Forward Cardiac Output Measurement with First-Pass Technique Using ^{99m}Tc-Labeled Myocardial Perfusion Imaging Agents

Junichi Taki, Akira Muramori, Seigo Kinuya, Kenichi Nakajima, Ichiro Matsunari, Yoshiharu Miyazaki, Yoshiharu Murata and Norihisa Tonami

Department of Nuclear Medicine, Kanazawa University School of Medicine, Kanazawa; Division of Nuclear Medicine, Department of Radiology, and Division of Cardiology, Department of Internal Medicine, Noto General Hospital, Nanao, Japan

The aim of this study was to develop and validate a new first-pass method for the measurement of forward cardiac output (CO) using ^{99m}Tc-labeled myocardial perfusion imaging agents. **Methods:** In protocol 1, to test the new method for measuring CO, the conventional method and the new method for CO measurement were performed in 1 d in 57 patients (32 men, 25 women; age 68 ± 11 y). In the conventional method, radionuclide angiography (1 frame/s) with in vivo ^{99m}Tc labeling (110 MBq) of red blood cells was performed for 2 min in the left anterior oblique projection. Five minutes later, a 1-min equilibrium image was obtained, and a blood sample was taken for calculation of the distribution volume. To obtain data for the new method, further radionuclide angiography (1 frame/sec) with ^{99m}Tc labeling (600–740 MBq) of red blood cells was then performed in the anterior projection. CO was calculated using the following equation:

$$CO = C_{max} \times V_{LV} / \int f(t)dt,$$

where C_{max} is the background-corrected peak count of the whole thorax during angiography, $\int f(t)dt$ is the area under the gamma variate-fitted left ventricular (LV) time-activity curve after background correction and V_{LV} is the LV volume obtained by the area length method applied to the radionuclide angiography and myocardial tomography. In protocol 2, to evaluate the new method, 24 patients (16 men, 8 women; age 71 ± 9.2 y) underwent radionuclide angiography with ^{99m}Tc-tetrofosmin (600–740 MBq), and the measured CO was compared with the CO obtained by the conventional method with ^{99m}Tc-labeled red blood cells. **Results:** In protocol 1, good correlation was observed between the CO by the new method (Y) and the CO by the conventional method (X): Y = 1.0X + 57 mL/min and r = 0.95. There was good agreement between the two methods (mean difference −56 ± 381 mL/min). Inter- and intraobserver correlation coefficients were 0.96 and 0.98, respectively. In protocol 2, the CO by the new method using ^{99m}Tc-tetrofosmin (Y) showed a good correlation with the CO by the conventional method (X): Y = 0.90X + 453 mL/min and r = 0.93. Good agreement between the two methods was observed (mean difference 73 ± 390 mL/min). Inter- and intraobserver correlation coefficients were 0.95 and 0.98, respectively. **Conclusion:** This new method permits accurate forward CO measurement using the first-pass data with ^{99m}Tc-terofosmin, which is applicable to other ^{99m}Tc-labeled myocardial perfusion imaging agents.

Key Words: forward cardiac output; ^{99m}Tc-labeled myocardial agents; tetrofosmin; radionuclide angiography

J Nucl Med 1999; 40:1874–1881

The most commonly used method for measurement of forward cardiac output (CO) is the thermodilution method (*1,2*). However, its invasive nature limits its wide clinical use. In the field of nuclear cardiology, forward CO measurement has been performed by the first-pass method using ^{99m}Tc-labeled red blood cells or albumin because it can offer accurate measurement of forward CO even in patients with arrhythmias or valvular regurgitation; this technique has been well validated against the thermodilution technique (*3,4*). In the radionuclide method, left ventricular (LV) equilibrium count data and blood sampling are necessary to measure CO. ^{99m}Tc-labeled myocardial perfusion imaging agents such as sestamibi and tetrofosmin have been introduced recently as a substitute for ^{201}Tl. Because these agents are labeled with ^{99m}Tc, they are suitable for first-pass data acquisition (*5–7*). However, these tracers rapidly disappear from the blood, and the equilibrium data, which are essential for CO measurement, therefore cannot be obtained. Thus, the technique for CO measurement with ^{99m}Tc-labeled perfusion tracers has been limited to the geometric method using first-pass data or electrocardiographically gated SPECT. In these methods, CO is measured by multiplying heart rate and stroke volume, which is obtained by subtracting the end-diastolic volume from the end-systolic volume. Accordingly, forward CO cannot be measured accurately under the condition of arrhythmias and valvular regurgitation.

It would be useful clinically if forward CO could be measured with these tracers during the first-pass transit concurrently with a myocardial perfusion study. Therefore, the aims of this study were to develop a new method for the measurement of forward CO using ^{99m}Tc-labeled myocardial

Received Jul. 13, 1998; revision accepted Apr. 9, 1999.

For correspondence or reprints contact: Junichi Taki, MD, Department of Nuclear Medicine, Kanazawa University School of Medicine, 13-1 Takara-machi, Kanazawa 920-8640, Japan.

perfusion imaging agents and to evaluate the new method prospectively against the conventional method.

MATERIALS AND METHODS

New Method of Cardiac Output Determination

The new method was designed to obtain CO with ^{99m}Tc-labeled myocardial perfusion imaging agents, such as sestamibi and tetrofosmin, using first-pass data and SPECT images.

The principle of this method is derived from the classic tracer dilution equation, which has been described as follows (*8*):

$$F = I/\int c(t)dt, \qquad \text{Eq. 1}$$

where F = blood flow or CO, I = total amount of injected dose of the tracer and c(t) = concentration of the tracer of the left ventricle during the radionuclide bolus passage at time t.

In the new method, first-pass data were obtained from the anterior view because the total injected dose of the tracer (I) was easily estimated as a maximum count of the whole thorax during first-pass data acquisition.

When f(t) is defined as the radioactivity measured from the LV region of interest (ROI) at time t, f(t) is expressed as follows: $f(t) = k_1 \times V_{LV} \times c(t)$, where V_{LV} is the LV volume (mL) and k_1 is the correcting factor for the counting rate from the left ventricle, including the attenuation factor and sensitivity of the gamma camera.

