Effect of Region of Interest Selection on First-Pass Radionuclide Cardiac Output Determination

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In principle, region of interest (ROI) selection should not affect the measurement of cardiac output by the first-pass technique with a radioactive intravascular indicator. Clinical application of the method requires that this theoretical hypothesis be tested. Sixty-eight left anterior oblique first-pass studies were acquired with a scintillation camera and computer using red blood cells labeled in vitro with ^{99m}Tc. Calculated mean cardiac output varied in the following order with respect to ROI: lung > right heart > left ventricle > whole heart (both ventricles) > aorta. Similar variations were observed in patients both with and without valvular regurgitation. Regions of interest over left ventricle or whole heart yielded the best correlations with cardiac output by thermodilution ($r = 0.96, 0.95$, respectively, $n = 28$) as well as the smallest interobserver variations ($r = 0.994, 0.995$, respectively, $n = 33$). First-pass studies with [^{99m}Tc]red blood cells labeled in vitro can yield accurate, reproducible determinations of cardiac output provided that the effect of ROI selection is recognized and that regions are properly selected.

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Principles of indicator-dilution have provided the basis for the earliest (*1–4*), as well as some of the most widely accepted current methods for estimating the output of the heart. The introduction of radioactive intravascular indicators prompted the use of the externally monitored radiocardiogram to determine cardiac output according to principles of indicator-dilution. This method has been evaluated with favorable results by several investigators (*5–11*), but less favorable results by others (*12–14*). Early first-pass measurements were performed with probes placed over the chest. While almost all investigators agreed that proper collimation and placement of the probe was critical to the success of the radionuclide method (*5,10,12,13,15,16*), there was no universal agreement in practice as to where or how the probes should be placed prior to injecting the patient. This proved to be a practical limitation in the application of the method. Why might the site of observation affect measurements of cardiac output based on external monitoring? In this regard, it is important to first examine briefly the basis of the first-pass method.

Following the injection of a quantity, I, of intravascular indicator, the integrated area, A, under the time-concentration curve, C(t), at a downstream sampling point is related by conservation of mass to a constant flow, F, by the equation

$$I = F \int_0^\infty C(t)\, dt. \qquad (1)$$

It can be shown (*15*) that Eq. (1) can be expressed in the form

$$F = \frac{\text{Dilution Volume} \times E}{A}, \qquad (2)$$

when monitoring is performed with an external detector, where A is area under the first-pass curve observed by the detector and E is the count rate of the detector at the time when dilution volume of the intravascular tracer is measured. Equation (2) is valid even when multiple sites of flow are observed. It is important, however, that the detector observe the same volumes of distribution of tracer during both first-pass and equilib-

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rium counting (*15,17,18*). Depending on the location of the detector, different volume distributions of tracer could be observed when E and A are measured. Detector location could also affect the accuracy with which the area, A, under the curve could be measured using the extrapolation method of Hamilton (*4*). Therefore, measurements of cardiac output might vary with location of an external detector.

Using modern scintillation cameras and computers it is possible to acquire data simultaneously from a large number of potential probe locations. Hence, the effect of varying the site of observations on measurement of cardiac output can be assessed. In this study, such an assessment was made, revealing that region of interest (ROI) selection has a systematic and predictable effect on cardiac output results.

METHODS

Subjects

Sixty-eight determinations of cardiac output were performed with first-pass radionuclide angiography in 66 patients: 24 females and 42 males with an age range of 14–79 yr and mean age 61 yr. Two patients were studied twice, at intervals of 1 hr and 1 wk, respectively, before and after therapeutic interventions. Equilibrium gated cardiac imaging was performed for clinical indications in each patient, and first-pass studies were acquired incidental to tracer injection. Patients with intracardiac shunts were excluded from the study.

Forty of the patients underwent contrast angiography within 2 wk of radionuclide imaging; 20 showed no evidence of mitral or aortic regurgitation and 20 showed mitral or aortic regurgitation ranging in severity from 1+ to 4+ as assessed by retrograde reflux of contrast (*19*) (six with 1+, five with 2+, five with 3+, and four with 4+ regurgitation). All 20 had physical findings of mitral or aortic regurgitation at the time of the radionuclide study. Principal cardiovascular diagnoses among these 40 patients included: coronary artery disease in 26, normal in three, rheumatic heart disease in three, hypertensive heart disease in two, ruptured chordae tendineae in two, bacterial endocarditis in two, periprosthetic valvular leak in one, and coronary artery disease plus rheumatic heart disease in one patient.

The other 28 determinations were performed in 26 hospital in-patients with right-sided thermodilution catheters in place as described below. Principal cardiopulmonary diagnoses among these 26 critically ill in-patients included coronary artery disease in 19, cardiomyopathy in three, chronic lung disease in two, rheumatic heart disease in one, and primary pulmonary hypertension in one. None of these 26 in-patients were anuric or in overt pulmonary edema at the time of study, and none were studied within 24 hr of arrival in the critical care unit.

