
Relative Accuracy of Three Scintigraphic Methods for Determination of Right Ventricular Ejection Fraction: A Correlative Study with Ultrafast Computed Tomography

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The accuracy of three scintigraphic methods for determination of right ventricular ejection fraction (RVEF) was tested in 29 patients using ultrafast computed tomography (UFCT) as the gold standard. RVEF measurements by the ECG-gated first-pass approach showed excellent correlation with the UFCT results ($r = 0.96$, $y = 0.06 + 0.91x$), while both the standard gated acquisition blood-pool imaging ($r = 0.71$, $y = 0.14 + 0.59x$) and the nongated first-pass curve approach ($r = 0.63$, $y = 0.18 + 0.37x$) significantly underestimated RVEF. The error can be ascribed to partial inclusion of the atrial activity in the region assigned to the right ventricle. The tricuspid valve plane was found to move by a distance equal to 9%–33% (mean = 20%) of the right ventricular long-axis between systole and diastole. This translational motion was more pronounced with higher EFs.

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Scintigraphic techniques for measurement of right ventricular ejection fraction (RVEF) play an important part in the management of patients with right ventricular dysfunction (1–4). Other modalities, including contrast ventriculography, echocardiography, and Doppler methods, are hampered by the lack of a suitable geometric formula that can reliably estimate the volume of the irregularly shaped right ventricle (RV) (5–7). A variety of radioisotopic methods have been employed for RVEF determination (8–12), but the most commonly accepted method is the first-pass curve (FP-Curve) approach (13,14) in which a bolus of radioactivity is injected intravenously and its transit through the RV is recorded dynamically. The time-activity data derived from a region of interest (ROI) placed over the RV provide instantaneous count rates corresponding to

the volume of the RV at end-diastole (ED) and end-systole (ES) and thereby enable computation of RVEF. Only a fixed ROI can be assigned to the aggregate RV data, as the individual data points have insufficient count density for reliable tracing of the RV outline on a frame-by-frame basis.

Two alternative techniques have thus been developed (15–20) to permit the use of variable ROIs. Maddahi et al. derived RVEFs from standard multi-gated equilibrium blood-pool images (Eq-GA) in a manner similar to that used for left ventricular ejection fraction determinations (15,16). Variable ROIs can be employed in this approach, but the presence of blood-pool activity outside the right heart poses a major problem. A third approach, introduced by McKusick et al. (19), retains the advantages of the first-pass technique, in that it enables selective visualization of the right heart structures, but also employs ECG gating to enable the summation of time-activity data from several consecutive cardiac cycles. The composite first-pass cycle so obtained (FP-GA) possesses sufficient count density to permit operator placement of individual ROIs at ED and ES.

In the past, RVEF measurements by various scintigraphic techniques have been compared to each other (20), but a rigorous analysis of their relative accuracy has not been attempted due to lack of an independent “gold standard.” Accurate assessment of RVEF by non-radionuclide methods has recently been made possible with the introduction of ultrafast computed tomography (UFCT) (21,22). Rapid sequence, transaxial images of the cardiac chambers can be obtained with this modality after intravenous administration of the contrast agent. The spatial resolution is comparable to that of conventional CT and the scanning time is short enough (~50 msec) to permit definition of chamber outlines at ED and ES. The RV volume can be determined precisely by summing the planimetric areas in the tomographic cuts spanning the length of the RV, and EF is derived in a conventional manner. The

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accuracy of this method for measurement of both the RV chamber volume and the RV stroke volume has been validated in animal studies (23–26). Utilizing this gold standard, we examined the accuracy of the three radionuclide methods currently available for RVEF determination in 29 subjects who were examined by UFCT and by the scintigraphic methods. The objective of the study was to determine which scintigraphic method correlated best with the truth data provided by UFCT.

METHODS

The study group was comprised of 5 normal volunteers and 24 adult patients who were consecutively admitted into the study from a population of patients referred for an UFCT examination of the heart. The inclusion criterion for the patients was availability of scintigraphic studies within 10 days of the UFCT examination. In normal volunteers and in about one-third of our patients, one or both imaging studies were obtained primarily for research. In this group, informed written consent was obtained from the subject, and the studies were approved by the Human Use Committee of The University of Iowa. In the remaining patients, data were collected retrospectively from clinically indicated studies obtained within the time interval specified by our protocol. Not all patients in this group had the full complement of scintigraphic studies. Thus, a total of 29 FP-GA and 27 each of FP-Curve and Eq-GA studies were available for comparison with UFCT.

