

Can right ventricular performance be assessed by equilibrium radionuclide ventriculography?

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ABSTRACT Although right ventricular function may be examined by following the passage (first pass) of a bolus of radionuclide through the right heart before it reaches the left heart, the counts detected with conventional gamma cameras in such a short time interval are low; moreover, repeated determinations would result in an unacceptable radiation burden to the patient. We have modified the gated equilibrium blood pool method to allow repeated assessment of the right ventricular ejection fraction (RVEF) and have compared the results with the first-pass method in 43 patients. Good agreement was obtained between the two methods ($r = 0.91$, $p < 0.001$). The mean difference between the two methods was 0.04 with an intra-observer variation for the equilibrium studies of 0.03 and an inter-observer difference of 0.04. The mean difference in RVEF for seven patients studied on two separate occasions 30 minutes apart was only 0.02.

In four patients the mean RVEF measured at rest was 0.44 ± 0.05 (SEM) and after exercise it was 0.48 ± 0.06 . After infusion of isoprenaline at $1 \mu\text{g}/\text{min}$ the mean rose to 0.64 ± 0.04 ($p < 0.02$) and after infusion of a new β_1 -sympathomimetic agent, prenalterol, at doses of 1 and 2 mg it was 0.56 ± 0.02 ($p < 0.02$) and 0.59 ± 0.03 ($p < 0.01$) respectively, where the significance levels are relative to the resting values. In nine patients with good ventricular function the vasodilator nifedipine caused right and left ventricular ejection fractions to increase by the same amount; while in six patients with severe impairment of left ventricular function due to ischaemic heart disease the RVEF increased from 0.58 ± 0.03 to 0.73 ± 0.03 ($p < 0.01$) after 2 mg of prenalterol, but the left ventricular ejection fraction increased only from 0.22 ± 0.04 to 0.26 ± 0.04 . We conclude that repeated estimation of right ventricular performance is possible by equilibrium radionuclide ventriculography.

Radionuclide techniques are now widely used for evaluating the left ventricular ejection fraction (LVEF). Two principal methods have been used. The first-pass method analyses the initial passage of a radionuclide bolus through the left ventricle by frequent sampling of the fluctuations in activity during several cardiac cycles. The second method is the gated equilibrium blood pool technique. Here an intravascular label is given and once equilibrium has been achieved within the blood pool a sequence of images throughout the cardiac cycle is stored in the computer memory and updated over several hundred heart beats by gating from the R-wave of

the patient's electrocardiogram. Both methods have advantages and disadvantages. The principal advantage of the first-pass method is that there is little background contribution from overlying cardiac chambers. With conventional gamma cameras, however, the counts detected in each short time interval are low, resulting in large statistical uncertainty in the calculated ejection fraction. Repeated determinations are impracticable as they would result in an unacceptable radiation burden for the patient. With the equilibrium technique the background contribution from overlying structures is higher; but on the other hand greatly improved counting statistics may be achieved, and as the intravascular label is present for several hours the method is suitable for repeated determinations.

The first-pass technique uses a right anterior oblique projection to separate the right atrium from the

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right ventricle,¹ and counts from the overlapping left ventricle can be prevented by detecting the bolus only as it passes through the right side of the heart, stopping the acquisition before it reaches the left side. To separate the right and left ventricles with the equilibrium method a left anterior oblique projection must be used. Until recently it was thought that this projection could not be used for the determination of the right ventricular ejection fraction (RVEF) because of the contribution from the right atrium. Recently, however, Maddahi and colleagues² suggested that this difficulty could be overcome by assigning separate regions of interest to the right ventricle at end diastole and end systole.² They admitted that in its present form the technique was subjective and required considerable experience for accurate assignment of region of interest.

To us it seemed that the principal difficulties were: (1) The right ventricle has an extremely irregular shape that varies from patient to patient. (2) The contribution from the right atrium to the counts in the right ventricular region of interest will vary, depending on the right atrial size. (3) A deformed or poorly contracting right ventricle may worsen the separation between the right and left ventricles. (4) Background counts come from all the structures around the right ventricle and the most suitable site for a background correction remains uncertain.