Radionuclide Studies

Autologous red blood cells were labeled with 20 mCi of technetium-99m (^{99m}Tc) by an in vitro procedure (*20*). The dose was divided into two aliquots of 10 mCi each. The first aliquot was injected as a bolus with particular attention to technique of injection. Thirteen of the 68 injections were performed through the proximal ports of indwelling thermodilution catheters into the right atrium or the region of its junction with the superior vena cava. Following completion of injection of the first 10-mCi aliquot in a volume of ~4 ml, immediate aspiration of blood back into the injectate syringe was begun in order to remove residual indicator from the catheter (*21*) and field-of-view. This also terminated the trailing edge of the radionuclide bolus.

Fifty-five peripheral injections were performed through either external jugular veins, right median basilic antecubital veins, or in one instance, through an indwelling catheter in a right iliac vein. External jugular and antecubital injections were performed through 21-gauge Butterfly needles with 12-in. tubing*. All injections and withdrawals of blood related to the procedure were performed through the i.v. line so that patients experienced only one venipuncture. Following external jugular injections, immediate reaspiration of blood back into the injectate syringe was performed as described above. Antecubital injections were performed as follows. A rubber tourniquet was applied in the right midhumeral region and the patient carefully taught to relax their right arm as it was passively raised and lowered with the tourniquet applied. The dose was then injected and the arm elevated by the injector as the tourniquet was released. The single injection into a right iliac catheter was accomplished as described for external jugular injections. With careful attention to injection technique as outlined above, problems with venous delay and poor bolus quality as described by Fouad et al. (*22*) have been eliminated.

All first-pass studies were performed in the 40° left anterior oblique (LAO) projection using a portable camera† interfaced to a computer‡. A high resolution, parallel hole collimator was employed in order to maximize spatial resolution. First-pass data were recorded in a 64 × 64 matrix at 0.4 sec per frame for 128 frames. Immediately following dynamic acquisition a postflow static image was acquired for 700,000 counts without repositioning either the patient or the scintillation camera. This ensured that ROIs were applied to identical anatomic areas in determining first-pass and equilibrium count rates, without intervening patient motion or elution of tracer from the vascular space. The duration of acquisition of the postflow static image was automatically recorded by the computer. All data were stored on floppy disks. Following completion of the postflow static image, the remainder of the 20 mCi dose of the ^{99m}Tc red blood cells was injected, and equilib-

rium gated cardiac imaging was performed with calculation of left ventricular ejection fraction by standard methods using variable ROIs.

Data Analysis

ROIs for determination of cardiac output were manually defined with a light-pen using the postflow static image. Regions were assigned over right or left lung, right heart, left ventricle, whole heart (over both right heart and left ventricle), proximal ascending aorta and pulmonary artery, and entire field-of-view of the camera as in Fig. 1. Anatomic ROIs were defined well inside the outer edges of the chamber of interest in the postflow static image; e.g., left ventricular regions were chosen so as to approximate the end systolic edges of the ventricle. Time-activity curves were then generated from the dynamic study and equilibrium count rates from the postflow static image for all six regions of interest. Background regions were not defined, and background subtraction was not performed. Time-activity curves from the ROI encompassing the entire field-of-view of the camera were used to correct for count losses due to system deadtime by the method of Adams et al. (*23*). A least squares exponential fit to the downslope of each curve was performed and total area under the curve calculated by the Hamilton approach (*4*). The dilution volume was estimated as predicted blood volume based on sex, height, and weight by the formula of Nadler and Hidalgo (*24*), and cardiac output calculated using Eq. (2) for each of the five anatomic regions in Fig. 1.

Thermodilution Studies

In 28 instances, cardiac output was measured by thermodilution immediately prior to the radionuclide studies. Simultaneous injections of radionuclide and thermal indicators were avoided due to potential distortion of the thermal curve by the [^{99m}Tc]red blood cells which were injected at room temperature. Thermodilution measurements were performed using seven French, quadruple lumen, flow-directed balloon-tipped catheters interfaced to a bedside computer[§]. Injections of 10 ml iced saline were repeated at minimum intervals of 2 min until three consecutive determinations agreed within 10%. The final thermodilution result was taken as the average of these three. Radionuclide injections were performed immediately after the last thermodilution study.

Statistical Analysis

To evaluate the effect of ROI selection on the first-pass results, it is important to compare results from different ROIs with each other as well as with a reference measurement. Thermodilution measurements were used as references in this study. Straightforward comparison of mean results is difficult, however, since all the results in any one patient are highly correlated with one another. Hence, multiple comparison testing

