Measurement of Aortic and Mitral Regurgitation by Gated Cardiac Blood Pool Scans

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SUMMARY A simple, noninvasive radionuclide technique which measures the severity of valvular regurgitation has been developed. The technique compares right and left ventricular stroke volume indices (change in counts between diastole and systole over the left and right ventricles) from 45° LAO gated cardiac blood pool scans. In 14 control subjects, the left-to-right ventricular stroke index ratio was near unity (1.15 ± 0.15 [SD]). In 26 patients with mitral and/or aortic regurgitation it was larger (range 1.36-5.30, mean 2.44). Comparison between the stroke index ratio and qualitative angiographic estimates of regurgitation revealed good agreement (F = 45.5, p < 0.001). Gated cardiac blood pool scans permit noninvasive assessment of the severity of valvular regurgitation.

EVALUATION OF THE SEVERITY of aortic and mitral regurgitation is difficult.1,2 Echocardiography and auscultation are still the best noninvasive methods to diagnose both the presence and the site of regurgitation, but they have disadvantages. Echocardiography can specifically diagnose aortic regurgitation and sometimes mitral regurgitation, but provides only indirect evidence for its severity by measuring the repercussions of volume overload on the left ventricular and left atrial dimensions.

Quantitative assessment of aortic or mitral regurgitation requires simultaneous measurement of the total stroke volume and the forward stroke volume. Biplane left ventriculograms can be used to calculate the left ventricular (LV) total stroke volume from the measurement of the left ventricular end-diastolic and end-systolic volumes. Forward stroke volume can be calculated from measurement of the heart rate and cardiac output.3 In the absence of pulmonary or tricuspid regurgitation, shunts or transpositions, the forward stroke volume can also be determined from the right ventricular (RV) stroke volume.4 However, radiologic assessment of valvular regurgitation requires extreme care in the performance and quality control of each measurement, and is difficult to perform routinely. Most angiographers prefer a subjective assessment which grades valvular regurgitation qualitatively.5,6

In this study we introduce a new technique based on gated cardiac blood pool scans. When performed in the left anterior oblique (LAO) 40-45° projection, these studies allow simultaneous visualization of the left and right ventricles as separate structures, and permit assessment of their volume variations without requiring geometric assumptions.7 Measurement of the change in counts between end-diastole and end-systole over the right and left ventricles reflects their respective total stroke volume variations, and a ratio of these count changes (stroke indices) can be calculated. In normal persons the RV stroke volume is equal to the LV stroke volume and the left-to-right stroke index ratio should be unity.9 In patients with aortic or mitral regurgitation the LV total stroke volume increases, and the left-to-right stroke index ratio should exceed unity. We studied the value of the stroke index ratio to estimate the severity of valvular incompetence.

Material and Methods

The study group of 40 patients was retrospectively selected from the files. Fourteen control patients (mean age 49 years, range 27-63 years, 71% male, 29% female) had no valvular heart disease. Two were normal volunteers; 12 had ischemic heart disease. None had physical signs of valvular disease. In 11 patients with angiographically documented coronary artery disease, angiography had documented the absence of mitral incompetence. The ejection fractions in this group ranged from 29-84% (mean 56%). Four of these patients had reduced global LV function (ejection fraction < 50%). Twenty-six patients had evidence of valvular regurgitation. Twenty were studied by contrast angiography; 12 had isolated mitral regurgitation, four had isolated aortic regurgitation, three had combined mitral and aortic regurgitation and one had mitral regurgitation and aortic regurgitation plus tricuspid regurgitation. The tricuspid valve abnormalities were suggested by prominent C-V waves in the jugular veins and a parasternal systolic murmur increasing with inspiration. No other patient had clinical evidence of right-heart valvular regurgitation. Six patients were not catheterized, but had clinical evidence suggesting mild-to-moderate mitral regurgitation (n = 4), mild aortic regurgitation (n = 1), or moderate aortic regurgitation of luetic origin (n = 1). The mean age of the 26 patients with valvular disease was 52 years (range 27-73 years, 62% male, 38% female). Fifteen of the 20 patients with valvular insufficiency who had cardiac catheterization were on chronic digitalis and/or diuretic therapy.
Cardiac catheterization was performed within 2–3 weeks of the gated cardiac blood pool study in the patients with valvular insufficiency. This time interval in the control patients was as long as 3 months. During this interval, there were no significant changes in any patient’s clinical condition, laboratory data or medications. LV angiograms were performed routinely in the right anterior oblique (RAO) 30° projection, after retrograde catheterization of the left ventricle with a pigtail catheter introduced through the femoral artery. Mitral regurgitation was assessed on a four-point scale (0.1.2.3) using criteria suggested by Austen et al. Aortography was performed in the LAO 45° projection with the catheter withdrawn approximately 3 cm above the aortic valve plane. Aortic regurgitation was graded on a similar scale using the Austen criteria.

