Volumetric evaluation of aortic regurgitation by combined first-pass/equilibrium radionuclide ventriculography

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KEY WORDS: Aortic regurgitation, stroke volume, regurgitant fraction, ejection fraction, cardiac catheterization, radionuclide ventriculography, transluminal coronary angioplasty.

In 16 men with normal valvular function (group I) and 23 men and one woman with isolated aortic regurgitation (group 2) effective stroke volume was determined by first-pass radionuclide ventriculography. Total left ventricular stroke volume was derived from equilibrium radionuclide ventriculography using a geometric approach for the end-diastolic volume multiplied by the ejection fraction. The difference between the two stroke volumes as a fraction of total left ventricular stroke volume was taken as radionuclide regurgitant fraction. Radionuclide lv/rv stroke count ratio was calculated as the ratio of end-diastolic–end-systolic count-rate differences from the left and right ventricles. All patients underwent left heart catheterization. Angiographic regurgitant fraction was evaluated by the method of Sandler and Dodge in 16 patients of group 2. In the others, aortic regurgitation was quantified in 5 grades of severity. Group 1 was classified correctly by both radionuclide regurgitant fraction and lv/rv stroke count ratio (specificity 100%). In group 2 the radionuclide regurgitant fraction was elevated in all (from +20% to +88%, sensitivity 100%), radionuclide lv/rv stroke count ratio in 19 of 24 cases (from 0-6 to 5-6, sensitivity 79%). The angiographic regurgitant fraction correlated well with the radionuclide regurgitant fraction (r=0.78), whereas no significant correlation was found between the angiographic stroke volume ratio (i.e. left ventricular stroke volume/cardiac output per beat) and radionuclide stroke count ratio (r=0.10) due to the high rate of false-negative results of the latter method.

In conclusion, in patients with moderate to severe isolated aortic regurgitation, using combined first-pass/equilibrium radionuclide regurgitant fraction allows a reliable noninvasive evaluation of aortic regurgitation which is superior to the evaluation of the radionuclide lv/rv stroke count ratio.

It is often difficult to assess the severity of aortic regurgitation from clinical, radiological, electrocardiographic and echocardiographic findings. Two angiographic methods are used in clinical routine. First, the amount of contrast medium appearing in the left ventricle after injection into the aortic root and the number of cycles necessary for clearing is used to estimate the severity of valvular regurgitation[4,5,6]. The second, more precise, technique is the method of Sandler and Dodge[11], the amount of blood regurgitated into the left ventricle is calculated from the difference between the left ventricular stroke volume, determined by left ventricular cineangiography, and the effective stroke volume, determined by Fick’s principle.

For follow-up studies, in severely ill patients (acute endocarditis, acute paravalvular regurgitation after aortic valve replacement), and in patients with dubious severity of aortic regurgitation, a noninvasive method is desirable to determine the regurgitant fraction. Recently, several authors have demonstrated the use of radionuclide methods for the evaluation of valvular regurgitation. The radionuclide lv/rv stroke count ratio as the ratio of end-diastolic–end-systolic count-rate differences of the left and right ventricles has been
recommended as a variable to quantify the regurgitant fraction\cite{8-19}. The disadvantage of this ratio is the relatively low sensitivity (under 80%), while specificity is high\cite{13,14,19}. The goal of the present study was to evaluate the reliability of the latter variable in comparison with the left ventricular regurgitant fraction derived from the radionuclide determination of the effective and total left ventricular stroke volume. This method, based on the technique of Sandler and Dodge\cite{7}, was first described by Van Dyke\cite{20} and Weber\cite{21}, but so far no systematic investigation has been performed to study its practical value in patients with aortic regurgitation.

**Methods**

**Patients**

Sixteen men with normal valvular function (but suffering from single vessel coronary disease and scheduled for transluminal coronary angioplasty) (group 1; mean age 52 years ± 12) were investigated and compared with 23 men and one woman with isolated aortic regurgitation (group 2; mean age 42 years ± 12). Four patients had acute aortic regurgitation (less than 6 months by history), 3 patients had paravalvular regurgitation after aortic valve replacement, while the remainder suffered from chronic aortic regurgitation. All patients were in regular sinus rhythm.

**Cardiac Catheterization and Angiography**

Aortic cineangiography and left heart catheterization were performed in all 40 patients. Left ventriculography was performed in deep inspiration by the biplane technique (32 frames per second) in right anterior oblique (RAO) 30° and left anterior oblique (LAO) 60° views using 30 to 50 ml sodium meglumine midotrizoate (Urografin® 76%). Patients with contrast medium regurgitation into the left atrium and all with induced arrhythmias were excluded. Total left ventricular stroke volume was calculated in 17 of the 24 patients in group 2 using the biplane technique as described by Schulz et al.\cite{22}.

