Quantitative radionuclide angiocardiology *Determination of left ventricular ejection fraction in children*

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A method is described for measuring left ventricular ejection fraction which uses high frequency computer recording of gamma scintillation camera data and peripheral venous injection of technetium-99m as sodium pertechnetate. Data from mechanical model experiments are used to show feasibility of this method. A phantom experiment is described which was used to develop a technique for accurate delineation of the ventricular outline in the presence of background. The left ventricular ejection fraction was measured in 12 patients by radionuclide angiocardiology and biplane cineangiography. Comparison of these two methods gave a correlation coefficient of 0.91. In addition, left ventricular ejection fraction was measured in 34 patients (aged 7 weeks to 18 years) without evidence of cardiac disease using the radionuclide method alone. Average ejection fractions of 0.66 and 0.70 were found for children over 2 years of age and children 2 years of age or younger, respectively. In addition, an interobserver comparison study was performed with the data from 10 patients, and only small differences were noted (SD 0.025).

Clinical assessment of left ventricular ejection fraction as a measure of ventricular performance is of value in the management of patients with heart disease. In the past, this measurement has been made by contrast angiography at cardiac catheterization. More recently, a number of techniques have been described which use radionuclides to measure left ventricular ejection fraction. Strauss *et al.* (1971) described the use of the electrocardiogram to control time intervals for the collection of end-diastolic and end-systolic images in the gamma camera during equilibrium of an intravascular radioindicator. The volumes and ejection fraction were then calculated from the area and length of the ventricular images (area-length method). Van Dyke *et al.* (1972) described the use of a television monitor recording from oscilloscope images of the first passage of a radionuclide through the left heart. They used a single 'region-of-interest' over the ventricular image to determine the relative end diastolic and end-systolic counts. They then used an extraventricular region-of-interest to determine the level of background radiation and subtracted this from the end-diastolic and end-systolic counts be-

fore calculating ejection fraction (background-subtraction method). Reports by other workers (Pierson *et al.*, 1973; Parker *et al.*, 1972; Secker-Walker *et al.*, 1973; Ashburn *et al.*, 1973; Kostuk *et al.*, 1973; Steele *et al.*, 1974a, b; Schelbert *et al.*, 1975) have described modifications of these two methods, using improvements in equipment and details of technique. The most recent report, that of Schelbert *et al.* (1975), shows excellent results in comparison with contrast angiography using a background-subtraction technique similar to that of Van Dyke *et al.* (1972).

However, there remain problems with these two basic techniques. Both methods, especially the former, are sensitive to choice of area, and neither has a generally-accepted method of making that choice. The latter method has the disadvantage that there is no justifiable *a priori* way of selecting the background region-of-interest; hence this is chosen empirically.

The purpose of this report is to present a new technique for the measurement of left ventricular ejection fraction. The method involves choosing separate areas for end-diastole and end-systole in a clearly-defined way. The counts in each region

during the respective cardiac phases are then used to calculate ejection fraction. This method differs from the area-length method in that the counts, rather than the areas, are used in the calculation; this gives the area a third dimension (i.e. count density). It differs from the background-subtraction method in that no area for determination of background is used; instead, different areas are used for end-systole and end-diastole rather than a single area for both. This avoids the difficult problem of empirical choice of background area. The specific technique for defining areas was developed using a series of phantom experiments, and the method was compared to contrast angiography in 12 patients. In addition, the normal range was established in 30 children.

Materials and methods

All radionuclide studies were performed using intravenous technetium-99m as sodium pertechnetate and recording with a gamma scintillation camera¹ interfaced with a digital computer system.² Recording was done on an event-by-event basis (list mode); the studies could be framed at a variety of frame rates for display on the computer oscilloscope in a 64×64 matrix.

To ensure that this equipment was adequate for the recording of rapidly changing images, a test was performed using a mechanical model of the ventricle.³ The model was set at a variety of heart rates and ejection fractions, and computer recordings were made of a bolus of 10 mCi of Tc-99m flowing through it without recirculation at each setting. The recordings were framed at 10 frames/second, and ejection fractions were measured using the counts within the 'ventricle' at end-diastole and end-systole from the formula: $\text{ejection fraction} = (\text{end-diastolic counts} - \text{end-systolic counts}) / (\text{end-diastolic counts})$. Actual and measured ejection fractions (the latter averaged over 10 beats) were in close agreement.