Gated cardiac blood scans were acquired in the LAO 40–45° projection after intravenous injection of 99mTc-labeled human serum albumin (20 mCi). For each patient, the angle of the projection was optimized for best separation of the left ventricle and right ventricle, but no caudal tilt was used. Data were recorded either in a systolic-diastolic mode using a Brattle cardiac synchronizer (n = 21) or in continuous ECG-synchronized mode (n = 19) with 16–28 frames spanning the cardiac cycle. Depending on the mode of acquisition and on the patient’s heart rate, the acquisition time ranged from 10–15 minutes and 250,000–500,000 counts were collected per frame. Frame duration ranged from 20–50 msec and was kept equal for systole and diastole. Studies were acquired with a conventional Anger-type scintillation camera (ON 100) interfaced to a dedicated computer system (ON-150, MDS or Informatek Simis 3). In the ECG-synchronized mode, the effective resolution was 64 × 64 pixels full screen.

Regions of interest (ROIs) were drawn over the left and right ventricles by visual inspection (fig. 1), taking care to include the entire RV or LV area while excluding as much of the atria, pulmonary artery, and aorta as possible. Selection of the ROI was aided by repeatedly viewing both end-systolic and end-diastolic frames (n = 21) or cinemtic blood pool studies (n = 19). Areas near the base of the heart that appeared more prominent during systole (e.g., atria, aorta) were not included in the ROI. The change in counts in each ventricular area between systole and diastole was then determined. Since the same ROIs were used for both systole and diastole, and since we were interested only in the absolute change in counts, background activity which was unrelated to the cardiac cycle was not subtracted. When patients were studied in the ECG-synchronized mode, the entire ventricular “time-activity curve” of the representative cycle was displayed and diastolic and systolic periods were selected separately for each ventricle at the peak and nadir of each ventricular curve (the nadir of the LV and RV curve occurred on a different frame in two-thirds of our studies). The results were expressed as a ratio of the change in counts in the LV area over the change in counts in the right ventricular area (LV/RV stroke index ratio). The reasons for choosing these techniques to determine the LV/RV stroke ratio are described in greater detail in the Appendix.

Analysis of the scans, including delineation of the ROIs, was performed by two independent observers who had no knowledge of the patients’ diagnoses. Analysis of the angiograms was performed by a single observer who was unaware of the clinical findings and scan results.

The null hypothesis that the LV/RV stroke ratios were similar in all groups of patients was tested by a paired t test. To test whether the mode of recording (systolic-diastolic or continuous ECG-synchronized mode) resulted in any systematic difference, we also used a paired t test. The observers’ independent results were compared by a linear regression analysis. LV/RV stroke ratios in patients with no angiographic regurgitation, patients with mild-to-moderate regurgitation and patients with severe regurgitation by angiographic grading were compared by a one-way analysis of variance and by multiple t tests.

