Use of Equilibrium (Gated) Radionuclide Ventriculography to Quantitate Left Ventricular Output in Patients With and Without Left-sided Valvular Regurgitation

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SUMMARY We examined the accuracy with which left ventricular output can be estimated by equilibrium radionuclide ventriculography. After red blood cells were labeled in vivo, we measured left ventricular end-diastolic and end-systolic count rates and the count rate in 5 ml of the patient's blood. After estimating the average ratio of counting efficiency for the left ventricle to counting efficiency for the blood sample (E_{LV}/E_s) in six patients, we calculated left ventricular output in 26 other patients as (left ventricular activity ejected per minute divided by activity per liter of blood) divided by the previously estimated E_{LV}/E_s. Radionuclide left ventricular output closely approximated Fick cardiac output (r = 0.94) in patients without mitral or aortic regurgitation and exceeded Fick cardiac output in all patients with valvular regurgitation. Regurgitant fraction, calculated as the difference between the radionuclide and Fick outputs divided by the radionuclide output, correlated with the severity of regurgitation as assessed angiographically. The equilibrium radionuclide ventriculogram is an excellent means for noninvasive estimation of left ventricular output.

AN ACCURATE, noninvasive method for calculating left ventricular output would be a valuable addition to cardiac evaluation, particularly for sequentially monitoring the efficacy of therapy in patients with congestive heart failure. First-pass radionuclide angiography has been used to estimate forward cardiac output, but measurements cannot be rapidly repeated, for the radioactive tracer must be largely cleared from the body before the examination can be repeated. For all standard radionuclide studies, at least 24 hours are needed for adequate decay. Recently developed two-dimensional echocardiographic techniques have been used to estimate left ventricular volumes and outputs. However, these methods cannot be applied to every patient, and they are subject to errors imposed by geometric assumptions.

Using a variation of recently described techniques for measuring left ventricular volume that involve comparison of the left ventricular activity with the activity in a sample of the patient's blood, we calculated radionuclide left ventricular minute outputs in patients with and without left-sided regurgitant lesions. To calculate left ventricular output in liters per minute, one must estimate the ratio of counting efficiency for counts within the left ventricle (E_{LV}) to the counting efficiency for counts within the blood sample (E_s). The degree of variability in E_{LV} from patient to patient affects the accuracy with which absolute left ventricular output can be estimated, although it should not influence the detection of changes in left ventricular output in an individual patient. We estimated the average E_{LV}/E_s using combined radionuclide and catheterization data in six patients, and then applied this estimate of E_{LV}/E_s to calculate radionuclide left ventricular output in 26 other patients, 16 without mitral or aortic regurgitation and 10 with valvular regurgitation. We compared our results with Fick cardiac output, thereby testing the interpatient variability in E_{LV} and assessing the accuracy with which left ventricular output can be estimated by equilibrium radionuclide ventriculography.

Methods

Subjects

We studied 32 patients (22 men and 10 women), ages 30–78 years, who were referred for routine diagnostic cardiac catheterization. The study group comprised patients referred for radionuclide ventriculography and patients selected because of valvular regurgitation. The primary diagnosis was valvular heart disease in 17 patients, coronary artery disease in nine, cardiomyopathy in two and primary pulmonary arterial hypertension in one patient. One patient had a previously repaired ostium secundum atrial septal defect and had no residual shunt by oximetry. Two patients had suspected coronary artery disease but had normal cardiac catheterizations. Each patient underwent radionuclide examination within 2 days of cardiac catheterization.

Twenty-two patients (group 1) had no clinical evidence of left-sided valvular regurgitation. Sixteen group 1 patients underwent contrast left ventriculography and none had evidence of mitral regurgitation. Ten patients (group 2) had typical findings of aortic or mitral regurgitation; regurgitation was confirmed in all 10 at cardiac catheterization. In eight group 2 patients, mitral regurgitation was documented by contrast left ventriculography, and in six group 2 patients, including four with mitral regurgitation, aortic regur-
gitation was documented by contrast aortography. In one of the eight group 2 patients with mitral regurgitation, aortography was not performed, but aortic regurgitation was diagnosed on the basis of typical findings on physical examination and echocardiography. Thus, 22 patients had no evidence of aortic or mitral regurgitation, three had evidence of mitral but not aortic regurgitation, two had evidence of aortic but not mitral regurgitation and five had evidence of both mitral and aortic regurgitation.

