Automated Computer Program for Radionuclide Cardiac Output Determination

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Radionuclides have provided a safe, reliable, and minimally invasive method for repeated determinations of cardiac output. A completely automated computer program for data analysis is described. Cardiac output values obtained by this technique correlated closely with values obtained by manual determination of the region of interest ($r = 0.90$ for right-ventricular and 0.98 for left-ventricular outputs, $p < 0.001$ for both). Further, cardiac output determined by computer selection of either left-ventricular area of interest or of the "whole heart region" correlated significantly with that simultaneously determined by dye-dilution technique (indocyanine green; $r = 0.86$, $p < 0.001$ for both). The automated approach allows greater objectivity in the selection of the regions of interest, faster turnaround of calculated results, and use of a smaller dose of radionuclide.

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The development of reliable methods to determine cardiac output in man has resulted in a major step in our understanding of cardiovascular function. As experience grew, however, it became clear that a single determination has limited value because of the many factors that can influence the evaluation of any cardiovascular disease. Not least among these factors is therapeutic intervention and the response that it provokes (*1*). To take but one example: in the study of hypertension, repeated determinations of cardiac output are frequently needed (*2*), rather than the isolated measurements used in the recent past. Reasons for this include evaluation of recent potent antihypertensive drugs, as well as investigation of controversies regarding autoregulation (*3,4*) and the evolution of hemodynamic abnormalities in hypertension.

For repeated determinations of cardiac output, radionuclides have provided a safe, reliable, and minimally invasive approach. Difficulties associated with early attempts (*5*) have been largely overcome with the development of short-lived, moderate-energy emitters, the scintillation camera, and computer techniques. Currently available methods have been proven reliable (*6–8*); they are practically noninvasive and the total-body radiation for one cardiac output determination by the use of Tc-99m HSA is low (0.018 rad/mCi). A possible disadvantage of these methods, however, is the time consumed by computer analysis following the acquisition of the information. Current methods of off-line analysis require several steps: the printing out of distribution data, the selection of areas of interest by a physician, the transfer of these areas once more for computer analysis to determine time-concentration curves, and calculation of the cardiac output from the area under the curve.

This delay can be alleviated by two methods. One would entail use of an on-line or interactive computer by which areas for determination of dilution curves must be selected by the physician following initial processing of data. This method, however, would greatly increase the time required of the physician for the procedure; in addition, unless a dedicated computer is available, the computer would not be used at its fullest efficiency. The second alternative would be to establish a computer program for automatic selection of the areas of interest and immediate calculation of the cardiac output. In this way, once the acquisition is completed, the entire analysis can be performed automatically with no further involvement of the physician or technical personnel.

Since we were concerned with the use of this technique for multiple studies on many patients, we have decided on the latter method in order to reduce as much as possible the interval between the procedure and availability

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of results. Comparison of the radionuclide method with the well-established dye-dilution (indocyanine green) (*9*) method provided evaluation of the accuracy of the radionuclide cardiac output determination. This paper describes this computer program and compares its results with values obtained in the same patients by manual selection of the regions of interest, as well as with values obtained by simultaneous determination of cardiac output with the dye-dilution method.

MATERIAL AND METHODS

Sixteen patients were studied; hemodynamic evaluation was required because of problems with either hypertension or idiopathic orthostatic hypotension. Their ages varied from 30 to 55; eight were females and eight were males. They gave their informed consent to determination of cardiac output with Tc-99m albumin simultaneously with its determination by dye dilution; most of them were taking part in our long-term studies of hypertension and were familiar with the invasive determination of cardiac output by indocyanine green.

Determination of blood volume (I-125 RISA) and cardiac output (indocyanine green). All studies were performed in the morning after an overnight fast. After a resting period of at least 30 min and placement of catheters, patients had plasma volume determined by i.v. injection of I-125 RISA and blood sampling 10 min after the injection (*10*). Blood volume was then calculated from the plasma volume and the hematocrit. Cardiac output was determined in triplicate using indocyanine green dye (5 mg) introduced into a right atrial catheter and then flushed into the circulation in less than ½ sec with 5 ml saline. Blood was withdrawn from the arterial catheter, which had been positioned under fluoroscopy in the root of the ascending aorta. Arterial-blood withdrawal was done through a Gilford densitometer using a constant-rate pump with the speed set between 0.3 and 0.5 ml/sec. Curves were inscribed on a fast-response recorder and blood was reinfused immediately after the curve inscription, thereby ensuring no blood loss during investigation (*9*). A fourth dye-dilution curve was then obtained by the same method simultaneously with the radionuclide dilution study, the dye being injected into the right atrium via the appropriate catheter while the radiotracer was delivered as a rapid bolus through a peripheral vein in the other arm as described previously (*8*). Proper calibration of the dye system was done at the end of each study, with known dye concentrations and the same pump speed used during output determinations (*9*).

