Gated Right Ventricular Studies Using Krypton-81m: Comparison with First-Pass Studies Using Gold-195m

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Krypton-81m, given by continuous i.v. infusion, has been successfully used for the equilibrium ECG-gated assessment of right ventricular function. We compared gated studies with ^{81m}Kr (half-life 13 sec) with first-pass studies using ^{195m}Au (half-life 30.5 sec). Krypton studies analyzed using variable regions of interest (ROIs) led to a significantly higher calculated right ventricular ejection fraction (RVEF) than with a fixed ROI, both with and without background correction. The differences between first-pass studies and gated studies without background correction were significant ($p < 0.01$), whereas they were not with background correction. These data suggest that large systematic errors exist in the calculation of RVEF depending on the analysis method and that background correction is important when different techniques are compared.

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Recognition of the importance of right ventricular function (*1*) has led to the interest in methods for its noninvasive assessment (*2*). Because of the right ventricle's complex geometry (*3*), radionuclide angiography, which is independent of ventricular shape, appears ideally suited to its study. A major problem associated with conventional ECG-gated equilibrium studies is that the left ventricle overlaps the right ventricle in the right anterior oblique (RAO) projection. This is the ideal projection for minimizing right atrial overlap. In the left anterior oblique (LAO) projection, which is most often used, the right atrium overlaps the right ventricle (*4*), although the ventricular septum is in profile and there is separation of the ventricles. Thus, chamber overlap may lead to errors in the calculation of ejection fraction. To overcome these problems, some investigators have used variable regions of interest (ROIs) in systole and diastole (*5*), and have used a variety of background corrections.

The development of krypton-81m (^{81m}Kr), which has both a very short half-life (13 sec) and is eliminated on its first pass through the lungs, has meant that right ventricular gated studies may be performed using the RAO projection, without left ventricular overlap (*6,7*). Methods of analysis vary between centers, and it has not yet been agreed if background correction is necessary (*6,7*). In this study, nine subjects had resting gated ^{81m}Kr images, which were then analyzed using four methods, variable or fixed ROIs, with or without background correction. These subjects also had first-pass radionuclide angiography using gold-195m (^{195m}Au) on the same day and the results were compared.

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PATIENTS AND METHODS

Patients

The study group consisted of nine patients, eight male, one female, ranging in age from 44–72 yr, mean ± s.d. (58 ± 9 yr), who were referred to the nuclear cardiology laboratory for assessment of resting ventricular function. Clinical details and the reasons for the study are given in Table 1. Six had coronary artery disease (CAD), two had congestive cardiomyopathy, and one had a left ventricular aneurysm. All subjects were able to lay flat and were in sinus rhythm. Informed signed consent was obtained, and the study had hospital ethical committee approval.

Gated ^{81m}Kr Studies

Patients were imaged in the supine 30° RAO projection using a GE 400T single crystal gamma camera linked to a gamma 11 computer sytem. Krypton-81m was eluted in 5% dextrose from a ^{81}Rb/^{81m}Kr generator

TABLE 1
Clinical Details and Results in All Subjects

Patient no.	Sex	Age	Diag*	EF†(Au10)‡	EF(Au1)§	EF(Kr1)¶	EF(Kr2)**	EF(Kr3)††	EF(Kr4)‡‡
1	M	52	CAD§§	28	28	44	22	46	28
2	M	58	CAD	36	38	38	23	33	22
3	M	60	CM¶¶	14	21	24	9	20	3
4	M	62	CAD	36	40	41	19	31	11
5	M	62	LVA***	31	37	50	27	49	34
6	F	47	CAD	33	34	45	21	36	19
7	M	72	CM	29	26	55	30	54	38
8	M	65	CAD	19	18	37	16	31	20
9	M	44	CAD	40	44	41	25	44	35
Mean		58		29.6	31.4	41.7	21.3	38.2	23.3
s.d.		9		8.4	9.0	8.7	6.2	10.8	11.6

* Diag = Diagnosis.
† EF = Calculated RVEF (%).
‡ Au10 = ^{195m}Au study injection rate 10 ml/sec.
§ Au1 = Gold study injection rate 1 ml/sec.
¶ Kr1 = ^{81m}Kr gated study analysis Method 1 (see text).
** Kr2 = Krypton study Method 2.
†† Kr3 = Krypton study Method 3.
‡‡ Kr4 = Krypton study Method 4.
§§ CAD = Coronary artery disease.
¶¶ CM = Cardiomyopathy.
*** LVA = Left ventricular aneurysm.

