CARDIAC EVALUATION FROM RADIOISOTOPE DYNAMICS

Donald Van Dyke, Hal O. Anger, Robert W. Sullivan, William R. Vetter, Yukio Yano, and Howard G. Parker

Donner Laboratory of Medical Physics, University of California, Berkeley, California, and the Department of Cardiology, USPHS Hospital, San Francisco, California

The use of radioactive isotopes to obtain quantitative information on the size of the blood-containing compartments in the cardiopulmonary circulation, and the rate of blood flow through these compartments had its beginnings over 20 years ago (*1*). In the last 10 years there have been significant advances in available isotopes and methods of preparation (*2*), in rapid, high-resolution imaging devices (*3*), and in quantitative area-of-interest recording techniques. These advances have contributed to the rapid recent development in the field and to the method to be described here (*4–7*).

According to Chapman et al (*8*), "The ideal system for following changes in ventricular volume is obviously one which is fully applicable to the free-living organism, which requires no injection of any sort, and which can be used repeatedly over long periods of time without danger or discomfort to the subject. Such a system, if it ever becomes available, can hardly be based on roentgenographic principles."

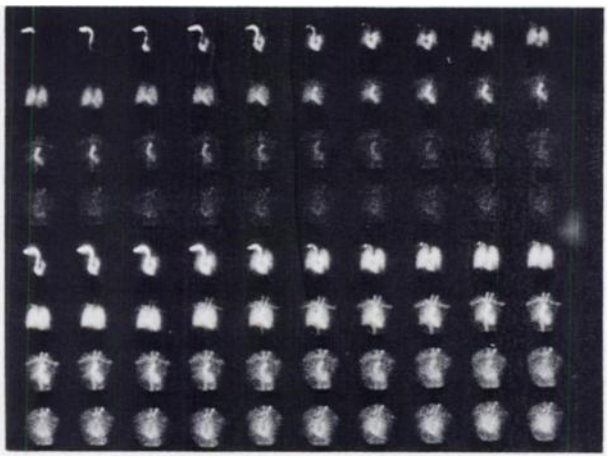

FIG. 1. Print from 80-lens camera negative showing two simultaneous sequential recordings of passage of ^{99m}Tc bolus through central circulation. Upper series of 40 pictures: starting time interval, 0.5 sec/picture; exposure time, 0.5 sec/picture. Lower series of 40 pictures, starting time interval, 0.5 sec/picture; exposure time, 2 sec/picture, to allow collection of large number of dots per picture.

Quantitative radioisotope angiocardiography makes a major step toward fulfilling these requirements. It is an essentially noninvasive technique which can be performed on an outpatient basis. The study can be repeated at frequent intervals for evaluation of clinical status, operative repair, or response to other forms of therapy with little danger or inconvenience to the patient.

MATERIALS AND METHODS

A specially built large-field scintillation camera with a 16-in.-diam sodium iodide crystal and 37 phototubes (*9*) was used. The large field of view allowed easy positioning of the heart, and the entire lung fields and great vessels were included in the field of view. However, the field of view of the standard commercially available scintillation camera is adequate.

For recording quantitative data from the scintillation camera, an interim data storage and readout system with very fast response using television techniques was used. A television camera viewed the cathode-ray tube of the scintillation camera and during passage of the isotope through the heart and lungs a recording was made on video tape. Quantitative information on the amount of radioactivity present in any area of interest as a function of time was obtained by measuring the light output from a television monitor during playback of the tape. The playback monitor was masked so that only one area of interest, such as the left ventricle, was uncovered at a time. A similar system has been described by Bitter et al (*10*). Area-of-interest masks were made by tracing the heart chambers as shown on a series of scintiphotos taken with a specially built 80-lens scope camera (*11*). This camera simultaneously takes two sets of pictures as shown in Fig. 1. In the

Received Jan. 10, 1972; revision accepted Mar. 14, 1972.

For reprints contact: Donald Van Dyke, Donner Laboratory, Univ. of California, Berkeley, Calif. 94720.

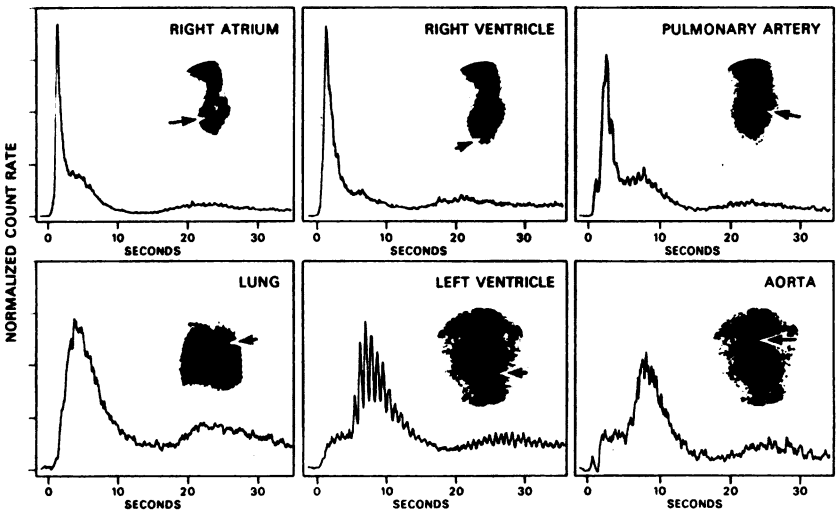

FIG. 2. Stripchart recordings of passage of isotope through six areas of interest in central circulation. Television playback monitor screen was masked around each area of interest in turn as tape was replayed. 80-lens camera pictures from time of maximum activity in each area of interest have been inserted for purposes of illustration. Arrows indicate anatomic structure unmasked for each recording.