In 20 patients of group 2, right heart catheterization was performed immediately prior to left heart catheterization and aortic cineangiography. Cardiac output was evaluated by the Fick method. The oxygen content was determined from samples of aortic and pulmonary artery blood. Effective stroke volume was calculated from the mean of the heart rate during the measurement of cardiac output.

Angiographic stroke volume ratio was defined as the ratio of left ventricular stroke volume and effective stroke volume. No determination of the right ventricular stroke volume was performed.

The difference between the total and effective stroke volume as a fraction of total left ventricular stroke volume was taken as the angiographic regurgitant fraction.

In 7 patients of group 2 (4 of them were in a critical clinical condition) the magnification factor, used to calculate the left ventricular end-diastolic and end-systolic volume from biplane angiography, was not determined for technical reasons (to abbreviate the investigation, after the appearance of sudden arrhythmias). In one patient of group 2 the left ventricular stroke volume was available, but the effective stroke volume was not evaluated. In these cases the amount of aortic regurgitation was estimated semiquantitatively using the classification of Hunt\cite{3}. Grade 0 corresponds to no contrast material reflux into the left ventricle during aortography, grade 5 to a reflux of contrast material clearly outlining the left ventricle with a density equal to that of the aortic root within three beats.

No drugs were administered during the investigation.

**Radionuclide Ventriculography**

In severely ill patients, radionuclide ventriculography was performed within one day before or after cardiac catheterization, in all others within 10 days. The drug regime remained unchanged during this time.

After in vivo labelling of the red blood cells\cite{23}, cardiac output was calculated from the first-pass study. 15 mCi 99-m-Tc in a bolus of less than 2 ml were injected into a brachial vein, followed by a flush injection of saline solution. The first passage of the bolus through the heart was registered in the LAO 45° position with a gamma camera-computer system (Picker small field of view camera 4/11 and Informatek computer SIMIS 3). No background subtraction was performed. The time-activity curve of the left ventricle was generated using intervals of one second. The downslope of the dilution curve was extrapolated to baseline by a monoexponential fit. Two minutes later the count rate did not change significantly and equilibrium activity ($c_{\infty}$) of the tracer was taken in the same camera position. Effective stroke volume ($SV_{eff}$) was derived from the product of blood volume ($BV$) (predicted from height, weight and sex of the patient) which permits the routine application
of this technique) and equilibrium count rate \( c_{\infty} \)
divided by the momentary heart rate (HR) and the integral of the extrapolated time-activity curve of first-pass investigation\(^{20,21,25} \)

\[
SV_{\text{eff}} = \frac{c_{\infty} \times BV}{HR \times \int_0^\infty c(t) \, dt}
\]

The momentary heart rate was determined as the mean heart rate during the time interval of the first bolus passage.

After finishing this process, the camera position was corrected, if necessary, to achieve a precise separation of the interventricular septum. Gated by the R-wave of the ECG, 64 frames (32 \times 32 pixels) were acquired for 5 min. For processing the equilibrium radionuclide data a self-developed fully automatic computer program was used\(^{26,27} \).

The criteria for the automatic determination of the left and right ventricular region of interest (ROI) are both morphological and functional. Using a single end-diastolic ROI the following parameters were calculated:

(a) Radionuclide lv/rv stroke count ratio given by

\[
\frac{\text{lv} \left[ \text{counts (ED)} - \text{counts (ES)} \right]}{\text{rv} \left[ \text{counts (ED)} - \text{counts (ES)} \right]}
\]

where ED stands for end-diastole and ES for end-systole. The normal range of the ratio is between 0.6 and 1.7\(^{28} \).