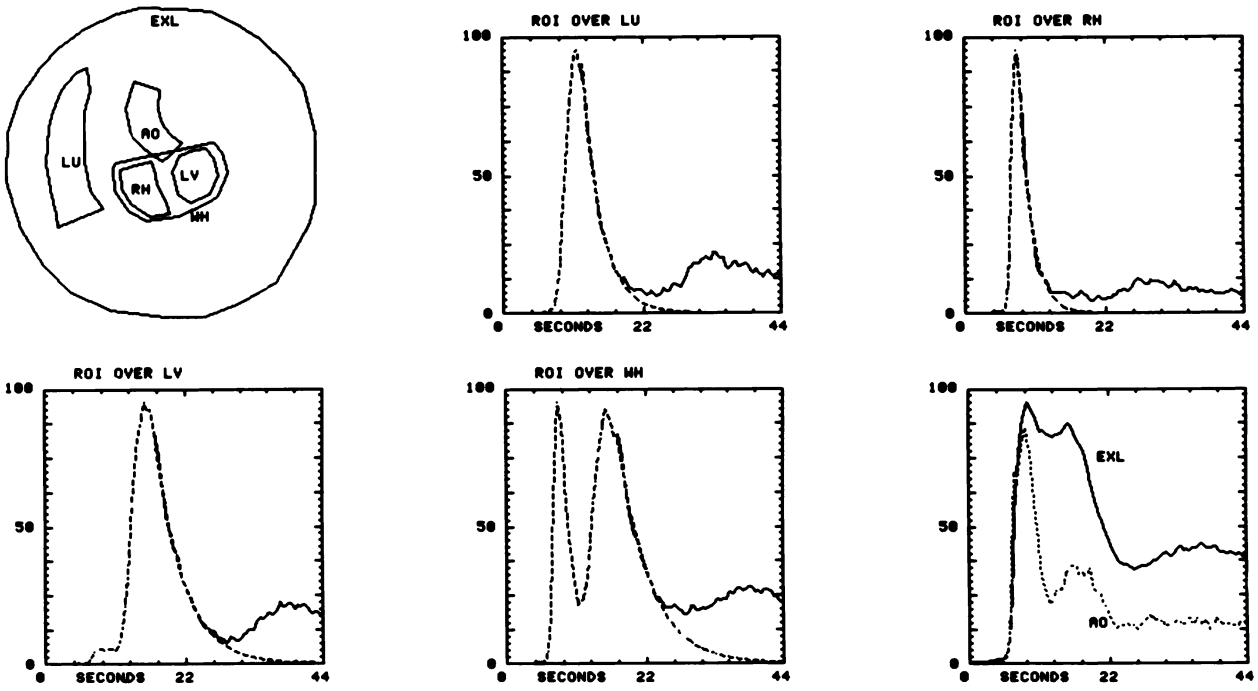

FIGURE 1
Upper left: ROIs employed. Other frames show normalized time-activity curves from ROIs. Solid curves are raw data; dashed curves are fitted and extrapolated to baseline by Hamilton method. Lower right: Normalized curves from ROIs over aorta and entire crystal showing relationship between total countrate and activity in central circulation. LU = Lung, RH = Right heart, LV = Left ventricle, WH = Whole heart, AO = Aorta, EXL = Entire crystal

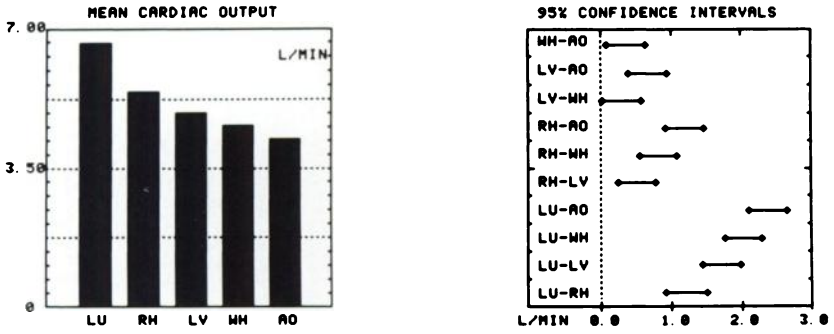

FIGURE 2
Left: Mean cardiac output results from different ROIs in 68 studies. Right: 95% confidence intervals for differences between mean results from different ROIs. Difference between left ventricle and whole heart demonstrates confidence interval that approaches zero difference (· · ·). See abbreviations in Fig. 1

that accounted for this correlation was employed. Cardiac output from different ROIs or by thermodilution were compared with Tukey multiple comparison tests applied to a one-factor, repeated measurement design matrix (*25*). A dependent variable, one value of cardiac output, was used for each determination of cardiac output by each method for each patient. Dummy variables were then employed in the matrix to indicate whether or not the dependent variable (dummy variable 1 or 0, respectively), cardiac output, was determined from any one of up to six possible sources (thermodilution and five ROIs studied) based on the Tukey procedure. Linear regression by ordinary least squares, Pearson correlation coefficients, t-tests, and chi-square tests were performed when more straightforward comparative procedures were required.

Reproducibility

Reproducibility in processing the raw radionuclide data to yield cardiac output from different regions of interest was evaluated in 33 studies, 20 of which had thermodilution studies as well. Radionuclide studies were processed by two independent observers, each without knowledge of the results of the other. All studies were initially acquired on erasable floppy disks. At the time that reproducibility was assessed all available or remaining disks were processed by the second observer.

RESULTS

Mean cardiac output results by the first-pass radionuclide method are shown in Fig. 2. A statistically significant systematic variation of results from different ROIs was observed with mean cardiac output values varying in the following order with respect to region of interest employed: lung > right heart > left ventricle > whole heart > aorta. This exact ordering of results was observed in 46 of 68 or 68% of the studies, and either this ordered sequence or only one change in this sequence was observed in 63 of 68 or 93% of studies. Mean output values from the five ROIs all differed significantly from one another at a confidence level of 95% (Fig. 2), but results from left ventricle and whole heart did not differ at a confidence level of 99% using multiple comparison testing.