upper 40 pictures the exposure times were ½ sec, while in the lower set there was time overlap (2 sec/picture), allowing collection of a large number of dots per picture.

The 80-lens camera film was projected by means of a View-Graph projector to the size of the television monitor screen to outline the areas of interest for subsequent masking of the television playback monitor around each area of interest in turn as the tape was replayed. The light output of the television monitor in the unmasked area was measured with a light-sensitive conduction cell, the output of which was recorded on a strip-chart recorder (see Fig. 2).

Human serum albumin was labeled with ^{99m}Tc by a modification of the electrolytic method of Benjamin et al and Burke et al (*2,12*). For adult human subjects, 8 mCi of ^{99m}Tc-labeled albumin was given. The radiation dose from 1 mCi of ^{99m}Tc-labeled albumin is 14 mrad whole body and 46 mrad to blood (*13*).

The EKG was monitored and recorded on one of the audio channels of the video tape during the study. This allowed subsequent gating of the replay monitor to obtain electrocardiographically-controlled cardiac images in end-systole and end-diastole (*6*).

Positioning of the patient under the scintillation camera varied with the patient's condition and the specific information desired. The right anterior oblique view (30 deg) is essential when left ventricular volume is to be determined by area measurement. Pictures of a radioactive "ruler" consisting of point sources along the x and y axis were taken to be used in measuring left ventricular volume by the direct technique of Sullivan et al (*14*) and Zaret et al (*6*).

With proper adjustment of the television camera sensitivity during recording and proper setting of brightness and contrast in the playback monitor, no correction for nonlinearity or baseline shift of the television system needs be made. An absorber wheel with ten steps giving a linear step function from 0 to 100% (see Fig. 3) absorption was used as an aid in adjusting the brightness and contrast of the television monitor so as to obtain satisfactory overall linearity

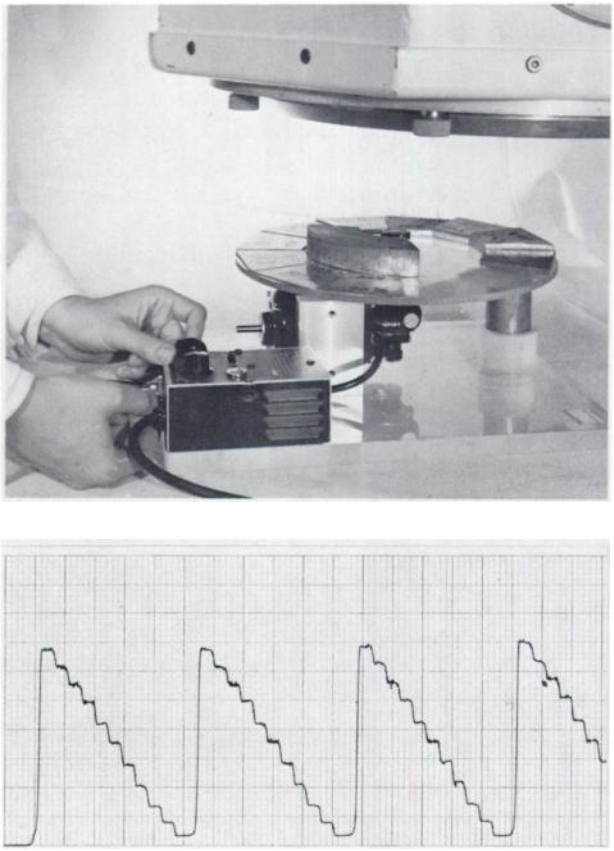

FIG. 3. Absorber wheel with ten steps giving linear step function from 0–100% absorption (top). Strip-chart recording (bottom) demonstrates satisfactory overall linearity of entire system.