If we assume that the stroke counts—that is, the difference in ventricular counts between end diastole and end systole—must be the same for each ventricle then we have a means of checking the assigned background region. We therefore undertook a study to determine whether a standardised and reproducible technique could be developed for the assessment of right ventricular performance.

Methods

PATIENTS

We studied 43 patients by both first-pass and gated equilibrium methods. We purposely selected patients in whom there would be a wide range of both right and left ventricular ejection fraction. Of the 43 patients, 11 had atypical chest pain and had a normal rest and exercising electrocardiogram and normal LVEF at rest and on exercise. Their subsequent follow-up suggested musculoskeletal chest pain and for the purpose of this study they were deemed normal subjects. Fifteen patients had documented ischaemic heart disease and seven of them had suffered a myocardial infarction. The remaining 17 patients had chronic bronchitis and emphysema with severe impairment of airway function (mean FEV₁ 0.70 ± 0.32 l). In addition, we

studied the response to exercise and drug treatment in 20 patients with ischaemic heart disease or hypertension who had a wide range of left ventricular ejection fraction. Details of our methods for examination and analysis of the left ventricle have previously been published.³⁻⁶ The patients with chronic bronchitis and emphysema freely consented to participate in the study, which had the approval of our institute's ethical committee. All the other patients had been referred to the laboratory as part of their clinical investigation.

RADIONUCLIDE METHODS

The patients were studied in the supine position beneath a Searle LEM gamma camera with a high-sensitivity parallel-hole collimator, and 740 MBq (20 mCi) of albumin labelled with technetium-99m was injected as a rapid bolus. Images were collected on a Cromemco (System 3) microcomputer in frame mode and were gated from the R-wave of the patient's electrocardiogram. For the first-pass technique a 10° right anterior oblique view was used, the acquisition being started as soon as the bolus had been injected and terminated once the activity was seen to be in the lungs.⁷ This usually allowed us to acquire 10 cardiac cycles. For the equilibrium method we waited for five minutes after injection so that the tracer was uniformly distributed in the blood pool. The angulation of the camera was then changed to a 20–30° left anterior oblique projection with a 20° caudal tilt and 500 heart beats were acquired for the equilibrium study. Images of the composite cardiac cycle were then displayed for both studies in "movie" mode on a TV monitor.

ANALYSIS OF FIRST-PASS STUDY

From the movie images we identified the right ventricle at end diastole and end systole. Background corrections were obtained from separate regions along the inferior margin of the right ventricle at the appropriate phases of the cardiac cycle and scaled to an area equal to that of the corresponding right ventricular region.⁷ RVEF was calculated from the relationship

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

where EDC and ESC are the background-corrected counts at end diastole and end systole respectively.

ANALYSIS OF EQUILIBRIUM STUDY

Inspection of the movie images showed that there was good separation between the right and left ventricles, but that during systole the right atrium overlapped the position occupied by the right ventricle at end diastole. The use of a fixed region of interest, as

is common in the determination of the left ventricular ejection fraction, was therefore inappropriate since the variable contribution from the right atrium would result in a significant underestimate of RVEF. In addition to the conventional movie sequence we used three specific computer programs to assist in identifying the right ventricle at systole and diastole. The first of these was a movie sequence which subtracted frame n from frame $n - 1$, and so on throughout the cardiac cycle. This allowed identification of the phase of emptying and filling by providing a movie display with maximum contrast between the ventricles and the atria.³ The second program used a phase analysis based on a Fourier transformation of the ventriculogram.⁸ This allowed clear identification of the right ventricle and in particular allowed definite identification of the outflow tract, which is difficult by any other technique (fig 1). The third program used an analysis based on the logarithm of the variance between each pixel and the pixels surrounding it. In effect this allows identification of a count gradient for each frame and is a form of edge analysis that permits the delineation of the ventricular outline at systole and diastole. Only a combination of these methods allowed complete identification of the right ventricle.