The next task was to develop a consistent method of outlining the ventricle in the presence of background. First, five consecutive patient studies were examined to determine the amount of background. Intrathoracic count rates outside the left heart and aorta were found to average about 18 to 33 per cent of the maximum intraventricular count rate during end-diastole. The extracardiac activity remained constant from end-diastole to end-systole, though of course the intraventricular counts decreased.

¹Nuclear Chicago Pho/Gamma HP, Chicago, Ill., or Nuclear Data Radi-camera.

²Gamma-11 (DP 11/20) Digital Equipment Corporation, Maynard, Mass.

³Thermo-Electron Corporation, Waltham, Mass.

From this it was decided to perform a static phantom experiment with containers of various sizes, using constant background levels of 15, 25, and 35 per cent of the maximum counts in the largest container; this spanned the entire range of patient study background levels. Containers with 100 ml, 50 ml, 40 ml, 30 ml, and 20 ml of water mixed with technetium-99m were imaged in the presence of these background levels. They were also imaged without background to determine the actual count rates. From these latter measurements, the actual 'ejection fractions' were found from the counts in the smaller containers and those in the largest container; this number could then be compared with the 'ejection fractions' measured in the presence of background. The images of the containers with background were displayed and, with the computer, isocount contours at percentages of the maximum count rate were superimposed. Outlines of the containers were drawn using these contours, and the counts inside them were totalled. These totals were used to calculate 'ejection fractions', as in the non-background case for each of five different isocount contour levels (75%, 65%, 55%, 45%, and 35%).

Twelve patients aged 2 to 40 years (mean 20) were examined by both cardiac catheterization and radionuclide angiocardiology. Four of the radionuclide angiocardiology studies were performed in the catheterization laboratory; the rest were done on the morning after catheterization. Catheterizations were performed for the usual indications, and informed consent was obtained for radionuclide angiocardiology.

The angiograms were done with either biplane cineangiography at 60 frames/second or biplane cut film¹ at 6 frames/second, with simultaneous recording of the electrocardiogram. Most volumes were calculated by the length-area method of Dodge *et al.* (1960), with two corrections: (1) a mathematical correction for magnification assuming a point source and linear spread, and (2) Graham's correction for ventricular wall irregularities (Graham *et al.*, 1971). In 3 cases, the Simpson's rule method of Chapman *et al.* (1966) was used. The left ventricular ejection fraction (EF) was calculated from the volume by the formula: $\text{EF} = (\text{end diastolic volume} - \text{end-systolic volume}) / (\text{end-diastolic volume})$.

The radionuclide angiocardiology studies were performed with a peripheral venous injection. The dose of Tc-99m as sodium pertechnetate was 200 $\mu\text{Ci/kg}$; specific activity was 20–60 mCi/ml. Recordings were made event by event (list mode) with the camera and computer system described above.

¹Elema-Schonander, Sweden.

FIG. 1 Left: Two second scintigraph (64×64) of the left ventricular and aortic activity. The scintigraphic frames corresponding to the superior vena cava, right atrium, right ventricle, and pulmonary artery were subtracted in the computer. Right: Time-activity curve at 10 frames per second obtained from a region-of-interest placed over the left ventricle.

Imaging was done in the anterior position. The data were framed at 10 frames/second in a 64×64 matrix unless the heart rate was greater than 120, for which framing was done at 15 frames/second. The next step was to choose end-diastolic and end-systolic frames. This was done using the computer display by placing a region-of-interest for time reference over the left ventricle as seen on a 2-second summed image of the laevophase of radio-

nuclide passage with the dextrophase subtracted. The number of counts in this region in each frame of the study was displayed graphically (Fig. 1), and equal numbers of end-diastolic and end-systolic frames were chosen from the peaks and troughs of this graph. By summing the frame matrices corresponding to these peaks and troughs, composite pictures were obtained of end-diastole and end-systole (Fig. 2). The planes of the aortic and mitral

FIG. 2 End-diastolic (left) and end-systolic (right) frames composed of 10 heart beats. Note the 'filling' of the ascending aorta with activity on the end-systolic frame. The frames corresponding to the superior vena cava, right atrium, right ventricle, and pulmonary artery were subtracted.