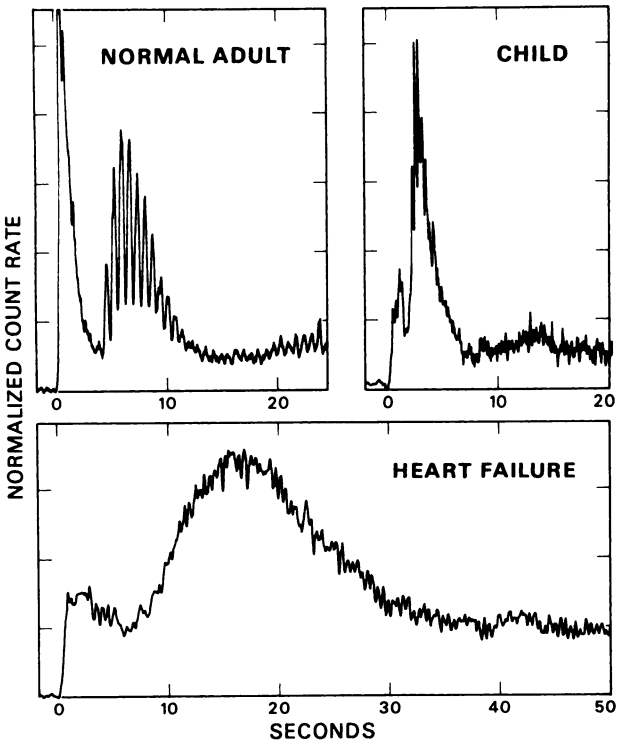

FIG. 4. Comparison of recordings of passage of isotope through left ventricle of normal adult, 5-year-old child, and patient in severe heart failure. First peak represents passage of bolus through right ventricle, method relying primarily on temporal separation. In patient in failure, fluctuations represent "noise", ejection fraction being too small to be recorded.

for the entire system. Two other corrections may be required. These are (A) the "deadtime" loss due to the 3-μsec deadtime of the scintillation camera, and (B) the "speed effect" due to the time response of the TV system, including the quantitative photometer, the pen recorder, and the integration time constant being used. The deadtime loss of a strong varying source (the isotope in the chest) can be determined by monitoring the instantaneous reduction in counting rate of a small reference source at the side of the scintillation camera field. Corrections for speed effect are obtained from a table prepared by running a heart phantom at different rates. Mechanical heart phantoms demonstrated the ability of the entire system to accurately determine stroke volumes at various pulse rates in the absence of background interference.

To accurately determine the ejection volume of the left ventricle, the area of interest must be as large as the ventricle in end-diastole. When the entire left ventricle is included in the area of interest, some counts from the right ventricle, left atrium, and aorta are also included. The contribution from the right ventricle on the first pass can easily be recognized (see Fig. 4) and is over before the left ventricle component is maximal. However, the second pass (rapid recirculation) through the right ventricle and contributions from the left atrium and aorta appear in the left ventricular area of interest, contributing significantly to the total counts. The magnitude of this background or "cross-talk" contribution must be determined in order to measure the ejection fraction.

After the first few studies it was apparent that ejection fraction, read from recording of the left ventricular area of interest without modification of baseline, was approximately one-half the true value (see Table 1, data column 1). Dynamic studies of a single-chamber model demonstrated that this was not a fault of the recording system and must therefore be due to activity in adjacent structures. As an accurate measure of ejection fraction was a prime object, success of the method depended on establishing the baseline from which the ejection fraction was to be measured. The true baseline must be one which results in a constant ejection fraction throughout the left ventricular phase. This requirement is met by any one of a family of baseline curves (see Fig. 5). By comparison with the results of contrast angiography, it was apparent that the correct baseline curve was one which intercepted the left ventricular curve at its low point after passage of the bolus and before recirculation. All curves above a certain value meet this requirement, indicating that the true value must be established from each patient's record. Ideally, one must look in front of, behind, and around the ventricle to measure the "cross-talk" and background interference. In practice, this can be approximated by recording a ring-shaped area of interest

TABLE 1. EFFECT OF BACKGROUND ERASE ON EJECTION FRACTION (%)

Patient	Isotope		Contrast
	Uncorrected	Minus background	
JO	25	63 (9)*	62 (3)*
BR	50	87 (14)	84 (1)
BE	25	52 (9)	53 (3)
SH	23	51 (13)	55 (1)
MA	26	47 (7)	48 (1)
SI	26	47 (5)	54 (2)
WM	21	43 (8)	56 (1)
OD	34	50 (6)	79 (3)
ME	40	54 (6)	57 (3)
SO	66	74 (6)	72 (3)
TA	28	58 (5)	59 (1)
OG	41	72 (7)	80 (3)
WH	37	79 (11)	70 (3)
JO	17	42 (13)	35 (3)
BO	55	86 (7)	86 (5)
JI	34	74 (6)	72 (4)
	Average†	61	64

* Number of beats analyzed in parentheses.
† Comparison of columns 2 and 3 gave an r value of 0.85, p value of <0.05.