Radionuclide Studies

Red blood cells were labeled in vivo by intravenously injecting unlabeled stannous pyrophosphate (5 mg Pyrolite, New England Nuclear), followed 15–20 minutes later by 15–25 mCi of technetium-99m ($^{99mTc}$) as pertechnetate.11

Gated radionuclide ventriculograms were obtained with an Anger scintillation camera and a high-sensitivity, straight-bore, 30°, slant-hole collimator (Engineering Dynamics) as described elsewhere.12 Five minutes after injection of the radionuclide, the camera was positioned in the modified left anterior oblique projection (30° caudal tilt). Ten million counts were acquired in matrix mode, using a matrix size of $64 \times 64$ elements. Data were acquired on magnetic disk using a standard digital computer and nuclear medicine software (PDP 11/34 and Gamma-11 system, Digital Equipment), with a 15% window centered on the $^{99mTc}$ photopeak.

Data acquisition was physiologically gated to the patient's ECG. The cardiac cycle was divided into 25-msec frames, with data acquisition triggered by the patient's R wave. Patients with more than 15% ventricular premature complexes were excluded. Patients with atrial fibrillation whose heart rates were controlled pharmacologically were included.

Data Analysis

Radionuclide data were analyzed without knowledge of catheterization results. The end-diastolic left ventricular perimeter was drawn manually, and the left ventricular background regions were defined automatically using a computer algorithm that we have described previously.13

The left ventricular background per cell was estimated as the mean counts per cell in three background regions calculated from the end-systolic frame. This background value was then subtracted from each cell of the end-diastolic and end-systolic frames.

An ejection fraction image was constructed as described previously.13 This image was used to redraw the left ventricular region, if necessary, and permitted calculation of the left ventricular end-diastolic and end-systolic counts. The number of seconds represented by each frame was calculated as the total number of cardiac cycles incorporated into the study multiplied by 0.025 second (because the duration of each frame was 25 msec). The left ventricular end-diastolic activity and end-systolic activity, in counts per second, were then calculated by the formulas: end-diastolic activity = end-diastolic counts/sec per frame; end-systolic activity = end-systolic counts/sec per frame. Stroke volume activity (counts/sec ejected per cardiac cycle) was then calculated as stroke volume activity = end-diastolic activity − end-systolic activity.

To obtain an index of activity per milliliter of blood, 5 ml of blood were drawn from the patient into a heparinized syringe at the midpoint of the radionuclide ventriculogram acquisition. After completion of data acquisition, the patient left the imaging room. Room background was counted for 5 minutes using the same Anger camera and collimator as were used for patient imaging, after which the syringe of blood was placed on the collimator face so that the counts projected at the center of the imaging field. The syringe content was counted for 5 minutes, after which the syringe was removed, and a repeat 5-minute background count was performed. Activity per ml of blood was calculated as $[(5$-minute syringe count$/300) − \text{background activity}] / d \times 5 \text{ ml}$, where background activity = the average counts per second derived from the two background counts, and d is the factor needed to account for the $^{99mTc}$ decay that occurred between the midpoint of the angiocardiogram acquisition and the midpoint of the blood sample count, based on a physical half-life of 6.04 hours.