Then,

$$c(t) = f(t)/k_1 \times V_{Lv}. \qquad \text{Eq. 2}$$

When Equation 2 is inserted into Equation 1,

$$F = I \times k_1 \times V_{Lv}/\int f(t)dt. \qquad \text{Eq. 3}$$

Because the radionuclide tracer was injected as a bolus, the total injected dose was counted as the maximum count, C_{max} (cpm), of the whole thoracic ROI. When the correcting factor for the counting rate from the whole thorax is k_2, $C_{max} = k_2 \times I$. Then Equation 3 is

$$F = (k_1/k_2)C_{max} \times V_{LV}/\int f(t)dt. \qquad \text{Eq. 4}$$

V_{LV} can be measured based on the area length method using the formula of Sandler and Dodge (*9*) as follows, $V_{LV} = 8A^2/3\pi L$, where A is the area of the left ventricle and L is the length of the LV long axis.

True LV area (A) and length of the long axis of the left ventricle (L; length between the midpoint of the aortic valve plane and apex) can be calculated using the LV ROI and SPECT images (Fig. 1). When, on the anterior image generated from radionuclide angiography, the horizontal and vertical components of the long axis of the left ventricle (L_{ROI}) are X and Y, respectively, and the angle between the LV long axis and the anterior surface of the thoracic wall (horizontal line) on the myocardial tomographic transverse image is α, the following equations are obtained.

$$L_{ROI}^2 = X^2 + Y^2, \quad L^2 = (X/\cos\alpha)^2 + Y^2.$$

Then,

$$L_{ROI} = \sqrt{X^2 + Y^2}, \quad L = \sqrt{(X/\cos\alpha)^2 + Y^2}.$$

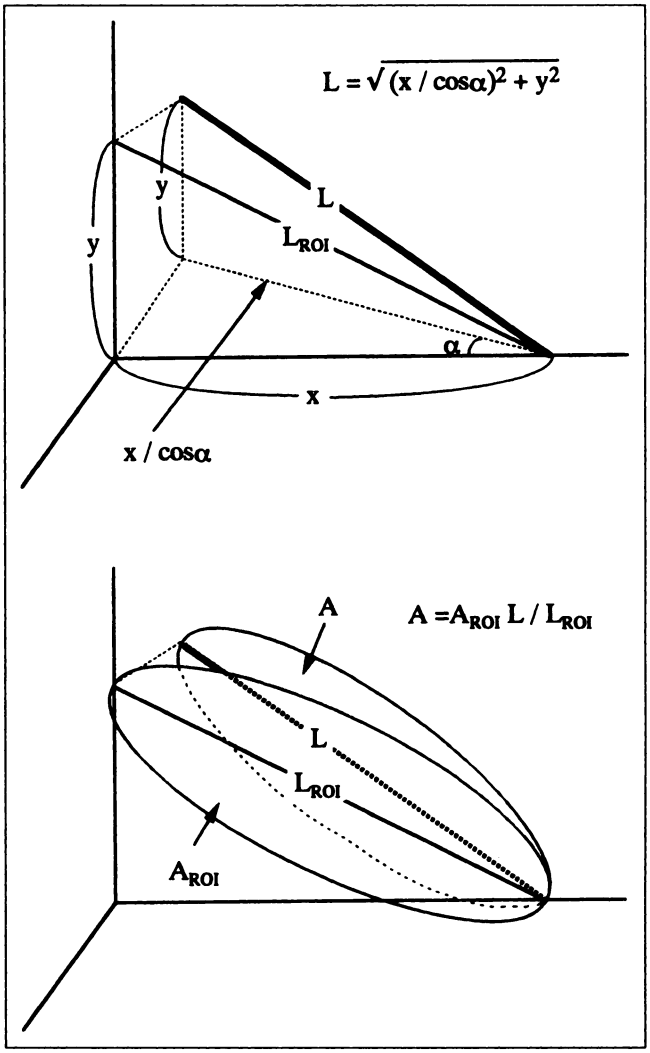

FIGURE 1. Method to calculate length of LV long axis (L) and LV area (A). From anterior image length of long axis of LV region of interest (L_{ROI}), horizontal and vertical component of L_{ROI} (x and y) can be obtained. From transverse image of SPECT, angle between gamma camera surface and LV long axis (α) can be obtained. A_{ROI} = area of LV ROI.

When the shape of the left ventricle resembles a prolate ellipsoid, $A = A_{ROI} \times L/L_{ROI}$.

On the summed image (duration 3–5 s) of the LV phase of the first-pass images, LV ROI was set by delineating the edge where the count was 40% of the ventricular peak count based on the phantom study in which 40% cutoff of the peak count of the syringe (3-cm diameter) with 50 mL ^{99m}Tc showed the most accurate edge detection. The aortic valve plane was delineated manually by detecting a slight narrowing or the angulation between the ascending aorta and the left ventricle. The length of the L_{ROI} was then obtained (Fig. 2A). When the valve plane was unclear, the anterior image obtained at tomographic imaging was used as a reference. $\int f(t)dt$ was obtained as the area under the first-pass time-activity curve from the LV ROI fitted by a gamma variate curve (*10*) (Fig. 2B). A gamma variate function was applied from the ascending limb of the LV time-activity curve to the point at which recirculation or overlapped activities such as descending aorta were seen to occur.