Results

The LV/RV stroke ratios measured by observers A and B, respectively, were 1.11 ± 0.14 (SD) and 1.19 ± 0.19 in the 14 control patients, 2.67 ± 1.32 and 2.74 ±
1.34 in the 16 patients with mitral regurgitation, 2.22 ± 0.74 and 2.03 ± 0.51 in the six patients with aortic regurgitation, and 1.89 ± 0.38 and 2.08 ± 0.47 in the four patients with combined lesions. For each group, these independent observations were compared using the paired t test, and no significant differences were found (p > 0.05). The absolute mean variation and the range of variation between both observers was 0.134 (0.03–0.32) in controls, 0.228 (0.01–0.76) in patients with mitral regurgitation, 0.25 (0.01–0.69) in patients with aortic regurgitation and 0.19 (0.08–0.32) in patients with combined lesions. There were no systematic differences between the LV/RV stroke ratios of patients studied in the systole and diastole only. The LV/RV stroke ratios determined by observers A and B were similar in controls and patients with valvular disease (r = 0.98, n = 40, SEE = 0.28) (fig. 2).

In 26 patients with valvular regurgitation, the mean LV/RV stroke ratio was 2.44 (range 1.36–5.30) (mean of both observers). The largest ratios were in three of the 12 patients with isolated mitral regurgitation (4.61, 5.20 and 5.30). The largest LV/RV stroke ratios in patients with aortic regurgitation were 2.92 and 2.86.

The patient with aortic regurgitation and mitral regurgitation associated with tricuspid regurgitation had a ratio of 1.36. In this patient concomitant RV and LV volume overload precluded the use of the stroke ratio to estimate left-sided regurgitation. Therefore, this patient was excluded from the following comparison of the LV/RV stroke ratio with angiographic estimates of regurgitation.

The comparison between angiographic grading and the LV/RV stroke ratio in 11 controls and 19 patients with valvular regurgitation is presented in figure 3. There was good agreement between the LV/RV stroke ratio and the angiographic grading. There were significant differences between the average LV/RV stroke ratios of control patients (1.15 ± 0.13 (SD)), patients with mild-to-moderate regurgitation (2.15 ± 0.48) and those with angiographically severe regurgitation (4.02 ± 1.15) (t test: t = 6.74 (normal vs mild-to-moderate), p < 0.001, and t = 5.1 (mild-to-moderate vs severe) p < 0.001). The difference between these three groups was also assessed by one-way analysis of variance: F = 45.5, p < 0.001.

Discussion

This study demonstrates the feasibility of using gated cardiac blood pool scans to measure a RV and LV stroke volume index that can be used to estimate left-sided valvular regurgitation. Measurement of the

FIGURE 2. Comparison of the stroke index ratios determined by observers A and B in all controls and patients with valvular regurgitation. MR = mitral regurgitation; AI = aortic insufficiency; TR = tricuspid regurgitation.
FIGURE 3. Comparison of the stroke index ratio with the angiographic assessment of the severity of valvular regurgitation. Eleven controls and 19 patients with valvular regurgitation are grouped according to the angiographic class. Statistical comparisons were performed between three groups: controls, slight-to-moderate regurgitation and severe regurgitation. The nine patients who were not catheterized are displayed for comparison. LV = left ventricular; RV = right ventricular; MR = mitral regurgitation; AI = aortic insufficiency.

The ratio in controls can be narrowed by improved techniques. Available data suggest that regurgitation cannot be diagnosed with confidence until it amounts to approximately 30% of the stroke volume.

The ratio in patients without valvular regurgitation slightly exceeds the theoretically expected unity. The reasons for this systematic error are not entirely clear. The slight delay in RV contraction might have produced an increase in the ratio in patients studied in the systolic-diastolic mode, but we also found a ratio greater than unity in control patients studied in the ECG-synchronized mode. Another possibility involves differences in depth or in thickness of the interposed tissue between the two ventricles and the plane of the camera, as differences in attenuation for the activity from the right and left ventricle would alter the ratio.