In comparing 40 patients assessed by contrast angiography (20 patients without and 20 patients with mitral or aortic regurgitation), similar distributions of results from different ROIs were observed for both groups (Fig. 3). Patients with regurgitation demonstrated lower cardiac outputs than patients without regurgitation. However, the two groups had similar left ventricular ejection fractions calculated from equilibrium gated blood-pool images: 49.2 ± 16% (mean ± s.d.) in patients without regurgitation compared with 44.9 ± 18.7%, $p > 0.10$ by t-test.

Essentially simultaneous radionuclide and thermodilution studies were performed in 28 instances in 26 patients, and comparative results are presented in Fig. 4. Cardiac outputs from ROIs over left ventricle or whole heart demonstrated the closest correlations with cardiac output by thermodilution ($r = 0.96, 0.95$, respectively) with the smallest s.e.e.s and smallest absolute variations compared with thermodilution (Table 1).

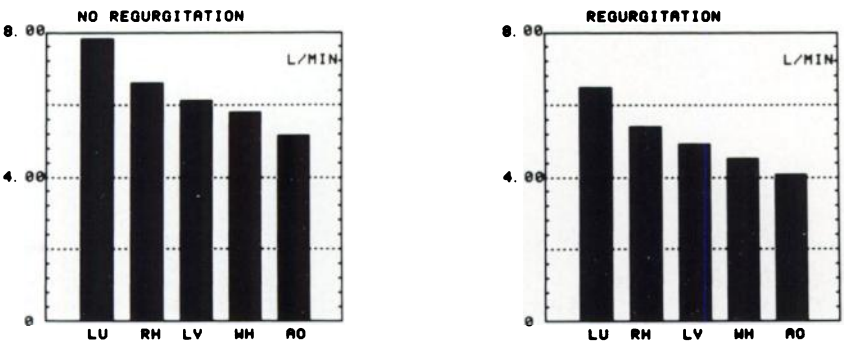

FIGURE 3
Left: Mean cardiac output results in patients without regurgitation. Right: Mean results in patients with aortic or mitral regurgitation. See abbreviations in Fig. 1

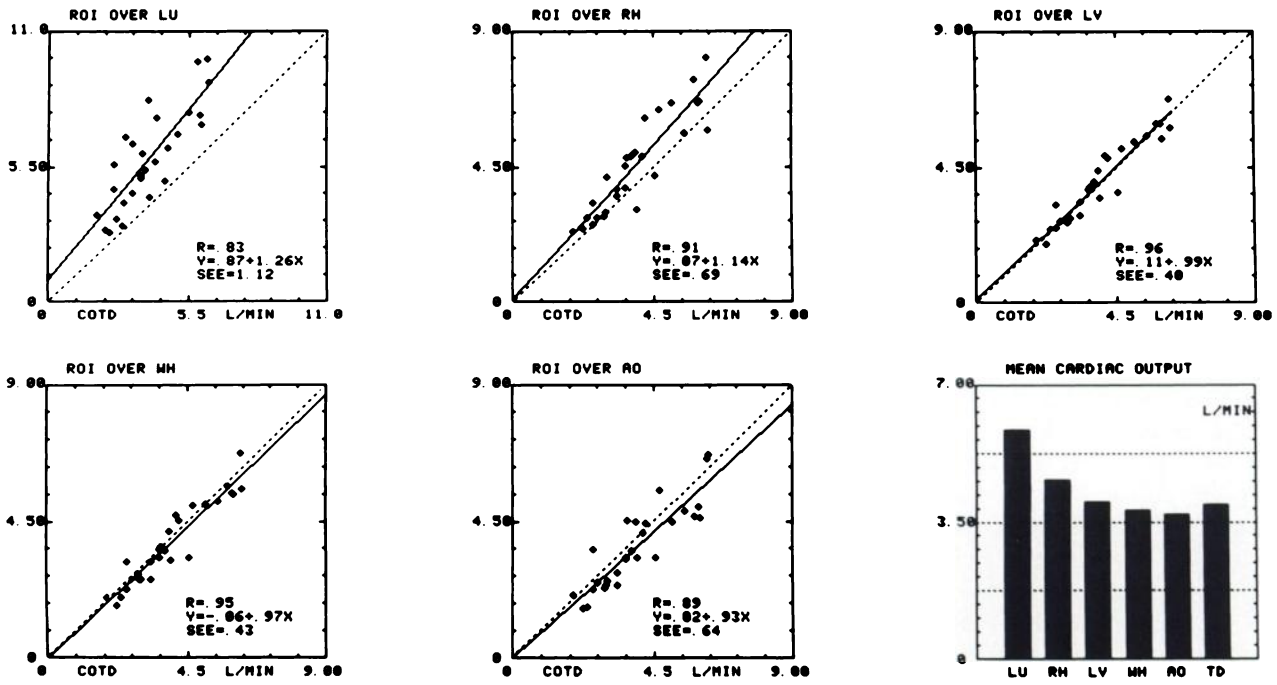

FIGURE 4

Correlation of thermodilution and radionuclide results from different ROIs in 28 studies. Thermodilution results on abscissa, radionuclide results on ordinate. (—) Represents lines of regression, (---) represents lines of identity. Lower right: Mean results. Values in l/min. COTD = Cardiac output by thermodilution, R = Correlation coefficient, s.e.e. = Standard error of estimate, TD = thermodilution. See Fig. 1 for other abbreviations

Radionuclide cardiac output results from ROIs over lung and right heart were too high and over aorta too low when compared with thermodilution.

