Quantification of valvular regurgitation using radioisotopes

P. Rigo AND M. Chevigné

University of Liège, Liège, Belgium

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Mitral and aortic regurgitations impose an abnormal volume overload on the left ventricle. Recent advances in radionuclide angiographic measurements of all cardiac volumes have made this a practical technique for the detection, quantification and functional assessment of valvular regurgitations and shunts. The method is based on the comparative evaluation of total and effective left ventricular stroke volume. In the radionuclide technique, the right ventricular stroke volume is most frequently used to represent the effective left ventricular stroke volume although techniques have been presented which used as reference the left ventricular stroke volume calculated from measurements of heart rate and cardiac output (Fick method or dye dilution or scintigraphic techniques). The technique can be performed either during first-pass or at equilibrium. Equilibrium measurements are performed in the left anterior oblique position. The stroke volume ratio and the regurgitant fraction are calculated. This technique has been shown to provide adequate quantitative measurements of mitral and aortic regurgitations. Its specificity is adequate with careful positioning and if regions of interest are determined and care is taken to exclude inadequate studies (as these can be prospectively recognized). The technique can separate moderate from severe regurgitation, provide follow-up values for both left ventricular volume and regurgitant fraction, and assess the effect of interventions on the amount of regurgitation. The technique is, however, not adequate to detect mild or minimal regurgitation.

In conclusion, equilibrium scintigraphic measurement of valvular regurgitation is an attractive new technique for measuring valvular regurgitation. Its clinical value lies in its simplicity, its reproducibility and its wide applicability. Its accuracy will be improved by performance of gated tomographic acquisitions.

Introduction

Radionuclide angiography is a non-invasive technique that provides most of the information previously available only through the use of contrast angiography. It can indeed measure ventricular volumes as well as systolic and diastolic function parameters, mainly ejection fraction, ejection rate and filling rate. The ability to evaluate simultaneously both the right ventricular and left ventricular parameters has proven particularly useful in patients with valvular regurgitations. Comparison of right and left ventricular stroke volumes can indeed be used to assess the severity of valvular regurgitation, while right ventricular function parameters can provide information on the repercussions of the left ventricular overload on the pulmonary circulation and right ventricular tolerance.

One of the main advantages of radionuclide angiography is the possibility of studying patients during exercise and measuring in absolute or relative terms the changes in cardiac output, ejection fraction and fractional volumes so as to derive information on the evolution of the pump and cardiac function during exercise.

In this review, we will describe the methodology of radionuclide angiography and its applications to the functional and prognostic characterization of patients with valvular regurgitation.

Methodology

THEORETICAL BASIS

The tracer after intravenous injection achieves rapid mixing in the blood. During first transit, although the tracer concentration varies with time, homogeneous filling, at least of the left ventricle, is considered to be obtained in most case. Uniform blood concentra-
tion is achieved within 5 min and considered stable during performance of the equilibrium studies. Count variations in a ventricular region of interest during the systolic phase for first-pass studies, or the whole cardiac cycle for equilibrium studies, are therefore considered to represent volume variations. This count-volume proportionality assumption is central to the application of radionuclide angiography in the study of cardiac function and valvular regurgitation. Despite several limitations due to tissue attenuation and in particular self absorption in enlarged ventricles, it has been substantiated over a wide range of chamber volumes.

**TRACER**

Technetium labelled red cells are most frequently used. Labelling can be performed in *vivo* or in *vivo*. The modified *in vivo* technique is most convenient. It requires preinjection of stannous pyrophosphate or stannous fluoride (0.02 mg kg⁻¹) intravenously. Blood is reaspirated 30 min later in a syringe containing free pertechnetate and labelling is allowed to proceed prior to reinjection. This provides a high labelling efficiency (>90%) with limited free pertechnetate. This tracer remains within the vascular compartment. In contrast, technetium labelled human serum-albumin diffuses quite rapidly out of the vascular compartment and the high background activity renders it improper for interventions such as equilibrium exercise studies.

For first-pass acquisitions, the use of a tracer remaining in the vascular space during first transit such as technetium 99m pertechnetate suffices. The short-lived radioisotopes recently proposed for first-pass angiography belong to this category: tantalum-178 (t/2: 9.3 min), iridium-191m (t/2: 4.9 s), gold-195m (t/2: 30.5 s) or H2 150 (t/2: 2 min).

**EQUILIBRIUM TECHNIQUE**

Equilibrium studies are performed in the left anterior oblique projection, after equilibration of the tracer. Use of a small detector (20 cm) or of a slanthole collimator can permit the necessary craniocaudal tilt and facilitates positioning that provides separation of the four cardiac chambers. The adequacy of positioning, usually a 35 degrees LAO must be verified using the persistence scope and later on functional images (mainly the Fourier amplitude image).