The study group included 19 men and 10 women whose ages ranged from 18 to 68 yr with a mean age of 47 yr. The clinical diagnoses of the patients studied were: coronary artery disease in 9, valvular heart disease in 6, atrial or left ventricular mass in 4, cardiomyopathy in 3, and pericardial disease in 2. The interval between the UFCT and the radionuclide studies averaged 3.3 days and ranged from 0 to 10 days. No major therapeutic interventions or changes in hemodynamic status of the patients occurred between the two studies. Patients with arrhythmia, specifically those with atrial fibrillation or frequent premature ventricular beats, were excluded from the study. Also excluded were those in whom the administration of radiographic contrast was contraindicated on basis of known allergy or impaired renal function (creatinine > 1.8 mg%).

RVEF Measurements by UFCT

Computed tomographic images were obtained with the Imatron C100 (South San Francisco, CA) scanner (21). A detailed description of this device has been previously published (26). The instrument utilizes a focused beam of electrons which is rapidly swept across four semicircular tungsten target rings. The X-rays thus generated are collected in a double ring of 432 stationary scintillation detectors. The combination of the four target rings and the two detector arrays provides eight tomographic images, each of which is 8 mm in thickness. Images from adjacent rings are separated by a 4-mm gap. The scanning time for each target ring is 50 msec with an 8-msec interscan delay. Thus, maximum scanning rate is 17 images/sec.

Patients were placed supine on the scanning table and positioned so that the apex of the left ventricle was in the lowest tomographic cut. The entire RV was encompassed

within the 16 slices obtained from two consecutive cine-mode data collections. The number of time-frames obtained at each slice level was 10. Ten seconds prior to the start of imaging, administration of a nonionic contrast agent, Iohexol (Sterling-Winthrop, New York, NY), was begun at the rate of 1.5 ml/sec.

Images were reviewed using a closed-loop cine display and ED and ES were identified. Using a threshold set at the midpoint between the density of the contrast-enhanced RV chamber and that of the surrounding myocardium, the outline of the RV was traced. The area of the RV cavity was then planimetered in each slice and the areas for all slices summed by a modified Simpson's formula to determine the chamber volume at ED and ES. The stroke volume was derived by subtracting the end-systolic volume from the end-diastolic volume and RVEF was determined by dividing the stroke volume by the end-diastolic volume. Volume determinations by UFCT have been shown to be highly reproducible. In a previous report from this institution, correlation of measurements by different observers yielded: $r = 0.98$, slope = 0.90, and y intercept = 1.66 ml (26).

Scintigraphic RVEF Measurements

Data Acquisition. Patients were positioned in a semi-recumbent position on the imaging table and an intravenous line was established via an antecubital vein. Standard ECG leads were then placed, and the patient was positioned under a small field of view gamma camera (LEM +, Siemens, Des Plaines, IL) for imaging of the heart in a 15° RAO projection. The gamma camera was equipped with a low-energy parallel-hole collimator fitted with a 3-mm thick lead collar, which limited the field-of-view to a central aperture measuring 17.5 cm in diameter. The collar shielded the unnecessary extracardiac activity and minimized count losses caused by camera dead time. The pulse-height analyzer was set for a 15% symmetrical window about 140 keV.

Prior to injection of radionuclide, 5.1 mg stannous pyrophosphate was administered intravenously to prepare the red blood cells for subsequent *in vivo* labeling. Ten minutes later, 30 mCi of technetium-99m-pertechnetate in a volume measuring 2 ml was introduced into the venous line and flushed through the line by a rapid injection of 20 ml normal saline. Data from the gamma camera and the ECG-gating device were recorded simultaneously for 30 sec in list mode by a commercial computer system (A², Medical Data Systems, Ann Arbor, MI).