The most probable cause for this error, however, is incomplete separation of the right and left ventricles from surrounding structures. When the heart is viewed in the LAO projection, the atria are superimposed on
a portion of the ventricular ROI. The degree of overlap can vary between the right and left ventricle and can vary during different portions of the cardiac cycle. Thus, the counts obtained from the ventricular ROIs reflect ventricular activity and a variable amount of atrial activity.

This problem is theoretically worse for the right heart than the left heart, since only a portion of the right atrium is usually visualized, even during systole. The portion of the right atrium that is visualized during systole can be largely excluded from the ROI, but some portions of the right atrium are almost surely present behind the RV ROI and contribute to right-heart counts. Similarly, a portion of the RV outflow tract probably extends above the aorta and cannot be included in the RV ROI.

Technical improvements might aid in the performance of the study. Use of a slant-hole collimator could improve patient positioning and allow better separation of all four chambers, the aorta and pulmonary artery. Use of 99mTc red blood cells rather than 99mTc-HSA might provide sharper, more easily analyzed images. Selection of the ROI might be improved by using a computer-generated "stroke volume image." This image is obtained by subtracting the end-systolic frame from the end-diastolic frame and displaying the difference. If this approach is used the difference image should represent the maximum change in counts in each ventricle. Since the nadir of the LV and RV curves may occur in different frames, multiple "stroke volume images" near end-systole will be needed to identify the maximum RV and LV difference independently.

We chose fixed ROIs over the left and right ventricles for simplicity and reproducibility. Maddahi et al. have shown that variable ROIs are needed to obtain a good correlation between RV ejection fractions from first transit and gated blood pool studies. However, we wished to obtain only the absolute change in counts between end-diastole and end-systole, not the ejection fraction. As our data (Appendix) show, either a fixed or variable ROI may be used. If variable ROIs are used, six areas have to be outlined instead of two (i.e., LV and RV end-diastolic regions and LV and RV end-systolic regions, plus LV and RV background regions). Using different end-diastolic and end-systolic regions requires background subtraction to correctly measure the change in ventricular activity, since the number of matrix points in the two regions is not the same. Using fixed ROIs avoids the problem of selecting background ROIs. This method assumes that the background activity surrounding each ventricle does not change during the cardiac cycle. Constancy of periventricular background has, in fact, been confirmed in several previous studies. In our patients, the mean change in background activity was only 3% of the ventricular end-diastolic activity (Appendix). By using a fixed ROI, the contribution of background counts to the total counts present in the ROI is equal at end-systole and end-diastole. The difference between the total end-systolic and end-diastolic counts therefore represents the net change in ventricular activity. Comparisons of LV/RV stroke ratios to quantitative measures of valvular regurgitation will be needed to further evaluate whether the fixed or variable ROI approach is best.

Recently, a number of techniques have been reported for assessing valvular regurgitation. Doppler echocardiography provides a qualitative estimate of valvular regurgitation. Mitral regurgitation has been measured by continuous infusion of 133-xenon in the left ventricle with sampling in the aorta or a peripheral artery and the left atrium. This technique seems to provide accurate results, but is highly invasive. Kirch et al. have presented a technique based on computerized first-pass radionuclide angiocardiography. Using a pulsatile flow model of the atrial-ventricular-arterial system, they have derived equations that can be applied to the patient after extraction of as many as four parameters derived from individual chamber time-activity curves. Disadvantages of this approach include the dependence on a discrete bolus delivered in the proximal atrium. If a blood pool tracer is injected, this technique could be combined with the stroke volume index approach by obtaining an equilibrium gated study after the first-pass study.

Another noninvasive approach that uses radioisotopes compares the cardiac output and stroke volume determination made during first-pass angiocardiography to the total stroke volume determination calculated from the LV ejection fraction and end-diastolic volume. Although this approach is attractive, as it is similar in principle to the classic angiographic approach, it suffers from the uncertainties of the scintigraphic evaluation of the LV end-diastolic volume. Because of the difficulties in determining the exact position of the valve plane, the volumes measured by area-length determinations on the scintigraphic images have relatively large standard errors of the estimate.