Reproducibility of the data processing method was assessed in 33 studies. Processing of raw radionuclide data was performed by two independent observers, each without knowledge of the results of the other. Cardiac output results from the two observers demonstrated excellent correlation for all five ROIs studied (Fig. 5). However, reproducibility was best for regions of interest over left ventricle or whole heart (r = 0.994, 0.995, respectively). The same ordering of mean cardiac output results from different ROIs was found by both observers. Radionuclide results from both observers showed highly similar correlation with cardiac output by thermodilution (Table 2). Both observers demonstrated best correlations with thermodilution using regions of interest over left ventricle or whole heart. Hence, ROIs over left ventricle or whole heart yielded the most accurate, compared with thermodilution, as well as most reproducible determinations of cardiac output. Results from other ROIs (lung, right heart, or aorta and pulmonary artery) were less accurate and less reproducible.

TABLE 1
Correlation of Thermodilution and Radionuclide Results (n = 28)

Region	r Value	s.e.e.*	% Difference†
LU‡	0.83	1.12	51.1
RH§	0.91	0.69	18.9
LV¶	0.96	0.40	8.4
WH**	0.95	0.43	9.9
AO††	0.89	0.64	15.8

* Standard error of estimate in l/min.
† Percent differences expressed as mean absolute percentage of result by thermodilution.
‡ Lung.
§ Right heart.
¶ Left ventricle.
** Whole heart.
†† Aorta.

In 13 instances central injections of radionuclide were performed through the proximal port of the thermodilution catheter into the right atrium or superior vena cava. These central injections yielded a slightly different distribution of cardiac output results among the ROIs as compared with those calculated for peripheral injections (Fig. 6). The ordering of results shown for central injections (lung > right heart > left ventricle > aorta > whole heart) was found after eight of 13 central injections but after only five of 55 peripheral injections, $p < 0.001$ by chi-square. Results from lung and right heart also showed wider separation after central injections.

DISCUSSION

This study demonstrates that selection of a site for observation of the circulation can have a significant

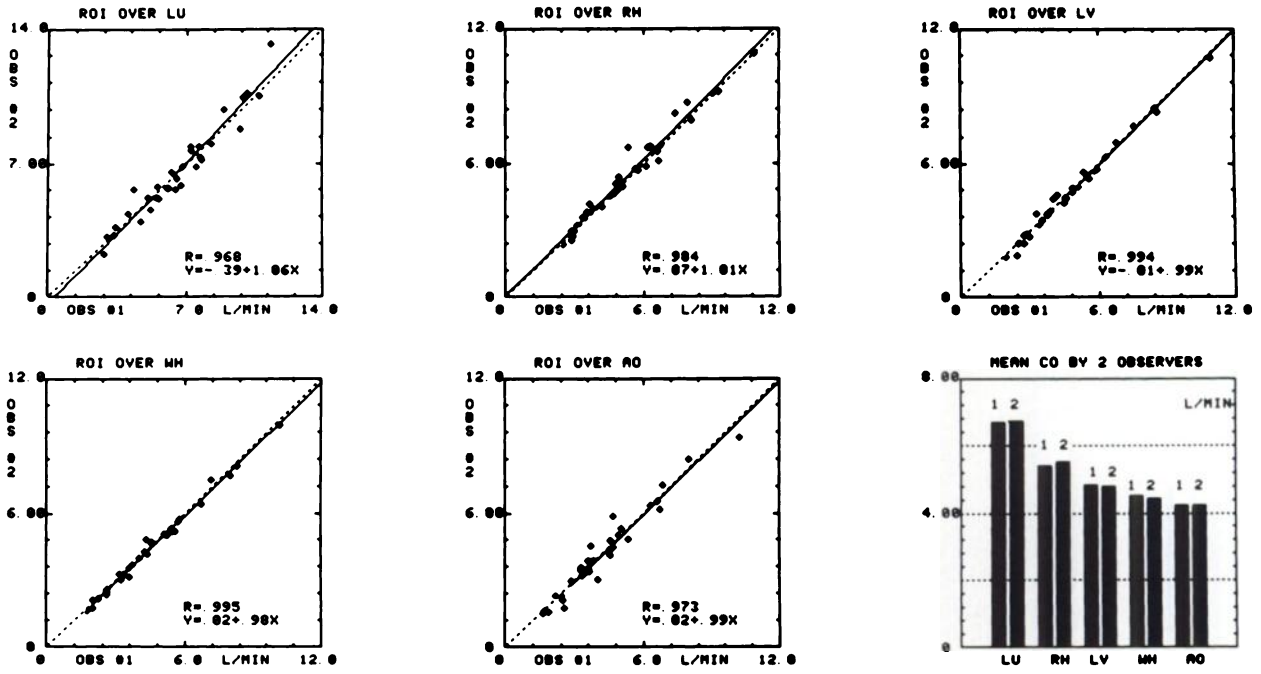

FIGURE 5
Interobserver reproducibility of results from different ROIs. (—) Represents lines of regression, often overlapping lines of identity (---). Lower right: Mean results by two observers. Values in l/min. OBS = Observer. For other abbreviations see Figs. 1 and 4

influence on the calculated cardiac output. If cardiac output is determined from several different sites of observation after a single injection, then variable results may be obtained. Variation in results from different sites must arise from differences in observation during equilibrium and first-pass measurements. This changes the E/A ratio in Eq. (2). Five anatomic ROIs were evaluated in this study: lung, right heart, left ventricle, whole heart, and proximal aorta. ROIs over the proximal aorta also included the pulmonary outflow tract since acquisition was performed in the LAO projection.