(b) Global left ventricular ejection fraction (EF) given by

\[
\text{counts (ED)} - \text{counts (ES)}
\]

\[
\text{counts (ED)} - \text{counts (background)}
\]

(c) Left ventricular end-diastolic volume (EDV). This is assumed to consist of cylindrical slices arranged perpendicularly to the long axis of the left ventricle, each slice having the height of one image element. The diameter corresponds to the left ventricular ROI. According to the formula

\[
EDV = f_{\text{cal}} \sum_{i=1}^n \frac{d_i^2}{4} \, h \, (\text{ml})
\]

where \( n \) is the number of rows, \( d_i \) the number of pixels in the horizontal row \( i \) of the end-diastolic ROI, \( h \) the height of one pixel (\( h \) has the value 1) (see Fig. 1). EDV is calculated with a calibration factor \( f_{\text{cal}} \) in consideration of the spatial dimension of one image element. The calibration factor was derived earlier from a study including 25 patients with acute myocardial infarction in whom the left ventricular stroke volume was determined simultaneously scintigraphically and by the thermodilution technique:

\[
f_{\text{cal}} = \frac{\text{stroke volume (thermodilution)}}{EF \times EDV-\text{units (radionuclide stroke units)}}
\]

A second study demonstrated the reproducibility of the EDV-calculation: in 32 men who suffered from coronary heart disease or congestive cardiomyopathy and who were in stable condition, repeated determinations of EF and EDV with a time interval of 1-3 hours were performed. The correlation between the first and second determination was 0.96\(^{27} \) and 0.91, respectively.
Regurgitated blood volume (RBV) was calculated from the difference between total and effective left ventricular stroke volume ($SV_{eff}$):

$$RBV = EF \times EDV - SV_{eff}$$

The radionuclide regurgitant fraction was the ratio of the regurgitated blood volume and total left ventricular stroke volume:

$$RRF = \frac{RBV}{EF \times EDV}$$

**Statistical Analysis**

All data are presented as mean ± standard deviation. The radionuclide and angiographic end-diastolic volume and regurgitant fraction were compared by linear regression analysis.

**Results**

The radionuclide data of patients of groups 1 and 2 (end-diastolic volume, ejection fraction, effective stroke volume, regurgitant fraction, lv rv stroke count ratio) are demonstrated in table 1 and 2, respectively. Table 3 provides information about the corresponding angiographic results and the aortographically determined degree of severity of the aortic regurgitation in patients of group 2.

**End-Diastolic Volumes**

Figure 2 compares the angiographically and scintigraphically determined end-diastolic volumes in

**EDV**—left ventricular end-diastolic volume, **EF**—ejection fraction, **Reg.**—regurgitant fraction, **L/R**—lv rv stroke count ratio.

**Table 1** Radionuclide data of 16 patients with normal valvular function (group 1, controls)

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<th>No.</th>
<th>EDV (ml)</th>
<th>EF (%)</th>
<th>Effective stroke volume (ml)</th>
<th>Reg. fraction (%)</th>
<th>L/R</th>
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</table>

**Table 2** Radionuclide data of 24 patients with isolated aortic regurgitation (group 2)

<table>
<thead>
<tr>
<th>No.</th>
<th>EDV (ml)</th>
<th>EF (%)</th>
<th>Effective stroke volume (ml)</th>
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</table>

Abbreviations as in Table 1.

**Figure 2** This figure compares the angiographic and radionuclide end-diastolic volumes in 17 patients of group 2.
Radionuclide evaluation of aortic regurgitation

Figure 3. Radionuclide lv/rv stroke count ratio in 16 controls (left) and 24 patients with aortic regurgitation (right).

Table 3. Angiographic data of 24 patients with isolated aortic regurgitation (group 2)

<table>
<thead>
<tr>
<th>No.</th>
<th>EDV (ml)</th>
<th>EF (%)</th>
<th>Effective stroke volume (ml)</th>
<th>Reg. fraction (%)</th>
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</table>

Abbreviations as in Table 1.

Figure 4. The relation between the angiographic stroke volume ratio and the radionuclide lv/rv stroke count ratio is demonstrated in this figure for patients with aortic regurgitation. ns—not significant.
17 patients of group 2. The correlation is 0.87
($P<0.001$).

**RADIONUCLIDE LV/RV STROKE COUNT RATIO**

In all 16 patients of group 1 radionuclide lv/rv stroke count ratio was within the normal range
(1.2 ± 0.4) (Table 1). Values were elevated in 19 of
24 patients of group 2 (from 2.0 to 5.6), while 5
patients demonstrated normal ratios (from 0.6 to
1.6; Table 2) (average value 3.2 ± 1.1). Therefore
the sensitivity of the radionuclide lv/rv stroke count
ratio was 79%, whereas specificity reached 100%
(Fig. 3). Figure 4 demonstrates the relation between
the radionuclide ratio and angiographic stroke
volume ratio in 16 patients of group 2 ($r=0.10$, not
significant) (Table 3).