The difference between both correcting factors (k_1 and k_2) was

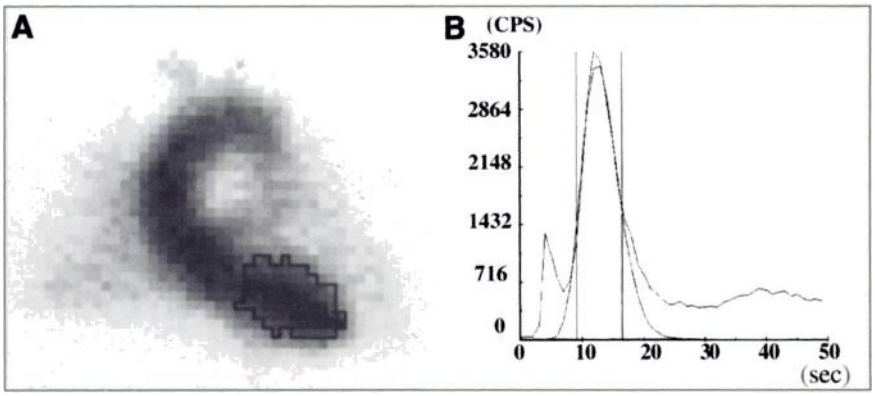

FIGURE 2. (A) Typical LV ROI delineated by 40% contour of LV maximal count on summed image of LV phase of first-pass image obtained in anterior view using ^{99m}Tc-tetrofosmin. (B) Area under first-pass time-activity curve from LV ROI obtained using gamma variate-fitted LV time-activity curve. CPS = counts per second.

considered to arise from the difference of the attenuation associated with the localization of the tracer when counting was performed. Because k_1 is applied when the tracer is in the left ventricle, a large part of the attenuation may occur by the thoracic wall and only a small part may occur through the right ventricle. In terms of k_2, C_{max} was obtained in almost all cases in which the tracer was distributed from the right ventricle to the both lungs; a large part of the attenuation may then occur by the thoracic wall and only a small part may occur through the mediastinum and sternum. Therefore, k_1 and k_2 were considered to be similar values, and, k_1/k_2 was arbitrarily assumed to be 1.0.

Cardiac Output Determination by Conventional Radionuclide Angiography

The principle of the conventional method, which is derived from the classic tracer dilution equation, also has been described as Equation 1, which can be expressed in the following form (*8*): CO = Vd × Ce/S, where Vd is the distribution volume of the tracer, Ce is the counting rate of the LV ROI at the time when Vd of the intravascular tracer is measured and S is the area under the first-pass time-activity curve derived from the LV ROI.

The Vd was calculated as follows. The same amount of ^{99m}Tc-pertechnetate (1.0 mL) that was injected into the patient was stirred into 999 mL water; 1.0 mL of specimen was then placed in a test tube and counted in a well counter [Cinj (cpm)]. A blood sample (1.0 mL) withdrawn immediately after acquisition of the equilibrium blood pool data was also counted in a well counter [Cb (cpm)]. The Vd was calculated by the following equation: Vd (mL) = 1000 Cinj/Cb. On the summed image (duration 3–5 s) of the LV phase of the first-pass images obtained from the left anterior oblique projection, the LV ROI was set by delineating the edge where the count was 40% of the ventricular peak count. The aortic valve plane was delineated manually. The area under the first-pass time-activity curve from the LV ROI (S) was obtained using a gamma variate-fitted LV time-activity curve (*10*). Using the same LV ROI, Ce was obtained as the counting rate of the left ventricle on the equilibrium image.

Study Patients

Fifty-seven consecutive patients (protocol 1) (32 men, 25 women; mean age 68 ± 11 y; range 48–94 y) who underwent first-pass radionuclide angiography with in vivo ^{99m}Tc-labeling of red blood cells for evaluation of various cardiac diseases were recruited for this study to establish the new method for the measurement of forward CO, which is applicable to use of ^{99m}Tc-labeled myocardial perfusion imaging agents. The mean height and body weight were 156 ± 8.3 cm (range 140–179 cm) and 55 ± 9.2 kg (range 35–79 kg), respectively. Twenty patients had old myocardial infarctions, 35 had angina pectoris, 1 had mitral stenosis and 1 had diabetes mellitus. Three patients had atrial fibrillation. No patients had regurgitant valvular lesions. All patients underwent SPECT with ^{201}Tl or ^{123}I-β-methyl-p-iodophenyl-pentadecanoic acid, from which the LV geometric information was obtained.

To confirm the feasibility of the new method for CO measurement, a subsequent 24 patients (protocol 2) (16 men, 8 women; mean age 71 ± 9.2 y; range 50–85 y) who met the following criteria were studied: ^{99m}Tc-tetrofosmin scintigraphy and first-pass radionuclide angiography with in vivo ^{99m}Tc-labeling of red blood cells performed within 1 wk, heart rate and systolic blood pressure change within 10% between the two radionuclide studies, no change in medications between the two studies and steady-state condition with no interventional therapy between the two studies. The mean height and body weight were 157 ± 7.7 cm (range 143–169 cm) and 56 ± 10 kg (range 36–77 kg), respectively. Eight patients had histories of previous myocardial infarctions, 13 had angina pectoris, 2 had congestive heart failure and 1 had previous aortic valve replacement. No patients had regurgitant valvular lesions or arrhythmias.

Study Protocols

Protocol 1. To test the new method for measuring forward CO, two consecutive first-pass studies, including the conventional method and the new method, were performed.

The patients received approximately 0.5–0.9 mg stannous ion as stannous pyrophosphate. Twenty minutes later, 110 MBq ^{99m}Tc-pertechnetate in a volume of 1.0 mL were injected from the right medial antecubital vein or the right jugular vein and flushed with 20 mL saline. In the 35° left anterior oblique view, first-pass radionuclide angiographic data were obtained every 1 s for 2 min using a large-field-of-view gamma camera equipped with a high-resolution parallel-hole collimator. Energy discrimination was centered on 140 keV with a 20% window. Imaging was performed using 64 × 64 matrices with a 1.5 zoom mode, giving 0.533 cm of matrix size. Equilibrium data were acquired for 1 min with the patient in the same position 5 min after radionuclide angiography. Immediately after acquisition of the equilibrium data, a 1.0-mL blood sample was drawn into a test tube and counted in a well counter for calculation of the distribution volume.