FIG. 3 Top row: End-diastolic (ED) frame, end-systolic (ES) frame, end-diastolic frame with an isocount contour of 55 per cent of the intraventricular maximum with end-diastolic region of interest superimposed and end-systolic frame showing the left ventricular outline within the end-diastolic region-of-interest. Bottom row: Time-activity curve at 20 frames per second after filtering with Fast Fourier Transform.

valves were chosen directly from the end-diastolic composite. Then, the isocount contour at 55 per cent of the intraventricular maximum was displayed on each of the composite pictures, and, with the valve planes superimposed, the remainders of the end-diastolic and end-systolic areas were chosen (Fig. 3). In cases where the isocount contour was irregular, a smooth outline was chosen such that its area was identical to that inside the contour.

Since previous workers (Strauss *et al.*, 1971; Van Dyke *et al.*, 1972; Pierson *et al.*, 1973; Parker *et al.*, 1972; Secker-Walker *et al.*, 1973; Ashburn *et al.*, 1973; Kostuk *et al.*, 1973; Steele *et al.*, 1974a, b; Schelbert *et al.*, 1975) have used various methods of combining cardiac cycles to yield the ejection fraction, the counts were obtained using these regions-of-interest in two ways: (1) placing the regions-of-interest over the summed diastolic and systolic frames as described and determining the counts within them ('static' method); (2) using the areas similarly to calculate an average beat-by-beat ejection fraction, using only the 3 beats including and after the bolus peak ('dynamic' method). In each case the ejection fractions were calculated from the formula: $EF = (\text{end-diastolic counts} - \text{end-systolic counts}) / (\text{end-diastolic counts})$. The final ejection fraction was taken as the average of these two numbers.

An additional 34 children (aged 7 weeks to 18 years, mean 9 years) without evidence of cardiac disease were studied. All were scheduled for non-cardiac radionuclide studies using Tc-99m as pertechnetate (brain and abdominal studies) or as diphosphonate (bone studies). In this way a group of 'normal' values was obtained without additional radiation exposure.

No attempt has been made to correct the dead-time losses. Though such a correction was considered, analysis of actual patient data made it clear that any such correction would be very small. Though high total count rates which cause dead-time losses were found in these studies, the rates do not change in a systematic way from diastole to systole. Thus, any such multiplicative correction factors would be nearly identical for systole and diastole, and would cancel when the ejection fraction was calculated.

A frequency analysis technique using the Fast Fourier Transform (FFT) (Brigham, 1974) for the time-activity curves for the regions as described was also developed. By eliminating the higher frequencies from these curves, a smooth clear curve could be obtained. This technique was tested in 15 patients.

The effect of choice of isocount contour was

TABLE 1 Phantom experiment results

Threshold used	Mean absolute error	Root mean squared error
75%	0.0725	0.0951
65%	0.0319	0.0422
55%	0.0237	0.0266
45%	0.0256	0.0335
35%	0.0314	0.0385

Note: Errors are comparisons of measured vs. actual 'ejection fraction' averaged over all containers and all background levels (total: 12 measurements for each average).

assessed in 12 patients. Calculations of ejection fraction were made using isocount contours of 45 per cent and 65 per cent of maximum intraventricular counts, as well as the standard 55 per cent.

A 'two independent observer' correlation study was done in 10 consecutive patients to test the consistency of the technique. The second observer (L.O.) was not a medically-trained person.

In addition, ejection fraction was calculated by the method described by Schelbert *et al.* (1975) in 15 patients for comparison with this method. The only differences between the Schelbert method as described and that applied here was that imaging was done in the anterior position and injections were in a peripheral vein rather than in the superior vena cava. Six of these patients had intracardiac left-to-right shunts and 9 did not.

FIG. 4 Comparison of left ventricular ejection fraction in 12 patients estimated by radionuclide angiocardiology and during angiography at catheterization.

Results

The results of the phantom experiment are shown in Table 1, which shows the average error of the measured vs. actual 'ejection fraction' for the five different isocount contour levels. The most accurate choice was 55 per cent; however, 45 per cent was not significantly worse. The former level was

TABLE 2 Left ventricular ejection fraction determined by left ventricular angiography and radionuclide angiocardiology

Case No.	Age (y)	Diagnosis	Ejection fraction Radionuclide angiocardiology			Biplane angiocardiology
			Static	Dynamic	Mean	
1	18	MR; s/p coarctation repair; aortic valvotomy	0.79	0.78	0.78	0.69
2	18	s/p DORV repair	0.59	0.65	0.62	0.57
3	10	cardiomyopathy	0.18	0.19	0.19	0.18
4	3	s/p TGA repair	0.67	0.67	0.67	0.84
5†	38	PFO; persistent LSVC; AS; AR	0.57	0.66	0.62	0.67
6†	23	AS; AR	0.69	0.68	0.69	0.69
7†	40	CAD	0.48	0.48	0.48	0.50
8†	21	s/p FT repair	0.54	0.60	0.57	0.51
9†	39	s/p ventricular aneurysm repair	0.38	0.35	0.37	0.39
10	23	AS; AR	0.56	0.56	0.56	0.45
11	6	VSD; AR	0.61	0.63	0.62	0.65
12	6	s/p TGA repair	0.77	0.78	0.77	0.73*