**RADIONUCLIDE REGURGITANT FRACTION**

In group 1 radionuclide regurgitant fraction on
average was slightly negative (−4.1% ± 7.1). In
contrast, patients of group 2 demonstrated values
between +20% and +88% (on average 58 ± 20%).
On the one hand in no patient with normal valvular
function did the regurgitant fraction exceed +10%;
on the other, in no patient with aortic regurgitation
was the radionuclide regurgitant fraction less than
+20%. Sensitivity and specificity of this procedure
were therefore 100% (Fig. 5). Figure 6 compares the
radionuclide and angiographic regurgitant fractions
in 16 patients of group 2 ($r=0.78$, $P<0.001$).

![Figure 5](https://academic.oup.com/eurheartj/article-abstract/5/4/317/507569)

**Figure 5** Radionuclide regurgitant fraction in 16 con-
trols (left) and 24 patients with aortic regurgitation (right).

![Figure 6](https://academic.oup.com/eurheartj/article-abstract/5/4/317/507569)

**Figure 6** The relation between the angiographic and
radionuclide regurgitant fractions is demonstrated for
patients with aortic regurgitation.

**Discussion**

Quantification of regurgitated blood volume in
patients with aortic valve regurgitation is still diffi-
cult. It is highly desirable especially for severely ill
patients and in cases of dubious severity of aortic
regurgitation to have a sensitive and specific non-
invasive diagnostic procedure. No precise tech-
nique has, however, been available.

**SEMIQUANTITATIVE ANGIOGRAPHIC ESTIMATION**

The semiquantitative estimation of aortic regur-
gitation during aortic cineangiography using 4 or 5
grades of severity can be altered by the size of
ventricular cavity (distribution volume of the con-
trast material), cardiac arrhythmias, cardiac output
and the position of the catheter during injection
into the aortic root. However, if the catheter is
placed properly in the aortic root, all patients
with normal valvular function will be classified
correctly.

**METHOD OF SANDLER AND DODGE**

Problems also occur with the method of Sandler
and Dodge. Determination of cardiac output by
Fick's principle might be incorrect in patients with
congestive heart failure. Furthermore, it is some-
times difficult to assess the exact end-diastolic and
end-systolic boundaries of the left ventricle during
cineangiography. For theoretical reasons it is
necessary to determine left ventricular stroke...
volume and cardiac output simultaneously. However, the reproducibility of cardiac output during left ventricular cineangiography is poor, probably due to the influence of deep inspiration and of arrhythmias.

Finally, since the heart rate and ventricular pressure at the time of angiography must be comparable to the rate and pressure at the time of determination of effective stroke volume, contrast material-induced arrhythmias will limit the value of this method.

**Radionuclide LV/RV Stroke Count Ratio**

In our study the sensitivity of the lv/rv stroke count ratio was 79%. This value is comparable with the findings of others. The lack of sensitivity even in patients with distinct aortic regurgitation is due mainly to two problems. For geometric reasons equilibrium radionuclide lv/rv stroke count ratio is normal up to about 1.7, corresponding to a regurgitant fraction of 41%.[13] Recently, more sophisticated methods have been developed to improve the separation between the two ventricles and between the ventricles and atria. Using the first-pass technique,[8] a slant hole collimator[12] or Fourier-amplitude analysis[31] the radionuclide lv/rv stroke count ratio could be approximated to the ideal value of 1.00 in healthy subjects. Further systematic investigations will have to examine the reliability of these new techniques.

The other essential problem cannot be overcome by these new procedures. In patients with concomitant right-sided regurgitation (due to tricuspid or pulmonary regurgitation, shunt lesions) elevated values, as seen in patients with aortic regurgitation, will be decreased or even completely normalized. In our study, normal lv/rv stroke count ratios were observed only in patients of group 2 who were in extremely poor clinical condition. Four of them showed severely depressed left ventricular function (EF less than 30%); one patient died shortly after the investigation, the others underwent immediate aortic valve replacement. The last patient suffered from paravalvular regurgitation after aortic valve replacement. All patients showed clinical signs of right heart failure.

We failed to demonstrate a significant correlation between the angiographic stroke volume ratio and the radionuclide lv/rv stroke count ratio in patients with aortic regurgitation. This is due to the fact that the angiographic ratio was defined as total left ventricular stroke volume divided by effective stroke volume (derived from cardiac output); the radionuclide ratio as left ventricular stroke counts divided by right ventricular stroke counts. Thus, discrepancies between these ratios mainly reflect additional right ventricular overload (tricuspid or pulmonary regurgitation). This is strongly supported by the fact that the largest differences were noted in patients with severely depressed left ventricular function. When three patients with radionuclide ejection fractions lower than 40% and one patient with an extremely dilated heart who died shortly after the investigation (patient 6), were excluded, the correlation is substantially improved (r=0.73, P<0.01). This compares with the results reported by Nicod et al.[13] who also noted an improved accuracy of the lv/rv stroke count ratio in patients with normal or almost normal left ventricular ejection fraction.

