## DIAGNOSTIC NUCLEAR MEDICINE

# Radionuclide Techniques for Valvular Regurgitant Index: Comparison in Patients with Normal and Depressed Ventricular Function

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**We compared contrast angiography with three techniques of quantitating valvular regurgitation from radionuclide ventriculograms in 70 patients: 45 with documented regurgitation graded 1–4+, and 25 without regurgitation. The radionuclide "regurgitant index" (ratio of L to R ventricular stroke counts) was measured from fixed end-diastolic regions of interest (method A), from separate end-diastolic and end-systolic regions of interest (method B), and from a "stroke-volume image" (method C). Sensitivities for detecting 1+ or more regurgitation were: method A = 57.8%, method B = 37.8% and method C = 62.2%. Sensitivities for detecting 2+ or more regurgitation were: method A = 74.2%, method B = 54.8%, and method C = 77.4%. All methods were >97% specific. Interobserver coefficients of variability were: method A = 9.1%, method B = 19.2%, and method C = 5.4%. The sensitivity of each method was improved when left-ventricular ejection fractions were >0.35. No method consistently differentiated between 2+, 3+, and 4+ valvular regurgitation.**

**J Nucl Med 23: 763–769, 1982**

Valvular regurgitation is the most common cause of chronic volume overload of the left ventricle. Myocardial compensation for volume overload leads to both dilatation and hypertrophy of the ventricle. Ultimately these compensatory mechanisms fail and severe, long-standing left-ventricular volume overload causes irreversible myocardial damage. Once overt cardiac failure occurs, long-term survival is limited despite operative intervention (*1*). Therefore, patients with valvular regurgitation should be followed closely for any change in hemodynamic variables.

Cardiac catheterization with contrast angiography has been the reference standard for the diagnosis and quantitation of valvular regurgitation. However, procedural risks, cost, and radiation burden limit the utility of catheterization for frequent patient follow up. Accordingly, there has been considerable interest in the use of noninvasive techniques to quantitate valvular regurgitation and to identify early ventricular decompensation (*2–9*).

Radionuclide techniques provide safe, reliable, and relatively noninvasive means of evaluating ventricular function. Examinations may be performed on outpatients and repeated at frequent intervals. In addition, several different methods for quantitating valvular regurgitation from equilibrium gated blood-pool data have been described (*5,7,8*). The purpose of this study was to compare the accuracy and reproducibility of three commonly used methods of measuring the radionuclide regurgitant index (ratio of L to R ventricular stroke counts).

## METHODS

**Study patients.** Cardiac catheterization with contrast ventriculography and radionuclide gated blood-pool imaging were performed in 70 patients (50 men, 20 women; mean age 47 yr) between January 1979 and December 1980. None of these patients had evidence of an intracardiac shunt or right-sided valvular regurgitation by physical examination, or a prominent right atrial V wave at catheterization. Cardiac medications

Received Feb. 25, 1982; revision accepted April 16, 1982.

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were not changed between the radionuclide and catheterization studies.

Radionuclide ventriculography was also performed in seven normal volunteers (six men, one woman; mean age 26 yr) who had no clinical evidence of valvular regurgitation.

**Cardiac catheterization and contrast angiography.** Left- and right-heart catheterization with oximetry were performed in all 70 patients. Indicator dilution curves were also recorded in cases of suspected intracardiac shunt. No patient had evidence of aortic or mitral stenosis. Single-plane contrast left ventriculograms were recorded in a 30° right anterior oblique projection. Left-ventricular ejection fractions and volumes were calculated using the area-length method and the Kennedy regression equation (*10,11*). Supravalvular aortograms were recorded in all patients with suspected aortic regurgitation and in all patients with rheumatic heart disease. Valvular regurgitation was graded on a scale of 0 to 4+, based upon the breadth of the regurgitant stream, the rapidity of regurgitant flow, the degree of chamber opacification, and the rapidity with which the contrast medium was cleared (*12,13*). Final grades represented the consensus opinion of two experienced observers.

**Radionuclide ventriculography.** Radionuclide ventriculography was performed at the time of cardiac catheterization and before contrast angiography in 25 of the 77 patients (22 with valvular regurgitation and three without). The remaining patients with valvular regurgitation were studied within 1–40 days of catheterization (8.9 ± 12.5 days, mean ± s.d.). The remaining patients without valvular regurgitation were studied within 1–150 days of catheterization (28.1 ± 37.6 days).

