First-Pass Radionuclide Determination of Cardiac Output: An Improved Gamma Camera Method

Henning Kelbaek, Ole J. Hartling, Knud Skagen, Ole Munck, Ole Henriksen, and John Godtfredsen

Department of Clinical Physiology and Nuclear Medicine, and Department of Cardiology, Herlev Hospital, Department of Magnetic Resonance, Hvidovre Hospital, University of Copenhagen, Denmark

A technique for noninvasive determination of cardiac output by aid of first-pass radionuclide cardiography is described. After intravenous injection of 10–15 mCi technetium-99m- (^{99m}Tc) labeled red blood cells the method requires (a) acquisition of a first passage time-activity curve recorded with a gamma camera over the left ventricle, (b) the background corrected left ventricular count rate recorded after complete mixing of the tracer in the circulation, and (c) determination of the distribution volume of the tracer. The method was applied in 14 patients with heart disease of various origins and evaluated against the conventional tracer dilution technique with arterial sampling of blood activity. Cardiac output determinations by external counting ranged from 2.30 to 8.56 l/min, mean ± s.d. 4.50 ± 1.66 l/min and by arterial blood sampling from 1.88 to 8.96 l/min, mean ± s.d. 4.52 ± 1.71 l/min. An excellent correlation was demonstrated between the two techniques, $r = 0.978$ ($p < 0.001$). When no background subtraction was applied to the left ventricular counts at equilibrium, radionuclide cardiac output values were ~40% higher than those obtained by arterial sampling. The new first-pass radionuclide cardiographic technique may prove a useful tool in the noninvasive evaluation of cardiac function, especially in patients with arrhythmias and/or valvular incompetence.

J Nucl Med 28:1330–1334, 1987

The gated equilibrium technique for assessment of left ventricular volumes and cardiac output by radionuclide cardiography is well established (*1–3*). The method, however, is not applicable to patients with cardiac arrhythmias and, because it does not measure a forward flow, the value of cardiac output measurements is limited in patients with valvular incompetence.

First-pass radionuclide cardiography allows determination of the cardiac output, even in the presence of arrhythmias and valvular regurgitation. In spite of this, the method has not yet become widespread, and only a few studies have been performed to evaluate the method clinically (*4–6*). The difficulties involved in the estimation of background radioactivity and the use of empirical correction factors (*7,8*) are major drawbacks of the previously employed methods, and may account for their limited use.

Received Aug. 4, 1986; revision accepted Feb. 27, 1987.

For reprints contact: Henning Kelbaek, MD, Dept. of Clinical Physiology and Nuclear Medicine, Herlev Hospital, Univ. of Copenhagen, DK-2730 Herlev, Denmark.

We have developed a technique that allows subtraction of background activity at the point of complete mixing of the tracer in the circulation (equilibrium) from the total activity recorded in the left ventricular region of interest in a way corresponding to that employed in the calculation of gated left ventricular ejection fractions and volumes (*1,3,9*).

The present study evaluates the method by simultaneous recording of cardiac output by the direct tracer dilution method involving fractional sampling of radioactivity in arterial blood.

METHODS

Patients

The study population was comprised of 13 male and one female patient, aged 39–74 yr (mean, 60 yr) with diagnoses as outlined in Table 1. Four patients had atrial fibrillation and four were suspected of having regurgitation of the mitral valve. All patients were hospitalized and consented to participate in the study after detailed instruction including written infor-