Left Ventricular Stroke Volume and Output

If stroke volume activity and activity per milliliter of blood, as measured above, represented the true stroke volume activity and the true activity per milliliter of blood respectively, the stroke volume could be calculated as true stroke volume activity/true activity per milliliter of blood. However, measured left ventricular activity and measured activity per milliliter of blood are actually less than the true values and depend on $E_{LV}$ and $E_s$, respectively: measured left ventricular activity = true left ventricular activity $\times E_{LV}$, where $E_{LV} < 1$; and measured activity per ml of blood = true activity per ml of blood $\times E_s$, where $E_s < 1$. Therefore, if $E_{LV}/E_s$ is known, stroke volume (ml) can be calculated as true stroke volume activity/true activity per ml of blood = (measured stroke volume activity/measured activity per ml of blood) $\times (E_{LV}/E_s)$ and left ventricular output (ml/min) can be calculated as (measured stroke volume activity/measured activity per ml of blood) $\times$ heart rate (min$^{-1}$) $\times (E_{LV}/E_s)$.

$E_{LV}$ and $E_s$ depend on imaging geometry, absorption of photons by the thorax and chest wall or by the syringe and by the collimator, the efficiency of absorption of photons by the scintillation crystal, and the intrinsic electronic efficiency of the Anger camera. The $E_s$ is constant because the blood sample is measured identically from patient to patient. Therefore, the variability in $E_{LV}$ from patient to patient influences the accuracy with which left ventricular stroke volume and left ventricular minute output can be estimated.

In patients without mitral or aortic regurgitation,
E_{LV}/E_{S} was estimated by combining radionuclide and catheterization data:

\[
\frac{\text{measured stroke volume activity}}{\text{measured activity per ml of blood}} \times \frac{\text{HR}}{E_{LV}/E_{S}}
\]

where HR = heart rate during radionuclide ventriculography. To prospectively evaluate the accuracy of radionuclide left ventricular output measurement, we calculated the average E_{LV}/E_{S} in the first six patients without valvular regurgitation and then applied this value to calculate radionuclide left ventricular output in the remaining 26 patients:

\[
\frac{\text{measured stroke volume activity}}{\text{measured activity per ml of blood}} \times \frac{\text{HR}}{E_{LV}/E_{S}}
\]

We correlated radionuclide left ventricular output with Fick cardiac output in 16 patients without valvular regurgitation (excluding the first six patients in whom E_{LV}/E_{S} was estimated) using standard linear regression analysis.

Left ventricular regurgitant fraction was calculated as (radionuclide left ventricular output − Fick output)/radionuclide left ventricular output. Regurgitant fractions were compared in patients with and without valvular regurgitation using the t test.

The reproducibility of the left ventricular output measurement was tested in 14 additional patients. In eight patients, the radionuclide ventriculogram was repeated 10 minutes after completion of the first study, after repositioning the camera, without injecting additional radiotracer. In six patients, the study was repeated 24 hours later, after administering additional stannous pyrophosphate and 99mTc in a manner identical to that used during the first study. For both the 10-minute and 24-hour studies, the activity in a second blood sample, drawn during the repeat study, was measured, and the left ventricular region of interest was redrawn. Left ventricular output measurements from the two studies were compared by standard linear regression analysis.

Catheterization

Cardiac catheterization was performed when the patients were in the resting, postabsorptive state. Oxygen content was measured (reflection oximetry, American Optical) in 5-ml systemic arterial (SA) and central pulmonary arterial (PA) blood samples drawn simultaneously during a 3-minute collection of the patient's expired air, permitting calculation of cardiac output by the formula:

\[
\text{oxygen consumption per minute/(SA oxygen content - PA oxygen content)}
\]

Left-to-right shunts were excluded in all patients by oximetry.

The presence of mitral regurgitation was determined from a right anterior oblique contrast left ventriculogram, examining only sinus beats. Care was taken to position the catheter to avoid artificial mitral regurgitation. The presence of aortic regurgitation was assessed by right anterior oblique or left anterior oblique cineaortography. Mitral and aortic regurgitation were each graded from 1+ to 4+. Total regurgitant grade, calculated as the sum of the grades of mitral and aortic regurgitation, was compared with the regurgitant fraction in group 2 patients.

Results

Hemodynamic data are provided in table 1. The E_{LV}/E_{S} ratios were estimated using equation 1 in all 22 patients without mitral or aortic regurgitation (table 2). For the first six patients, the mean estimated E_{LV}/E_{S} was 0.218 ± 0.039 (± sd). For all 22 patients, the mean estimated E_{LV}/E_{S} was 0.212 ± 0.031.