Radionuclide ventriculograms were performed with technetium-99m-labeled red cells (*14*). Thirty-two-frame equilibrium gated blood-pool image sets were acquired with a mobile gamma scintillation camera, equipped with a low-energy, all-purpose, parallel-hole collimator and interfaced to a dedicated nuclear medicine computer system. Subjects were studied in the supine position with the detector positioned in a left anterior oblique projection, modified with 5–10° of caudal angulation so as to provide optimal visualization of the interventricular septum. Individual images contained a minimum of 150,000 counts.

Left-ventricular ejection fraction was determined from the background-corrected ventricular time-activity curve (*15*). Left-ventricular end-diastolic and end-systolic volumes were determined from the background-corrected ventricular activity, normalized for peripheral venous blood activity and corrected using the Dehmer regression equation (*16,17*). Volumes were indexed for body surface area.

**Radionuclide quantitation of valvular regurgitation.** Three methods were used to calculate a radionuclide index of valvular regurgitation. The following procedural steps were common to all three:

1. The left-ventricular time-activity curve was used to identify the ventricular end-diastolic and end-systolic frames.
2. The ventricular end-diastolic and end-systolic frames were isolated from the gated series and smoothed using a nine-point center-weighted filter kernel.
3. A periventricular region of interest (ROI) was constructed just lateral to the apex of the left-ventricular activity. The average activity per pixel within this ROI was subtracted from each pixel of the end-diastolic and end-systolic frames.
4. A "stroke volume" image was created by subtracting the background-corrected end-systolic frame from the background-corrected end-diastolic frame.
5. A "reverse stroke volume" image was created by subtracting the end-diastolic frame from the end-systolic frame.
6. The radionuclide "regurgitant index" (RI) was calculated from the following formula:

$$RI = \frac{\text{LV stroke counts}}{\text{RV stroke counts}} = \frac{\text{LV ED counts} - \text{LV ES counts}}{\text{RV ED counts} - \text{RV ES counts}}$$

where LV is left ventricle, RV is right ventricle, and ED and ES are end-diastolic and end-systolic, respectively.

*Method A.* (Fig. 1) Using the stroke-volume and reverse stroke volume images as guides, a single fixed ROI that followed the end-diastolic boundary was constructed manually for each ventricle. This ROI was used to determine both the end-diastolic and end-systolic counts. The regurgitant index was then calculated according to the formula given above.This is the method originally described by Rigo and associates (*5*).

*Method B.* (Fig. 2) Separate ROIs were constructed manually for each ventricle at end-diastole and end-systole. The regurgitant index was then calculated as for method A. This is the "variable region of interest" method described by Sorensen et al. (*8*).

*Method C.* (Fig. 3) This method differs from the other two in that ventricular stroke counts were measured directly from the stroke-volume image. Regions of interest were constructed manually over the stroke-volume image of each ventricle. When the boundary of the stroke image was not clearly defined, the boundary of the reverse stroke image was used to define the region of interest further. The regurgitant index was then calculated directly from the ratio of ventricular stroke counts as in the formula above.

All studies were analyzed using each of the three methods by two independent and experienced observers