Consideration of the distribution of activity during first-pass and equilibrium counting aids considerably in explaining the variation in cardiac output determined from different ROIs. As the bolus of activity enters the right heart, essentially no background activity is initially present to perturb count rates taken from the right heart since activity will not yet have arrived in the chest wall, lung, and other overlapping structures. During equilibrium counting, however, these other structures contribute to observed count rates. Furthermore, the contribution of Compton scatter will be different during first-pass and equilibrium counting. Thus, right heart E/A ratios in Eq. (2) and, hence, cardiac outputs are higher than they would be if all structures contributing to equilibrium count rates had also contributed proportionately to the area, A, under the first-pass curve. This effect is somewhat more pronounced for ROIs over the lung than for the right heart due to the relatively lower blood content per unit volume in lung than within the right heart. It is also possible that incomplete mixing of blood within the right heart (*26,27*) could increase its E/A ratio if the tracer flowed predominantly through regions in the right heart with relatively high flow.

TABLE 2
Correlation of Thermodilution and Radionuclide Results of Two Observers (n = 20)

Region	Observer 1	Observer 2	Interobserver
LU	0.86	0.93	0.96
RH	0.91	0.89	0.99
LV	0.97	0.94	0.99
WH	0.97	0.95	0.99
AO	0.90	0.92	0.96

As the bolus traverses the left ventricle, some tracer is still flowing from the lungs as well as arriving in the aorta, bronchial arteries, coronary arteries, and chest wall. Hence, background activity contributes to the observed left ventricular count rate during first-pass (*28*) as well as equilibrium counting, and the conditions for application of Eq. (2) are more nearly satisfied. Accordingly, cardiac output determined from ROIs over the left ventricle demonstrated the best correlation with simultaneous results by thermodilution.

ROIs over both ventricles or whole heart would similarly generate curves that would partially span the period during which chest wall and other systemic vascular compartments first received activity and, similarly, cardiac output from these ROIs correlated well with thermodilution values. In patients with prolonged transit times, however, some recirculation of tracer back into the right heart can occur before tracer

has completely cleared from the left ventricle. This would flatten the washout phase of the whole heart time-activity curve, and therefore reduce the magnitude of the exponential rate constant. These effects increase the extrapolated and total area, A, under the curve. This reduces the E/A ratios and cardiac outputs from ROIs over the whole heart. Similar arguments apply to results from ROIs over proximal aorta which also include the pulmonary artery or right ventricular outflow tract. Cardiac output from aortic ROIs were the lowest observed, and fell below the results by thermodilution. This reasoning does not explain why results from aorta were slightly lower than those from whole heart, however.

Excluding results from lung and whole heart, a trend of sequentially lower values of E/A and cardiac output was demonstrated (right heart > left ventricle > aorta) as more downstream sampling sites were examined by external monitoring. This effect is in agreement with the results of Swan et al., who demonstrated an increase in total area under time-concentration curves taken from progressively downstream catheter sites following injections in the right heart (*26*). Such sequential increases in curve area lead to decreases in calculated cardiac output by Eq. (2), in agreement with our findings for right heart, left ventricle, and aorta. Hence, the intravascular behavior of indicator may contribute to the observed, ordered dispersion of radionuclide results independent of relationships between equilibrium and first-pass counting or E/A ratios, and independent of contamination of the observed curves by activity in overlying compartments and by scattered radiation.

The total area, A, under the curve consists of both observed and extrapolated components. Extrapolation is required because of recirculation of indicator, and is usually performed as a monoexponential continuation of the downslope of a time-activity curve (*4*). Alternatively, extrapolation and curve fitting have been performed with a gamma variate. This function usually yields a relatively smaller curve area and therefore a relatively higher cardiac output (*29*) than the more conventional Hamilton approach. Therefore, the gamma variate was not utilized in this study. The contributions of extrapolated areas to total areas under the curves differed greatly among the ROIs studied. Areas under curves from right heart or lung included relatively small extrapolated components, whereas curves from aorta or whole heart included relatively large extrapolated components, with left ventricular curves having intermediate contributions (Fig. 1). Any contamination of the late, but not early, phase of the downslope of a time-activity curve by recirculation of tracer into the ROI would prolong the apparent washout, add area under the curve, and thereby decrease the calculated value of cardiac output from that ROI. Accordingly, the data demonstrate relatively greater extrapolated areas and relatively lower cardiac output results from ROIs over aorta or whole heart and relatively higher results from lung or right heart which showed relatively small extrapolated areas. Finally, the use of only a single exponential to describe the washout phenomenon and to extrapolate the curves represents a simplification of a much more complicated process (*30*).