Radionuclide dilution curves. *Instruments.* A portable scintillation camera with a medium-sensitivity, low-energy collimator was used for precordial recording of the radiotracer's passage. The camera head was positioned in a left anterior oblique position at 30–45°, parallel to the longitudinal body axis and tilted 0–5° upward to help visualize the subclavian veins.

The camera output was transferred to a storage system, with individual frames stored on magnetic tape. Recording, storing, and playback functions were effected by an off-line computer. This procedure permitted recording and storage of sequential full frames of the multichannel analyzer at 0.5-sec intervals without loss of transfer time from the gamma camera. The procedure of data acquisition has been described previously in detail (*8*).

Radionuclide. Technetium-99m-labeled human serum albumin (Tc-99m HSA) used was prepared by unit dose reagent kit.* The preparation and the stability of the bond between Tc-99m and HSA have been described (*8*). A dose of 8 mCi was used if the patient were to have one hemodynamic study; in the case of two consecutive studies in the same patient, the first dose was only 4 mCi, and 8 mCi were given for the second determination. The radiation dose to the whole body is estimated at 0.018 rad/mCi (*11*). The material was injected intravenously, and rapid-flush technique (*12*) provided delivery of the radioactive material to the heart as a bolus. Injection was done via an antecubital vein. In 70% of cases it was via the left arm; the catheters for dye-dilution measurements were passed via the vessels of the right arm. Whenever possible, the injection was given via the basilic vein, this being preferred to the cephalic or peripheral veins because of its direct course via the axillary vein into the subclavian vein without passage across the shoulder area.

Calculations. Cardiac output, F, was calculated from Stewart-Hamilton formula (*13*):

$$F = \frac{I}{\int_0^\infty c.dt}$$

In the dye method, I is the amount of indicator injected in milligrams. In the case of Tc-99m cardiac output, calculations were made as previously described (*5*), I being the product of the volume of dilution (blood volume in milliliters as measured 10 min after RISA injection) and the counting rate at final dilution, recorded 10 min after injection of Tc-99m HSA. Cardiac output was calculated separately from dilution curves obtained from the right and left ventricles.

A background frame was recorded before each injection and subtracted from all of the succeeding frames for each sequence.

AREAS OF INTEREST

The data for computer processing were contained in a 64 × 64 array of integer words. For the dynamic study needed for cardiac output determination, one such array was produced by the gamma camera each 0.5 sec. The camera was positioned so that the septum was viewed on edge.

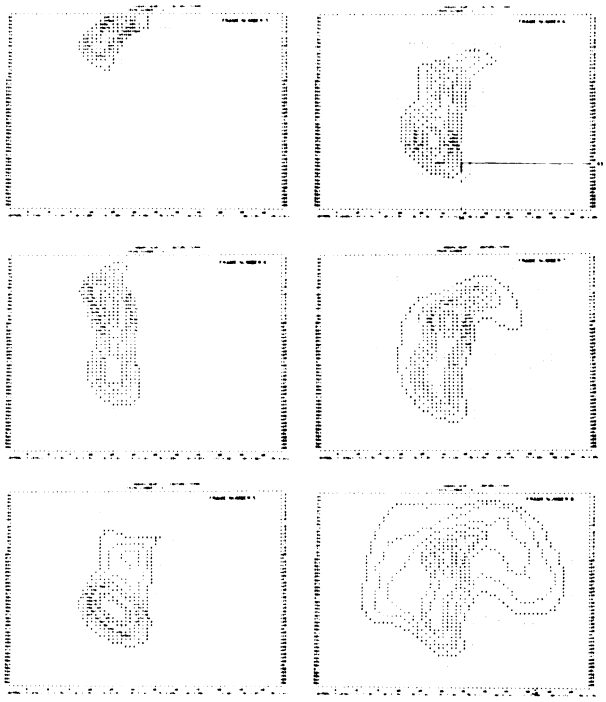

FIG. 1. Serial smoothed frames of data illustrating selection of a pixel in the septum near the lower left border of the right ventricle (see text). In above example, the pixel selected is defined by row 43 and column 34 in frame number 6. Tracer: Tc-99m.