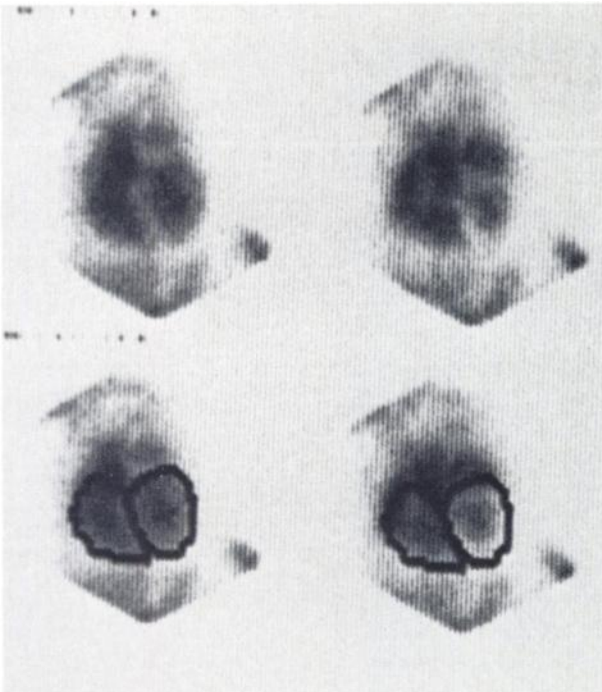

**FIG. 1.** "Fixed region of interest" method (Method A). End-diastolic (top left) and end-systolic (top right) frames from radionuclide ventriculogram performed on patient with isolated mitral regurgitation. Bottom row shows duplicated end-diastolic and end-systolic images with superimposed fixed regions of interest that follow end-diastolic ventricular boundaries. The single region of interest on each side is used to determine both end-diastolic and end-systolic ventricular counts.

who had no knowledge of the clinical or catheterization data. In addition, one of the observers repeated the complete analysis on a separate occasion.

**Statistical analysis.** Radionuclide ventriculograms from the normal volunteers, and from patients without demonstrable valvular regurgitation who had left-ventricular ejection fractions >0.35, were analyzed to determine the normal range of the regurgitant index for each of the three models. The normal range was defined as those values within two standard deviations of the mean.

The reproducibility of each method was assessed by determining the inter- and intraobserver coefficients of variability (C.V.).

Comparison of proportions was done using an adjusted Chi-square analysis (*21*). The multiple comparison test of Newmans–Keuls was used to compare means (*21*). Radionuclide indices of valvular regurgitation were compared with those from contrast angiography. Catheterization estimates were used as the reference standard. The diagnostic value of each radionuclide method was determined by calculating the sensitivity and specificity for detecting valvular regurgitation. In order to assess the effect of left-ventricular volume and ejection fraction on the accuracy of each of the three techniques, sensitivity and specificity figures were also calculated separately for patients grouped according to left-ventricular ejection fraction and left-ventricular end-diastolic volume index.

## RESULTS

**Cardiac catheterization.** These results are summarized in Table 1. Forty of the 70 patients had contrast angiographic evidence of regurgitation involving one left-sided valve (18 mitral and 22 aortic). Five patients had both aortic and mitral regurgitation. The remaining 25 patients had no evidence of valvular regurgitation either clinically or at cardiac catheterization.

**Radionuclide ventriculography.** Twenty-five of the 77 subjects had left-ventricular ejection fractions $\leq$0.35 (0.23 $\pm$ 0.07, mean $\pm$ s.d.; range 0.12–0.35). Fifty-two of the 77 subjects had left-ventricular ejection fractions >0.35 (0.64 $\pm$ 0.12, range 0.39–0.85; $p < 0.001$). Left-ventricular volume indices were significantly different between these two groups. In the patients with left-ventricular ejection fractions $\leq$0.35, the left-ventricular end-diastolic volume indices averaged 168 $\pm$ 82 ml/m$^2$ (mean $\pm$ s.d.) and the left-ventricular end-systolic volume indices averaged 129 $\pm$ 69 ml/m$^2$. In the patients with left-ventricular ejection fractions >0.35, the corresponding indices averaged 98 $\pm$ 45 and 38 $\pm$ 21 m/m$^2$. Differences were significant ($p < 0.001$) for both end-diastolic and end-systolic volume index.