Several recent studies have emphasized the use of gated blood-pool imaging for determination of cardiac output through determination of ventricular volume which, with heart rate and ejection fraction, yields cardiac output (*31,32*). These methods are cumbersome to apply. They require a difficult determination of counting efficiency either directly, or by regression against invasive catheterization results which are not available in many facilities. Additionally, these volumetric methods cannot be applied in patients with valvular regurgitation, a common finding even in patients with coronary artery disease (*33*). Volumetric results also require precise definition of ventricular edges (*34*), and small changes in the definition of ventricular edges can produce large variations in calculated cardiac output even with counts-based methods that are, in a sense, nongeometric (*32*). Radionuclide determinations of cardiac output based on estimates of ventricular volume and ejection fraction, therefore, are of limited usefulness in many routine clinical settings.

The first-pass method based on indicator-dilution is free of many of these limitations. Ventricular edges do not have to be precisely defined, and in this study ROIs over the cardiac blood pool were defined well inside the outer borders of the cardiac silhouette in order to sample the chambers throughout the cardiac cycle. Background correction was not employed, whereas some form of background correction is required for most counts-based volumetric methods.

The first-pass approach should be equally valid in patients with and without valvular regurgitation. Valvular regurgitation does not affect the applicability of Eqs. (1) and (2) because they are based upon the average forward flow of the indicator. However, if the degree of mixing during first-pass compared with equilibrium counting differed significantly in the presence of left-sided regurgitation, the left ventricular E/A ratio in Eq. (2) would be affected more than E/A ratios from nonregurgitant regions such as the right heart or lung. As a result, cardiac output values from different ROIs would be expected to show relatively different patterns in patients with and without left-sided valvular regurgitation. The data did not support this since a similar pattern of results was observed in both groups (Fig. 3). Valvular regurgitation should enhance first-pass mixing within the left ventricle; this also supports application of the first-pass method in patients with valvular regurgitation. An effect of valvular regurgitation on the shape

of indicator curves is well recognized (*35,36*), with prolongation of the washout phase. This prolongation may affect the Hamilton extrapolation procedure and, therefore, cardiac output calculated from an ROI over or distal to a regurgitant chamber. This study does not support such a disproportionate effect on results from different ROIs in patients with regurgitation (Fig. 3). ROI selection affects results in a similar manner in patients with and without regurgitation.

These arguments indirectly support application of the first-pass method in patients with regurgitation. This is important since volumetric methods for determining cardiac output cannot be directly applied in patients with valvular regurgitation. A more direct assessment of the applicability of the first-pass method in patients with or without regurgitation could be obtained by performing nearly simultaneous first-pass radionuclide, thermodilution, and contrast angiographic studies. This study did not include such evaluations, however, and hence its support for the first-pass method in patients with regurgitation remains indirect. The similar effect of ROI selection in patients with and without valvular regurgitation also indicates that comparison of results from different regions in the same patient does not permit the detection or quantitation of regurgitation. For example, relative differences in results from right heart and left ventricle were similar in the two groups of patients (Fig. 3), with no clear relationship to the presence or severity of regurgitation.

First-pass and equilibrium volumetric determinations are not mutually exclusive. Accurate determinations by both methods in the same patient would permit quantitation of valvular regurgitation. Since the two approaches are based on different principles, however, both results would need to be absolutely accurate in order for quantitation of regurgitation to be performed.

Although the first-pass method based on indicator-dilution possesses several advantages over volumetric methods for determining cardiac output, a number of potential difficulties must be addressed if the method is to be successfully applied. Camera deadtime losses affect both equilibrium and first-pass counting, but to a different extent. As a result, the E/A ratio in Eq. (2) and, therefore, calculated output will be affected by the performance of the detector. In this study count losses were minimized by limiting the injected doses to 10 mCi and by the use of a high resolution collimator, which also served to optimize spatial resolution and definition of ROIs. Deadtime corrections were then performed for both equilibrium and first-pass acquisitions by the method of Adams et al. (*23*). Net corrections in final results averaged only 3–4% in this study, but significantly greater corrections might be necessary depending upon camera deadtime, efficiency of the detector, and amount of radionuclide.

Accurate estimates of dilution volume of the intravascular tracer employed are also required for absolute determinations of cardiac output by the first-pass method. In accordance with the use of Eq. (2) this dilution volume should be determined at the time of equilibrium counting (*15*). This study, however, was designed primarily to evaluate the effect of ROI selection on cardiac output determinations, and the method used to estimate dilution volume for Eq. (2) actually is not relevant to this purpose. Accordingly, a simple estimate of dilution volume based on height, weight, and sex of the patient (*24*) was employed. This estimate could potentially introduce errors into determinations of absolute cardiac output, particularly in patients with greatly expanded or contracted blood volumes (*37*).