MR=mitral regurgitation; TGA=transposition of great arteries; PFO=patent foramen ovale; LSVC=left superior vena cava; CAD=coronary artery disease; AS=aortic stenosis; AR=aortic regurgitation; FT=Fallot's tetralogy; DORV=double outlet right ventricle; VSD=ventricular septal defect.

*Only single plane available for ejection fraction calculation. †Radionuclide angiocardiology performed in catheterization laboratory. s/p=postoperative state.

TABLE 3 *Left ventricular ejection fraction estimated by radionuclide angiocardiology in 25 patients without cardiovascular disease*

Patient	Age (y)	Heart rate	Ejection fraction		
			Static	Dynamic	Average
1	14	60	0.65	0.64	0.64
2	6	107	0.61	0.61	0.61
3	6	100	0.62	0.60	0.61
4	7 wk	89	0.72	0.70	0.71
5	13	91	0.81	0.78	0.79
6	15	86	0.75	0.75	0.75
7	13	107	0.73	0.75	0.74
8	11	80	0.74	0.74	0.74
9	9	100	0.70	0.71	0.70
10	4	106	0.69	0.68	0.69
11	13	105	0.57	0.58	0.57
12	7 mth	185	0.73	0.79	0.76
13	10	111	0.70	0.71	0.70
14	12	92	0.62	0.62	0.62
15	5	92	0.54	0.53	0.53
16	2	89	0.66	0.67	0.66
17	17	67	0.62	0.64	0.63
18	8	124	0.67	0.69	0.68
19	7	71	0.60	0.60	0.60
20	8	93	0.58	0.56	0.57
21	6	107	0.69	0.70	0.70
22	15	95	0.70	0.74	0.72
23	8	103	0.67	0.72	0.69
24	2	153	0.59	0.65	0.62
25	8	86	0.74	0.72	0.73
26	16	77	0.58	0.64	0.61
27	11	83	0.67	0.70	0.69
28	5	97	0.61	0.62	0.62
29	11	71	0.64	0.63	0.64
30	6	150	0.71	0.73	0.72
31	12	82	0.59	0.60	0.60
32	14	97	0.70	0.74	0.72
33	18	100	0.67	0.64	0.66
34	9	92	0.56	0.58	0.57

chosen by operator preference to be used in all patient studies.

The comparison study data are shown in Table 2, along with pertinent patient information. Ejection fraction by angiography is plotted against ejection fraction by radionuclide angiocardiology in Fig. 4. The correlation coefficient was 0.91, and the standard deviation 0.072. Note that there is one patient in whom a large difference between angiography and radionuclide angiocardiology was found; this patient had partial obstruction of the superior vena cava, and thus had a slow bolus, with unusually high background levels which partially obscured the regions.

The ejection fractions measured in the 34 children without known heart disease are shown in Table 3. The average was found to be 0.66 ± 0.065 (SD) in the 30 children over 2 years. This is statistically significantly higher ($P < 0.05$) than the average of 0.63 ± 0.05 (SD) reported by Graham *et al.* (1971) for children aged 2 to 18. Our average for the children of 2 years and under was 0.70 ± 0.05 (SD), but as there were only 4 children in this group, no meaningful comparison can be made with the published value (0.68 ± 0.05) (Graham *et al.*, 1971).

The Fast Fourier Transform smoothing technique made only slight differences in the calculation

of the ejection fraction in the 15 patients in whom it was tested; on average, it changed the measured ejection fraction by only -0.009 , with a range from -0.030 to $+0.020$. Because of the time-consuming nature of this method and its small contribution, the technique was not adopted.

The testing of different isocount contours for the selection of regions-of-interest resulted in modest changes in the calculated ejection fraction. As one would expect, using the 45 per cent instead of the 55 per cent contour yielded lower ejection fractions, since both the end-diastolic and end-systolic area increased in size. The average decrease was 0.022 for the 12 cases; the ejection fraction actually increased in 3 cases. Similarly, when the 65 per cent contour is used, one would expect an increase in ejection fraction from the 55 per cent contour. The average increase was 0.032 for the 12 cases; decreases occurred in only 3 cases.