**Combined First-Pass/Equilibrium Technique**

The improved sensitivity of the first-pass/equilibrium technique over the lv/rv stroke count ratio is due to several factors. Geometric problems, i.e. an overlap of the heart chambers, play only a minor role. The effective stroke volume, determined by the described first-pass method, is not influenced by valvular heart diseases or shunt lesions (especially right ventricular volume overload).

The time needed to determine the radionuclide regurgitant fraction by this procedure is 15 min including 3 min for data processing.

The latter was performed by a self-developed fully automated computer program in which the left and right ventricular end-diastolic regions are defined on morphological and functional bases.[26,27] We avoided subjectively-set right and left ventricular regions. Because of poor reproducibility the lv/rv stroke count ratio evaluated by manually drawn regions cannot distinguish between normal, mild/moderate and severe regurgitation.[19] In our own study, manual corrections were necessary only in 2 of 40 cases. In these we noted a bad separation between the left and right ventricles; the automatically computed ROI was rejected and corrected manually.

Several factors can influence the reliability of the combined first-pass/equilibrium technique. An additional mitral regurgitation leads to an estimation of the 'total left ventricular regurgitant fraction' consisting of mitral and aortic regurgitation. Calculation of blood volume from height, weight and sex of the patient might not be accurate in cases with congestive heart failure or in those receiving potent diuretic therapy. In patients with coronary heart disease (control group), effective stroke...
Volume can be underestimated due to a reduced blood volume. This could lead to a false-positive regurgitant fraction. Underestimation of total left ventricular stroke volume can occur if the assumed geometric model differs from the real ventricular cavity. This might be responsible for the (generally) slightly negative radionuclide regurgitant fraction in patients with normal valvular function. With increased end-diastolic volume—as in patients with aortic regurgitation—the left ventricle resembles more a spheroid causing a distinct reduction of this deviation.

The left ventricular end-diastolic volume still shows large individual variations. A patient who has a 250 ml volume by contrast angiography can have anywhere between 200 and 400 ml by the radionuclide method. This is in part not the fault of our radionuclide technique, but is also related to our ‘gold standard’ (angiocardiology). Therefore, although we found a good correlation between the angiographic and radionuclide regurgitant fraction, caution is advised in the interpretation of the regurgitant fraction in an individual patient.

Several authors have demonstrated that count-based end-diastolic volume measurement is superior to geometric approaches. However, these methods are less reliable in end-diastolic volumes larger than 300 ml, as observed in patients with aortic regurgitation. Furthermore, in our laboratory, it is too time-consuming to evaluate the activity of a blood sample during the daily routine.

As to the method of Sandler and Dodge, we did not determine total and effective stroke volume simultaneously. However, all patients were in the supine position during and between the investigations. They were in regular sinus rhythm, and the heart rate showed only slight changes during the time of observation (maximal 9 beats per minute). Therefore, changes in left ventricular stroke volume are probably negligible.

Angiographic and radionuclide techniques cannot reveal identical values for ejection fraction, end-diastolic volume and regurgitant fraction. Influences of the contrast material, differences in pre- and after-load and the different number of heart cycles used to evaluate these variables must be taken into account. Furthermore, during radionuclide investigation the patient is completely relaxed, while angiographic investigation represents a stress situation; the volumes of the heart chambers can only be evaluated during deep inspiration.

Despite these methodologic considerations, we believe that the radionuclide regurgitant fraction is a valuable method for quantitative evaluation of aortic regurgitation. Furthermore, the first-pass/equilibrium technique clearly identified and separated patients with aortic regurgitation from those with normal valvular function.

In conclusion, the usual determination of the radionuclide lv/rv stroke count ratio represents a simple technique for noninvasive evaluation of aortic (and mitral) valve regurgitation. The disadvantage is the reduced sensitivity in patients with depressed left ventricular function. Radionuclide regurgitant fraction estimated by the combined first-pass/equilibrium technique demonstrated in all cases a reliable quantitative evaluation of aortic regurgitation. Patients with haemodynamically insignificant reflux are not represented in this study because they were not subjected to cardiac catheterization. The accuracy of the described technique for these cases cannot be derived from this study.

References
Radionuclide evaluation of aortic regurgitation