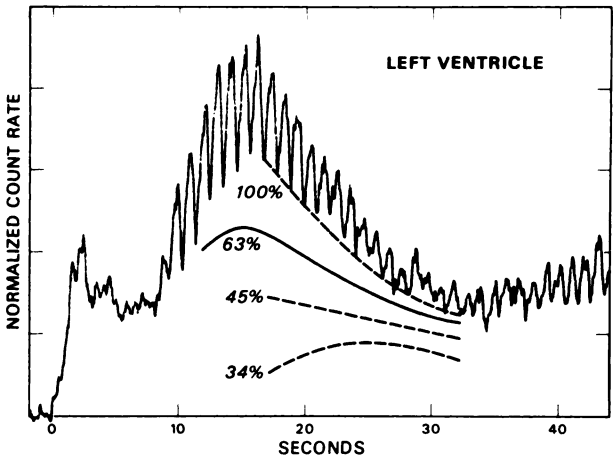

FIG. 5. Recording from left ventricle showing some of "family" of curves which result in constant ejection fraction through left ventricular phase. Solid curve (63%) represents correct baseline obtained by recording 3-mm-wide window around left ventricle and confirmed by simultaneous quantitative angiocardiography (first patient in Table 1).

around the left ventricle (see Fig. 6). The optimum width of the ring was determined by trial and error. With the monitor size employed, this was a 3-mm ring whose area happened to be approximately equal to the area of the left ventricle in end-diastole. By recording the activity in the ring immediately surrounding the ventricle, one sees fluctuations due to "cross-talk" when the ventricle is full. By taking only the low points of that curve (when the ventricle itself is contracted and out of sight) and recording at a sensitivity which brings the low point to the same value as the low point of the left ventricular curve, a satisfactory baseline curve is established (see Fig. 7 and Table 1). As can be seen from the table, the isotope method allows averaging the results of several beats in all cases whereas contrast angiography must frequently rely on a single beat. Although discrepancies appear in the comparison (r value = 0.85), this method of establishing the baseline appears to be satisfactory.

When the counts from the left ventricle are spread out by using a faster paper speed, such as provided by an electrocardiograph or Electronics for Medicine recorder, higher frequency details of the pattern of left ventricular volume changes (dV/dt) can be seen (upper portion of Fig. 8). The changes in left ventricular volume (dV/dt) are determined by direct recording of the electrically-determined derivative (lower portion of Fig. 8). From such a record the maximum rate of change in volume with time and duration of systolic, diastolic, and isovolumic phases can be measured. A clear, noise-free record of rate of change of volume during left ventricular ejection, such as in Fig. 8, is obtained only in a small proportion of cases when a dose of 8 mCi is used. Such data could be obtained consistently by increasing the dose of isotope administered.

RESULTS

The normal pattern, dynamic and static, is sufficiently characteristic that marked abnormalities are immediately recognized on seeing the sequential pictures, viewing the television monitor during repeated

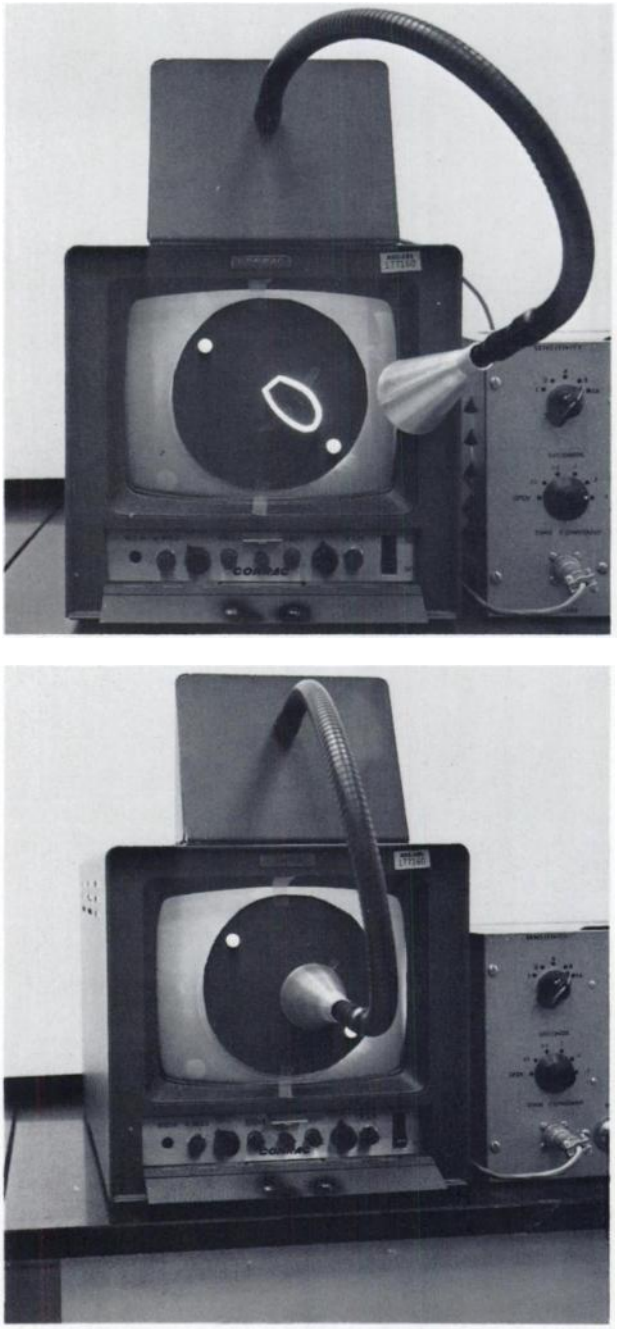

FIG. 6. Illustration of method of masking left ventricle to record "cross-talk" and background interference. Top, window, 3 mm wide, opened (cut out of black paper) surrounding left ventricular outline. Bottom, light collecting funnel with light sensitive conduction cell in place over window. Two additional windows in mask are positioned over sources fixed to camera face to assure proper magnification and orientation of mask.