Equilibrium blood-pool imaging was initiated in a LAO projection 10 min after the injection of the radionuclide. The camera position was adjusted to obtain the best separation of the left ventricular activity from the right ventricular activity. Our standard MGA technique utilized 20 image frames per cardiac cycle and 200,000 counts/image at ED. None of the first-pass or blood-pool studies were rejected or had to be repeated for poor technical quality.

Data Analysis

All data were analyzed by a single operator who is quite experienced in processing first-pass and equilibrium blood-pool studies on an MDS computer. The operator was blinded to the results of RVEF measurements by UFCT.

FP-Curve Method. For the beat-by-beat analysis, the raw data stored in list mode were formatted into serial 40-msec frames and, additionally, into a single frame containing the entire first transit data for the RV. The latter was used for defining a single ROI for the RV. The operator drew the ROI along the ED contour of the RV and carefully traced it through the planes of the tricuspid valve and the pulmonary valve. Utilizing the 40-msec-framed images, a time-activity curve was then generated from the transit of the radioactive bolus through this ROI and the three consecutive beats exhibiting the highest count rates were selected for analysis. Ejection fraction was determined for each beat by dividing the difference of the maximum and minimum count rates in that cycle by the maximum count rate in that same beat. Typical RV count densities obtained in this manner were on the order of 500 counts/frame for ED and 250 counts/frame for ES. The best estimate of the EF was taken to be the average of EFs for the three consecutive beats. A background region adjacent to the apex of the RV was found to have no significant activity in any of the patients studied and, therefore, no background subtraction was implemented.

FP-GA Method. The raw data recorded in list mode were initially formatted into serial 0.5-sec frames for visual identification of the times at which the bolus entered and left the RV on cine display. List mode data for events recorded between the entrance of the bolus into the RV and before its first appearance in the lungs then were summed utilizing the standard ECG gating technique into 16 frames that constituted one average cardiac cycle. This composite GA cycle possessed sufficient count density to permit the placement of an operator-defined ROI for each of the 16 frames in the study. The plane of the tricuspid valve and the pulmonary valve could be determined visually on virtually all frames in all patients. Count densities obtained from the RV region typically ranged from 3000 counts per frame for ED to 1500 counts per frame for ES. Ejection fraction was derived in a standard manner.

In order to assess the extent of the translational motion of the tricuspid valve plane in different subjects, the operator marked the center of the tricuspid valve plane at ED and ES and measured the distance between the two points. This measurement was then computed as a percent fraction of the RV long-axis defined as the distance from the center of the valve plane to the apex of the RV at ED (Fig. 1).

Eq-GA. For RVEF determinations with the equilibrium blood-pool technique, each of the 20 standard composite image frames in the cardiac cycle was fitted with an operator-defined ROI depicting the boundary of the RV as seen on that frame (variable ROI technique). In about one-third of the cases, the superior margin of the RV could not be defined reliably. In these patients, the superior margin of the RV was demarcated at the level of the superior border of the LV. A standard ROI was also defined adjacent to the apex of the heart for sampling the background count rates. The time-activity curve derived from this region was subtracted from the curve obtained from the RV region after normalization for differences in the sizes of these ROIs. RVEF was then computed in a standard manner.

Statistical Analysis. Pairwise Pearson product-moment correlation coefficients were determined for each of the three sets of scintigraphic measurements with the UFCT measurements. Intercepts and slopes were estimated for each scintigraphic