Manually selected areas. Rectangular areas of interest for the bolus passage through the right and left ventricles were selected (X, Y coordinates of corners). From the computer printout in counts per time interval, time-activity curves were then generated. The areas under the curves were obtained by computer integration and least-squares fitting of the trailing edge (9); cardiac output was calculated as presented in the previous formula. It was important to select areas of interest that did not contain activity from adjacent or superimposed chambers.

Computer-selected regions of interest. In order to achieve automatic determination within the 64 × 64 arrays of the picture elements (pixels) corresponding to the right and left ventricles, it was decided to initiate the process by specifying a pixel that would correspond to a location in the septum near the lower left extremity of the right ventricle. The reason for choosing such a point was that the radioactive bolus is still relatively intact during its passage through the right heart, and the counting rate is relatively high. These conditions allow one to obtain reasonably accurate determinations of the right-heart chamber from data frames.

The procedure is illustrated in Fig. 1, in which several frames of the data are reproduced after processing. Working frame by frame, average counts for each row were calculated in each frame, and the row number "r" with the maximum average noted. When in succeeding frames the computer identifies a frame "F" in which the row number for maximum average count "R" is less than the corresponding row number from the previous frame, and the maximum average count has decreased, it is assumed that the bolus has passed its maximum downward excursion into the right chamber and has started flowing up into the pulmonary vessels. The frame immediately preceding frame "F" is thus the one that best exemplifies the right heart; in that "right ventricular frame" the row that has the maximum average count determines the row coordinate of the "leading edge" of the bolus, or the row number of the effective lower limit of the right ventricle. A similar procedure is carried out on the columns of the same data frame to obtain the column coordinate of the "left edge" of the right ventricle. In the study illustrated in Fig. 1, the bolus was flowing downward through frame No. 6, after which it flowed upward into the pulmonary vessels; in this case the initial point for computations was determined to be the pixel defined by row 43 and column 34 of data frame No. 6.

Empirically determined delineations led to a first approximation of the right ventricle by a rectangular region of 15 × 12 pixels from the initial point defined above. This region, outlined with the printout symbol "R," is superimposed on the contour outlines from the frame in which this region contains the maximum number of counts (Fig. 2). A region is chosen immediately to the left of the right-heart region, again subject to some empirical assumption in size. This second region serves as a first approximation to the left ventricular region (Fig. 2, right).

The total counts from each of these regions are plotted against frame number, thus outlining two dilution curves, one for the approximation of the right ventricular region and one for the left (Fig. 3). In a following step, a group of sequential frames is automatically selected from the highest counting rates of each curve, as shown in Fig. 3. These frames are assumed to carry most information regarding the outlines of the heart chambers, and analysis of this information is put to two further uses:

1. The sequence of frames at the top of the curve for each region is summed to obtain a 64 × 64-sum array;

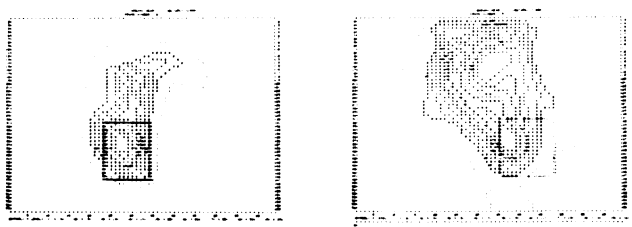

FIG. 2. Rectangular areas approximating right and left ventricular regions (12 × 17 and 14 × 17 pixels, respectively) by using pixel localized in frame 6 of Fig. 1. These represent first approximations for right and left ventricular regions (left and right portions of figure, respectively).