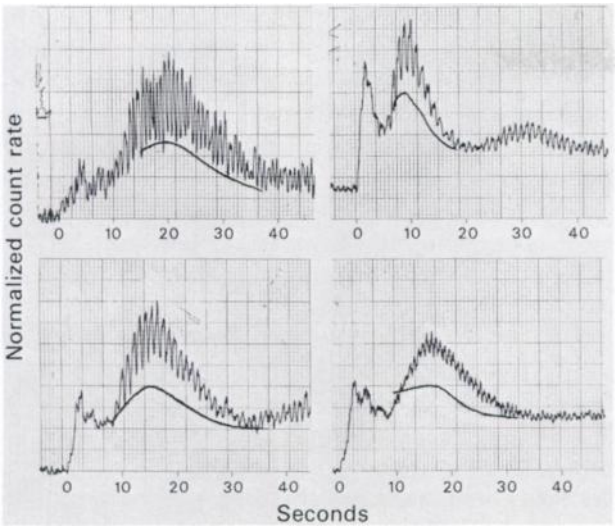

FIG. 7. Examples of baseline as determined by recording 3-mm window around left ventricular borders in four patients. Determination of baseline is essential for calculating ejection fraction.

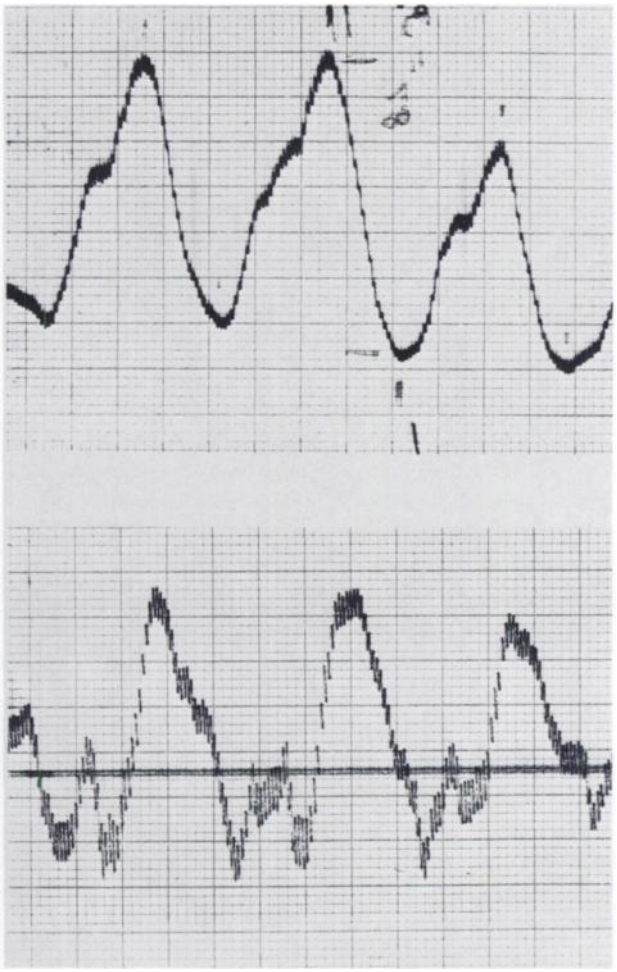

FIG. 8. Details of pattern of left ventricular volume changes (dV/dt) seen by spreading out recording using fast paper speed (top). Electrically determined derivative (bottom) provides graphic presentation of rate of change in volume as function of time. Line was drawn through isovolumic phase of graph (rate of filling below, emptying above).

playback of the study, and on seeing the curves generated from the areas of interest. Before quantitation the experienced observer is aware of major abnormalities in the central circulation by inspection of the patterns alone (*15*). These include abnormal anatomy, chamber size, transit times, shunt, and whether the ejection fraction is large or small.

A typical record from areas of interest including right atrium, right ventricle, pulmonary artery, lung, left ventricle, and aorta of a normal subject is shown in Fig. 2.

Figure 4 compares records from the left ventricle of a normal subject, a five-year-old child with a heart rate of 175 beats/min, and a patient with severe heart failure. The sharp first peak represents the passage of the bolus through the right ventricle, a part of which is also seen in the left ventricular area of interest. The second saw-toothed peak represents passage of the bolus through the left ventricle. The fluctuations represent ventricular contractions, the high point representing the filled ventricle (end-diastole) and the low points representing the end of emptying (end-systole).