Processing of the average cardiac cycle first consists of normalization for the variable acquisition times resulting from cardiac arrhythmias during acquisition. Temporal and spatial smoothings of the images follow which are helpful in recognizing cardiac borders. Although automatic programmes have been proposed for the definition of the left ventricular area of interest, none is satisfactory for the right ventricle. We therefore prefer to trace the regions of interest by hand relying heavily on the information provided by the functional images. Fourier phase and amplitude images are particularly useful. They do not require preliminary information such as the time of systole and account for all volume variations irrespective of timing. We trace the left ventricular, right ventricular and background regions of interest by concomitant examination of four images, the end-diastolic image, the end-systolic...
image, and the Fourier phase and amplitude images. Only the diastolic regions of interest are used to calculate the stroke volume ratio while the background and systolic regions of interest serve for the ejection fraction. We prefer the use of single region of interest over both ventricles rather than end-systolic and end-diastolic regions of interest. Indeed, we found that the improved accuracy of the latter technique in normal subjects was associated with an increased complexity and a higher measurement variability. The use of functional images enables to define the smallest region of interest that includes all stroke counts. Calculation should not however be done on functional images but rather on the left and right ventricular volume curves. It is specially true for the amplitude image as this reflects count variations that do not contribute to stroke volume. Gross inaccuracies may therefore result in patients with asynchronous contractions of dyskinetic regions as frequently observed in coronary artery disease, in cardiomyopathies or in patients with marked left ventricular dysfunction.

PARAMETERS CALCULATED

Ventricular volumes

Estimation of ventricular volumes can be either relative or absolute. Relative volume can be directly obtained through consideration of ventricular counts, all volumes being standardized to the end-diastolic volume at a given time. Absolute volume can be measured through geometric or count-based method. The latter cannot be used for first pass studies as the tracer concentration varies during each diastole. Geometric measurements depend on accurate border recognition and the assumption of the ellipsoid formula. The count-based method can be used with equilibrium studies. It consists first of count normalization for the time of acquisition, radioactive decay and tracer concentration. This is done by comparison with a blood sample drawn during acquisition. Calculation of absolute volume further depends on correction for attenuation both within the ventricle and in the chest wall. Several methods have been devised to estimate mean ventricular depth. Although quite accurate, none has achieved widespread clinical use, however, mainly because of the increased complexity.

Ejection fraction

The ejection fraction (EF) is calculated on the left and right ventricular volume curves after background correction, according to the classical formula:

$$\text{EF} = \frac{\text{EDC} - \text{ESC}}{\text{EDC}},$$

where EDC is end-diastolic counts and ESC is end-systolic counts.

Stroke volume ratio

The stroke volume ratio (SVR) is simply the ratio of the left ventricular (LV) stroke counts over the right ventricular (RV) stroke counts taken as reference (provided no concomitant right ventricular volume overload occurs):

$$\text{SVR} = \frac{\text{LV-DC} - \text{LV-SC}}{\text{RV-DC} - \text{RV-SC}},$$

where DC and SC are diastolic and systolic counts, respectively. As we prefer to keep the reference stroke volume in the denominator, we use an inverted ratio to assess patients with right ventricular volume overload:

$$\text{SVR} = \frac{\text{RV-DC} - \text{RV-SC}}{\text{LV-RC} - \text{LV-SC}}.$$

Regurgitant fraction

The regurgitant fraction (RF) is the fraction of the stroke volume that is regurgitated. It can easily be calculated as:

$$\text{RF} = \frac{\text{LV stroke counts} - \text{RV stroke counts}}{\text{LV stroke counts}}.$$

A more general formulation:

$$\text{SVR} - \frac{x}{\text{SVR}},$$

where x is 1 or rather the mean SVR in normal subjects allows adjustment of the regurgitant fraction to each laboratory’s normal values and permits the assessment of left and right ventricular volume overload by LV/RV or RV/LV ratio keeping the reference output in the denominator.

Other methods have been proposed to calculate the regurgitant fraction. Konstam et al. compared the total stroke volume (absolute end-diastolic volume times ejection fraction) to the forward stroke volume measured by Fick or a standard thermodilution technique. Klepzig et al. measured the effective forward stroke volume by first-pass radionuclide cardiac output and heart rate determination. These approaches and especially the Fick method should be particularly useful in cases where the right ventricular...
stroke volume cannot be used as the reference because of tricuspid regurgitation or other causes of right ventricular volume overload.