Various attempts were made to identify suitable regions for background correction of the right ventricle. It is important to emphasise that all background corrections that are now used for the left ventricle have been empirically determined. We found that a background assigned along the inferior margin of the right ventricle (taking the counts there at end systole) provided a value for stroke counts equal to that of the left ventricle. The background-corrected counts were then used to calculate the right ventricular ejection fraction as above.

ASSESSMENT OF REPRODUCIBILITY

For the equilibrium technique the intra-observer variation in the measurement of RVEF was determined in 40 patients and the inter-observer variation was assessed in 15 studies. The correlation between the first-pass and equilibrium methods was measured in 43 patients. In seven subjects RVEF was determined by the equilibrium method at rest on two separate occasions 30 minutes apart.

PHARMACOLOGICAL STUDIES

We conducted two studies to determine whether the effects of exercise and drug intervention on right ventricular performance could be assessed by the equilibrium technique. In the first study four patients with moderately good left ventricular function were studied at rest, during supine exercise at 50 watts, and after isoprenaline infused at $1 \mu\text{g}/\text{min}$.

Then the effect of a new β_1 -sympathomimetic agent, prenalterol, was examined at two different dose levels, 1 mg and 2 mg. Details of the left ventricular function studies have already been published.⁹ In the second study we examined the response of both ventricles to a vasodilator (nifedipine 10 mg) in nine patients with hypertension. In the third we examined the response of both ventricles to a 2-mg dose of prenalterol given to six patients with severe impairment of left ventricular function due to ischaemic heart disease (LVEF < 0.30).

Results

Using background selection for the right ventricle, as shown in figure 2, we observed close correlation between stroke counts for the right and left ventricles. The mean difference between the counts for the two ventricles was only 4.9%.

The values of RVEF determined by the equilibrium technique are compared with those from the first-pass method in figure 3 ($r = 0.91$, $p < 0.001$). The mean difference between the two methods was 0.04.

The analysis of 40 equilibrium studies by the same observer on two separate occasions is shown in figure 4. The mean intra-observer variation was only 0.03. When two observers independently analysed 15 studies the mean inter-observer variation in RVEF was 0.04.

The values of RVEF measured by the equilibrium method on two separate occasions 30 minutes apart are shown in figure 5. There was no significant difference between the two measurements, the mean difference being only 0.02. In addition, RVEF for one subject lying at rest remained unchanged when measured at 30-minute intervals for two hours.

The responses of the right and left ventricles to exercise, isoprenaline, and prenalterol in the four patients with ischaemic heart disease are shown in figure 6. The mean values of RVEF at rest, during exercise at 50 watts, after infusion of isoprenaline at $1 \mu\text{g}/\text{min}$, and after 1 and 2 mg of prenalterol were 0.44 ± 0.05 (SE), 0.48 ± 0.06 , 0.64 ± 0.04 ($p < 0.01$), 0.56 ± 0.02 ($p < 0.02$), and 0.59 ± 0.03 ($p < 0.01$) respectively, where the significance levels are relative to the resting values. The corresponding values of LVEF were 0.38 ± 0.07 , 0.41 ± 0.09 , 0.53 ± 0.09 ($p < 0.01$), 0.45 ± 0.09 ($p < 0.01$), and 0.47 ± 0.10 ($p < 0.01$), significance levels again relative to the resting values.

In the nine patients with hypertension LVEF was initially 0.62 ± 0.04 (SE), increasing to 0.69 ± 0.03 after nifedipine. RVEF was initially 0.58 ± 0.03 and 0.73 ± 0.03 after nifedipine (fig 7). In patients with ischaemic cardiomyopathy the resting LVEF was