TABLE 1
Patient Data

Patient number	Age (yr)/Sex	Diagnosis	Cardiac rhythm
1	39/M	Variant angina	Sinus rhythm
2	63/M	Ischemic heart disease	Sinus rhythm
3	46/M	Dilated cardiomyopathy	Sinus rhythm
4	59/M	Ischemic heart disease	Sinus rhythm
5	55/M	Ischemic heart disease	Sinus rhythm
6	70/M	Ischemic heart disease	Sinus rhythm
7	74/F	Ischemic heart disease	Sinus rhythm
8	51/M	Hypertensive heart disease	Atrial fibrillation
9	65/M	Aortic stenosis	Sinus rhythm
10	73/M	Mitral stenosis	Atrial fibrillation
11	56/M	Ischemic heart disease	Atrial fibrillation
12	65/M	Aortic stenosis	Sinus rhythm
13	59/M	Hypertensive heart disease	Atrial fibrillation
14	67/M	Ischemic heart disease	Sinus rhythm

mation. The study protocol had the approval of the local ethical committee.

Study Protocol

The patients were studied in the afternoon in the recumbent position; no medical treatment was discontinued. An intracatheter was placed in the right subclavian vein via a cubital vein, and a 1.2 × 200 mm polyethylene catheter* was inserted into a femoral artery by the Seldinger technique.

In vitro labeling of autologous red blood cells with technetium-99m (^{99m}Tc) was performed as described recently (*10*). A labeling efficiency of more than 95% was assured. A dose of 12–15 mCi (444–555 MBq) labeled cells in a volume of 0.7 ml was injected and flushed with 20 ml saline through the subclavian vein catheter.

Simultaneous registration of the bolus passage through the central circulation was performed by external recording over the heart with the gamma camera, and by fractional sampling of blood from the femoral artery catheter.

Cardiac Output Determination by Noninvasive Method: External Recording

The principle of this method, which is derived from the classic tracer dilution equation, has been described previously as follows (*11,12*).

$$F = \frac{D}{\int_0^\infty c(t)\,dt},$$

where F = blood flow, D = amount (dose) of tracer, c = blood concentration of tracer during the bolus passage, and t = time. It is assumed that

$$\frac{\int_0^\infty c(t)\,dt}{C_{eq}} = \frac{\int_0^\infty q(t)\,dt}{Q_{eq}},$$

where C_{eq} = the blood concentration of tracer after complete mixing, q = the mean height of the tracer curve during the bolus passage as recorded externally, and Q_{eq} = the height of the tracer curve after complete mixing. Thus,

$$F = \frac{D}{\int_0^\infty q(t)\,dt \times C_{eq}/Q_{eq}} \quad \text{or} \quad F = \frac{Q_{eq}}{\int_0^\infty q(t)\,dt} \times \frac{D}{C_{eq}}.$$

Because D/C_{eq} represents the distribution volume (V_d) of the tracer, and $\int_0^\infty q(t)\,dt$ represents the area (A) under the externally recorded passage of the tracer bolus, the calculation of blood flow can be determined as

$$F = \frac{Q_{eq}}{A} \times V_d.$$

The external data acquisition was performed with a cardiac gamma camera† equipped with a low-energy, all purpose parallel hole collimator in the left anterior oblique position and a 5–10° caudal tilt over the precordium. The first-pass data were acquired in list mode in a 256 × 256 matrix by connection of the gamma camera to a Scintiview II nuclear medicine computer‡. After 10 min of tracer mixing in the circulation, a 10-sec static image was acquired to determine the height of the activity curve, Q_{eq}. The data were processed in a 128 × 128 frame format by manually delineation of the left ventricle and a background area in a region of least activity just inferolateral to the apex of the heart (Fig. 1). The area under the low frequency (0.5 sec/frame) left ventricular time-activity curve, A, was calculated automatically by aid of a