After the blood sampling, 1-min radionuclide first-pass data acquisition every 1 s in the anterior view was performed immediately after the bolus injection of 600–740 MBq ^{99m}Tc-pertechnetate. At this time, the patient's entire thorax was covered by the field

of the gamma camera. The first-pass time-activity curve of the LV ROI was obtained by subtracting the previously injected radionuclide activity. C_{max} was also obtained from the time-activity curve of the entire thorax after subtraction of the previously injected radionuclide activity.

Then 35° and 70° left anterior oblique electrocardiographically gated blood pool imaging was performed for assessment of regional and global LV function.

Protocol 2. To evaluate and confirm the accuracy of the new method, the patients underwent the 1-min radionuclide first-pass study (1 frame/s) with ^{99m}Tc-tetrofosmin (600–740 MBq) in a manner similar to that described for the second injection of ^{99m}Tc-pertechnetate in protocol 1. An electrocardiogram was recorded during the study to obtain the heart rate during administration of the radionuclide. Approximately 1 h later, SPECT was performed. Within 1 wk of the ^{99m}Tc-tetrofosmin study, conventional radionuclide angiography with in vivo ^{99m}Tc-labeling of red blood cells in the left anterior oblique view was performed to measure forward CO.

To evaluate the bolus integrity, the full width at half maximum (FWHM) of the time-activity curve generated from the square ROI (5 × 5 pixel) set on the superior vena cava was calculated.

To test the interobserver reproducibility of the new methods, in both protocols, two well-experienced observers analyzed the same data independently throughout all processes of the analysis. Observer 1 repeated all processes of the analysis to evaluate intraobserver reproducibility.

Statistical Analysis

Data are presented as mean ± SD. Simple linear regression analysis was used to compare COs measured by the conventional and new methods and to analyze inter- and intraobserver reproducibilities. A paired *t* test was applied to test the difference between the COs by the new and conventional methods and between the bolus integrities. To assess systemic error and agreement between COs by conventional and new methods, the method of Bland and Altman (*11*) was used. $P < 0.05$ was considered significant.

RESULTS

Protocol 1

The mean CO by the new method was 5725 ± 1272 mL (range 2934–8490 mL); the mean CO by the conventional method was 5667 ± 1213 mL (range 2838–8456 mL). There was no significant difference between the COs measured by the two methods ($P = 0.25$). The CO by the new method (Y) showed an excellent correlation with the CO by the conventional method (X): Y = 1.0X + 57 mL/min, $r = 0.95$ and SEE = 245 mL (Fig. 3A). The method of Bland and Altman (*11*) showed a good agreement between the two methods (mean difference −56 ± 381 mL/min) and no significant degree of systematic measurement bias (Fig. 3B). Intra- and interobserver correlations were also excellent: Y = 0.98X + 47 mL/min, $r = 0.98$ and SEE = 153 mL/min; and Y = 0.94X + 392 mL/min, $r = 0.96$ and SEE = 219 mL/min, respectively.

Protocol 2

Bolus integrities of the radionuclide angiography with tetrofosmin (FWHM = 2.7 ± 1.2 s) and the conventional method with ^{99m}Tc-labeled red blood cells (FWHM = 2.5 ± 0.77 s) were similar ($P = 0.60$). No fractionated bolus was observed.

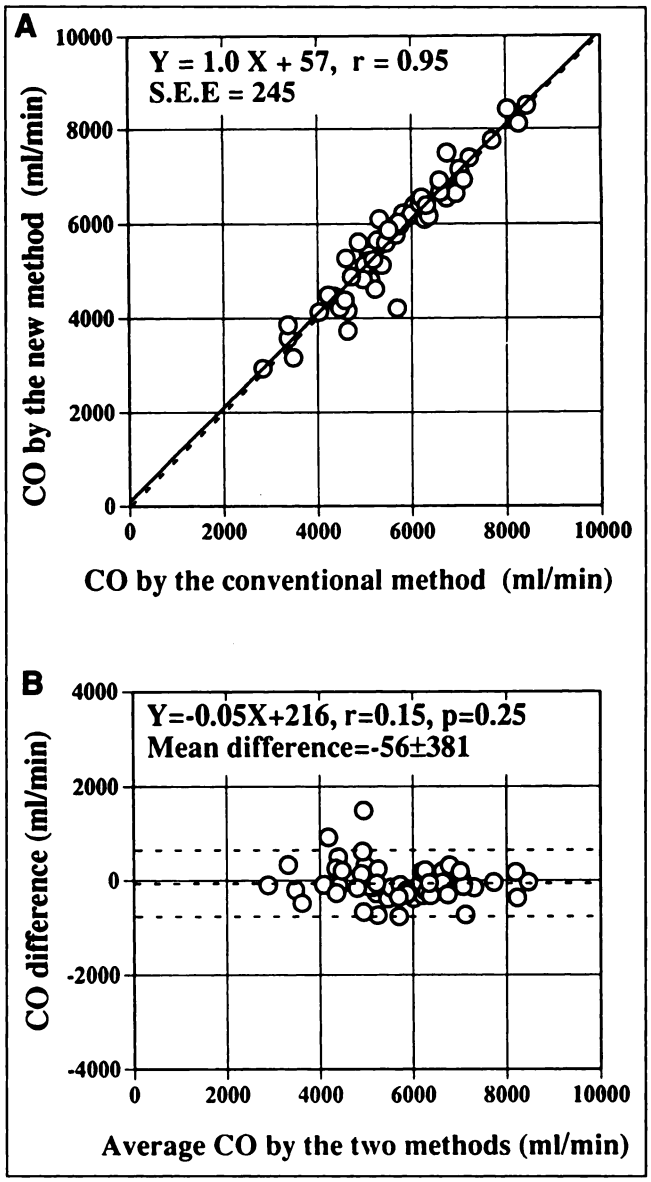

FIGURE 3. (A) Relationship between cardiac outputs (COs) by conventional method with ^{99m}Tc-labeled red blood cells and COs by new method with ^{99m}Tc-tetrofosmin. Dashed line is line of identity. (B) Scatterplot of CO difference (CO by conventional method minus CO by new method) against mean CO obtained by two methods. Dashed lines represent mean and ±2 SDs.