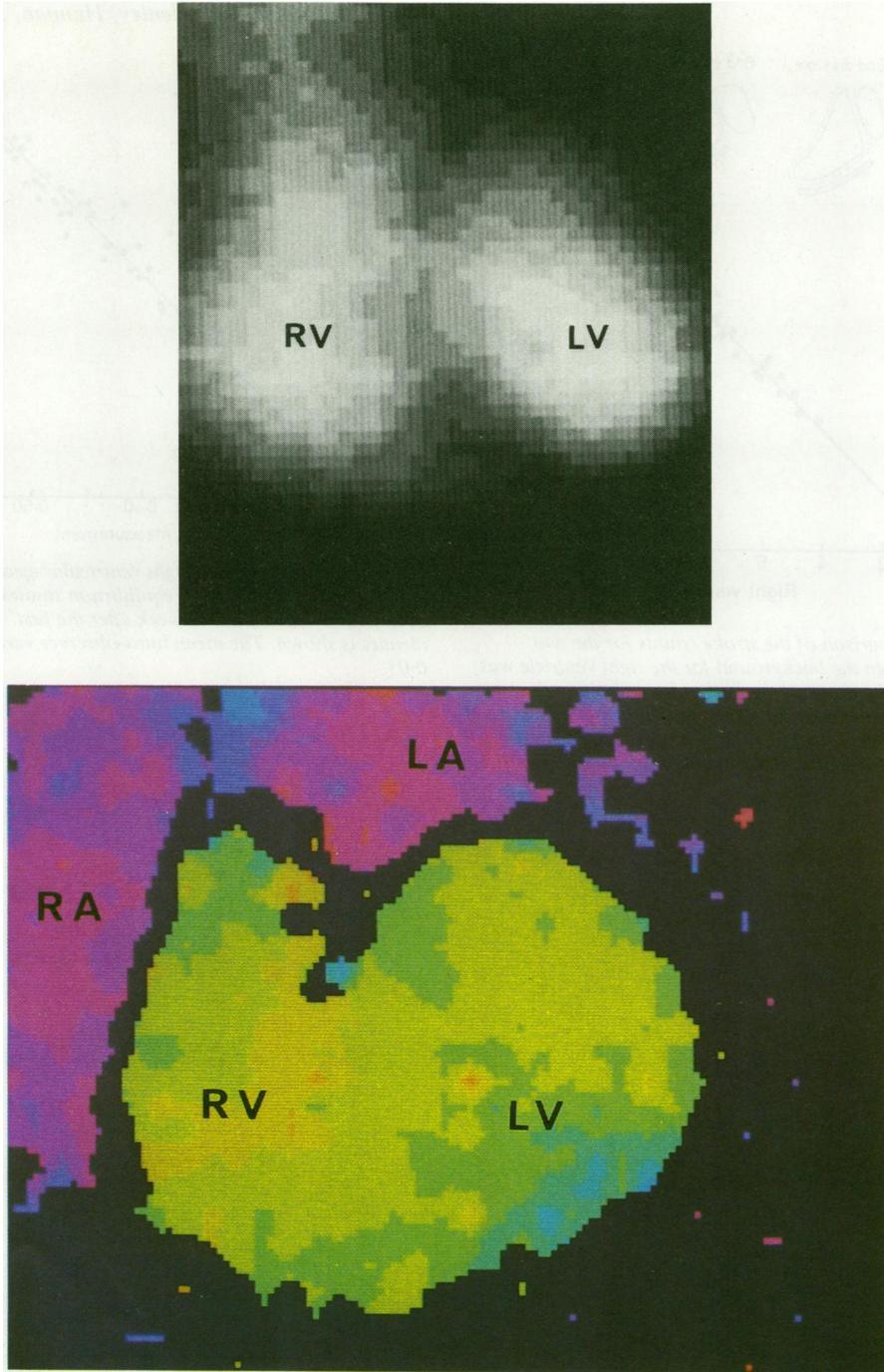


Fig 1 *A gated blood pool image taken at end diastole (above) illustrating the separation between the right and left ventricles in the modified left anterior oblique projection. The Fourier phase image (below) was generated from the sequence of images throughout the cardiac cycle and illustrates the separation between the right ventricle and right atrium and identifies the outflow tract of the right ventricle.*