(*6*) (MRC Cyclotron Unit, Hammersmith) and infused through a Millipore filter and a 21-gauge butterfly into an arm vein. Infusion rate was controlled at ~ 10 ml/min using a peristaltic infusion pump. Electrocardiographic gating was performed using R-wave triggering with 18 frames/cycle, and data were collected until 5×10^6 counts were acquired (~ 15–20 min).

Data Analysis

Data were analyzed using four methods described below.

Method 1. Variable ROIs without background correction. An initial provisional ROI was entered over the visually identified right ventricle, and an 18-point time-activity curve was generated. End-diastole was taken as the frame with the highest counts, and end-systole was taken as the frame with the lowest counts. New ROIs were then entered, one using a visually identified end-diastolic ROI, and the other a visually identified end-systolic ROI. The position of the lateral (septal) and inferior borders of the right ventricle were easily identified, but assessment of the approximate position of the medial (tricuspid) and superior (pulmonic) borders required generation of a cine cycle from which the tricuspid and pulmonic valve planes were identified. These positions were then checked against a stroke volume image that was generated by subtraction of the end-systolic image from the end-diastolic image (*8*). New time-activity curves were generated from the ROIs and the right ventricular ejection fraction (RVEF) was derived from the peak (end-diastolic) counts from the diastolic ROI and the trough (end-systolic) counts from the systolic ROI by the formula:

$$\text{RVEF (\%)} = \frac{(\text{EDC} - \text{ESC})}{\text{EDC}} \times 100,$$

where RVEF = right ventricular ejection fraction, EDC = end-diastolic counts, and ESC = end-systolic counts.

Method 2. Fixed ROI without background correction. An initial time-activity curve was produced and a stroke volume image described as in Method 1. The updated ROI was then formed from the perimeters of the stroke volume image. This produced an ROI similar to the end-diastolic ROI in Method 1. The rationale for using the stroke volume image is that it represents the region in which counts change from systole to diastole, and thus contribute to the ejection fraction counts. Care was exercised to include all pixels within the lateral and inferior borders of the right ventricle identified from the end-diastolic frame, even if from the stroke volume frame they did not appear to contribute counts due to impaired function. The right atrium, identified by the medial border of the stroke volume image and pulmonary artery, as identified by the superior border of the stroke volume image, do not contribute changes in counts to the ejection fraction and were thus excluded. A major problem with using a fixed ROI is movement of the tricuspid valve plane from systole to diastole. In order to ensure that right atrial activity is excluded from the right ventricular ROI during systole, the medial border of the ROI has to be positioned such that some end-diastolic right ventricular counts are excluded. Method 2 differs from Method 1 in that the single ROI means the end-systolic counts are derived from a much

larger area, whereas end-diastolic counts are derived from a slightly smaller area. A new time-activity curve was generated and the ejection fraction calculated from peak and trough counts.

Method 3. Variable ROIs with background correction. Variable ROIs were identified as in Method 1. A background ROI, 2 pixels wide, was entered laterally and inferiorly to the diastolic ROI. Care was taken to ensure that the background did not extend into the right atrium or pulmonary artery as identified by the valve planes on the stroke volume image. A normalized background time-activity curve was subtracted from the appropriate systolic and diastolic time-activity curves and the ejection fraction calculated as in Method 1.

Method 4. Fixed ROI with background correction. A fixed ROI was derived as in Method 2, and a background ROI as in Method 3. A normalized background time-activity curve was subtracted from the right ventricular time-activity curve and ejection fraction calculated from the resultant curve.