To critically evaluate the quantitative technique, the system was installed in a standard fluoroscopic angiocardiographic catherization laboratory (USPHS Hospital, San Francisco) so that the isotope and fluoroscopic techniques could be compared in the same patient at virtually the same time. The scintillation camera was placed adjacent to the fluoroscope over the mobile procedure table. Sixteen patients were studied by quantitative radiocardiography during selective x-ray angiocardiography. In these patients, cardiac output by the isotope method showed good agreement with output by the Fick method.

Left ventricular ejection fraction from the isotope studies is compared with that obtained with contrast media in Table 1. From the table it can be seen that there was reasonable agreement in the majority of the 16 patients studied (r value of 0.85), with serious discrepancy in one.

Left ventricular end-diastolic volume by area measurements of scintiphotos and contrast radiograms are compared in Table 2. Only the nine patients in whom both studies were done in the right oblique (30-deg) projection are compared. There was good agreement in all but one, with an r value of 0.875.

DISCUSSION

A counting-rate recording of the passage of a bolus of isotope through the central circulation is a reflection of many parameters of dynamic cardiac function. It was the object of this research to determine

TABLE 2. COMPARISON OF LEFT VENTRICULAR END-DIASTOLIC VOLUME OBTAINED BY ANGIOCARDIOGRAPHY OR BY ISOTOPE DYNAMICS

Patient	Angio.	Isotope*	No. of frames
TA	134	141 cc	1
WH	224	216 cc	3
OG	132	129 cc	3
BE	188	182 cc	3
SO	165	163 cc	2
SH	234	238 cc	1
PI	186	131 cc	1
JO	203	187 cc	6
SM	116	104 cc	4

* Drawn from enlarged Polaroids. All others measured from enlarged 80-lens camera negative.

the information that could be extracted. To accomplish this, one must have a reliable standard for comparison. Whatever its limitations, contrast cineangiography is clearly the standard by which the new technique must be judged. Because of the lability of dynamic cardiac function, comparisons done days or weeks apart would not provide the rigid comparison desired. Because of the nature of the imaging equipment, simultaneous studies are not possible, but with the fluoroscope and scintillation camera side by side, the comparisons were made a few minutes apart. Reasonable values for cardiac output and left ventricular end-diastolic volume were expected on the basis of previous studies (*16–18*).

This paper emphasizes measurement of left ventricular ejection fraction from the high-frequency beat-by-beat oscillations in the isotope counting-rate curve, and estimation of left ventricular end-diastolic volume from area measurements on the scintigrams. This provides a workable system that is in accord with the results of contrast angiography. However, we must also mention here some of the additional efforts we have been making to develop a more comprehensive analysis of the (low frequency) isotope dilution curves along the classical lines of compartment-system or deconvolution analysis. At the present writing we do not feel that they contribute materially to the workup of the patient, but we share with many authors the conviction that eventually such analyses will yield useful information. Although the isotope dilution curves from the various areas of interest obtained with the camera are better than any previously available, the study of the "background" in the 3-mm ring around the left ventricle and similar studies of the other areas established that even with the present refinements there is still a very sizable mutual interference between counts from the various heart chambers, lung, and chest wall. Adequate correction of these curves for their mutual interference remains an unsolved problem. For anything more than assessment of ejection fraction, the ring technique should probably be considered only an interim device; we have not attempted to apply it systematically to all areas of interest. One might obtain the relative counting efficiencies needed for a "cross-talk" correction with an injection into each major region, but this would mean having access to all heart chambers with a catheter.

Prior to the realization that the curves obtained were still not adequate representations of the isotope content of single anatomical regions for the purposes of a simple compartment-system or deconvolution analysis, we made a particular effort to treat the left heart as a compartment with the isotope curve from the lung as its input function in order to obtain a curve and a washout slope more characteristic of the left heart itself. This was done with a variety of digital computer programs including a fitting program to find the best values for the exponential functions used. It has so far not contributed to a useful estimate of left ventricular end-diastolic volume. The study has shown that the downslope of the presently obtainable low-frequency left ventricular curve cannot be used to estimate EDV, even if corrected for the slow input from lung. A purely empirical relationship between such slopes and known EDV was also searched for but without success.

For the right heart, on the other hand, the high-frequency information from the isotope dilution curves has so far been unproductive, while treating the right ventricle as a compartment is simpler than for the left. Also, right ventricular contrast angiography has not been available for detailed comparison and area measurements of this ventricle on the scintigrams is a less practicable procedure than for the left ventricle. Thus in the list of procedures below the measurement of right ventricular parameters is based on simple compartment-system concepts previously used by many authors.

In addition, we have made an effort to obtain information from the (low-frequency) isotope dilution curves by deconvolution methods. Fourier transform and numerical deconvolution methods described in the literature were tried and rejected because of serious instabilities in the solutions. They seem unlikely to provide a method that could be automated and used routinely. Instead, we turned to simulation and fitting programs that deconvolute by repeated trial convolutions, using simple 3- or 4-parameter curves to fit the low frequency data. This may eventually simplify methods of obtaining mean transit times through individual segments of the central circulation

and in addition show transit-time distributions characteristic of certain disorders. The likelihood of these methods providing true numerical values for individual heart chamber volumes seems small. At present, however, the real test of such ideas must await low-frequency curves that are uncomplicated by significant mutual interference (*19*).

