of homogeneous variances.14

Results
Each method yielded a high correlation coefficient for the relationship between radionuclide and contrast angiographic volumes (table 2). This high correlation was in large part due to the wide range of heart sizes, which varied from 104–544 ml at end-diastole and 12–316 ml at end-systole. In fact, for several of the methods, the scatter in the middle range was considerable and was reflected by the relatively high standard errors of the estimate.

Geometric Volume Methods
The first method examined was that using directly measured long and short axes from the Polaroid picture of the right anterior oblique first-pass left ventricular phase to calculate end-diastolic volume (fig. 1A). End-systolic volume was then calculated using the first-pass ejection fraction. Despite the high correlation coefficient \( r = 0.95 \) for end-systolic and end-diastolic volumes together; \( r = 0.93 \) for end-diastolic and \( r = 0.94 \) end-systolic volume), the standard error was high (29 ml for end-diastolic and end-systolic volumes together). Therefore, the 95% confidence limits for the contrast angiographic volume of a patient with a nuclear volume of 150 ml ranged from 95–240 ml.

The closeness of fit was considerably improved by measuring a second short axis from the left anterior oblique Polaroid positioning picture (method 2, fig. 1B). Although the correlation coefficient was similar using the biplane data \( r = 0.96 \) for the two volumes together), the standard error was smaller (25 ml instead of 29 ml) and the 95% confidence limits were narrower.

The third geometric method, the single-plane area-length analysis, provided correlation coefficients and standard errors comparable to those obtained by directly measuring the long and short axes (fig. 2A). The total counts in the composite end-diastolic region of interest for four to six cycles evaluated ranged from 3500–6000. Therefore, drawing the left ventricular outlines was difficult.

When the biplane data were subjected to area-length analysis (method 4), using the end-diastolic and end-systolic frames from the left anterior oblique blood pool study, the correlation was again slightly higher \( r = 0.96 \); see = 26 ml for end-diastolic and end-systolic volumes together; fig. 2B). However, the area-length and directly measured axes methods were not appreciably different.

Counts-based Nongeometric Method
Figure 3 illustrates the relationship between left ventricular volume (in nuclear units) and contrast angiographic volume using the counts-based method (method 5). The correlation coefficients for end-diastolic and end-systolic volumes together and for the two individually (all \( r = 0.98 \) are each higher than for the geometric methods, although these differences do not achieve statistical significance \( p < 0.12 \). The standard errors, when converting from nuclear units to milliliters using the regression relationship, are all lower as well (18 ml for the end-diastolic and end-systolic volumes together, 21 ml for end-diastolic volume and 17 ml for end-systolic volume; the smaller variance with the counts-based method was statistically significant \( p < 0.05 \)). Most impressively, and most important clinically, the 95% confidence limits of contrast angiographic volume for a patient with 40-unit nuclear volume (equivalent to 150 ml using the regression equation) range only from 120–185 ml. The relationship appears to remain linear over the entire range of nuclear volumes.

Interobserver and Intraobserver Variability
Interobserver and intraobserver variability were assessed for the counts-based method. One observer analyzed all 20 studies twice at intervals of 3–6 months, achieving an average difference in volume measurements of 5% (3% for end-diastolic volumes and 6% for end-systolic volumes). When two observers independently analyzed the studies, their calculations differed by a mean 6% (4% at end-diastole, 7% at end-systole).

Discussion
Background
Although measurements of left ventricular function are important in the evaluation and follow-up of patients with cardiac disease, several recent developments have emphasized the added value of

| Table 2. Comparison of Findings with Various Methods in Relation to Contrast Angiography |
|-------------------------------|-------------------|-------------------|-------------------|
|                               | EDV               | ESV               | Combined          |
|                               | \( r \) \( \text{SEE} \) (ml) | \( r \) \( \text{SEE} \) | \( r \) \( \text{SEE} \) | Range for 150 ml nuclear volume* |
| Measured axes-RAO             | 0.93  32          | 0.94  23          | 0.95  29          | 95–240                           |
| Measured axes-biplane         | 0.96  25          | 0.96  21          | 0.96  25          | 115–225                          |
| Area-length–RAO              | 0.94  29          | 0.94  24          | 0.95  29          | 80–220                           |
| Area-length–biplane          | 0.95  27          | 0.95  21          | 0.96  26          | 90–220                           |
| Counts-based                 | 0.98  21          | 0.98  17          | 0.98  18          | 120–185                          |

*95% confidence limits of angiographic volumes from regression analysis.
Abbreviations: RAO = right anterior oblique; ESV = end-systolic volume; EDV = end-diastolic volume.
measurements of left ventricular size.\textsuperscript{16} Until recently, studies that require left ventricular volume measurements have entailed contrast angiography, a procedure that exposes the patient to some risk, allows only a limited number of determinations, and may itself affect left ventricular volume. Echocardiography has been used for this purpose, but it has severe limitations in many patients with ischemic heart disease.\textsuperscript{16, 17}

Radionuclide angiography has made the noninvasive measurement of left ventricular volume more feasible. Several groups have reported their findings with this technique in relationship to cardiac catheterization.\textsuperscript{1-7} and more studies have used this method. Two general approaches have been used:

**FIGURE 1.** (A) Regression line and 95% confidence limits for points of relationship between radionuclide volume measurement (Vol-N) and contrast angiographic volumes (Vol-A). Scintigraphic volumes were determined from directly measured long and short axes from right anterior oblique first-pass images. (B) Scintigraphic volumes were determined from directly measured long and short axes from the right anterior oblique first-pass images and from a second short axis measured from the positioning film of the left anterior oblique equilibrium study. LGV = left ventricular gradient; EDV = end-diastolic volume; ESV = end-systolic volume.