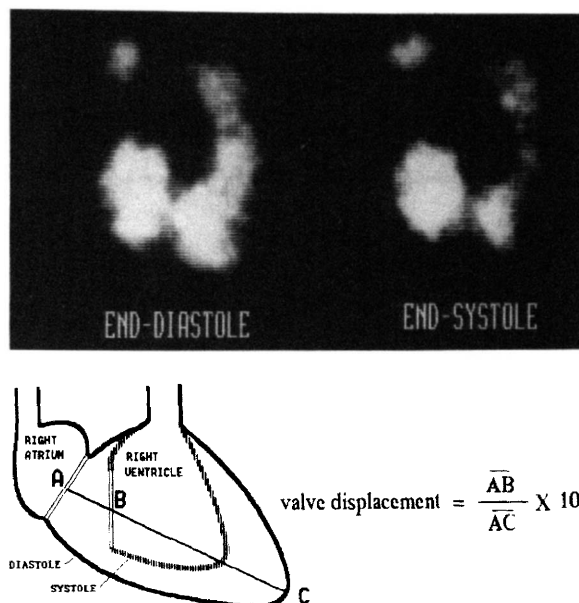


FIGURE 1

Two frames of a gated first-pass study (top) depict radioactive tracer in the superior vena cava, the right atrium, the RV, and the pulmonary outflow tract. The tricuspid valve plane, denoted by the indentation between the right atrium and the RV, was noted to move toward the center of the RV at systole on cine display of the RV images. This translational motion was measured in all patients as a percent-fraction of the right ventricular long-axis according to the formula shown on the bottom.

$$\text{valve displacement} = \frac{\overline{AB}}{\overline{AC}} \times 100$$

method using the least-squares approach, where the UFCT measurements were taken as the independent variable and the scintigraphic measurements were taken as the dependent variable. Ninety-five percent confidence intervals were constructed for each slope and intercept. Tests of hypotheses used 0.05 as the level of significance.

RESULTS

A wide range of RVEF determinations were obtained with the UFCT method from the study population. The lowest and highest values obtained were 16% and 87%, respectively. Table 1 lists the results of RVEF studies with UFCT and the scintigraphic methods and Figure 2 shows the correlation of each of the three scintigraphically-derived measurements with the values determined by UFCT.

It can be seen that the RVEF values obtained with the gated first-pass technique are in excellent agreement with the UFCT-derived measurements. There is minimal scattering of the data points around the regression line and the *r* value for this analysis is equal to 0.96. Furthermore, the intercept and the slope values calculated for the regression line ($y = 0.06 + 0.91 x$) place this line very close to a line of identity. The estimated slope is not significantly different from unity ($p > 0.05$) and therefore any small deviation from a line of identity

TABLE 1
RVEF Measurements by Three Different Scintigraphic Methods Compared to UFCT

Subject	UFCT	Gated first-pass	Non-gated first-pass	Eq-GA
1	35	33	40	38
2	65	66	—	54
3	49	49	33	41
4	63	62	43	—
5	48	50	30	—
6	46	49	34	33
7	32	30	25	28
8	52	52	35	67
9	47	52	31	33
10	37	40	31	37
11	41	52	30	27
12	59	55	40	43
13	29	36	32	33
14	63	61	56	61
15	43	45	30	50
16	46	50	39	37
17	37	37	33	39
18	58	60	25	51
19	48	51	38	34
20	52	51	30	31
21	60	60	—	41
22	38	39	24	34
23	71	71	54	60
24	41	56	50	66
25	36	36	26	36
26	16	15	24	21
27	66	66	48	52
28	87	87	38	65
29	80	74	52	60

with UFCT data is probably within the range of measurement uncertainty inherent in either technique.

The agreement between the UFCT-derived RVEF measurements and those from the FP-Curve method, however, is less satisfactory. As shown in Figure 2A, there is wide scattering of the data points around the regression line and the correlation coefficient is only 0.63 (significantly < 1; $p < 0.005$). Moreover, the slope of the regression line is only 0.37 (significantly < 1; $p < 0.0001$) and its intercept value is 18%, indicating that this conventional method of assessing RVEF systematically underestimates the values above 30% by as much as 40% and, conversely, overestimates RVEF values that fall into the extremely low range of measurements.

A somewhat better correlation was found for the Eq-GA versus UFCT-derived sets of data. The fitted line for this analysis has a slope of 0.59 (significantly < 1; $p < 0.01$) and an intercept value of 14%. These parameters describe a line closer to the line of identity than those obtained for the FP-Curve method; however, they again demonstrate a tendency to significantly underestimate RVEF in the range of values commonly seen in clinical applications.