First-Pass ^{195m}Au Studies

Within 6 hr of the ^{81m}Kr study the patients were studied using ^{195m}Au. They were studied in the supine 30° RAO projection using a multicrystal gamma camera (Baird Atomic System 77). An 18-gauge cannula was inserted into a large antecubital fossa vein, preferably a medial vein, and connected to a tube with a dead space of <2 ml. This was connected to a three-way tap which allowed radioisotope to be injected into the tube and then flushed into the patient using a 20-ml syringe of saline. Aliquots of ^{195m}Au, ~0.5 ml (550–770 MBq), were eluted from a portable ^{195m}Hg/^{195m}Au generator as previously described (*9*). The ^{195m}Au was injected at two injection rates, 10 and 1 ml/sec. Because ^{195m}Au has a half-life of only 30.5 sec it was possible to repeat the injection after only 3 min (i.e., >5 half-lives) without correcting for residual activity which was <2% of that injected. Data were collected for 30 sec at 30 msec framing intervals and were corrected for instrument dead time and crystal nonuniformity using a uniform ^{203}Hg flood which has a similar energy to ^{195m}Au.

Data Analysis

Right ventricular ejection fraction was calculated from high frequency time-activity curves, using a method that has been shown to be reproducible and to correlate reasonably well with contrast angiographic studies of the right ventricle (*10*). Data were corrected for rapid decay of the radioisotope and temporally smoothed (*11*).

The study was replayed using 1-sec serial frames and the right ventricle identified visually. A time-activity curve was generated from an initial right ventricular ROI and the peak (end-diastolic) and trough (end-systolic) frames identified. The initial peak was not used as this may represent passage of the bolus of radioisotope directly through the open tricuspid valve into the pulmonary outflow tract without mixing. All subsequent peaks are thus preceeded by systolic mixing in the right atrium. By adding the individual end-diastolic and end-systolic frames, end-diastolic and end-systolic images could be produced. A stroke volume image could then be produced by subtraction as outlined in Method 1 of the kyrpton studies. The right ventricular ROI could thus be adjusted to ensure that all right ventricular pixels were included, and by using an iterative approach a final ROI was produced. Background correction was made using a ROI, 2 cm wide, around the lateral and inferior borders of the right ventricle. The limits of this background ROI were defined in the same way as in Method 3 of the krypton studies. A planar background correction was made using the normalized counts/pixel derived from the background ROI, and ejection fraction was then calculated from the background corrected residual counts within the right ventricular ROI.

Radiation Dosimetry for ^{81m}Kr and ^{195m}Au

Krypton 81m. Because of its short half-life and almost total elimination by the lungs, the radiation exposure from krypton is principally to the right ventricle. Although the extent of decay in its passage from the generator to the heart is not known with certainty, this will greatly affect any calculation of radiation dose to the heart. Despite these limitations, the dose to the right ventricle for a 20-min study has been calculated as 1 rem (*12*).

Gold-195m. Calculated dosimetry for the Harwell ^{195m}Hg/^{195m}Au generator, assuming a 0.01% ^{195}Hg breakthrough, for two studies per patient is 50 mrem to the kidneys, a maximum of 6 mrem to the gonads, and a whole-body dose of 12 mrem. The equivalent burden from 1,100 MBq of technetium-99m (^{99m}Tc), as pertechnetate, which would be enough for two studies, is 300 mrem to the whole body and 3,000 mrem to the kidneys.

Statistical Analysis

Analysis was performed using paired and unpaired t-tests and standard errors of the estimate as appropriate, using a standard software program and a desktop microcomputer. A p value of <0.05 was taken as significant.

Adverse Effects

No adverse effects were noted during either the krypton or gold studies.

RESULTS

Comparison of Ejection Fractions from the Four Methods of Analysis of the Gated ^{81m}Kr Studies

Table 1 and Fig. 1 show the mean ± s.d. for the four krypton methods and the two gold studies. The values