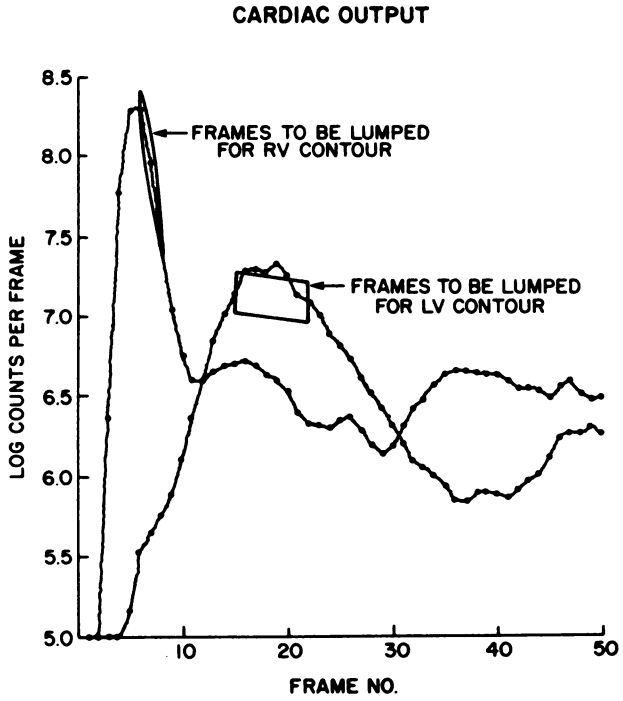

FIG. 3. Time-activity curves obtained from right and left ventricular areas of Fig. 2. Box at top of each curve includes frames carrying highest counts in respective ventricular chamber.

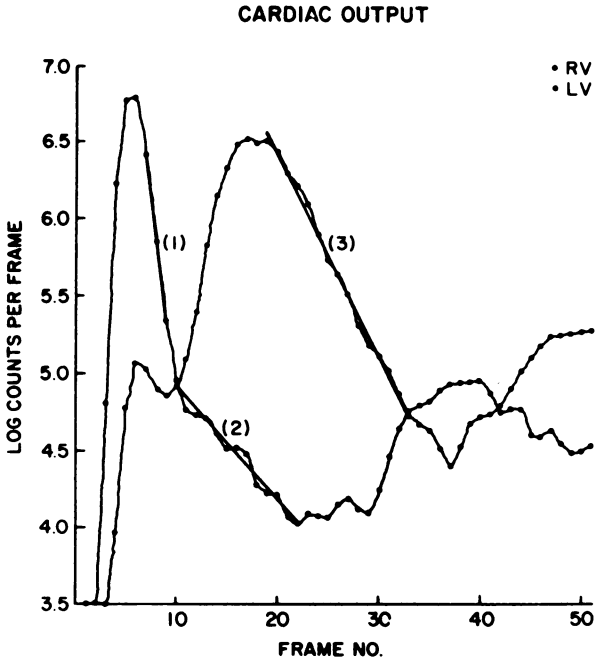

FIG. 5. Time-activity curves obtained from areas of interest defined in Fig. 4. Curves are smoother than corresponding curves obtained from first-approximation areas of interest (Figs. 2 and 3).

the pixel that contains the maximum counts within boundaries of the original "R" or "L" preliminary region is assumed to indicate the center of the corresponding ventricular chamber. A smaller "refined data" region is constructed about this pixel as center (Fig. 4). The counts in these two smaller regions are again plotted as a function of frame number (Fig. 5), with obvious improvement in the shape of the corresponding dilution curves (RV of Fig. 3 compared with RV of Fig. 5; LV of Fig. 3 compared with LV of Fig. 5). The data obtained from these "refined regions" are used to calculate cardiac output from the right and left chambers.

2. The data from the frame sequences outlined above were also used to obtain irregularly shaped regions corresponding to the heart chambers, by the following procedure. Two of the frames from that sequence were added together, smoothed, and contoured. All pixels whose contour values were large enough (≥ 7), and that lay within the boundary of the initial rectangular region, served as a central region about which additional pixels were accrued. The region corresponding to each ventricle is created (Fig. 6) by running through the appropriate frame sequence previously defined in Fig. 3. The final regions are obtained by annexation of neighboring pixel layers to an extent where increments are minor, indicating that the chamber wall has been reached.

Finally, these two regions are combined to give a "total

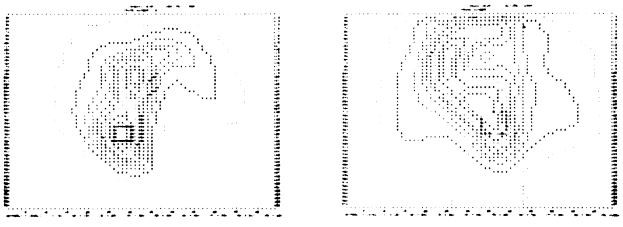

FIG. 4. Refined right and left ventricular area of interest (see text).