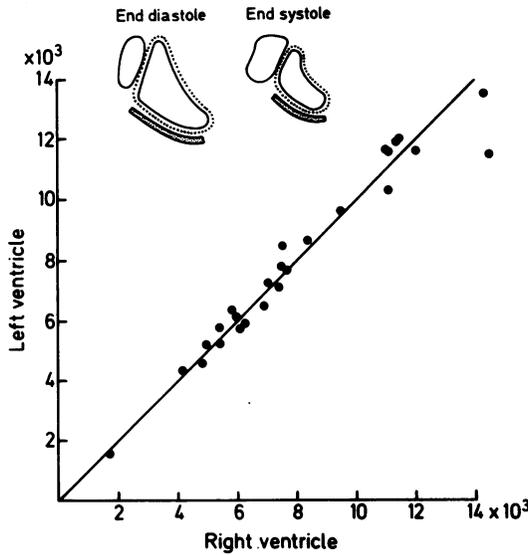


Fig 2 Comparison of the stroke counts for the two ventricles when the background for the right ventricle was taken along the paraventricular border and along the inferior margin outside the right ventricle at end diastole and end systole. The line of identity is shown. The mean difference between the stroke counts from the two ventricles was 4.9%.

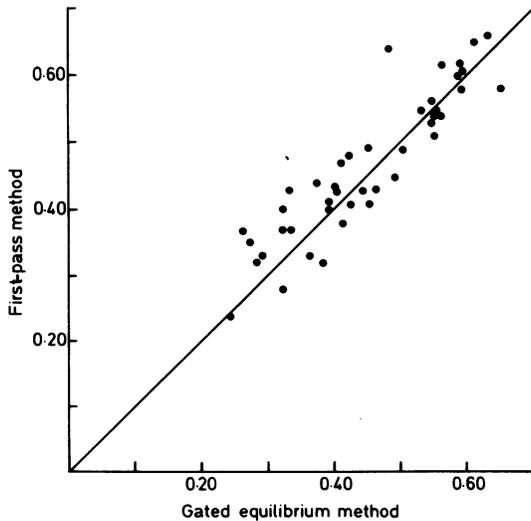


Fig 3 Comparison of the right ventricular ejection fraction by the first-pass and equilibrium methods. The line of identity is shown. The mean difference in RVEF by the two methods was 0.04.

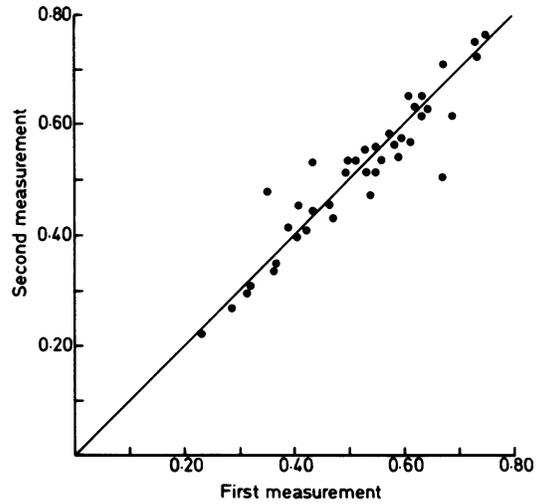


Fig 4 Repeat analysis of right ventricular ejection fraction by the same observer on 40 equilibrium studies; the second observation was made one week after the first. The line of identity is shown. The mean intra-observer variation was 0.03.

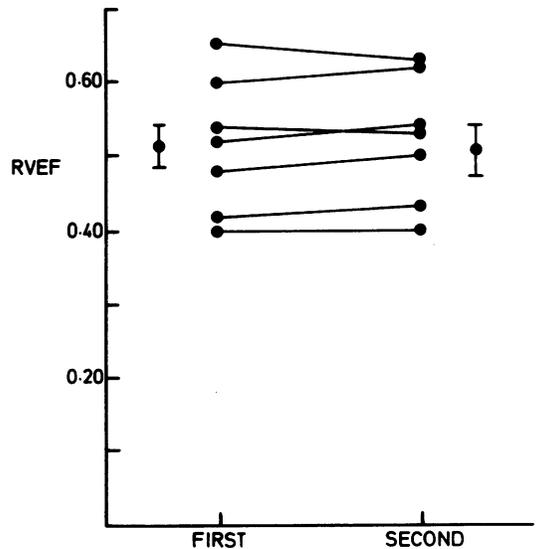


Fig 5 Repeat measurements of right ventricular ejection fraction in seven subjects on two separate occasions 30 minutes apart. Mean values and standard errors (vertical bars) are also shown. The mean difference between successive measurements was 0.02.