While the current study was limited to the use of the LV/RV stroke index ratio to measure mitral and aortic regurgitation, the concept may have wider applicability. Comparison of the RV and LV stroke index could be applied to other lesions that overload only one ventricle, whether right or left. Measurement of the stroke index ratio might thus be used to estimate right-sided valvular regurgitation, unidirectional shunts, anomalous pulmonary venous return, and the relative output of each circuit in complete transposition of the great vessels.

The LV/RV stroke index ratio extends the usefulness of gated cardiac blood pool imaging in analyzing ventricular function. The greatest advantage of the technique is its simplicity. Virtually any nuclear medicine facility that can acquire gated cardiac studies can apply the technique. It is not dependent on the quality of the injected bolus, and does not require complex data processing. Although further validation of the technique is needed, the initial clinical results with mitral and aortic regurgitation suggest that the technique can detect regurgitant flow and provide at least a qualitative estimate of its severity.
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Appendix

Three methods for obtaining the LV/RV ratio were compared in 15 patients with available ECG-synchronized digital data who had angiography. Eight of these patients were normal and seven had documented valvular insufficiency. The methods used were 1) fixed LV and RV end-diastolic ROIs, as described in the text; 2) the same end-diastolic regions, and end-systolic ROIs drawn over the left and right ventricle; and 3) the same end-diastolic and end-
systolic ROIs plus a background subtraction. A rectangular back-
ground (bgk) ROI was drawn lateral to the end-diastolic ROI of the left ventricle and right ventricle, respectively. Net end-diastolic counts were obtained using the following formula: end-diastolic counts — (bgk counts/cell) × (number of cells in end-diastolic ROI). Similarly, net end-systolic counts were obtained by end-
systolic counts — (bgk cts/cell) × (number of cells in end-systolic ROI). The differences in background counts between diastolic and systolic averaged 3.1% of the end-diastolic counts for the right and left ventricles.

The end-diastolic/end-systolic ROI method without background subtraction showed the greatest deviation from unity and greatest variability in normals (tables 1 and 2). It did not distinguish mild and moderate insufficiency as well as the other methods. These data

| Table 1. Left Ventricular/Right Ventricular Ratios in Normal Subjects |
|-----------------|------------------|-----------------|
|                 | ED ROI           | ED/ES ROIs minus background |
| 1               | 0.91             | 0.53             | 0.73 |
| 2               | 1.01             | 1.23             | 1.15 |
| 3               | 1.15             | 0.81             | 1.08 |
| 4               | 1.16             | 0.66             | 0.56 |
| 5               | 1.22             | 0.36             | 0.57 |
| 6               | 1.25             | 0.89             | 0.84 |
| 7               | 1.25             | 0.73             | 0.86 |
| 8               | 1.32             | 0.74             | 0.94 |

| Mean = sd       | 1.16 ± 0.14      | 0.74 ± 0.26      | 0.84 ± 0.22 |

Abbreviations: ED = end-diastolic; ES = end-systolic; ROI = region of interest.

| Table 2. Left Ventricular/Right Ventricular Ratios—Valvular Regurgitation |
|-----------------|------------------|-----------------|
|                 | ED ROI           | ED/ES ROIs minus BKG |
| 1               | 1.39             | 1.21             | 1.15 Mild MR |
| 2               | 1.75             | 1.36             | 1.43 Mild MR |
| 3               | 2.19             | 1.94             | 1.80 Mod AI  |
| 4               | 2.10             | 1.42             | 1.28 Mod MR  |
| 5               | 2.23             | 1.10             | 2.16 Mod MR  |
| 6               | 3.26             | 1.27             | 2.10 Mod MR  |
| 7               | 5.20             | 4.92             | 6.79 Severe MR |