**Radionuclide index of valvular regurgitation.** Mea-

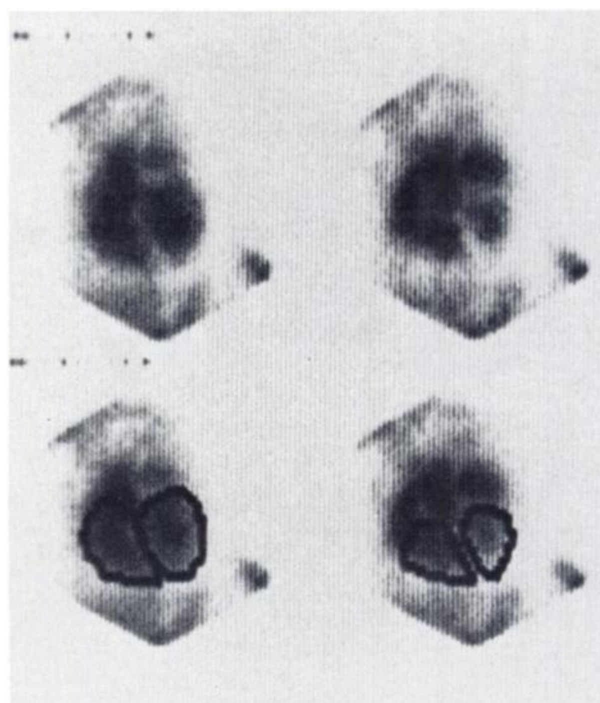

**FIG. 2.** "Variable region of interest" method (Method B). Radionuclide ventriculogram images and format are as in Fig. 1. Bottom row shows end-diastolic and end-systolic images with superimposed ROIs. Each end-systole and end-diastole has its own ROI.

**TABLE 1. ANGIOGRAPHIC ASSESSMENT OF VALVULAR REGURGITATION**

| | 0 | 1+ | 2+ | 3+ | 4+ | Total |
|---|---|---|---|---|---|---|
| Patients with one, or no, regurgitating valve | 25 | 13 | 14 | 11 | 2 | 65 |
| Patients with aortic and mitral regurgitation* | — | 1 | 3 | — | 1 | 5 |
| Normal volunteers | 7 | — | — | — | — | 7 |

* The degree of regurgitation of the predominant valvular lesion is given.

surements of the radionuclide regurgitant index calculated by each of the three methods are compared with contrast angiography in Figs. 4–6. Patients with left-ventricular ejection fractions ≤0.35 are designated by open circles. In the patients with both aortic and mitral regurgitation, only the angiographic grading of the predominant lesion is plotted. These patients are indicated by arrows. For each of the methods, there was considerable overlap in the values of the regurgitant index between patients with 2+, 3+, and 4+ valvular regurgitation by contrast angiography (Figs. 4–6).

The sensitivity and specificity of each of the methods for measuring the regurgitant index are shown in Table 2.

**Method A.** The radionuclide regurgitant index measured from fixed end-diastolic regions of interest is compared with contrast angiography in Fig. 4. In patients without valvular regurgitation, values for the

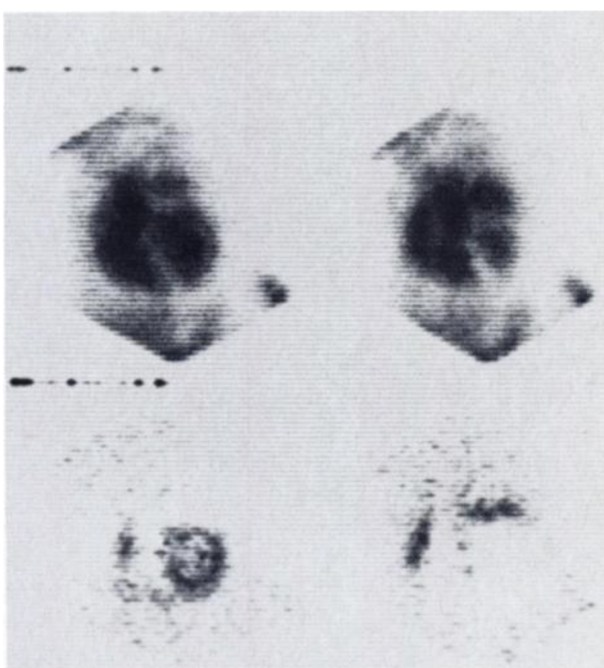

**FIG. 3.** "Stroke/volume image" method (Method C). Upper row again shows end-diastolic and end-systolic images from same patient as in Figs. 1 and 2. Bottom row shows "stroke-volume image" at left and "reverse stroke-volume image" at right.