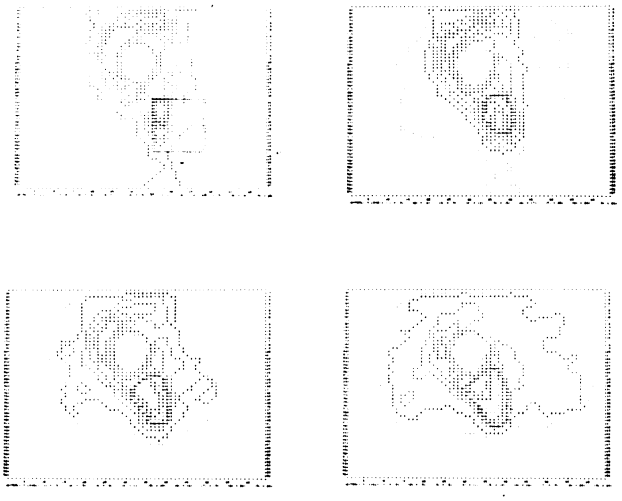

FIG. 6. Irregularly shaped contours corresponding to left ventricle obtained by sequentially adding and smoothing frames defined in Fig. 3 (box on top of curves). Gradual accrual of area is accomplished by annexation of neighboring pixel layers (see text). A similar procedure is applied to right ventricular region.

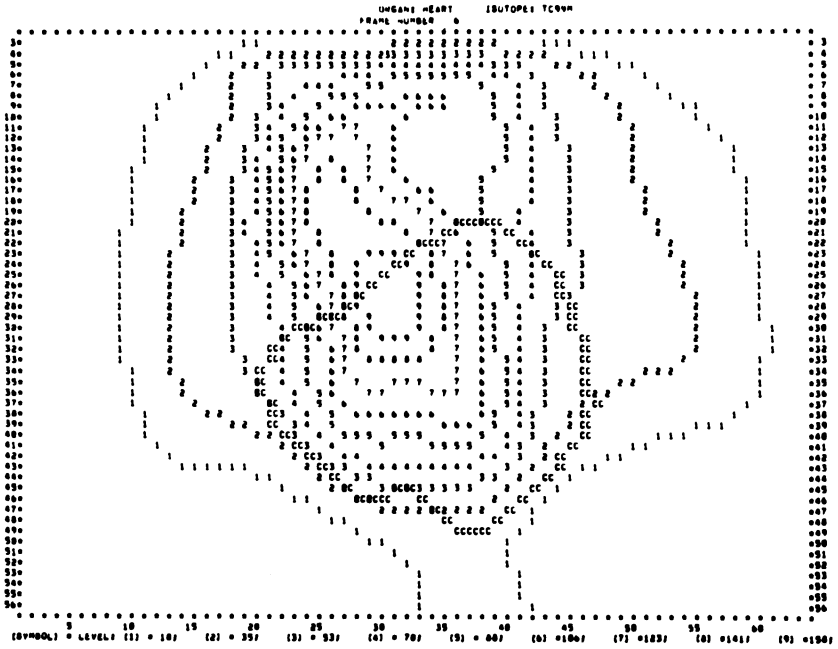

FIG. 7. Total heart region (area "C") obtained by combining irregular right and left ventricular areas of Fig. 6.

heart" outline (area "C" in Fig. 7) from which a dilution curve can be plotted (Fig. 8) and cardiac output calculated.

Since the plots are semilogarithmic (the logarithm of counts per frame plotted against time or frame number), an exponential dilution curve translates into a straight line, and a least-squares linear fit can be used for extrapolation of the dilution curve and applied to cardiac output calculations. Automatic computer selection of the frame sequence to obtain the best fit is performed, and the calculations proceed routinely.

STATISTICAL ANALYSIS

On comparison of the various techniques, data were analyzed as follows:

1. Correlation between radionuclide cardiac output values obtained from manually selected areas (for left and right ventricles) and the cardiac output determined simultaneously by dye dilution.
2. Correlation between radionuclide cardiac output values obtained from automatic computer-selected areas (right and left ventricles and whole heart) and the simultaneously determined dye-dilution cardiac output.
3. Correlation between radionuclide cardiac output values obtained from manually selected (right and left ventricles) and computer-selected areas (right and left ventricles).
4. Correlation between radionuclide "whole heart area" and radionuclide cardiac output obtained from manually selected left-ventricular area.