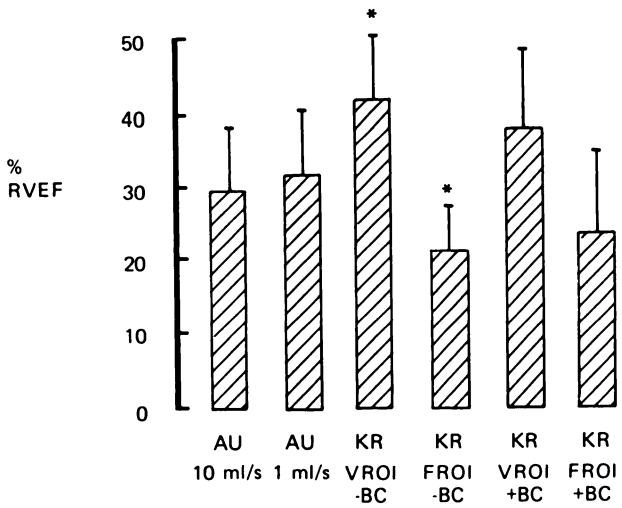

FIGURE 1
Mean ± s.d. of RVEF in nine subjects using ^{195m}Au and krypton. n = 9; * = $p < 0.01$ vs. ^{195m}Au study (injection rate 10 ml/sec). Au = ^{195m}Au study, KR = ^{81m}Kr study, VROI = variable region of interest, FROI = fixed region of interest, −BC = without background correction, +BC = with background correction

for the krypton studies were 41.7 ± 8.7% for Method 1, 21.3 ± 6.2% for Method 2, 38.2 ± 10.8% for Method 3, and 23.3 ± 11.6% for Method 4. The values using variable ROIs were significantly higher than using a fixed ROI, $p < 0.001$, both with and without background correction. The mean difference between variable and fixed ROIs without background correction (Methods 1 and 2) was 20.3 ± 4.0%, with six values differing by >20%, and three between 10 and 20%. With background correction (Methods 3 and 4) the difference was 14.9 ± 3.7%, with eight values differing by between 10 and 20% and only one by <10%. The effect of background correction in itself was not significant whichever ROIs were used. With variable regions the mean difference was 3.4 ± 4.6% with six values differing by 5% or less, and a maximum difference of 10%. With a fixed region the mean difference was −2.0 ± 6.5% with three values of 5% or less and a maximum of −10%.

Comparison of Gated ^{81m}Kr Studies and First-Pass ^{195}Au Studies

The values for the group are shown in Table 1 and Fig. 1. Two gold injection rates were used as the rate of 10 ml/sec is what is most often used in clinical practice, but the compact bolus limits the number of cardiac cycles available for analysis. The slower injection rate has been shown to have no effect upon the calculation of RVEF using this method (*8*), but does increase bolus duration, the number of cardiac cycles available for analysis, and as Table 4 shows the end-diastolic counts. Mean RVEF for the gold studies was 29.6 ± 8.4% at an injection rate of 10 ml/sec (range 14–40%), and 31.8 ± 9.0% (range 18–44%) at an injection rate of 1 ml/sec, p not significant. There were significant differences between the ejection fractions from the gold studies and from the krypton studies without background correction (Methods 1 and 2), $p < 0.01$. However, when background corrected (Methods 3 and 4) the differences were not significant.

TABLE 2
Significance Values (p) by Paired t-Test Comparing Each Method of Assessing RVEF with the Others

Au 10	—					
Au 1	N.S.*	—				
Kr 1	<0.01	<0.05	—			
Kr 2	<0.01	<0.01	<0.001	—		
Kr 3	N.S.	N.S.	N.S.	<0.001	—	
Kr 4	N.S.	N.S.	<0.001	N.S.	<0.001	—
	Au 10	Au 1	Kr 1	Kr 2	Kr 3	Kr 4

*n.s. = Not significant.

Table 2 shows the p values for each method or type of study when compared with each of the others. In summary, there were no significant differences between the gold studies, the krypton studies using given ROI(s), with or without background correction, or the gold studies and krypton studies background corrected. There were significant differences between krypton studies using different regions of interest, and between gold studies and krypton studies without background correction.

Table 3 has the same format as Table 2. It shows the standard errors of the estimates (s.e.e.s) (%) for each set of results when compared with each of the others. We have previously shown that the s.e.e. of RVEF in first-pass studies to be ~4%, over a wide range of ejection fractions and bolus injection rates (*8*). When the krypton methods are compared with the gold studies, this figure is considerably higher ranging from 4.9–11.9%, mean 9.0 ± 2.6%. When the krypton methods are

TABLE 3
Standard Errors of Estimates in % Comparing Each Method with the Others

Au 10	—					
Au 1	3.5	—				
Kr 1	8.0	8.9	—			
Kr 2	4.9	5.8	2.7	—		
Kr 3	10.3	11.1	4.7	4.4	—	
Kr 4	11.0	11.9	7.3	5.0	4.0	—
	Au 10	Au 1	Kr 1	Kr 2	Kr 3	Kr 4

compared, the s.e.e. ranges from 2.7–7.3%, mean 4.7 ± 1.5%.