The mean CO by the new method was 5323 ± 1009 mL (range 3665–8130 mL); the mean CO by the conventional method was 5396 ± 1037 mL (range 3644–8046 mL). There was no significant difference between the COs measured by the two methods ($P = 0.37$). CO by the tetrofosmin method (Y) showed an excellent correlation with the CO by the conventional method (X): Y = 0.90X + 453 mL/min, $r = 0.93$ and SEE = 425 mL/min (Fig. 4A). A good agreement between the two methods was observed (mean difference 73 ± 390 mL/min), and no significant degree of systematic measurement bias was observed (Fig.

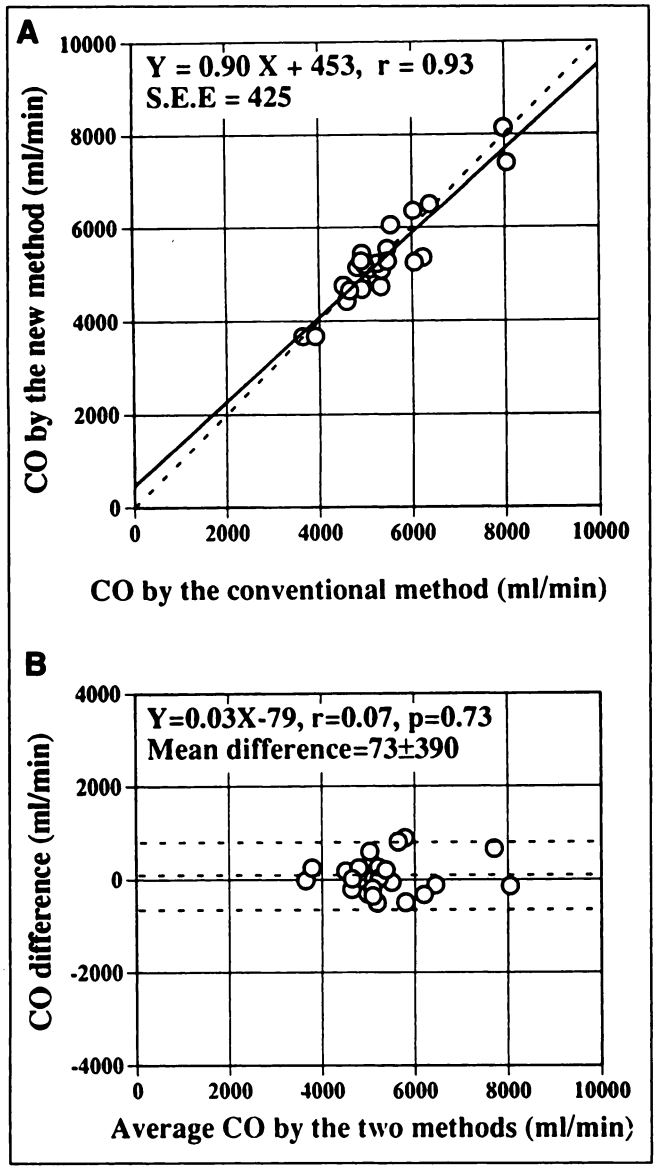

FIGURE 4. (A) Relationship between cardiac outputs (COs) by conventional method with ^{99m}Tc-labeled red blood cells and COs by new method with ^{99m}Tc-tetrofosmin. Dashed line is line of identity. (B) Scatterplot of CO difference (CO by conventional method minus CO by new method) against mean CO obtained by two methods. Dashed lines represent mean and ±2 SDs.

4B). Intra- and interobserver correlations were also excellent: Y = 0.96X + 102 mL/min, r = 0.98 and SEE = 102 mL/min; and Y = 0.97X + 130 mL/min, r = 0.95 and SEE = 351 mL/min, respectively (Figs. 5A and 6A). There were good agreements between two repeated measurements of observer 1 (mean difference 97 ± 195 mL/min) and between two independent observers' measurements of COs (mean difference 43 ± 309 mL/min) (Figs. 5B and 6B). There was also no significant degree of systematic measurement bias.

DISCUSSION

The physical properties of the ^{99m}Tc-labeled myocardial perfusion imaging agents such as ^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin permit assessment of both cardiac function and myocardial perfusion with a single injection of radiopharmaceutical. The LV ejection fraction and regional wall motion are now available during first-pass angiography or electrocardiographically gated SPECT using these ^{99m}Tc perfusion tracers (*5–7,12*). However, forward CO measurement with the injection of these tracers has yet to be developed. Therefore, we aimed to establish the method for measuring forward CO using ^{99m}Tc-labeled myocardial perfusion imaging agents. Our data show that first-pass data acquisition during the injection of ^{99m}Tc-tetrofosmin coupled with subsequent SPECT imaging permits accurate measurement of forward CO. The CO measured by ^{99m}Tc-tetrofosmin correlated closely with that measured by the conventional