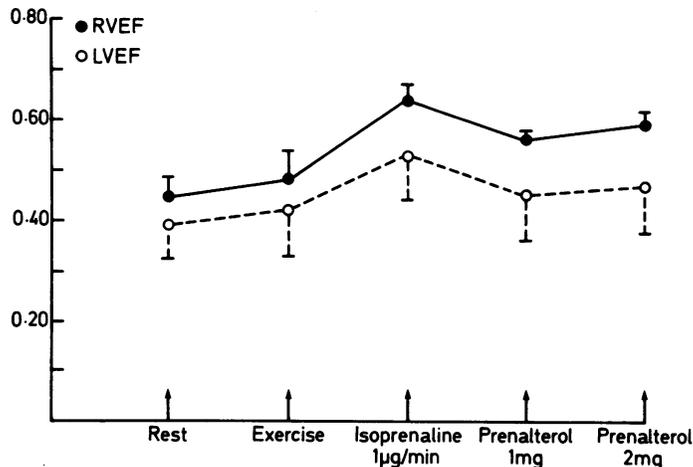


Fig 6 Left and right ventricular ejection fraction measured at rest, during exercise at 50 watts, after infusion of isoprenaline at 1 µg/min, and after 1 mg and 2 mg of prenalterol in four patients with chronic ischaemic heart disease. Mean values and standard errors are shown.

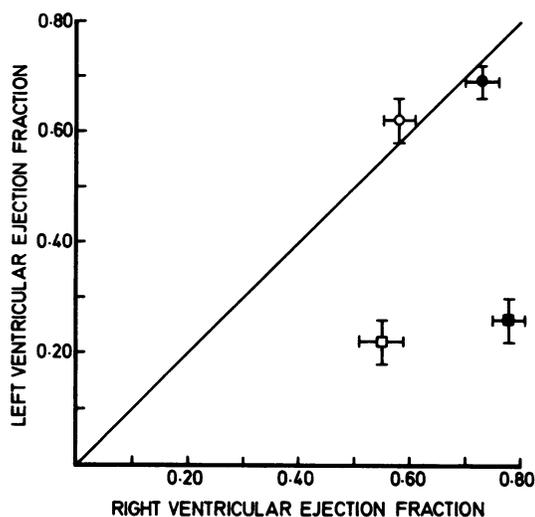


Fig 7 Right and left ventricular ejection fraction (RVEF and LVEF) before (○) and after (●) nifedipine in nine patients with hypertension and "good" left ventricular function (LVEF > 0.40) contrasted with RVEF and LVEF in six patients with severe left ventricular dysfunction (LVEF < 0.30) before (□) and after (■) the β_1 -sympathomimetic agent prenalterol. Mean values and standard errors are shown. There is a parallel increase in ventricular performance in response to nifedipine in those with good left ventricular function (○, ●), but in those with severe left ventricular dysfunction (□) the left ventricle does not respond to prenalterol (■), while there is a normal response of the right ventricle ($p < 0.01$).

low (0.22 ± 0.04) while RVEF was 0.55 ± 0.04 . There was little left ventricular response to prenalterol (0.26 ± 0.04) but RVEF increased to 0.78 ± 0.03 . Presumably this indicates the inability of the

left ventricle in these patients to respond adequately to inotropic stimulation, while the right ventricle can respond normally. The findings demonstrate the capacity of this technique to show differential responses of the ventricles.