regurgitant index ranged from 0.86–2.42 (1.36 ± 0.39, mean ± s.d.). The calculated normal range was thus 0.57 to 2.15 (1.36 ± 0.79, mean ± 2 s.d.). The sensitivity for detecting 1+ or greater valvular regurgitation was 57.8%, similar to that of method C (62.2%, $p = 0.830$), but somewhat higher than that of method B (37.8%, $p = 0.091$). The sensitivity for detecting 2+ or greater regurgitation was 74.2%, whereas sensitivities of methods B and C were 54.8 ($p = 0.184$) and 77.4% ($p = 0.767$), respectively. The specificity of the technique was 98.7%. When patients with left-ventricular ejection fractions ≤ 0.35 were excluded, the sensitivities for detecting 1+ or greater and 2+ or greater regurgitation increased to 71.4% and 80.0%, respectively, without change in specificity. The interobserver coefficient of variability was 9.1% (Fig. 4) while the intraobserver C.V. was 8.3%. By a multiple comparison test (*21*), both coefficients were significantly lower than those of method B ($p < 0.05$) and higher than those of method C ($p < 0.05$).

**Method B.** The regurgitant index measured from separate end-diastolic and end-systolic ventricular regions of interest is compared with angiography in Fig. 5. In patients without regurgitation, values ranged from 0.56–1.82 (0.98 ± 0.35, mean ± s.d.). The normal range was thus 0.28–1.68 (0.98 ± 0.70, mean ± 2 s.d.). The sensitivities for detecting 1+ or greater and 2+ or greater regurgitation were 37.8% and 54.8%, respectively, thus lower than those of method A (57.8%, $p = 0.091$ and 74.2%, $p = 0.134$) and those of method C (62.2%, $p = 0.035$ and 77.4%, $p = 0.107$). The specificity was 98.7%. When patients with left-ventricular ejection fractions ≤0.35 were excluded, the sensitivities for detecting 1+ or greater and 2+ or greater regurgitation increased to 53.6% and 60.0%, respectively. The specificity was 98.1%. Variability in the measurement of the regurgitant index by this method was considerably greater than those for methods A and C ($p < 0.05$). The interobserver coefficient of variability was 19.2% (Fig. 5) while the intraobserver C.V. was 14.8%.

**Method C.** The regurgitant index measured from the stroke-volume image is compared with angiography in Fig. 6. In the patients without valvular regurgitation, values ranged from 0.88–2.05 (1.22 ± 0.25, mean ± s.d.). The normal range was thus 0.73–1.71 (1.22 ± 0.49,

**TABLE 2. THE SENSITIVITY AND SPECIFICITY OF EACH RADIONUCLIDE TECHNIQUE**

| | Sensitivity* for detecting 1+ or more regurgitation | | | Sensitivity* for detecting 2+ or more regurgitation | | | Specificity† | | |
|---|---|---|---|---|---|---|---|---|---|
| | Method A (%) | Method B (%) | Method C (%) | Method A (%) | Method B (%) | Method C (%) | Method A (%) | Method B (%) | Method C (%) |
| All patients | 57.8 | 37.8 | 62.2 | 74.2 | 54.8 | 77.4 | 98.7 | 98.7 | 97.4 |
| Patients with LVEF† >0.35 | 71.4 | 53.6 | 85.7 | 80.0 | 60.0 | 92.0 | 98.1 | 98.1 | 98.1 |

* Sensitivity = number of true positives detected/total number of positives present.
† Specificity = number of true normals detected/total number of normals present.
‡ LVEF = left ventricular ejection fraction.

mean ± 2 s.d.). The sensitivity for detecting 1+ or greater regurgitation was 62.2%, thus higher than that of method B (37.8%, $p = 0.035$) but comparable with that of method A (57.8%, $p = 0.830$). The sensitivity for detecting 2+ or greater regurgitation was 77.4% compared with 54.8% ($p = 0.107$) for method B and 74.2% ($p = 0.767$) for method A. The specificity was 97.4%. When patients with left-ventricular ejection fractions ≤0.35 were excluded, the sensitivities for detecting 1+ or greater regurgitation increased to 85.7% (B) and 92.0%, (A), respectively. The interobserver coefficient of variability was 5.4% (Fig. 6) and the intraobserver C.V. was 3.0%, both significantly lower than those of methods A and B ($p < 0.05$).