The results of the two-observer correlation study are shown in Table 4. The average absolute

TABLE 4 Interobserver correlation in estimation of left ventricular ejection fraction by radionuclide angiography

D.K.	L.O.
0.66	0.70
0.62	0.63
0.66	0.67
0.59	0.59
0.58	0.56
0.70	0.74
0.70	0.73
0.67	0.67
0.54	0.56
0.70	0.67

Comparison of measured ejection fractions from identical data in 10 patients by two independent observers.

difference was only 0.019 , and the standard deviation of the regression line only 0.025 .

Results obtained with the background subtraction method of Schelbert *et al.* (1975) compared quite closely with those using our method in the 9 patients without left-to-right shunts. The average absolute difference was only 0.027 , and the square root of the mean squared error was 0.038 over a range of ejection fractions of about 0.5 to 0.8 . Overall, Schelbert's method gave ejection fractions 0.022 higher than those from our method for non-shunt patients. However, in the patients with left-to-right shunts, the ejection fractions from the background subtraction technique averaged 0.077 above those from this technique. The range of ejection fractions for this latter group was about

0.6 to 0.8 . This difference between the shunt and non-shunt patient groups, though small, was statistically significant ($P < 0.01$), despite the small sample sizes.

Discussion

The static phantom experiment shows that it is possible to use isocount contours to measure relative counts in the presence of background with good accuracy. The 45 and 55 per cent isocount contours give the best results; the 55 per cent contour has the advantage that the regions tend to be less irregular, thus making the outlining process easier.

The close correlation between ejection fraction from radionuclide angiography and from conventional angiography compares well with that found in other studies (Strauss *et al.*, 1971; Van Dyke *et al.*, 1972; Pierson *et al.*, 1973; Parker *et al.*, 1972; Secker-Walker *et al.*, 1973; Ashburn *et al.*, 1973; Kostuk *et al.*, 1973; Steele *et al.*, 1974a, b; Schelbert *et al.*, 1975). Since this technique was to be applied to children aged 2 to 18, it would have been preferable to make the comparison in patients of that age. Unfortunately, in our centre, few catheterized children have low ejection fractions; for this reason, 6 adults with a wide range of ejection fractions were catheterized in addition to the 6 children in order to validate the technique.

'Normals' in our study had significantly higher average ejection fraction than the normal value obtained from contrast angiography. There is, of course, no way of telling whether this is the result of a systematic error in one technique or the other, or whether it reflects some effect of contrast medium (Karliner, Bouchard, and Gault, 1972).

One of the most important features of this technique is the interobserver correlation. The average difference of only 1.9 per cent is considerably smaller than that of 5.4 per cent reported by Schelbert *et al.* (1975). The primary reason for this is probably the precise standardization of this technique.

The high correlation between this technique and that of Schelbert *et al.* (1975) in non-shunt patients is also important. Without many more studies with correlations with catheterization, it would not be possible to determine which technique is better in non-shunt patients.

The difference between this technique and that of Schelbert *et al.* (1975) in the shunt patients is also significant. Since the background area as described by Schelbert includes lung and right heart, anything which increases the activity in these structures relative to the left heart would tend to increase the measured ejection fraction. Since intra-cardiac shunts have this effect, an increase in

measured ejection fraction by the background subtraction technique might be expected. However, the difference could also be the result of decrease in measured ejection fraction by our technique, resulting from the presence of higher background activity.

The technique of smoothing curves by removing high frequencies using the Fast Fourier Transform is potentially useful. It could be used as part of an automatic procedure to eliminate spurious peaks or troughs resulting from statistical fluctuation.

Conclusion

A new method of measuring left ventricular ejection fraction by radionuclide angiocardiology has been developed. This method overcomes the problem of empirical choice of background area. Details of the technique were refined using phantom experiments, and the method was validated by comparison with contrast angiography in 12 patients. Regression analysis on these data yielded the correlation coefficient $r=0.91$. A normal range of 0.66 ± 0.065 (SD) for children aged 2 to 18 years has been established. Measurements by two independent observers showed excellent correlation, with average differences of only 1.9 per cent. A good correlation between this method and another radionuclide method (Schelbert *et al.*, 1975) has been shown in patients without intracardiac shunting. However, a significant difference was found between the two techniques in patients with intracardiac shunts; this is not yet explained.

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