Nevertheless, this study demonstrated a good correlation of absolute cardiac output results by the radionuclide and thermodilution methods, despite the fact that dilution volume was estimated as predicted blood volume, rather than measured directly. The thermodilution-radionuclide correlations were all performed in critically ill patients in critical care environments, although none were anuric or in overt pulmonary edema at the time of study, and none were studied within 24 hr of admission to critical care units. Greater errors in measurement of absolute cardiac output might be encountered in other patient groups, however, and the use of predicted blood volume will result in some error by the first-pass technique. Although the magnitude of the error resulting from the use of predicted blood volume cannot be precisely assessed in this study, such errors undoubtedly were present. They were, however, of sufficiently small magnitude so as to be obscured by other sources of error inherent in the thermodilution and radionuclide methods employed, since a good correlation was found when ROIs were properly selected. Results from regions over the left ventricle or whole heart yielded s.e.e. and absolute differences when compared with thermodilution (Table 1) that are in agreement with previous reports comparing thermodilution and other modalities (*11,38–40*). Previous studies have suggested that the overall biologic error inherent in any indicator method for cardiac output is in the range of 10–20% (*40–43*).

It is also pertinent that the use of an alternate intravascular tracer could shift the absolute cardiac output results. If the same predicted blood volume is used but the tracer diffuses out of the intravascular space before or during equilibrium counting, the assumptions of Eq. (2) are violated. Such conditions could arise with the use of in vivo labeling, for example. Errors due to either the measurement or prediction of dilution volume could be mitigated by expressing cardiac output in units of blood volume per min rather than in absolute units of volume per unit time. Dilution volume during equilibrium counting and blood volume are herein assumed to be similar for purposes of estimating cardiac output,

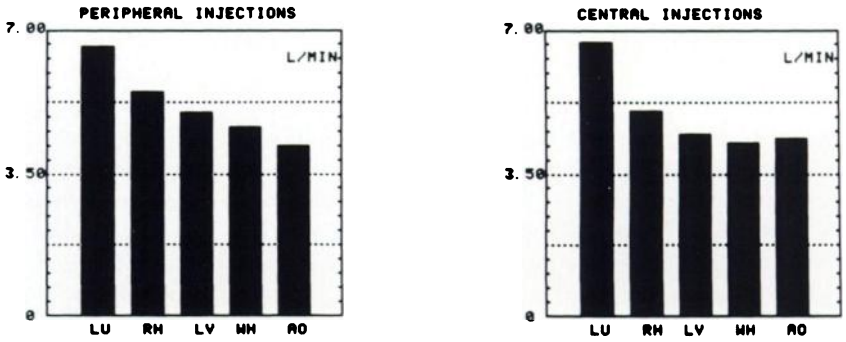

FIGURE 6
Mean results for peripheral and central injections

given that an excellent intravascular tracer is employed such as [^{99m}Tc]red blood cells labeled in vitro, as used in this study.

The first-pass method requires that the entire injected dose contribute to both first-pass and equilibrium counting in Eq. (2). Venous delay or poor bolus technique could allow additional activity to enter the circulation after completion of the bolus, adding additional equilibrium counts and causing a relative overestimation of cardiac output as per Eq. (2). Fouad et al. (*22*) found venous delay to be such a source of error, and in the present study meticulous attention was directed to bolus technique, as described in the section on methods. As a result, problems with venous delay were essentially eliminated as assessed by visual inspection of bolus clearance from subclavian and brachiocephalic veins. Injections into the right external jugular vein, followed by aspiration, have yielded optimal results in our experience.

Central injections into the right atrium through an indwelling catheter yielded prompt boluses but a somewhat less predictable distribution of results among different ROIs. This could relate to variable mixing of the bolus in the right heart. Poorly mixed tracer could distort the relationship between first transit and equilibrium counting in Eq. (2) and thereby account for the slightly different distribution of results in patients who received central injections (Fig. 6). Studies using catheter sampling of vascular tracers have shown that such nonmixing does occur with central injections (*26,27*). The slightly different results observed with central and peripheral injections (Fig. 6) suggests that site of injection as well as ROI selection can affect calculated cardiac output.

Of the five ROIs studied, ROIs over the left ventricle or whole heart yielded the most accurate as well as most reproducible results. Overgeneralization of these observations should be avoided, however. The use of still other ROIs or combinations thereof, or data acquisition in other projections, such as the right anterior oblique or anterior views, could yield different results of potentially differing accuracy. Similarly, the use of other intravascular tracers could shift the absolute accuracy of the results from any particular ROI. Nevertheless, using the techniques described here, ROIs over left ventricle or whole heart have yielded determinations of cardiac output that have proven quite satisfactory for many clinical purposes. The speed and simplicity of the first-pass method, once programmed, make it highly attractive for routine clinical application, and the method is suitable for a high degree of automation (*44*). ROI selection has an important and systematic effect on the results obtained, however, and clinical application of the first-pass method requires that ROIs be selected properly. The results also suggest that many of the difficulties reported by early investigators of the first-pass method may have resulted from problems they experienced in reliably sampling and choosing ROIs with the external probe detectors they employed.

FOOTNOTES

* Abbott Hospitals, Inc., North Chicago, IL.

† Low Energy Mobile Camera, Seimens Medical Systems, Inc., Iselin, NJ.

‡ CAM II Portable Computer, ADAC Laboratories, San Jose, CA.

§ SP5107 catheter with SP1435 Cardiac Index Computer, Gould, Inc., Oxnard, CA.

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