**Influence of large left-ventricular volumes on the radionuclide regurgitant index.** Twenty-two patients with left-ventricular ejection fractions >0.35 had left-ventricular end-diastolic volume indices >100 ml/m$^2$ (range 104–257, mean = 139 ± 23 ml/m$^2$). In these patients, the sensitivities for detecting 2+ or greater valvular regurgitation were: method A = 86.0%, method B = 65.0%, and method C = 100%. The specificities were: method A = 95.4%, method B = 100%, and method C = 95.4%.

DISCUSSION

The patient with chronic valvular regurgitation may present a therapeutic dilemma. The presence of valvular regurgitation is usually demonstrable by physical examination and/or noninvasive testing. However, it may be prognostically or therapeutically important to assess the severity of regurgitation, the impact of regurgitation on left-ventricular performance, and the changes in these variables with time, stress, medical therapy, or surgical intervention. Although contrast angiography has been regarded as the most accurate means of detecting and quantitating valvular regurgitation and ventricular function, it is not a practical technique for stress or serial studies. Consequently there has been considerable interest in the development of noninvasive techniques for this purpose (*2–9*).

Radionuclide ventriculography has been used to assess both the degree of valvular regurgitation (*5–9*), and ventricular function both at rest and during exercise stress (*18–20*). Common to most techniques for measuring valvular regurgitation from equilibrium gated blood-pool data is the use of the ratio of left- to right-ventricular stroke as an index of regurgitation. However, there are considerable procedural differences between

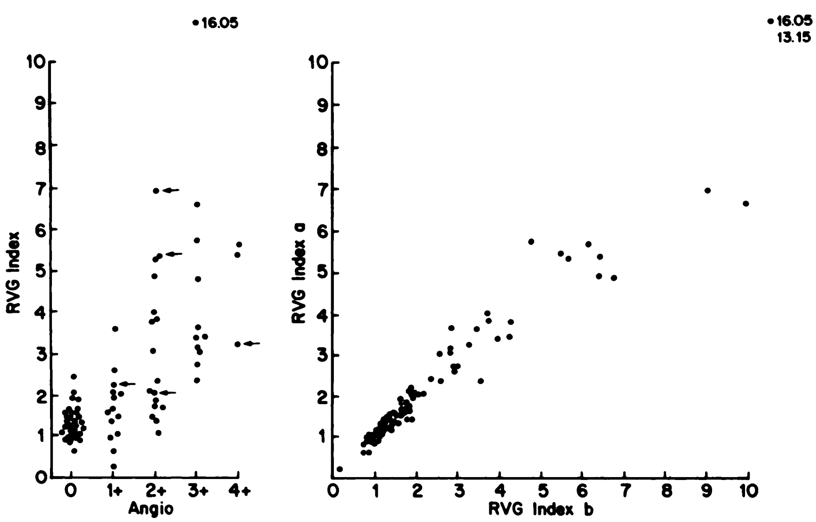


FIG. 4. Radionuclide regurgitant index by Method A (ordinate) plotted against angiographic grade of severity (abscissa). Interobserver variability for this technique is shown at right. Patients with LVEF ≤ 0.35 are designated by open circles. Arrows indicate patients with both mitral and aortic regurgitation, in which case plot refers to grade for predominant lesion only.

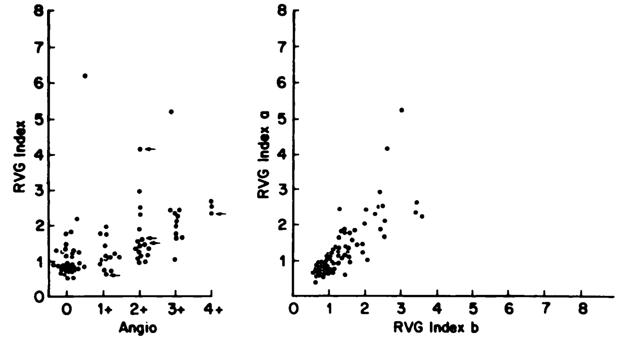


**FIG. 5.** Radionuclide regurgitant index by Method B plotted against angiographic grade of severity. Format as in Fig. 4. Interobserver variability for this technique is shown at right.