The estimated E_{LV}/E_{S} derived from the first six patients (0.218) was applied to calculate the radionuclide left ventricular outputs in the remaining 26 patients (including those with mitral or aortic regurgitation), using equation 2 (table 2). In patients without valvular regurgitation, radionuclide left ventricular output correlated strongly with Fick output (r = 0.94; S_{yx} = 0.58 l/min) (fig. 1). As expected, in all 10 patients with mitral or aortic regurgitation, radionuclide left ventricular output exceeded Fick output (fig. 2).

Reproducibility of the radionuclide left ventricular output measurement, tested in 14 additional patients (eight after 10 minutes and six after 24 hours), is shown in figure 4 (r = 0.98).

Discussion

An ideal method for calculating left ventricular output is one that is noninvasive, accurate, and permits multiple rapidly repeated measurements. Such a method is of great clinical value, particularly for sequentially evaluating the acute and chronic efficacy of pharmacologic therapy in congestive heart failure, in which a reduction in cardiac output is a major cause of incapacity and where improvement in cardiac output is a major therapeutic goal.

Changes in left ventricular count rate that occur during the cardiac cycle, as detected by equilibrium radionuclide ventriculography in animals, correlate well with changes in left ventricular volume. Sorenson et al. showed that a change with exercise in the left ventricular counts ejected per minute accurately reflected a change in the Fick cardiac output when the two sets of measurements were taken several minutes apart. Because the intravascular tracer concentration was not measured, absolute left ventricular output could not be calculated, and left ventricular output...
could not be compared in different patients or on different days in the same patient. Because our measurement is an index of absolute left ventricular output, it may be used to compare different patients or to sequentially monitor patient progress and therapeutic efficacy over any time interval.

Cardiac output has been estimated from first-pass radionuclide angiography using a variation of the indicator-dilution technique. By this method, the count rate is monitored over a region of interest in the heart (or any portion of the vascular pool) after i.v. injection of a radioactive tracer, and cardiac output is calculated as \( K_e \times \text{blood volume}/V \text{dt} \), where \( K \) is the instantaneous count rate detected at time \( t \), and \( K_e \) is the count rate at equilibrium. In addition to the necessity for independent calculation of the total blood volume, several problems are inherent to this method. First, a difference between the blood volume containing counts within the region of interest at equilibrium and during the first pass results in variable overestimation of the cardiac output. A second potential error is introduced by assumptions needed to estimate the expected area under the time–count rate curve in the absence of recirculation.
TABLE 2. Results

<table>
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<tr>
<th>Pt</th>
<th>$E_{LV}/E_S$</th>
<th>Fick CO (l/min)</th>
<th>RNLVO (l/min)</th>
<th>MR</th>
<th>AR</th>
<th>RF</th>
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<td>3.7</td>
<td>0</td>
<td>0</td>
<td>-0.27</td>
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</table>

| Group 2 |
| 23  | —             | 3.3            | 11.3          | 2  | 4  | 0.71 |
| 24  | —             | 3.1            | 7.5           | 3  | *  | 0.59 |
| 25  | —             | 6.1            | 7.9           | 2  | 2  | 0.23 |
| 26  | —             | 4.1            | 4.7           | 0  | 2  | 0.13 |
| 27  | —             | 4.5            | 10.7          | 2  | 3  | 0.58 |
| 28  | —             | 3.8            | 5.0           | 2  | 0  | 0.24 |
| 29  | —             | 4.1            | 5.0           | 1  | 0  | 0.18 |
| 30  | —             | 3.6            | 5.4           | 1  | 3  | 0.33 |
| 31  | —             | 5.2            | 7.0           | 0  | 3  | 0.26 |
| 32  | —             | 3.4            | 4.4           | 2  | 0  | 0.23 |

*Clinically obvious aortic regurgitation, but severity was not angiographically assessed.