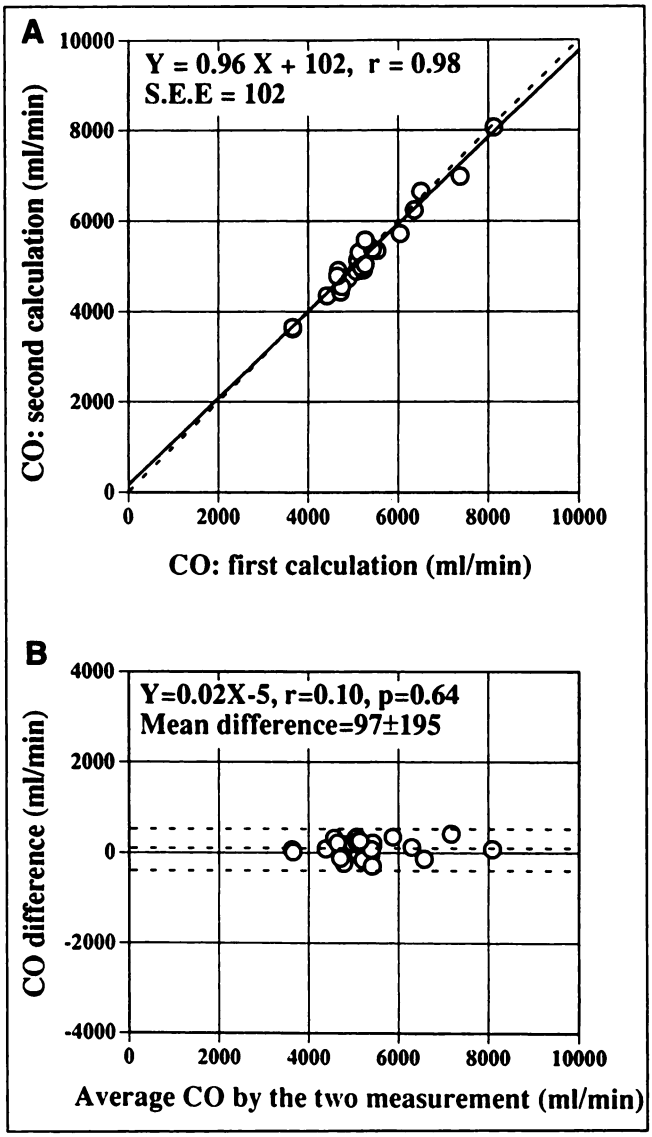

FIGURE 5. (A) Intraobserver reproducibility of cardiac output (CO) measurement by new method with ^{99m}Tc-tetrofosmin. Dashed line is line of identity. (B) Scatterplot of CO difference (CO by first calculation minus CO by second calculation) against mean CO obtained by two measurements. Dashed lines represent mean and ±2 SDs.

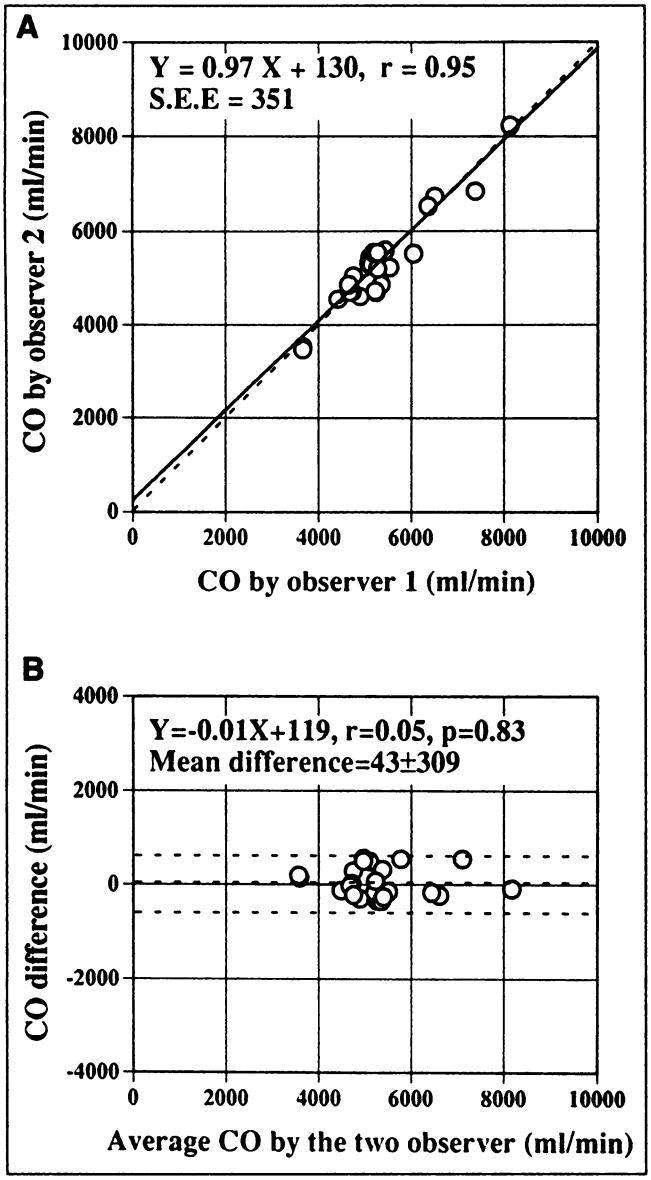

FIGURE 6. (A) Interobserver reproducibility of cardiac output (CO) measurement by new method with ^{99m}Tc-tetrofosmin. Dashed line is line of identity. (B) Scatterplot of CO difference (CO by observer 1 minus CO by observer 2) against mean CO obtained by two observers. Dashed lines represent mean and ±2 SDs.

method using ^{99m}Tc-labeled red blood cells (r = 0.93), and a good agreement between the two methods was observed (mean difference 73 ± 390 mL/min). This new method is intuitively considered to be applicable to all ^{99m}Tc-labeled perfusion imaging agents.

The CO measurement has been performed by indicator dilution methods, the Fick method and angiographic or geometric methods. The Fick method has not been in wide clinical use because it requires measurement of oxygen consumption and arterial and venous blood sampling. The method suffers primarily from the difficulty of obtaining accurate oxygen consumption measurements and lack of applicability in the steady state under certain conditions. It is necessary to collect the expired air for at least 1 min and ideally for about 3 min in the steady state to measure oxygen consumption, and this is the greatest source of measurement variability (*13*). In geometric methods, including angiography with contrast media or radionuclide angiography, CO is calculated by multiplying heart rate and stroke volume, which is obtained by subtracting the end-systolic volume from the end-diastolic volume. Therefore, it is inaccurate under the condition of valvular regurgitation and arrhythmias. In indicator dilution methods, the thermodilution technique, which uses cooler liquid as an indicator, has been used in many laboratories because it obviates withdrawal of blood from an arterial site and permits rapid display of the results using computerized methods. However, because of the invasive nature of the thermodilution method, it is not suitable for repeated follow-up studies. The radionuclide first-pass method using ^{99m}Tc-labeled red blood cells or albumin, also one of the indicator dilution techniques, is a standard method for measuring forward CO in nuclear cardiology (*3,4,14,15*). This method requires radiopharmaceuticals that stay in the vascular space and blood sampling for the calculation of the distribution volume of the tracer. Accordingly, this method cannot be applied to myocardial perfusion tracers, in which radioactivities disappear rapidly from the blood. With the new method, CO can be measured by <2-min first-pass data acquisition coupled with subsequent SPECT without blood sampling and equilibrium blood pool data. Furthermore, this method can be applied to patients with valvular regurgitation and arrhythmias because it is based on the indicator dilution method. In patients with mitral or aortic regurgitation without arrhythmias, the regurgitation fraction would be available (*16*) from simultaneous measurement of the forward stroke volume obtained by first-pass data acquisition (CO divided by heart rate) and LV end-diastolic and end-systolic volumes with subsequent gated myocardial tomography.