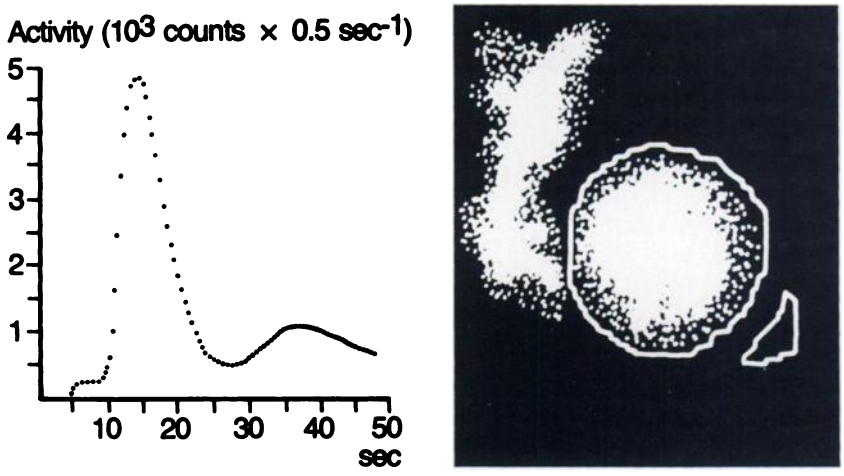

FIGURE 1
Smoothed low frequency time-activity curve from left ventricular region of interest (left) delineated together with the background area on the scintigram (right).

gamma variate function excluding (a) the initial "hump" due to Compton scatter from the bolus passage through the right ventricle and/or any activity arising in the pulmonary tissue in the left ventricular region of interest before entering the left ventricle, and (b) avoidance of recirculation activity by gamma variate extrapolation of the washout part of the curve (*13*) (Fig. 2). The count rate in the background area at the time of complete tracer mixing was normalized for the area of the left ventricle and subtracted from the count rate in the left ventricular region of interest (ROI).

A low frequency time-activity curve generated from the manually delineated left ventricular ROI is displayed in Figure 1. In Figure 2A the visual zero point of the ascending limb of the left ventricular curve is indicated by the first cursor to avoid activity from sources other than the left ventricle. A computerized gamma variate function is applied from the ascending limb of the curve to the point in which recirculation is seen to occur (indicated by the second cursor). The appropriate gamma variate curve that fits the left ventricular curve best is selected among several by superimposition of the gamma variate on the ventricular curve (Figs. 2b and c).

Cardiac Output Determination by Invasive Method: Arterial Blood Sampling

Cardiac output determination with arterial blood sampling, also based on the conventional tracer dilution equation (*14*) was carried out simultaneously. One-second samples of ~0.5 ml of arterial blood were obtained during 1 min after the bolus injection. After Saponine hemolysis exact volumes of 300 μl from each sample were transferred to glass tubes and the radioactivity of the samples was measured in a well counter. Correction for decay during counting time was applied and a time-activity curve was generated. Recirculation was corrected for by monoexponential extrapolation of the descending limb of the curve on semilogarithmic paper. The area under the curve was calculated by planimetry.

Calculation of Injected Dose and Distribution Volume

The tracer dose, D, was determined by measuring the radioactivity and weight of a standard of the injected material and comparing it with the weight of the injected bolus.

To determine the distribution volume, V_d, D was divided by the specific radioactivity of a blood sample drawn at the time of complete mixing of the tracer in the circulation, simultaneously with the assessment of the height of the externally recorded background corrected activity curve.

Statistical Analysis

The processing of the radionuclide cardiographic data was performed by two independent observers without knowledge of the results of the invasive method. The results of the noninvasive determinations are presented as the average values obtained by the two observers and plotted against the results of the invasive calculations. Correlation analysis was performed by the least squares method. A significance level of $p < 0.05$ was chosen.

RESULTS

Simultaneous collection of arterial and venous blood samples for calculation of the distribution volume resulted in mean values of 5.262 l (s.d. ± 0.931) and 5.237 l (s.d. ± 0.859), respectively. The mean difference of these determinations was 0.15% (range −9.7%–8.3%).