Regurgitant stroke volume (RSV) to end-diastolic volume (EDV) ratio

To assess the functional importance of regurgitation and more importantly to evaluate the potential for left ventricular volume regression after successful valvular replacement, Levine and Gaasch have proposed the calculation of the RSV/EDV ratio. This ratio can be calculated through radionuclide angiography without determination of absolute volume. Indeed the regurgitant stroke volume equals regurgitant fraction times total stroke volume and total stroke volume equals ejection fraction times end-diastolic volume. Therefore

\[
\frac{RSV}{EDV} = \frac{RF \times EF}{ESV}
\]

both RF and EF being normalized parameters.

Calculation of the RSV/ESV volume ratio might also be useful as the end-systolic volume is less dependent on the regurgitant stroke volume than the end-diastolic volume. It could be obtained as:

\[
\frac{RSV}{ESV} = \frac{RF \times EF}{1 - EF}
\]

Limitations of the techniques—future developments

Limitations of the techniques are twofold. First, the techniques are unable to evaluate complex lesions adequately. If both ventricles are overloaded, the method will lack a reference ventricle; in case of combined valvular regurgitation, mitral and aortic for instance, the combined repercussions are assessed and there is no possibility of separating the effects of each lesion.

Second, there is a difficulty in adequately separating the left and right ventricles from each other and from the surrounding structure. This is specially true for the right atrium which cannot be completely separated from the right ventricle. This overlap can, however, be identified on the amplitude image as the combination of discordant phase result in a reduced or absent amplitude. Overlap is also true for the right ventricular outflow tract which is usually superimposed on the image of the ascending aorta. This results in a rather wide range of normal values, thereby reducing the sensitivity and specificity of the technique. Although the immediate reproducibility is good, long-term reproducibility might be influenced by changes in the biventricular geometry. Also the determinants of ventricular regurgitation independent of the valve orifice are many and complicate the issue of long-term reproducibility.

Gated blood pool tomography although more complex to acquire and analyse has potential for more accurate volume determination and for better ventricular separation. This is also the case for nuclear magnetic resonance which has already been shown to provide precise determination of both left and right ventricles with a stroke volume ratio close to 1. The use of these tomographic techniques during exercise appears impossible, however.

Clinical results

RESULTS OF RESTING STUDIES

Results in normal subjects

The stroke volume ratio in a series of 24 subjects without any sign of valvular lesion and in whom an adequate study could be obtained was 1.20 ± 0.15 SD. Several groups using variations of the initial technique have reported normal values closer to the expected value of unity. Bough et al. report values of 1.08 ± 0.06 with a slanthole collimator; Janowitz et al. report values between 1.0 and 1.13 using a first-pass method. Subtraction of the right atrial contribution as performed by the Besançon and the Los Angeles groups and the use of tomographic acquisition also result in normal values closer to unity.

The specificity of the technique is discussed elsewhere in this issue (P. Gobert et al.). False positive results occur in some 20% of routine studies. They are, however, of limited grade and can usually be suspected prospectively as most result from inadequate positioning or persistent ventricular superimposition. We did not find a diminished left ventricular ejection fraction to be by itself a cause of false positive results.

Results in patients with valvular regurgitation

Several groups have reported a good correlation between scintigraphic and angiographic regurgitant fraction or qualitative results. In patients with chronic regurgitation, severe regurgitation corresponds to a stroke volume ratio of approximately 4 or a regurgitant fraction of around 0.7. We took moderate regurgitation to be in the range of ±2 stroke volume ratio or a regurgitation fraction of 0.4. Mild regurgitation probably cannot be adequately separated from normals using this technique.

Patients with acute regurgitation should not be
assessed using this scale, however, as the absence of atrial or ventricular dilatation limits the regurgitant volume independent of the severity of the valvular lesion.

Studies of tricuspid regurgitation with radionuclide angiography are few. Indeed, the stroke volume ratio is seldom applicable as most patients have concomitant left-sided valvular lesions. Recognition of tricuspid regurgitation is possible however through the observation of phasic count variations in the liver blood pool.

After valvular replacement, the decline of the regurgitation fraction can be demonstrated in successful cases. Residual regurgitation due to paravalvular leakage or prosthesis dysfunction can be separated from ventricular dysfunction as a cause of persistent or recurrent failure.

VENTRICULAR ADAPTATION DURING EXERCISE

Aortic regurgitation

There are 4 determinants of the aortic regurgitant flow: the size of the aortic orifice during diastole, the duration of the diastole per beat (a function primarily of heart rate) and the pressure in the aorta and left ventricle during diastole. Increasing the heart rate with atrial pacing leads to a reduction in ventricular volume and regurgitant flow. During exercise, a decreased regurgitant fraction can result from changes in diastolic duration as well as from an increase in the left ventricular diastolic pressure. These latter changes are most prominent in patients with severe aortic regurgitation or when produced by isometric rather than dynamic exercise. These changes in regurgitant fraction alter end-diastolic volume and preload and influence the ejection fraction response to exercise. In patients with aortic insufficiency, a drop in ejection fraction cannot therefore be interpreted to represent decreased left ventricular function without knowledge of the changes in end-diastolic volume, regurgitant volume and most importantly end-systolic volume.