Abbreviations: $E_{LV}/E_S$ = estimated ratio between the counting efficiency for the left ventricle and that for the blood sample; CO = cardiac output; RNLVO = radionuclide left ventricular output; MR = angiographic severity of mitral regurgitation (0-4); AR = angiographic severity of aortic regurgitation (0-4); RF = regurgitant fraction calculated from Fick and radionuclide outputs.

The frequency with which repeated measurements may be made using the first-pass technique is limited because the tracer must be largely eliminated from the blood pool before a repeat study. Approximately 1 day is required for 95% decay of $^{99m}$Tc (physical half-life, 6.04 hours). With the equilibrium method, measurements may be repeated frequently for several hours without administration of additional tracer. The equilibrium method is therefore more suited than the first-pass method for assessing the acute effect on left ventricular output of a drug or of an intervention such as exercise.

Because the first-pass method measures forward flow and the equilibrium method measures left ventricular output, the two methods are complementary in patients who have aortic or mitral regurgitation or left-to-right shunts at the ventricular or aortic level. In such patients, a change in left ventricular output may represent a change in forward flow or a change in the degree of regurgitation or shunt.

Estimation of left ventricular output by M-mode echocardiography is severely limited because it is based on the motion of only two points on the endocardial surface.1-8 Output estimation is particularly
susceptible to error in the presence of ventricular asynergy.\textsuperscript{36,32} Two-dimensional echocardiography is potentially superior to M-mode for estimation of ventricular output,\textsuperscript{6,7} but it is limited to examining one cross-sectional slice of the left ventricle at any one moment and therefore poses difficulties in integrating global ventricular function. Further, echocardiographic techniques rely on a geometric analysis of left ventricular volume, which may become invalid with alterations in ventricular configuration. Because the radionuclide method which we used depends on measuring the total count rate within the ventricle, it

![Graph 1](image1.png)

**Figure 1.** Comparison between radionuclide left ventricular (LV) output and Fick cardiac output in 16 patients without evidence of mitral or aortic regurgitation.

![Graph 2](image2.png)

**Figure 2.** Comparison between radionuclide left ventricular (LV) output and Fick cardiac output in 10 patients who had mitral regurgitation (MR) or aortic regurgitation (AR) or both documented by contrast angiography. The regression line derived from non-regurgitant patients (fig. 1) is shown. In every case, radionuclide left ventricular output, reflecting the sum of forward flow and regurgitation, exceeded the Fick output.

![Graph 3](image3.png)

**Figure 3.** Comparison between radionuclide-Fick regurgitant fraction and the total regurgitant grade, calculated as the sum of the angiographic grades of mitral regurgitation (MR) and aortic regurgitation (AR). The regurgitant fractions were significantly higher in patients with regurgitation than in those without regurgitation (p < 0.0001), tended to increase with increasing grades of regurgitation, and were particularly high in patients with both mitral and aortic regurgitation. Patient 24, whose regurgitant fraction was 0.59, had 3+ mitral regurgitation, but was excluded from this figure because of clinical evidence of aortic regurgitation that was not graded angiographically.

![Graph 4](image4.png)

**Figure 4.** Reproducibility of the radionuclide left ventricular (LV) output measurement in 14 patients. The second study was performed 10 minutes (eight patients) or 24 hours (six patients) after completion of the first study.
has the advantages of integrating global function and of being less dependent on geometric assumptions.

Our technique for calculating left ventricular outputs is based on the principles used by Slutsky et al. and by Dehmer et al., who estimated left ventricular volumes using equilibrium radionuclide ventriculography and found excellent correlation with measurements made from contrast ventriculograms. Slutsky et al. found that left ventricular volume was estimated more accurately when left ventricular activity was divided by the simultaneous intravascular activity concentration than when left ventricular activity was merely normalized for the radiotracer dose and body surface area. The inaccuracy of the latter method is likely to result from variability in intravascular volume and in extravascular leakage of the tracer.