Cardiac output determinations by external recording ranged from 2.30 to 8.56 l/min (mean ± s.d. 4.50 ± 1.66 l/min) and by arterial blood sampling from 1.88 to 8.96 l/min (4.52 ± 1.71 l/min). The difference of the noninvasive results in percentage of those obtained by the invasive calculation ranged from −9.6% to 32.4% with a mean of 0.7%. The mean cardiac output difference of the four patients with atrial fibrillation was 1.2% (range −6.6%–9.2%).

After mixing of the tracer the mean activity ± s.d. in the background area normalized for ventricular size was 175 ± 68 and 176 ± 72 counts × sec^{-1} for the two observers, representing 27% and 29%, respectively, of the total activity in the left ventricular ROI. Cardiac output values recorded without background correction were ~40% higher than those obtained from arterial sampling (Fig. 3).

Correlation analysis showed excellent correlation of the new external counting method with the conventional invasive method, r = 0.978, s.e.e. = 0.36 ($p < 0.001$) (Fig. 3).

DISCUSSION

An inherent problem of the first-pass radionuclide determination of cardiac output is the noncardiac radioactivity arising from pulmonary tissue and thoracic wall at the time of equilibrium in the left ventricular region of interest (*15,16*). Usually, an empirical correction factor of 0.81–0.85 is applied to the calculation

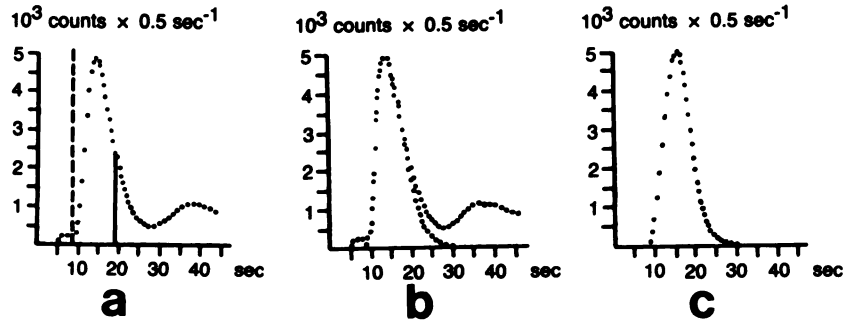

FIGURE 2
a: Low frequency left ventricular time-activity curve with cursors placed at the expected bolus appearance time in the left ventricle (left cursor) and at the start of recirculation (right cursor). b: The curve shown in C superimposed on the A curve. c: Gamma variate curve fitted to the left ventricular curve.