Shunting, if large, may be apparent from viewing the studies on the TV playback monitor or the sequential pictures obtained with the 80-lens camera or other sequential imaging methods. Quantitation of the magnitude of a shunt, or recognition of lesser degrees of shunt, is made from characteristic changes in the isotope dilution curves for the various regions in a way similar to that used for analysis of abnormal dye indicator dilution curves (*20*) or radioisotope dilution curves (*21*).

Superimposition of the images of the right and left heart can give valuable information regarding anatomical relationships (*4,7*). This can be done by photographing the TV playback monitor, opening the camera shutter only at the appropriate phases of the study.

Quantitative analysis presently includes the following:

1. Blood volume (from plasma volume and central hematocrit).
2. Cardiac output. (BV $\times$ height of equilibrium/area of first pass.)
3. Net stroke volume. (CO/heart rate.)
4. Right ventricular end-diastolic volume by slope analysis (*16*). (CO $\times$ mean time.) (Mean time = 1.44 $\times$ half-time of the downslope of the isotope washout curve.)
5. Right ventricular ejection fraction. [SV (#3)/rt. ventr. EDV (#4)] or [1/(mean time $\times$ heart rate).]
6. Analysis of lung curve for evidence of shunt, qualitatively (*20*) and quantitatively (*21*).
7. Left ventricular ejection fraction from strip-chart record with baseline corrected for "cross-talk" (see Figs. 5 and 7).
8. Left ventricular end-diastolic volume by area measurement (*6,14*).
9. Left ventricular end-diastolic volume (assuming no regurgitation). [Net stroke volume (#3)/ejection fraction (#7).]
10. Comparison of #8 and #9 to calculate percent regurgitation. [(EDV (from 8) — EDV (from 9))/EDV from 8.] The accuracy of the two values for EDV is such that differences of 30% or less cannot be relied upon as evidence of regurgitation.
11. Rate of change of volume (dV/dt) during left ventricular ejection from recording of left ventricle at fast paper speed (see Fig. 8).

Additional determinations can be made from transit time analysis, e.g., estimation of pulmonary blood volume (*22*)*. Also, assessment of left ventricular wall contraction can be made by superimposition of end-systolic and end-diastolic tracer images (*6*).

Unlike the injections of larger volumes of hypotonic medium used in angiography, the small volume of isotonic solution injected does not disturb blood viscosity, and this technique is entirely nonirritating to the myocardium. This feature is particularly important when normal physiological states are being studied, or subtle interventions planned, or for repeated evaluation of very sick patients with myocardial infarction or following heart surgery.

Changes in counting rate during ventricular contraction are directly related to volume changes rather than area changes which must be converted to volume as with the use of contrast media and fluoroscopy. In the fibrillating heart, the isotope method allows one to obtain an average ejection fraction from more beats than are usually obtained in the angiographic method. The absorbed radiation dose is on the order of 2% of that received from a comparable angiographic study.

Disadvantages of the noninvasive isotope technique as compared with the invasive contrast technique are failure to obtain measurements of blood gases or cardiac chamber pressures. Resolution of scintillation camera pictures is much less than that obtained by fluoroscopy, and much anatomic detail cannot be seen.

Although the authors have limited experience with this technique in small children, substitution of this technique for the standard fluoroscopic method should be considered wherever possible because of the reduction in radiation dose alone (*23*).

Information obtained by the technique described must be extensively evaluated in the clinical setting to determine its practical value. Clinical application of the technique has already demonstrated its ability to definitively confirm the clinician's impression in some cases, thereby eliminating the need for further study. In other cases certain possibilities in the differential diagnosis are clearly ruled out, thereby defining the nature of further studies and justifying the need for invasive procedures. In all cases the technique provides a large amount of added information, easily obtainable and not obtainable by other simple techniques. It is likely that application of this

* [C.O. $\times$ (peak time of LV — mean time of RV)], where "mean time of RV" = mean time as defined in #4 + arrival time at RV.

method will find great use in situations requiring serial study.

SUMMARY

A method for radioisotope angiocardiography using the scintillation camera and a quantitative television data system for rapid data recording and readout is described. This essentially noninvasive, risk-free, outpatient procedure, which can be repeated at frequent intervals, shows promise of being a significant supplement to conventional x-ray angiocardiography.

By precise area-of-interest masking and the use of fast-response counting-rate recording, a stroke-by-stroke reading of the left ventricular ejection fraction is obtained. Cardiac output is determined from the same record. In the absence of valvular insufficiency, end-diastolic volume is computed from these numbers. Comparison of this value with end-diastolic volume determined from area of measurements of the pictures provides an estimate of the degree of regurgitation when present. Direct comparison of this technique with standard contrast angiocardiography has been made in 16 patients with confirmatory results which are presented. Clinical application has already demonstrated the ability of isotope cardiography to provide a large amount of information not obtainable by other simple techniques. It is likely that this method will also prove useful in situations requiring serial study such as the management of intensive-care cardiac patients.