Limitations and Technical Considerations

We used in vivo ^{99m}Tc-labeled red blood cells to obtain a reference CO with the conventional first-pass method. The labeling efficiency of in vivo ^{99m}Tc-labeled red blood cells (85%–95%) is lower than that of in vitro ^{99m}Tc-labeled red blood cells (95%), resulting in an overestimation of total blood volume (distribution volume) and an underestimation of equilibrium ventricular count (tracer concentration) because part of the unlabeled ^{99m}Tc may distribute outside the vascular space (*17–19*). However, even if part of the tracer distributes to the extravascular space, the total injected dose of ^{99m}Tc (obtained by multiplying the distribution volume by the ventricular concentration of the tracer) would show a constant value and minimal error because the ventricular concentration of the tracer is in inverse proportion to the distribution volume. Because the LV concentration of the tracer is practically measured by a gamma camera, the effect of extracardiac tissue tracer activity would be a source of overestimation of the ventricular tracer concentration, resulting in an overestimation of the CO (*20*). Therefore, to

minimize error, the LV equilibrium pool data were acquired immediately after the mixing of the tracer (5 min after tracer injection) when the unlabeled ^{99m}Tc that may distribute to the extravascular space would be small, and the blood sample was obtained immediately after the data acquisition.

There are several sources of error in the new method, including quality of the bolus (*21*), fitting of the LV time-activity curve, dead time of the gamma camera, ventricular volume measurement and the potential difference of the correcting factors k_1 and k_2. The first three factors should also be considered in the conventional method. To avoid poor bolus, only the right medial antecubital vein or right jugular vein was used in this study and were flushed with 20 mL saline. Bolus integrities were good and were not fractionated, and no difference in the FWHM of the time-activity curve from the superior vena cava was observed in the conventional and the new method with ^{99m}Tc-tetrofosmin. Gamma variate fitting of the LV time-activity curve is a widely accepted technique for calculating the area under the LV time-activity curve and provides reliable results (*10,22*). Advances in Anger camera electronics improved the counting rate capacity, and new single-crystal gamma cameras provide counting rates comparable with those of the first generation of multicrystal detectors (*23*). With the gamma camera used in this study, count losses associated with dead time were negligible up to 800 MBq ^{99m}Tc. The radionuclide first-pass technique in the anterior view using geometric methods permitted accurate measurement of the LV volume (*24–27*). These studies used the area length method for calculating LV end-diastolic volume by measuring LV area by planimetry and LV length by direct measurement on the radionuclide image. Its accuracy should depend largely on the accurate LV edge determination. In the method used in this study, mean LV volume estimation was based on the ROI technique, which delineated the ventricular edge by 40% threshold of the maximal ventricular count on the summed image of the LV phase based on the phantom study. Large pixel size would bring about a larger error of geometric measurement. To decrease the unit of measured volume, imaging was performed by 64 × 64 matrices with a 1.5 times zoom mode, in which the gamma camera still covers the whole chest, rather than without zooming. Because of zooming, pixel size decreased from 0.80 to 0.53 cm and voxel size decreased from 0.51 to 0.15 cm^3. In this method, error of the LV volume determination does not directly affect the error of CO measurement. When an oversized ROI is placed on the left ventricle (usually by valve plane overestimation), the count of the ROI increases, resulting in the augmented area under the LV time-activity curve. For example, if the ROI is oversized purely to aortic area and only LV length is overestimated from 1 to x, LV volume will be overestimated from 1 to x. On the other hand, the area under the LV time-activity curve will be overestimated from 1 to x if the speed of tracer transit through the LV to the aorta is unchanged. The error of CO measurement can then be completely canceled out (Eq. 4). Although, practically, the situation is more complicated: the ROI error arises not only from valve plane identification but also from ventricular edge detection, even based on the percentage threshold method. Tracer transit speed is faster in the aorta than through the left ventricle, resulting in an incomplete proportional increase of the area under the time-activity curve in relation to the increase in ROI size. Similarly, an undersized LV ROI resulted in a decrease in the area under the LV time-activity curve. Accordingly, both over- and underestimation of the CO associated with error of LV volume estimation would be partially canceled by the increase or decrease in area under the LV time-activity curve. In the new method, correcting factors k_1 and k_2 were assumed to be similar. The difference between the correcting factors was believed to arise from the difference of the attenuation when the tracer is distributed through the right ventricle to both lungs (k_2) and when the tracer is in the left ventricle (k_1). In terms of the photons from the left ventricle, a large part of the attenuation may occur by the thoracic wall and only a small part may occur through the right ventricle. In terms of the photons from the right ventricle to the lungs, most of the attenuation may occur by the thoracic wall and only a small part may occur through the mediastinum and sternum. Therefore, k_1 and k_2 were considered to be similar values, and k_1/k_2 was arbitrarily assumed to be 1.0. However, k_1/k_2 might fluctuate in a different patient population, such as in patients with huge body size and in pediatric patients, and might be the source of error, although this variation was inconsequential in the patient population studied.