**FIGURE 2.** Scintigraphic volumes determined from the single-plane area-length analysis of the digitized, composite end-diastolic and end-systolic images of the right anterior oblique first-pass study. Format is the same as that in figure 1. (B) Scintigraphic volumes determined from the biplane area-length analysis of the end-diastolic and end-systolic images from the first-pass and equilibrium studies. LGV = left ventricular gradient; EDV = end-diastolic volume; ESV = end-systolic volume.

generic and counts-based, nongeometric methods.

In theory, a nongeometric method should have several advantages over a geometric one. A geometric technique requires spatial or temporal separation of the left ventricle from other cardiac chambers. In the right anterior oblique projection, which is optimal for evaluating the left ventricle since it is perpendicular to the plane of its long axis, this can only be accomplished during first-pass studies. These suffer from relatively low count density or suboptimal spatial resolution, even if a multicrystal camera is used. The first-pass technique also does not lend itself to serial studies because of the required doses of radiopharmaceutical. Equilibrium blood pool scintigraphy, which yields high-resolution, high-data density studies, only visualizes the left ventricle without right ventricular superimposition in the left anterior oblique projection, which by itself is not well suited for
geometric volume analysis. Even if left ventricular geometry is accurately characterized by these radionuclide techniques, volume analysis generally still depends on the use of the prolate ellipse model, which is at best an approximation and may be invalid in patients with ventricles of unusual shapes.

In contrast, the counts-based method uses the inherent advantages of the scintigraphic approach. It does not depend on geometric models. It does not depend on precise spatial resolution and does not require the right anterior oblique projection. Finally, it is well suited for serial studies, which allow the evaluation of the effects of interventions. However, factors such as background, tissue attenuation, and self-attenuation of activity within the blood pool either have to produce negligible effects or have a constant predictable effect in order for nuclear volumes to correlate closely with contrast angiographic volumes. Previously published studies have suggested that this is so. 8, 7

Findings of the Present Study

Although both the geometric and counts-based methods have high correlations with contrast angiography, the latter correlation was considerably closer. This was best reflected by the lower standard errors, indicative of significantly smaller variances, with the nongeometric method and the correspondingly narrower 95% confidence limits (figs. 1–3, table 2).

There was no significant difference between the two geometric approaches — the directly measured axes and the area-length calculation. This might seem surprising in view of the rather crude methods for measuring the axes which we used and the widely accepted advantage of calculating a short axis rather than measuring it. However, it was extremely difficult to outline the left ventricle from the right anterior oblique digitized images. This was probably why we could not show an advantage with the area-length technique. The biplane data improved the correlation with both geometric methods. Method 2, which uses directly measured long and short axes from both scintigraphic projections, offers a simple and relatively accurate method for the gross estimation of volumes.

The first-pass studies were performed with a single-crystal camera equipped with a medium-sensitivity collimator. While most nuclear medicine departments use similar equipment for these studies, a high-count-rate multicyrystal camera or a high-sensitivity collimator may have improved our geometric analysis. The biplane geometric correlations may also have been higher if truly orthogonal views had been used and if the small amount of caudal angulation had not been used.

Our findings with the counts-based method are remarkably similar to those of others. The correlation was high and the standard error low. Most important, the 95% confidence limits of the measurements were narrow enough to permit reliable discrimination between patients with small, normal and enlarged ventricles. Our theoretical concerns did not invalidate the correlation with contrast angiographic volumes. In part, this resulted from a consistent approach to the drawing of both background and left ventricular regions of interest. As a result, a single observer could achieve reproducible results. There was also close agreement between observers. Automated programs for drawing left ventricular outlines will further facilitate the achievement of such consistency. Our patients were all adult men; thus, tissue attenuation was a relatively constant factor. Although our findings cannot be extended to women and children, in whom more variable tissue attenuation could be expected, other workers have validated the counts-based approach in more heterogeneous populations. 6, 7 Self-attenuation within the blood pool appears not to be important; we found no tendency to underestimate volume with the nuclear technique in large ventricles. Our findings in this regard agree with those in some previous reports, 6, 7 but not with others. 18

Volumes were determined angiographically by single-plane techniques. This may not be an ideal gold standard, particularly in patients with severe asynergy. 19 However, the seven patients with wall motion abnormalities did not consistently provide the outlying points with any nuclear method and the correlations were similar at end-diastole and end-systole, suggesting the acceptability of using single-plane angiography for comparison.

Implications

Our findings indicate that the most accurate radionuclide approach to measuring left ventricular volume is a counts-based, nongeometric method based on equilibrium blood pool scintigraphy. Despite the high correlations achieved with the geometric methods, the scatter of data is such that it is difficult to apply them to many clinical and research situations. In addition, the counts-based method is reproducible and adds little further processing time to the usual analysis of blood pool scintigrams. Finally, equilibrium blood pool scintigraphy can be repeated without additional
radiation exposure, allowing the study of interventions such as exercise and drug administration.

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