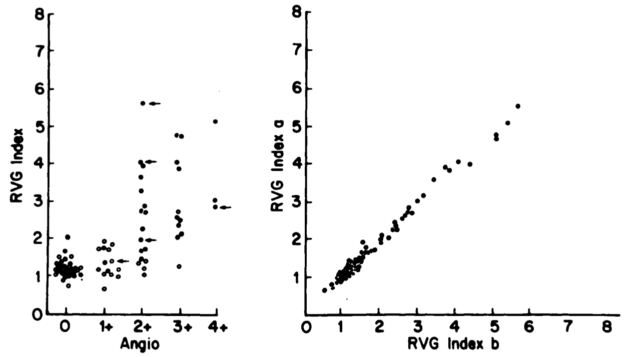


**FIG. 6.** Radionuclide regurgitant index by Method C plotted against angiographic grade of severity. Format as in Figs. 4 and 5. Interobserver variability for this technique is shown at right.

the reported techniques, which might result in considerable variation in the accuracy of radionuclide ventriculography for detecting and quantitating valvular regurgitation. Accordingly, we compared the relative accuracy and reproducibility of three radionuclide techniques with contrast-angiographic estimates of valvular regurgitation, graded in the conventional manner from 0 to 4+.

Measurements of the regurgitant index using fixed end-diastolic regions of interest (method A) and using the stroke-volume image (method C) were both sensitive and specific for detecting regurgitation graded as 2+ or greater by contrast angiography. These results were reproducible with small inter- and intraobserver coefficients of variability. Most of the patients misdiagnosed by these two methods had significant left-ventricular dysfunction (left-ventricular ejection fraction $\leq 0.35$). Measurements of the regurgitant index from separate end-diastolic and end-systolic regions of interest (method B) were less sensitive for detecting regurgitation $\geq 2+$, and the reproducibility of this method was poor. These limitations probably relate to difficulty in defining ventricular boundaries at end-systole since the ventricular end-diastolic boundaries are usually well defined by the stroke-volume and reverse-stroke-volume images that are used to guide placement of the end-diastolic regions of interest.*

Previous studies have suggested that radionuclide estimates of valvular regurgitation may be particularly unreliable in patients with considerable left-ventricular dysfunction (*9*). Our results concur. Possible explanations for this finding include: (a) a greater frequency of segmental ventricular dyskinesis in such patients, resulting in the failure of the ROI constructed over the end-diastolic boundary to include all end-systolic activity; (b) increasing difficulty in separating atrial from ventricular activity because of chamber dilatation; and (c) increasing attenuation effects with larger ventricular volumes. Although attenuation effects can certainly result in considerable errors in activity-based calculations of ejection fraction and stroke volume, in our patients with left-ventricular ejection fractions >0.35 and end-diastolic volume indices $>100$ ml/m$^2$, the sensitivities of all methods of measuring the regurgitant index for detecting 2+ or greater regurgitation were excellent. Right-ventricular dysfunction may also limit the accuracy of the radionuclide assessment of valvular regurgitation, but since none of our patients had isolated right-ventricular failure, we were unable to evaluate this possibility.

Thus our data suggest that radionuclide ventriculography permits the detection of valvular regurgitation graded as 2+ or greater by contrast angiography. Less severe regurgitation is frequently missed by current radionuclide techniques. Measurement techniques that use either fixed end-diastolic regions of interest, or the stroke-volume image to calculate the regurgitant index appear to be superior to methods using variable regions of interest. Although there was a general trend toward a greater regurgitant index with increasingly severe regurgitation as assessed by contrast angiography, there was considerable overlap between the patient groups. Of course, this overlap may be due, at least in part, to limitations of the contrast angiographic technique.

Although the techniques used in the current study failed to differentiate consistently among 2+, 3+, and 4+ valvular regurgitation by contrast angiography, these methods are not without considerable value in the evaluation of a patient with valvular regurgitation. The ability to monitor serial changes in left-ventricular ejection fraction, volumes, and indices of global and segmental contraction and relaxation may be vitally important in patient management, particularly when the degree of regurgitation has already been quantitated by invasive means.

## FOOTNOTES

* The accuracy for detecting regurgitation was not significantly different in 25 additional patients in whom slant-hole collimator was used, caudally directed 25–30°.

ACKNOWLEDGMENTS

This work was supported in part by the NIH Ischemic Heart Disease SCOR Grant HL-17669 and by the Harry S. Moss Heart Fund, Dallas, TX.

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