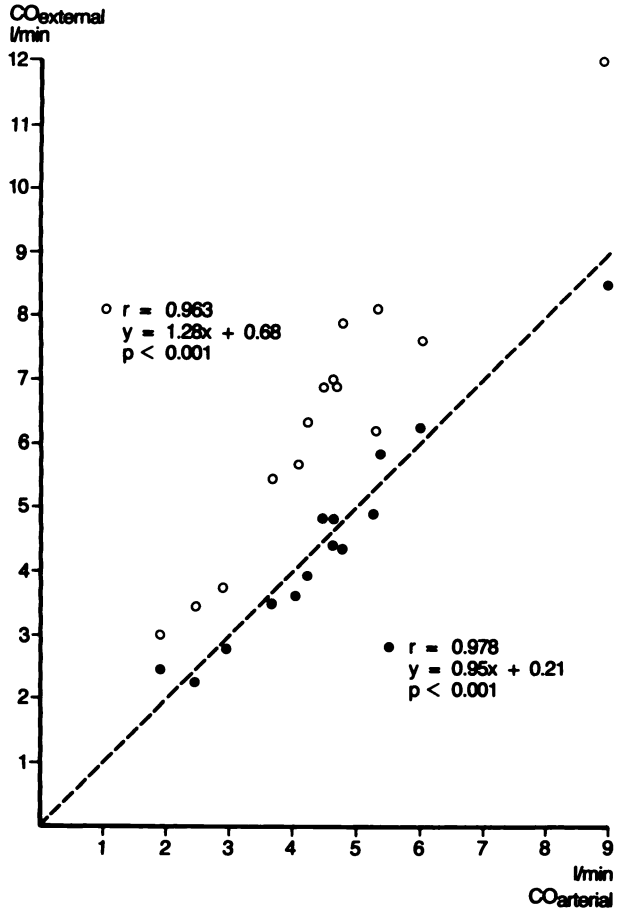

FIGURE 3
Correlation analysis between cardiac output determined by external recording ($CO_{external}$) and arterial blood sampling ($CO_{arterial}$). Open and closed circles represent values recorded *without* and *with* background subtraction at equilibrium. Dashed line indicates the line of identity.

because of this noncardiac equilibrium activity (*7,8,15*). However, great individual variations in background radioactivity weaken this correction method (*17*). In the present study we used a background subtraction from the equilibrium activity in the left ventricular ROI, which corresponds with that employed in the calculation of left ventricular ejection fraction and volumes by the multigated radionuclide equilibrium technique: A radioactivity-poor region just inferolateral of and behind the apex of the left ventricle normalized in size for ventricular area (*1,18*). This background activity was subtracted from the total activity in the left ventricular ROI at the time of equilibrium, whereas, no background subtraction was applied to the first-pass curve. The present results showed a high correlation of this new noninvasive method with the conventional invasive method.

Most of the activity in the lung tissue in front of the heart is temporally separated from the time-activity curve generated from the left ventricular cavity. Some residual activity may be present in the lung, serving to increase the height of the curve; however, this increase is counterbalanced by the absence of the residual activity in the left ventricular cavity. This is the rationale of ignoring background activity over the left ventricle during the first transit.

The result of the dilution volume calculations from arterial and venous equilibrium blood samples indicate that a possible difference between the hematocrits in various vascular beds (*19*) does not influence this result systematically.

Determination of background activity after tracer mixing in the circulation represents a crucial point in this new approach to noninvasive radionuclide measurement of the cardiac output. The background results of the two independent observers did not show any systematic deviation. These findings indicate an acceptable level of reproducibility of the background determination.

The major advantage of the gamma camera method compared with previously employed single detector (nuclear stethoscope) techniques for first-pass radionuclide determination of cardiac output (*6,8,12*) is the possibility of exact delineation of left ventricular and background ROI allowing determination of a background corrected left ventricular activity after tracer mixing. Compared with other first-pass gamma camera methods (*4,20*) the present technique considers and corrects for the overestimated left ventricular activity at the time of tracer mixing due to activity in extracardiac tissue. Further, the high in vivo stability of ^{99m}Tc-labeled red blood cells used in the present study (*10*) adds to a high precision in both the area delineation on the scintigrams and the determination of the tracer distribution volume.

As opposed to the radionuclide equilibrium technique (*1–3*), the first-pass technique as described in the present report allows calculation of the cardiac output in spite of cardiac arrhythmias. This conception was substantiated by the fact that the difference between noninvasive and invasive cardiac output values in the four patients with atrial fibrillation were within the range of the corresponding values of the patients with sinus rhythm. In addition, the first-pass method measures a cardiac forward flow, which represents the functional cardiac output. This is especially important in patients with valvular incompetence. Simultaneous noninvasive radionuclide determinations of cardiac output with first-pass and multigated equilibrium techniques will make it possible to quantitate the regurgitation fraction in patients with mitral and aortic incompetence, provided they have no arrhythmias.

NOTES

* Surgimed, Oelstykke, Denmark.
† (Siemens ZLC) Searle-Siemens Medical Systems, Inc., Des Plaines, IL.
‡ Searle-Siemens Medical Systems, Inc., Des Plaines, IL.

ACKNOWLEDGMENT

This work was supported by the Danish Medical Research Council, the Danish Heart Foundation, and the Foundation of King Christian X. The technical assistance of Kirsten Bülow is gratefully acknowledged.