Tests of statistical significance were calculated by standard methods (*14*); results were considered significant when $p < 0.001$ and of questionable significance when $p < 0.05$.

RESULTS

Table 1 lists the r value, slope, and intercept in the comparison obtained between the cardiac output values obtained from the right ventricle and left ventricle (physician-selected and computer-selected) against the simultaneously measured dye-dilution cardiac output. Comparison of the values of cardiac output obtained from manually selected areas of interest with values calculated from computer-selected areas showed an r

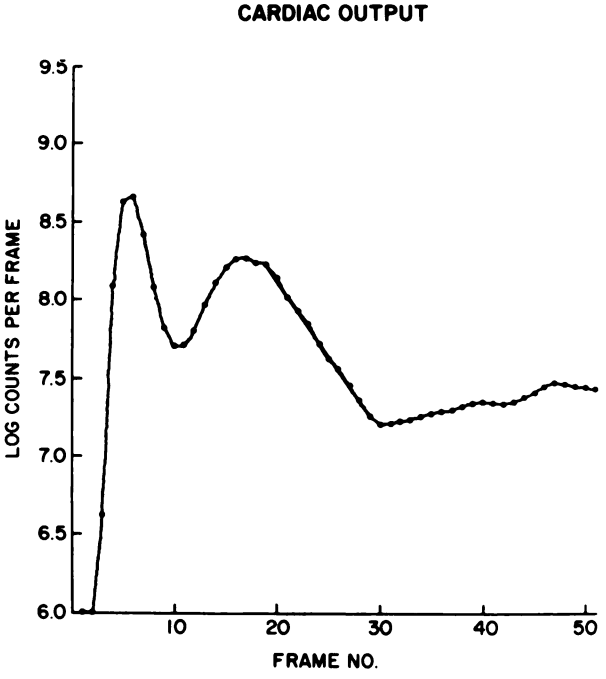

FIG. 8. Dilution curve obtained from "whole heart" area; two peaks for right and left ventricles are clearly defined.

TABLE 1. CORRELATION BETWEEN CARDIAC OUTPUT VALUES OBTAINED BY RADIONUCLIDES AND DYE-DILUTION TECHNIQUES*

	Correlation			
	Coefficient (r)	Significance (P)	Slope	Intercept
Computer vs manual				
RV	0.90	<0.001	0.93	0.47
LV	0.98	<0.001	1.08	−0.43
Computer vs DD (indocyanine green)				
RV	0.72	<0.001	0.71	1.88
LV	0.86	<0.001	0.74	1.25
"Heart"	0.86	<0.001	0.90	0.66
Heart vs LV area				
LV (manual selection)	0.96	<0.001	1.27	−1.28
LV (computer selection)	0.96	<0.001	1.16	−0.57

* Cardiac output was determined simultaneously by dye (indocyanine green) dilution (DD) and by Tc-99m albumin; values for radionuclide studies were calculated either from manually selected regions of interest or from automated computer program. LV refers to region of interest in left ventricle; RV to corresponding region in right ventricle; "Heart" to total cardiac area. "Heart" represents the cross-sectional area outlined on the outer surface of the combined right and left heart areas as shown in Fig. 7.

value of 0.90 ($p < 0.001$) for the right ventricle and 0.98 ($p < 0.001$) for the left ventricle (Fig. 9). Comparison of values obtained by radionuclides with simultaneously measured dye-dilution cardiac output showed a similar correlation between computer- and manually selected areas from the left ventricle (0.86) while in the case of the right ventricle the correlation was higher when the areas were selected by computer (0.72 compared with 0.67).

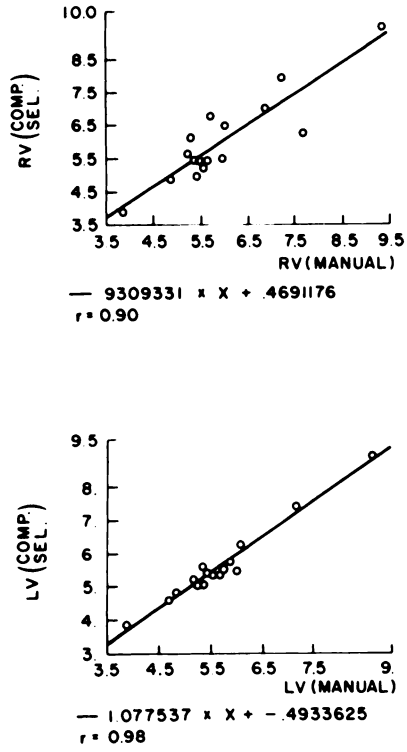

FIG. 9. Correlation between radionuclide cardiac output values obtained from computer-selected and manually-selected areas (right ventricle (RV) in upper frame and left ventricle (LV) in lower frame).