ACKNOWLEDGMENTS

The authors are indebted to Thomas Budinger and Richard Pierson, Jr., for invaluable contributions to this project. This work was supported in part by Grant No. W-7405-eng-48 from the U.S. Atomic Energy Commission.

REFERENCES

1. DONATO L: Selective quantitative radiocardiography. *Progr Cardiovasc Dis* 5: 1–18, 1962

2. BENJAMIN PP, RIEJALI A, FRIEDELL H: Electrolytic complexation of ^{99m}Tc at constant current: Its applications in nuclear medicine. *J Nucl Med* 11: 147–154, 1970

3. ANGER HO: Gamma-ray and positron scintillation camera. *Nucleonics* 21: No. 10, 56–59, 1963

4. KRISS J, MATIN P: Diagnosis of congenital and acquired cardiovascular diseases by radioisotopic angiocardiography. *Trans Ass Amer Physicians* 82: 109–120, 1969

5. MATIN P, KRISS JP: Radioisotopic angiocardiography: Findings in mitral stenosis and mitral insufficiency. *J Nucl Med* 11: 723–730, 1970

6. ZARET BL, STRAUSS HW, HURLEY PJ, et al: A noninvasive scintiphotographic method for detecting regional ventricular dysfunction in man. *New Eng J Med* 284: 1165–1170, 1971

7. MASON DT, ASHBURN WL, HARBERT JC, et al: Rapid sequential visualization of the heart and great vessels in man using the wide-field Anger scintillation camera. Radioisotope angiography following the injection of technetium-99m. *Circulation* 39: 19–28, 1969

8. CHAPMAN CB, BAKER O, MITCHELL JH, et al: Experiences with a cinefluorographic method for measuring ventricular volume. *Amer J Cardiol* 18: 25–30, 1966

9. ANGER HO: Scintillation camera and multiplane tomographic scanner. *Jap Soc Nucl Med* 6: 125–148, 1968

10. BITTER F, BESCH W, SCHÄFER N, et al: Integrierte Herz-Kreislaufanalyse mit Hilfe der quantitativen Funktionsszintigraphie. In *Frontiers of Nuclear Medicine*, Horst W, ed, Berlin, Springer-Verlag, 1971, pp 250–261

11. ANGER HO: Eighty-lens optical camera for recording dynamic studies with the scintillation camera. *UCRL-20699*, National Tech. Infor. Service, 1971

12. BURKE G, HALKO A, PESKIN G: Determination of cardiac output by radioisotope angiography and the image-intensifier scintillation camera. *J Nucl Med* 12: 112–116, 1971

13. MCAFEE JG, STERN HS, FUEGER GF, et al: ^{99m}Tc labeled serum albumin for scintillation scanning of the placenta. *J Nucl Med* 5: 936–946, 1964

14. SULLIVAN RW, BERGERON DA, VETTER WR, et al: Peripheral venous scintillation angiocardiography in determination of left ventricular volume in man. *Amer J Cardiol* 28: 563–567, 1971

15. KRISS JP, ENRIGHT LP, HAYDEN WG, et al: Radioisotopic angiocardiography: Wide scope of applicability in diagnosis and evaluation of therapy in diseases of the heart and great vessels. *Circulation* 43: 792–808, 1971

16. NEWMAN EV, MERRELL M, GENECIN A, et al: The dye dilution method for describing the central circulation. An analysis of factors shaping the time-concentration curves. *Circulation* 4: 735–746, 1951

17. MULLINS CB, MASON DT, ASHBURN WL, et al: Determination of ventricular volume by radioisotope-angiography. *Amer J Cardiol* 24: 72–77, 1969

18. STRAUSS HW, HURLEY PJ, ZARET BL, et al: Measurement of systolic and diastolic cardiac chamber volumes without cardiac catheterization. *J Nucl Med* 11: 364, 1970

19. ISHII Y, MACINTYRE WJ: Measurement of heart chamber volumes by analysis of dilution curves simultaneously recorded by scintillation camera. *Circulation* 44: 37–46, 1971

20. FOLSE R, BRAUNWALD E: Pulmonary vascular dilution curves recorded by external detection in the diagnosis of left-to-right shunts. *Brit Heart J* 24: 166–172, 1962

21. FLAHERTY JT, CANENT RV, BOINEAU JP, et al: Use of externally recorded radioisotope dilution curves for quantitation of left to right shunts. *Amer J Cardiol* 20: 341–345, 1967

22. GIUNTINI C, LEWIS ML, SALES LUIS A, et al: A study of the pulmonary blood volume in man by quantitative radiocardiography. *J Clin Invest* 42: 1589–1605, 1963

23. WESSELHOEFT H, HURLEY PJ, WAGNER HN, et al: Nuclear angiocardiography in the diagnosis of congenital heart disease in infants. *Circulation* 45: 77–91, 1972