In patients who did not have regurgitation, we estimated the \( \frac{E_{LV}}{E_s} \) ratio by applying radionuclide and catheterization data to equation 1. This equation is based on the following premises: (1) left ventricular minute output equals true left ventricular activity ejected per minute divided by the true activity per volume of blood; (2) true activity equals measured activity divided by counting efficiency. We applied the average estimate of \( \frac{E_{LV}}{E_s} \) from the first six non-regurgitant patients to prospectively calculate left ventricular outputs in the remaining 26 patients.

Because \( E_{LV} \) depends, in part, on tissue absorption of photons, \( E_{LV} \) should vary with differences in the patient’s body habitus, the degree of left ventricular hypertrophy, and the size and configuration of the left ventricular chamber. The variability in \( E_{LV} \) among our patients is indicated by the range of estimated values of \( \frac{E_{LV}}{E_s} \) (table 2) and by the standard error for left ventricular output estimation (0.58 l/min). Previous studies have shown that the variability in \( E_{LV} \) is not sufficient to preclude reasonably accurate estimation of left ventricular volume, and our study confirms this fact by demonstrating reasonably accurate estimation of left ventricular output.

Variability in \( E_{LV} \), although important in estimating absolute left ventricular output, is less important in monitoring changes in output in a single patient over time. In a given patient, \( E_{LV} \) is not likely to change significantly. Measurements of left ventricular volume and ejection fraction by equilibrium radionuclide ventriculography are highly reproducible, and our present data demonstrate excellent reproducibility for calculation of left ventricular output. The output measurement, therefore, represents an important tool for monitoring patient progress. By calculating relative output as the ratio between counts ejected per minute and counts per volume of blood, measurement is not restricted to the time during which a dose of radiotracer remains detectable, but rather may be repeated at any time after administration of additional tracer. As explained above, a method that merely normalizes left ventricular counts for dose administered is subject to error resulting from variability in the volume of tracer distribution, even in a given patient with time. The constancy of our measurement from one day to the next justifies our comparison with data obtained at catheterization within 48 hours of radionuclide study.

Other imaging systems, including those not using the slant-hole collimator, will yield different counting efficiencies. Therefore, a repeat estimation of \( \frac{E_{LV}}{E_s} \) by comparison of radionuclide and catheterization data is necessary before applying our method to estimate absolute left ventricular output using different imaging systems. However, an estimate of \( \frac{E_{LV}}{E_s} \) is not necessary in monitoring relative output in an individual patient, in which case measurement of activity ejected per minute divided by activity per volume of blood is sufficient.

Using the same region of interest for end-systole and end-diastole, estimation of left ventricular output should theoretically be more accurate than volume estimation. Output estimation entails subtraction of end-systolic from end-diastolic counts, thereby eliminating the need for background subtraction (assuming background counts remain fairly constant throughout the cardiac cycle). If different regions of interest are chosen for end-systole and end-diastole, background subtraction would be needed because the background counts would be different for the two regions.

Errors resulting from overestimating the left ventricular region of interest should be less important for output than for volume measurement as long as the erroneously included zone contains only stationary background counts. The resulting error would cancel out when end-systolic counts are subtracted from end-diastolic counts. However, region-of-interest errors that result in exclusion of part of the left ventricle or inclusion of a moving structure, such as the right ventricle or the left atrium, could result in a significant error. The 30° caudally tilted slant-hole collimator diminishes this error because its use results in improved separation between the left ventricle and left atrium. A method using a variable region of interest might decrease errors resulting from movement of count-containing structures into the diastolic region during systole.

Because left ventricular output exceeds forward flow in patients with mitral or aortic regurgitation, the radionuclide left ventricular output exceeds the Fick cardiac output in the regurgitant group. Several investigators have diagnosed and quantified left-sided valvular regurgitation noninvasively by comparing left and right ventricular stroke volume counts. In the absence of pulmonary or tricuspid regurgitation or intracardiac shunt, right ventricular output equals forward cardiac output; therefore, the comparison between left and right ventricular stroke counts is analogous to our comparison between radionuclide left ventricular output and Fick output. The regurgitant fraction, calculated as the difference between radionuclide left ventricular output and Fick output divided by radionuclide left ventricular output, may be
References

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