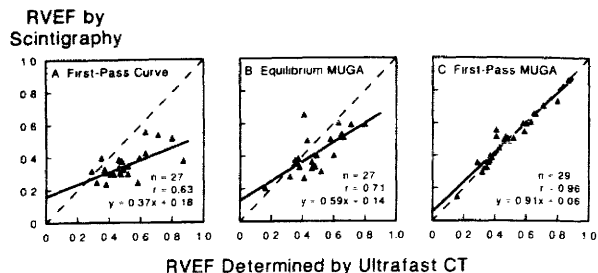


FIGURE 2
Results of RVEF measurements with three scintigraphic methods are plotted against the truth data generated by UFCT. Both the conventional non-gated first-pass approach (A) and the standard blood-pool gated acquisition technique (B) show poor correlation with the UFCT results and demonstrate a tendency to underestimate RVEF. Measurements with the ECG-gated first-pass method (C) are in excellent agreement with the results of UFCT; the slope and the correlation coefficient values calculated for this method are not statistically different from unity.

Figure 1 shows two frames of a typical FP-GA study depicting the RV at ED and ES, respectively. Of note is the magnitude of the shift in the position of the tricuspid valve plane from its end-diastolic position toward the center of the RV cavity at ES. Measured as a fraction of the RV long-axis, this translational motion ranged from 9% to 33% among the study population. The mean and standard error were $20\% \pm 1.2\%$. Furthermore, the displacement of the tricuspid valve plane appeared to be proportional to the magnitude of the RVEF. Table 2 lists the magnitude of the valve displacement associated with RVEF values of 50% or greater versus those with RVEF determination below 50%. The movements of the valve were more marked in patients with RVEF measurements of 50% or greater, averaging to be 25%, while in those with RVEF determinations below 50%, its mean value was 16%. The difference between the two groups is statistically significant ($p < 0.05$).

DISCUSSION

Radionuclide techniques provide a readily available means of evaluating right ventricular function noninvasively. However, the three scintigraphic methods that have been applied in the evolution of this test, have not been rigorously compared to an independent clinical method. Correlation with the proven technique of UFCT in this paper indicates that the ECG-gated first-pass approach is by far the most accurate radionuclide method for quantitating RVEF, while the equilibrium blood-pool imaging approach and the more widely used non-gated first-pass approach tend to underestimate RVEF significantly.

The superior performance of the FP-GA technique is largely attributable to its unique ability to isolate the RV both temporally and spatially from other blood-

TABLE 2
Systolic Displacement of Tricuspid Valve Plane
Expressed as a Fraction of RV Long-Axis

RVEF	No.	Range	Mean \pm 1 s.e.
≥ 0.50	18	19%–33%	25% \pm 1.4%
< 0.50	11	9%–26%	16% \pm 1.5%
All cases	29	9%–33%	20% \pm 1.2%

pool structures. ECG-gated images of the RV obtained from the first transit of a radioactive bolus through the RV permit visual delineation of this chamber at ED and ES without any significant interference arising from the blood-pool activity in the left heart chambers, the pulmonary parenchyma, or the thoracic wall structures. This is not easily achieved with either the Eq-GA or the FP-Curve methods.

Presence of substantial blood-pool activity outside the right ventricle obligates a LAO approach on Eq-GA studies. This view at best can only separate the RV from the LV. Delineation of the tricuspid valve plane is difficult on this projection because the valve plane is inclined with respect to the axis of the gamma camera and may not present a distinct profile. In our experience, in about one-third of the cases the superior margin of the RV could not be defined reliably on Eq-GA images and its location had to be inferred from the superior margin of the LV. Methods have been described whereby a functional image of the RV is generated from the difference of the ED and ES images in order to help distinguish RV from the oppositely phased image of the right atrium (27,28). Total elimination of right atrial contributions to the RV ROI, however, remains problematic when the two chambers overlap considerably. Separation of the RV from the right atrium can be improved somewhat if a slant-hole collimator is used (15,29) or if a caudad angulation is applied to the camera head, but a slant-hole collimator is not routinely available in all institutions, while the oblique positioning of the camera head degrades resolution and is difficult to reproduce.

The problem of atrial overlap is more pronounced with the FP-Curve method due to the use of a single "fixed" ROI for both the systolic and diastolic frames of the cardiac cycle. The average count density obtained in each frame used to construct the FP-Curve from a 30-mCi technetium-99m dose is on the order of 250–500 counts in about 900 pixels. This count density is insufficient for delineation of the RV edges either visually or by automated algorithms. One is therefore obligated to assign to a composite of many images a single ROI, which typically conforms to the end-diastolic contour of the RV (12). As shown in Figure 1, the tricuspid valve plane has an inward motion during systole which averages about 20% and could be as much as 33% of the length of the RV (Table 2). Because of

this, a substantial portion of the right atrium is included during systole in this single "fixed" ROI and results in underestimation of the RVEF.