Among patients with aortic insufficiency, three exercise pattern are common: An increased ejection fraction resulting mainly from a decreased end-systolic volume is a normal response and reflects mainly mild to moderate well tolerated regurgitation. A decreased ejection fraction with an increased end-systolic volume is an abnormal response that reflects exercise-induced left ventricular dysfunction. A decreased ejection fraction can also occur despite a diminution of the end-systolic volume because of a marked reduction in the regurgitant and end-diastolic volumes. This pattern is mainly observed in young patients with a large aortic regurgitation. End-systolic volume changes during exercise rather than ejection fraction changes should therefore be considered when evaluating the exercise tolerance of patients with valvular regurgitation. The end-systolic pressure over end-systolic volume ratio should also prove more useful.

Mitral regurgitation

Few exercise studies have been reported in mitral regurgitation. Although Bassand et al. observe an increase in regurgitation, Henze et al. report a decreased regurgitant fraction in mitral regurgitation as well as in aortic regurgitation. The right ventricular ejection fraction response to exercise differs, however, for these authors: it frequently tends to decrease in mitral regurgitation. This difference could reflect technical factors or more severe changes in pulmonary artery pressure consecutive to greater left ventricular contractile dysfunction unmasked by changes in its loading conditions.

Here again analysis of all volumes (including the right ventricle) and of the end-systolic volume pressure index should be more useful than simple consideration of the ejection fraction changes. Concomitant analysis of pulmonary blood volume during exercise should also be performed.

CLINICAL VALUE OF RADIONUCLIDE ANGIOGRAPHY IN PATIENTS WITH VALVULAR REGURGITANT LESIONS

Although the diagnosis is usually evident, clinical evaluation of patients with mitral and mainly aortic incompetence and the timing of surgery remain difficult. Indeed, compensatory changes can mask the development of left ventricular dysfunction and delay the onset of symptoms. Evolution of left ventricular ejection fraction, left ventricular volumes, systolic wall stress, regurgitant fraction and right ventricular ejection fraction may help precise the stage of the disease or document its evolution. Such precise determination appears most useful in patients with volume overload and severe ventricular dysfunction.

Radionuclide angiography provides a useful tool to study the natural history of the disease, the degree of tolerance to valvular regurgitation and the predictors of evolution.

At an early stage, detection of a diminished left ventricular reserve and of exercise-induced dysfunction is important if one wishes to avoid the development of irreversible ventricular damage before surgery. We have seen that the ejection fraction changes suggested by Borer should be replaced by end-systolic volume changes or more complex...
parameters. Concomitant analysis of pulmonary blood volume and of right ventricular function during exercise also appears important especially in patients with mitral valve disease.32–33 Depressed right ventricular function at rest reflects both increased pulmonary vascular resistances and concomitant left ventricular dysfunction. It probably has prognostic significance and might signal an increased risk for post-operative tricuspid insufficiency.

Ventricular volume changes resulting from pacing induced tachycardia could also provide data on the ventricular response to a diminished regurgitant fraction and preload in aortic regurgitation. Serial measurements of ventricular volumes, ejection and regurgitant fraction should also provide important data to help determine the timing of surgery. An increase in volumes, specially the end-systolic volume, in the face of a stable or decreasing regurgitant fraction provides evidence for progressing myocardial dysfunction. This could be best followed by the regurgitant stroke volume/end-diastolic volume or regurgitant stroke volume/end-systolic volume ratio as suggested by Levine and Gaasch171. Changes in ventricular volume and regurgitant fraction induced by drug can also be documented by this technique. This can substantiate the rationale for the use of drugs such as converting enzyme inhibitors in patients with aortic regurgitation. It would be worthwhile to evaluate whether such drugs could alter the natural history of the disease.

After valvular replacement, radionuclide angiography is useful to document the extent of post-operative improvement and assess the cause of failure: persisting left ventricular dysfunction or recurrent valvular or paravalvular insufficiency.

**Conclusions**

Radionuclide angiography is a useful technique for evaluating patients with valvular regurgitation. Its main advantages are its potentials for serial follow-up and its ability to study patients during exercise. Analysis of all volumes and of ventricular interactions are more promising than the simple consideration of ejection or regurgitant fraction. The advance of radionuclide tomography and the application of these principles to nuclear magnetic resonance will further enhance the utility of this approach.

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