Discussion

We have used a gated first-pass method as a control to assess the validity of the gated equilibrium technique. We do not have independent corroboration of RVEF determined by the first-pass method. Because of the anatomical shape of the right ventricle, determinations of right ventricular volumes and ejection fraction are difficult, although biplane angiographic techniques have been described¹⁰ and the results compared with radiographic measurements of postmortem casts.¹¹ Our own values of RVEF in normal subjects and patients with ischaemic heart disease and chronic bronchitis and emphysema correspond with other published values,^{1,12} however, so that we feel justified in using the first-pass method as the reference standard. The first-pass technique is unsuitable for multiple studies but, if the observations of Maddahi *et al*² could be validated, the multiple-gated equilibrium method would provide an understanding of right ventricular performance not only at rest but when the ventricle is stressed by exercise or pharmacological intervention. Our observations suggest that the equilibrium method is well suited to repeated studies of right ventricular performance. The technique requires the separate assignment of regions of interest to the right ventricle at end diastole and end systole. It calls for considerable experience for accurate assignment of region of interest but both inter-observer and intra-observer variability is small. The

results of the method correlate closely with those of the first-pass method and the reproducibility is satisfactory. The right ventricle behaves in an analogous fashion to the left ventricle in response to exercise or to β -sympathomimetic agents; but where the left ventricle is severely impaired we can show disparity in function between the two ventricles.

PROJECTION

Although there may be considerable variations in the shape of the right ventricle the counts detected by the radionuclide technique are proportional to volumes so that RVEF is independent of geometry. Thus variation in the shape of the right ventricle will not influence the calculation of RVEF provided that there is no overlap of chambers. In most patients separation between the left and right ventricles is easily achieved in a 20–30° left anterior view, but in each patient the degree of obliquity must be checked to obtain maximal separation of the ventricles. To check the contribution of the right atrium to the right ventricle in various projections a fixed human heart was obtained and placed in tissue-equivalent scattering material. The right ventricle was filled with particles of ion-exchange resin labelled with technetium-99m. Imaging was carried out in the right anterior; anterior; and 10°, 20°, 30° and 40° left anterior oblique projections. In each projection images were also collected at a 10°, 20°, and 30° caudal angulation. The right atrium was then also filled with ^{99m}Tc-labelled resin and the effect of the right atrial contribution to the counts obtained from the right ventricle in the various projections was assessed. It was found that the best projection that could be used to separate left and right ventricles and right ventricle from right atrium was a 20° left anterior oblique projection with a 20° caudal angulation. In this projection the proportion of the total counts in the right ventricular region due to the underlying right atrium was 30%.

BACKGROUND

In calculating LVEF investigators have developed empirical background subtraction methods and we have had to use a similar empirical approach for the right ventricle. Theoretically, the background should arise from three major sources: firstly, the pulmonary vascular bed; secondly, scatter from the left ventricle; and, thirdly, scatter from the right atrium. We compared four different possible background regions: superior and inferior left and right paraventricular regions. We found the most consistently reproducible results were obtained by using a right paraventricular and inferior border correction. Separate backgrounds at end-diastole and end-systole were assigned and subtracted from the

counts in the two different ventricular regions in these phases. With this method the relative stroke counts of the two ventricles were virtually identical and intra-observer and inter-observer variations were small.

PHARMACOLOGICAL EFFECTS

The purpose of this study was not to identify the effects of drugs on patients with chronic bronchitis and emphysema. Instead, as we were trying to validate the method, we chose to examine patients with ischaemic heart disease, examining the effects of rest and exercise and the effects of β -sympathomimetic stimulation with isoprenaline and prenalterol. As these patients with ischaemic heart disease had suffered previous myocardial infarction their left ventricular ejection fractions at rest were lower than their right ventricular ejection fractions. Given the different starting points, however, the responses in terms of ejection fraction appeared identical. This contrasts with the response in patients with severe ischaemic cardiomyopathy, who have left ventricles that respond poorly to inotropic stimulation. The disparity in function between the ventricles may have important implications for the management of heart failure.

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