Inclusion of non-RV counts in the ROI selected for this chamber can account for the systematic underrepresentation of RVEF exhibited both by the Eq-GA and the FP-curve methods (Fig. 2A-B). It follows from the EF formula that presence of extraneous activity added to both the end-diastolic and the end-systolic counts would invariably result in a lower calculated EF. The error is even greater when the extraneous activity varies cyclically in a phase opposite to that of the RV. Counts arising from the atria impart such an error to the RVEF measurement and behave in a manner similar to the presence of a dysknetic segment within the RV chamber.

We elected to position our subjects for the UFCT and the radionuclide studies not identically, but according to the norm practiced in our institution and many other institutions. Thus, subjects were supine for the UFCT and semi-recumbent for the scintigraphic studies. While there may have been slight hemodynamic differences between the two positions, such differences in our view are unlikely to have had significant impact on the relative accuracy of the three radionuclide methods we investigated.

Our FP-Curve method was similar to that originally described by Berger et al. (13) in 1976, but differed with respect to the type of imaging instrument employed. They used a multicrystal camera with a higher count rate capability than the Anger-type camera used in the present study. The multicrystal camera is no longer available as a realistic option and virtually all nuclear medicine centers currently employ Anger-type gamma cameras for clinical radionuclide studies. Modern Anger cameras, on the other hand, have improved measurably in their count rate response and currently are capable of handling count rates generated by routine doses of technetium-99m, typically in the range of 20–30 mCi. In this study, we took the added precaution of fitting our camera with a collar that shielded the bulk of extra-cardiac activity and thereby reduced the count rate burden on the camera. At any rate, the problem of systematic underestimation of RVEF by the FP-curve method cannot be explained by camera count rate limitations. From a theoretical standpoint, the total activity recorded by the camera during systole and diastole is nearly constant and, therefore, any count rate-dependent changes in camera sensitivity will have no significant effect on RVEF determinations. Had this been the case, the FP-GA results in this study would have also shown a similar error, because for the majority of cases they were drawn from the same set of first-pass data used in the FP-Curve analysis. On the other hand, the obligatory use of a fixed ROI, implemented both by Berger et al. and in our FP-Curve analysis, fails to

completely exclude the right atrium and, therefore, predisposes to RVEF underestimation. Berger et al. were cognizant of this problem (12) and suggested the remedy of obtaining a time-activity curve from a region over the interface between the right atrium and the RV and subtracting it from the right ventricular first-pass curve. This is hard to accomplish in a reproducible manner in all patients and may not be warranted when accurate RVEF measurements can be obtained in a straight forward manner with the FP-GA method.

Radionuclide techniques are likely to remain the preferred modality for RVEF determination. UFCT is handicapped by high cost, limited availability, and the requirement for intravenous injection of radiographic contrast. Our findings indicate that ECG-gated first-pass scintigraphy provides extremely accurate RVEF determinations. Both the standard Eq-GA technique and the nongated first-pass approach are subject to methodologic errors that degrade their accuracy. As an additional advantage, the FP-GA technique provides for limited wall motion analysis on the cine display of ECG-formatted right ventricular images. Centers currently employing beat-by-beat analysis of the first-pass curve can easily shift to the FP-GA method by merely adding ECG gating and applying the variable ROI methodology that is used already in LVEF measurements.

Neither UFCT nor any of the first-pass radionuclide methods can provide reliable RVEF measurements in the presence of pronounced cardiac arrhythmia. These techniques generally sample only a few cardiac cycles and therefore cannot provide a "mean RVEF" from a large number of cardiac cycles. In these situations, the Eq-GA technique may have a theoretical advantage over the other methods. The Eq-GA approach is also advantageous in circumstances where serial RVEF determination are to be obtained with a single radiopharmaceutical injection, such as in assessment of RV response to interventions.

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