Cardiac output values that were obtained from "whole heart" areas were compared with the dye-dilution values and with the cardiac output values obtained from areas of the left ventricle chosen by physician; the r value was 0.86 in the former comparison and 0.96 in the latter (Fig. 10). Cardiac output values calculated from the "whole heart" correlated very closely with values determined by computer selection from left-ventricular regions (Table 1).

DISCUSSION

The reference procedure for determination of cardiac output (dye-dilution technique) is well recognized. The high correlations obtained between this method and the radionuclide method indicate that the latter is a dependable technique provided certain precautions are taken (*8*). With this new program, complete automation of data analysis is now possible. Obvious advantages of this technique include (a) greater objectivity in selection of areas of interest, and (b) faster utilization of results and hence more efficient hemodynamic analysis, since the final calculations can be obtained with no physician or operator intervention. Thus, computer analysis can proceed immediately with no intermediate or subjective selection required.

In addition, an important benefit accrued from the high correlation found between cardiac output values calculated from "whole heart" area and those obtained either by the dye-dilution method or from the left-ventricular region by radionuclide techniques (whether derived manually or by computer). This high correlation

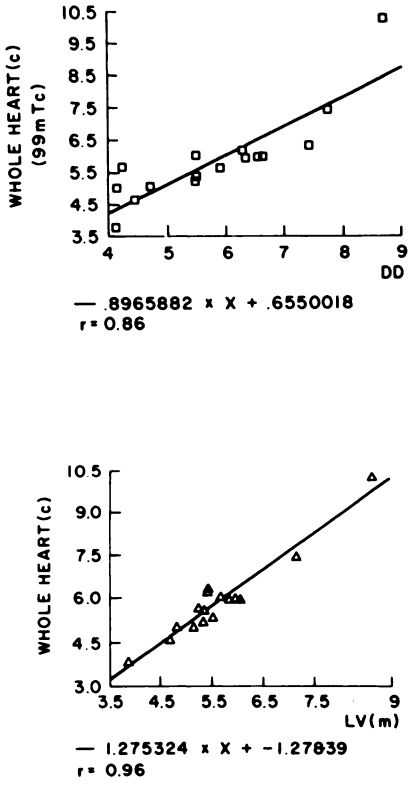

FIG. 10. Cardiac output determined from "whole heart" area correlates closely with both dye-dilution value (DD) (upper frame) and that obtained by manual selection of a region within left ventricle (LVm) (lower frame); r = 0.86 and 0.96, respectively, $p < 0.001$ for both.

suggested the possibility of using a smaller dose of radiotracer for a single study. The counting rate from "whole heart" was usually found to be six times the counting rate from an individual ventricular area (right or left). Therefore, a reduction of dose by this factor can be accomplished without sacrificing the statistical certainty of the results. As a result, the total-body exposure to radiation from a single dose would be decreased further and more tests can be made for hemodynamic evaluation and follow-up.

The poorer correlation of the right ventricle's cardiac output with the dye dilution is not unexpected. The Stewart-Hamilton equation makes no assumption about bolus delivery but does require that the dilution curve be recorded from the entire dose injected. It has been shown (*8*) that mild delays or hang-up of the bolus may occur in 61% of the cases. In some of those cases a portion of the injected dose is thus temporarily trapped in the venous input and does not contribute to the dilution curve recorded from the right ventricle. In general, it has been found that this hang-up seldom persists as long as the time of the left ventricle dilution curve, and it can be safely assumed that the entire dose has been included in the latter curve, thus providing a valid determination.

The radionuclide determination is an addition to the battery of already existing methods for measurement of cardiac output. It gives a greater choice of the method to be applied; in addition, it allows measurement of appearance time, mean transit times, and central blood volume. Its automation makes it faster, safer because of the smaller doses needed, and more objective. Its accomplishment with the use of a peripheral venous injection, without the necessity of introducing a catheter, makes it possible in patients with poor veins. In addition, it does not require arterial sampling, thus avoiding the many complications and discomfort that can occur with arterial puncture.

FOOTNOTE

* Union Carbide, Tuxedo, NY.

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