REFERENCES

1. Slutsky R, Karliner J, Ricci D, et al. Left ventricular volumes by gated equilibrium radionuclide angiography: a new method. *Circulation* 1979; 60:556–564.
2. Dehmer GJ, Firth BG, Lewis SE, et al. Direct measurement of cardiac output by gated equilibrium blood pool scintigraphy: validation of scintigraphic volume measurements by a nongeometric technique. *Am J Cardiol* 1981; 47:1061–1067.
3. Massie BM, Kramer BL, Gertz EW, et al. Radionuclide measurement of left ventricular volume: comparison of geometric and count-based methods. *Circulation* 1982; 65:725–730.
4. Alazraki NP, Schelbert HR, Verba JW, et al. Utilization of radionuclide cardiac angiogram for determination of cardiac output and ejection fraction. *J Nucl Biol Med* 1975; 19:127–134.
5. Kloster FE, Bristow JD, Greiswold HE. Cardiac output determination from precordial isotope-dilution curves during exercise. *J Appl Physiol* 1969; 27:465–468.
6. Pritchard WH, MacIntyre WJ, Moir TW. The determination of cardiac output by the dilution method without arterial sampling: validation of precordial recording. *Circulation* 1958; 18:1147–1154.
7. Donato L. Basis concepts of radiocardiography. *Semin Nucl Med* 1973; 3:111–130.
8. Kuikka J. In-113m radiocardiographic measurements of cardiopulmonary parameters in healthy subjects and in cardiac patients [Thesis]. University of Jyvaeskylae, Finland, 1976.
9. Kelbaek H, Gjørup T, Brynjolf I, et al. Acute effects of alcohol on left ventricular function in healthy subjects at rest and during upright exercise. *Am J Cardiol* 1985; 55:164–167.
10. Kelbaek H, Gjørup T, Fogh J. In vivo stability of in vitro labelled ^{99m}Tc-red blood cells. *Nucl Med Commun* 1986; 7:541–547.
11. Shipley RA, Clark RE, Liebowitz D, et al. Analysis of the radiocardiogram in heart failure. *Circ Res* 1953; 1:428–438.
12. MacIntyre WJ, Pritchard WH, Moir TW. The determination of cardiac output by the dilution method without arterial sampling: analytical concepts. *Circulation* 1958; 18:1139–1146.
13. Thompson HK, Starmer CF, Whalen RE, et al. Indicator transit time considered as a gamma variate. *Circ Res* 1964; 14:502–515.
14. Asmussen E, Nielsen M. The cardiac output in rest and work determined simultaneously by the acetylene and the dye injection methods. *Acta Physiol Scand* 1953; 27:217–230.
15. Lassen NA, Perl W. Volume, flow or mass, flux ratio (mean transit time): bolus injection. In: Tracer kinetic methods in medical physiology. New York: Raven Press, 1979:76–101.
16. Pierson RN, Alam S, Kemp HG, et al, Radiocardiography in clinical cardiology. *Semin Nucl Med* 1977; 7:85–100.
17. Kelbaek H, Gjørup T, Hartling OJ, et al. The influence of a background correction that considers the heart volume on radionuclide left ventricular ejection fraction determinations. *Br J Radiol* 1986; 59:993–996.
18. Pfisterer ME, Ricci DR, Schuler G, et al. Validity of left ventricular ejection fractions measured at rest and peak exercise by equilibrium radionuclide angiography using short acquisition times. *J Nucl Med* 1979; 20:484–490.
19. Larsen OA. Studies of the body hematocrit phenomenon: dynamic hematocrit of a large vessel and initial distribution space of albumin and fibrinogen in the whole body. *Scand J Clin Lab Invest* 1968; 22:289–295.
20. Fouad FM, Tarazi RC, MacIntyre WJ, et al. Venous delay, a major source of error in isotopic cardiac output determination. *Am Heart J* 1979; 97:477–484.