Mean = 2.59 ± 1.89

Abbreviations: ED = end-diastolic; ES = end-systolic; ROI = region of interest; BKG = background; MR = mitral regurgitation; AI = aortic insufficiency.
show that either a single, fixed end-diastolic ROI over each ventricle, or six ROIs (end-diastolic, end-systolic, and background ROI for each ventricle), can be used for determining the severity of valvular regurgitation. The fixed ROI method showed less variability in normals ($F = 12.4, p < 0.01$). Both methods deviated from the expected value of unity in normals. The fixed ROI method usually gave LV/RV ratios $> 1$ and the variable ROI method usually gave ratios $< 1$. The lower ratios in normals and regurgitation given by the variable ROI method were probably related to 1) better separation of the right atrium and right ventricle during systole, but continued overlap during diastole; 2) inadvertent exclusion of a portion of the right ventricle in the systolic ROI; 3) greater systolic overlap of the left atrium and left ventricle than the right atrium and right ventricle; or 4) a combination of these factors. Comparison with quantitative measures of valvular regurgitation is needed to determine whether the fixed or variable ROI method for obtaining LV/RV ratios is best. We chose the fixed ROI method because of its simplicity and reproducibility.

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**A Comparison of Simultaneous Measurements of Systolic Function in the Baboon by Electromagnetic Flowmeter and High Frame Rate ECG-Gated Blood Pool Scintigraphy**

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**SUMMARY** Left ventricular (LV) systolic timing and relative volume variations were simultaneously measured by electromagnetic flowmeter (EMF) and high frame rate ECG-gated blood pool scintigraphy in five baboons. No significant differences ($p > 0.1$, paired $t$ test) were observed in the time (from R wave) to peak aortic flow (maximum LV ejection rate), time to cessation of aortic flow (end-systole) or in the duration of aortic flow (LV ejection time). A small (~15 msec) but significant systematic difference ($p < 0.02$) was noted in the time to onset of aortic flow.

The shape of each scintigraphic time-activity curve during systole was compared to an equivalent curve synthesized from 10 EMF flow profiles obtained in the same baboon. Comparison of these paired curves over systolic ejection yielded an average correlation of $r = 0.95$ (range 0.90–0.99), The ratio of peak flow to stroke volume determined from these data did not differ significantly ($p > 0.05$).

In the baboon, quantitative high temporal resolution ECG-gated scintigraphy appears to reflect closely the detailed timing and relative magnitude variation of LV volume during the entire period of systolic ejection. We conclude that the assumptions underlying the scintigraphic method are valid in the baboon during the ejection interval.

**HIGH FRAME RATE** ECG-gated blood pool scintigraphy yields a scintigraphic image sequence that spans an average cardiac cycle. The time course of net total counts over the left ventricle in such a sequence is thought to reflect closely the time variation of left ventricular (LV) volume throughout the cardiac cycle; if true, this method not only offers the possibility of visualizing cardiac movement when the image sequence is cyclically displayed, but also provides a noninvasive method for routinely measuring intrasystolic and intradiastolic events, e.g., peak ejection and filling rates.

The quantitative accuracy of multi-image equilibrium studies in the measurement of such detailed, rate-related phenomena has not yet been established. Moreover, we are unaware of studies in which the assumptions underlying the scintigraphic method have been directly tested by experiment in vivo.

The present work addresses these issues (in part) by comparing simultaneous scintigraphic and electromagnetic flowmeter (EMF) measurements of instantaneous systolic LV function in the baboon.

**Methods**

Five male baboons (average weight 24 kg) constituted the study group. Under anesthesia and with controlled ventilation, a left anterior thoracotomy was performed through the fourth intercostal space. The ascending aorta was dissected free and one of several previously calibrated EMF flow probes installed about the aorta as near as possible to the aortic valve. The probe that most closely fit the aorta without compromising aortic flow was chosen. The probe electrical leads were exteriorized through a separate puncture.
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