Comparison of Total End-Diastolic Counts Between the Krypton Methods and the Gold Methods

Table 4 shows the mean and s.d. of the total end-diastolic counts of each of the krypton methods and the gold studies. Since the krypton Methods 1 and 2 were without background correction, the data include results from the gold studies both before and after background correction. Total end-diastolic counts were highest using krypton Method 1, 33,792 ± 11,236 counts, and were lowest from the gold studies at an injection rate of 10 ml/sec after background correction, 8,573 ± 3,685 counts. The difference in counts between the krypton methods were highly significant ($p < 0.01$), with the exception of krypton Methods 3 and 4 ($p < 0.05$). When the krypton methods without background correction (1 and 2) were compared with the gold methods the results were again significantly different ($p < 0.01$). However, when background corrected krypton studies (Methods 3 and 4) were compared with background corrected gold studies the difference in counts was not significant for the gold injections and 1 ml/sec, and only just significant at the faster injection rate ($p < 0.05$).

Differences in end-diastolic counts between the methods might have some relationship to the variability in calculated ejection fraction between the gold and krypton studies. To assess this, the mean background corrected counts were calculated in two groups, first those observations in which the variability between the gold and krypton results was less than the mean (10%), and second in those where the variability was greater than the mean. In the 19 observations in which the variability was <10%, end-diastolic count difference was 9,195 ± 7,669 counts, and in the 17 observations where the variability in ejection fraction was, >10%, the count difference was 8,694 ± 10,589 counts, (p not significant).

TABLE 4
Means and Standard Deviations of Total End-Diastolic Counts for Each Method of Calculating RVEF

	Mean	s.d.
Au 10	8573	3685
Au 10 (−BG)*	12,015	5126
Au 1	10,993	4434
Au 1 (−BG)†	15,321	5996
Kr 1	33,792	11,236
Kr 2	29,321	8211
Kr 3	19,132	7914
Kr 4	16,504	5789

*Au 10 (−BG) = ^{195m}Au studies at injection rate of 10 ml/sec without background correction.

†Au 1(−BG) = gold studies, injection rate 1 ml/sec without background correction.

DISCUSSION

Lack of a universally accepted standard, such as is provided by contrast left ventriculography for left heart studies, is a particular problem when new methods for assessing right ventricular function become available. Contrast right ventriculography and echocardiography have the inherent disadvantage that assessment of right ventricular volumes requires assumption about its complex and changing geometry (*13–14*). This is of importance since the relationship between the ventricles and, hence, right ventricular shape changes during the cardiac cycle and with respiration (*15*). Radionuclide techniques, which are independent of geometry, have been successfully used to assess RVEF. Right ventricular studies with conventional radioisotopes using the equilibrium gated technique have the disadvantage of chamber overlap. This has led to the search for radiopharmaceuticals that have short half-lives and are exhaled by the lungs.

Krypton-81m has a half-life of 13 sec and is expired by the lungs on its first transit, with minimal overlap by left-heart structures. Its short half-life means that environmental contamination is very small, and in this respect it compares very favorably with xenon-133, where exhaled gas has to be trapped (*16*). There is, however, no agreement in the methodology for assessing RVEF. It has been argued that no background correction is required since the left-heart structures do not contribute counts (*7*). This ignores the fact that scatter from the right atrium and pulmonary artery may contribute to measured counts. In the analogous situation in first-pass left ventricular studies with an injection through the distal port of a pulmonary artery catheter, it has been shown that despite the lack of activity in the right heart, background correction is still necessary (*17*).

This study was designed to assess the effect of different analysis protocols for the estimation of RVEF using ^{81m}Kr. These were compared with first-pass studies using ^{195m}Au, using a method of analysis which has shown to be reproducible, with a correlation of 0.93 and a s.e.e. of 4% (*8,10*). Comparing the method with single-plane contrast right ventriculography correlation was 0.74, with a s.e.e. of 6.5% (*10*). This correlation improves considerably (0.87) when biplane studies are used (unpublished data). This is despite the difficulties inherent in the assessment of RVEF from contrast studies. Use of the two short half-life radiopharmaceuticals limited the radiation exposure.