CONCLUSION

We developed a method for measuring forward CO using ^{99m}Tc-labeled myocardial perfusion imaging agents from first-pass and SPECT data without blood sampling; this method was compared with the standard first-pass method using ^{99m}Tc-labeled red blood cells. The CO measured by the first-pass study with ^{99m}Tc-tetrofosmin correlated closely with that measured by the conventional technique. Thus, forward CO can be measured accurately by the first-pass method and SPECT imaging with ^{99m}Tc-labeled myocardial perfusion agents.

REFERENCES

1. Ganz W, Donoso R, Marcus HS, Forrester JS, Swan HJC. A new technique for measurement of cardiac output by thermodilution in man. *Am J Cardiol.* 1971;27:392–396.
2. Weisel RD, Berger RL, Hechtman HB. Measurement of cardiac output by thermodilution. *N Engl J Med.* 1975;292:682–684.
3. Minssart P, Chatal JF, Grolleau JY, Guihard R, Agnely J, De Vernejoul P. A correlative study of the measurement of human cardiac output as determined by thermodilution and radiocardiography. *Eur J Nucl Med.* 1978;3:147–152.
4. Glass EC, Rahimian J, Hines HH. Effect of region of interest selection on first-pass radionuclide cardiac output determination. *J Nucl Med.* 1986;27:1282–1292.
5. Borges-Neto S, Coleman RE, Jones RH. Perfusion and function at rest and treadmill exercise using technetium-99m-sestamibi: comparison of one- and two-day protocols in normal volunteers. *J Nucl Med.* 1990;31:1128–1132.

6. Iskandrian AS, Hoe J, Kong B, Lyons E, Marsch S. Use of technetium-99m isonitrile (RP-30A) in assessing left ventricular perfusion and function at rest and during exercise in coronary artery disease, and comparison with coronary arteriography and exercise thallium-201 SPECT imaging. *Am J Cardiol.* 1989;64:270–275.
7. Boucher CA, Wackers FJT, Zaret BL, Mena IG. Technetium-99m sestamibi myocardial imaging at rest for assessment of myocardial infarction and first-pass ejection fraction. *Am J Cardiol.* 1992;69:22–27.
8. MacIntyre WJ, Pritchard WH, Moir TW. The determination of cardiac output by the dilution method without arterial sampling. *Circulation.* 1958;18:1139–1146.
9. Sandler H, Dodge HT. The use of single plane angiocardiograms for the calculation of left ventricular volume in man. *Am Heart J.* 1960;60:762–776.
10. Thompson HK, Starmer F, Whalen RE, Mcintosh HD. Indicator transit time considered as a gamma variate. *Circ Res.* 1964;14:502–515.
11. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet.* 1986;1:307–310.
12. Germano G, Erel J, Lewin H, Kavanagh PB, Berman DS. Automatic quantitation of regional myocardial wall motion and thickening from gated technetium-99m sestamibi myocardial perfusion single-photon emission computed tomography. *J Am Coll Cardiol.* 1997;30:1360–1367.
13. Fagard R, Conway J. Measurement of cardiac output: Fick principle using catheterization. *Eur Heart J.* 1990;11:1–5.
14. Burke G, Halko A, Peskin G. Determination of cardiac output by radioisotope angiography and the image-intensifier scintillation camera. *J Nucl Med.* 1971;12: 112–116.
15. Fouad FM, Houser T, MacIntyre WJ, Cook SA, Tarazi RC. Automated computer program for radionuclide cardiac output determination. *J Nucl Med.* 1979;20:1301–1307.
16. Kelbaek H, Aldershvile J, Svendsen JH, Folke K, Nielsen SL, Munck O. Combined first pass and equilibrium radionuclide cardiographic determination of stroke volume quantitation of valvular regurgitation. *J Am Coll Cardiol.* 1988;11: 769–773.
17. Hamilton RG, Alderson PO. A comparative evaluation of techniques for rapid and efficient in vivo labeling of red blood cell with Tc-99m pertechnetate. *J Nucl Med.* 1977;18:1010–1013
18. Hegge FN, Hamilton GW, Larson SM, Ritchie JL, Richards P. Cardiac chamber imaging: a comparison of red blood cells labeled with ^{99m}Tc in vitro and in vivo. *J Nucl Med.* 1978;19:129–134.
19. Pavel DG, Zimmer AM, Patterson VN. In vivo labeling of red blood cells with ^{99m}Tc: a new approach to blood pool visualization. *J Nucl Med.* 1977;18:305–308.
20. Kelbaek H, Hartking OJ, Skagen K, Munck O, Henriksen O, Godtfredsen J. First-pass radionuclide determination of cardiac output: an improved gamma camera method. *J Nucl Med.* 1987;28:1330–1334.
21. Fouad FM, Tarazi RC, MacIntyre WJ, Durant D. Venous delay, a major source of error in isotopic cardiac output determination. *Am Heart J.* 1979;97:477–484.
22. Starmer CF, Clark DO. Computer computations of cardiac output using gamma function. *J Appl Physiol.* 1970;28:219–220.
23. Nichols K, DePuey EG, Rozanski A. First-pass radionuclide angiocardiography with single-crystal gamma cameras. *J Nucl Cardiol.* 1997;4:61–73.
24. Sullivan RW, Bergeron DA, Vetter WR, Hyatt KH, Haughton V, Vogel JM. Peripheral venous scintillation angiocardiography in determination of left ventricular volume in man. *Am J Cardiol.* 1971;28:563–567.
25. Iskandrian AS, Hakki AH, Kane SA, Segal BL. Quantitative radionuclide angiography in assessment of hemodynamic changes during upright exercise: observations in normal subjects, patients with coronary artery disease and patients with aortic regurgitation. *Am J Cardiol.* 1981;48:239–246.
26. Upton MT, Rerych SK, Newman GE, Bounous EP, Jones RH. The reproducibility of radionuclide angiographic measurement of left ventricular function in normal subjects at rest and during exercise. *Circulation.* 1980;62:126–132.
27. Rerych SK, Schilz PM, Newman GE, Sabiston DC Jr, Jones RH. Cardiac function at rest and during exercise in normals and in patients with coronary heart disease: evaluation by radionuclide angiocardiography. *Ann Surg.* 1978;187:446–464.