The results show that end-diastolic counts are considerably higher in krypton studies than in gold studies, even when considering background correction. Slowing the rate of the gold injection in the first-pass studies reduced the difference, and this technique might increase the statistic accuracy of first-pass studies when

right ventricular function is of primary interest. The duration required for acquisition of right ventricular studies using krypton limits its usefulness in intervention studies where ventricular function may change rapidly. It should be remembered that the right ventricular counts of the krypton studies were acquired over at least 15 min, whereas those for the gold studies over 3 or 4 sec only.

Conventional gated right ventricular studies, which use the LAO projection, have employed both fixed (*18*) and variable (*5*) ROIs, the latter in an attempt to minimize right atrial contribution to right ventricular counts. When first-pass studies and gated studies using a fixed ROI (*18*) were compared, the RVEF values correlated moderately well, but ejection fraction tended to be higher in the gated studies possibly due to right atrial overlap. Our data on the calculation of ejection fraction show that the values of RVEF derived from krypton studies are highly dependent upon the method of data analysis. The use of a single ventricular ROI led to considerably lower values than using two. The addition of background correction slightly lessened the difference, but it was still very significant. Background correction, per se, did not significantly alter the values. However, it was not surprising that background correction did appear to significantly improve the agreement as compared with the first-pass method. When the s.e.e.s were compared, the differences between gold and krypton studies appeared to be quite large, whereas there was a reasonable relationship between krypton methods. In a study comparing bolus injections of xenon-133 and ^{99m}Tc in the assessment of right ventricular function using the first-pass technique (*16*) there was an excellent correlation. However projections, methods of analysis, and background correction were the same for both radioisotopes.

It is difficult to explain why there is such great difference between krypton and gold studies. It does not appear to be related to differences between total end-diastolic counts as our data show. However, work in progress in our laboratory has shown that there is a significant change in RVEF on maximal inspiration compared with maximal expiration (*19*). It may be that the observed differences between gold and krypton studies are due to the difference in data acquisition time discussed above. This will blur any changes during the respiratory cycle and may alter calculated RVEF. The difference in values between the fixed and variable ROIs is easier to explain. Since the end-systolic ROI is always smaller than the end-diastolic, both peak and trough counts from this region are lower. This means that ejection fraction, which is calculated from the end-diastolic time-activity curve peak and the end-systolic time-activity curve trough, will be higher when variable rather than fixed ROIs are used.

Background correction did not significantly alter the values, and this is of interest since background correction is of great importance in studies of the left venticle (*17*). It may be that the lack of overlap by other cardiac chambers in right ventricular studies reduces the contribution of background counts to overall right ventricular counts. The results of this study reveal an apparent paradox. Background correction increased mean RVEF when a fixed ROI was used (Methods 2 and 4), but reduced ejection fraction when variable ROIs were used (Methods 1 and 3). This may be due to the nature of the background counts curve which is phasic, being greatest at end-diastole and least at end-systole. Subtraction of this curve from both systolic and diastolic ventricular ROI curves proportionately reduces end-diastolic counts more than end-systolic counts thus reducing calculated ejection fraction. When this curve is subtracted from a single ventricular ROI curve both end-systolic and end-diastolic counts are reduced in the same proportion, and thus calculated ejection fraction is increased. Although in this study the methods of background correction for gold and krypton differ slightly, these data confirm the importance of background correction when different techniques are compared. In right ventricular studies, scatter is primarily from within the right ventricular itself and methods which use right atrial pixels to produce a background correction tend to increase the calculated RVEF (*4*). It must be stressed that it is not known which technique gives a "correct" value for RVEF, but that the variation in results from the krypton methods means that comparison between groups performing these studies is difficult.

In conclusion, ^{81m}Kr imaging is a useful technique for the assessment of right ventricle function. There are, however, large systematic errors which may be introduced into the calculation of ejection fraction unless the analysis protocol is chosen with care. Background correction appears to be important despite the lack of activity in left-heart structures. These data suggest that background correction should be employed in the analysis, but that until there is some agreement on analysis protocols, caution should be applied in comparing results between centers.

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