DUAL-ISOTOPE METHOD FOR DIAGNOSIS OF INTRACARDIAC SHUNTS

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Presently, cardiac catheterization and contrast angiography is the accepted method for the demonstration of intracardiac shunts in children and adults. The procedure is an essential part of the presurgical workup—but it is time consuming, expensive, and not without risk.

Dual-isotope (^{133}Xe in saline, ^{99m}Tc-sulfur colloid) angiocardiography is a simple, inexpensive technique for diagnosing intracardiac shunts. The technique requires only a single venipuncture, is without risk to the patient, and detailed evaluation of the study can be performed without the patient being present. This method will permit reliable noninvasive screening for diagnosis of intracardiac shunts of hemodynamic and surgical significance.

Twenty-five patients were studied: 7 without shunts, 4 with right-to-left shunts, and 14 with left-to-right shunts. No false-positives were encountered in the normals, and all patients with shunts, except three with left-to-right shunts, were diagnosed by the dual-isotope technique.

Visualization of the heart chambers by radioisotope angiography has proven to be, with occasional exceptions, adequate for the qualitative diagnosis of intracardiac shunts. Several authors have reported the results of rapid sequential visualization of radioactive boluses with scintillation cameras on either Polaroid or 35-mm film for the diagnosis of intracardiac shunts (*1–6*).

Recently, videotape and computer systems have become available and offer two valuable adjuncts to radioisotope angiocardiography: (A) the ability to permanently record the original data and (B) the ability for delayed and subsequent replay and analysis of the original study. This replay allows the possibility for semiquantitative analysis of selected areas of interest such as the flow pattern through individual heart chambers or major blood vessels and greatly increases the diagnostic potential of radioisotope angiocardiography (*7,8*).

The present method, known as the dual-radioisotope technique, requires the sequential bolus intravenous administration of two nuclides: (A) ^{133}Xe in saline and (B) ^{99m}Tc-sulfur colloid. Xenon-133, which is completely cleared by the lungs, is used to delineate only the right heart and pulmonary circulation flow patterns exclusive of pulmonary venous return, and ^{99m}Tc-sulfur colloid allows visualization of the pulmonary circulation and right and left heart-flow patterns. The "empty" or "cold" space within the cardiac region on the ^{133}Xe in saline flow corresponds to the left (arterial) side of the heart on the ^{99m}Tc-sulfur colloid flow. This dual-isotope procedure supplements visualization techniques with dynamic semiquantitative density information by the recording of time-activity curves from regions of interest over the right and left heart chambers for the evaluation of intracardiac shunts.

Theoretically, the simultaneous analog time-activity curves obtained from the right and left heart chambers after the sequential bolus intravenous administration of the radioisotopes should show characteristic curve patterns for normal patients and patients with left-to-right or right-to-left intracardiac shunts (Fig. 1). These time-activity curves are expressed as counts per minute versus time in seconds. In a normal individual, the passage of the bolus through a heart chamber can be described by a single rising exponential as the bolus enters a chamber and by a single falling exponential as the chamber empties. This accumulation and disappearance of radioactivity expressed as counts per minute versus

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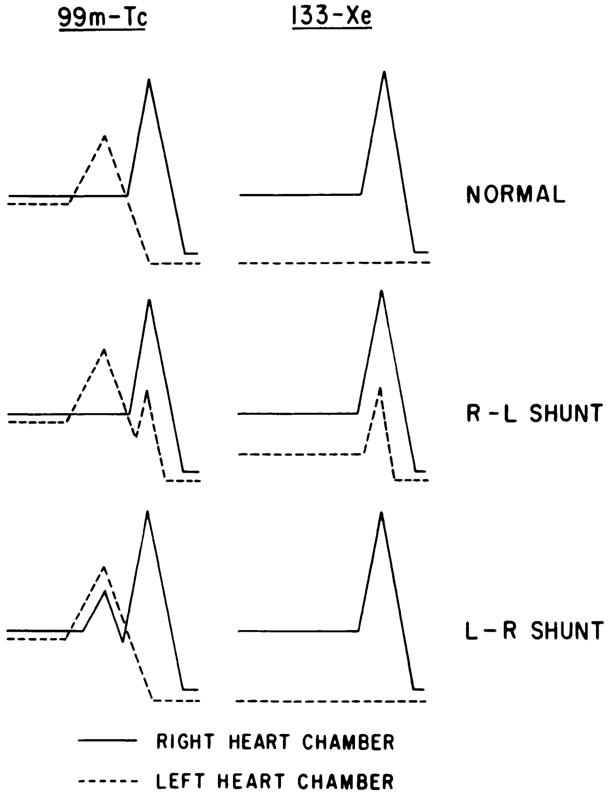


FIG. 1. Theoretical curves obtained from passage of bolus of ^{133}Xe in saline and ^{99m}Tc-sulfur colloid in normal and shunt patients.

time will result in clearly defined single peaked time-activity curves shown either over the right heart only or successively over the right and left heart. The injection of ^{133}Xe in saline will result in a single peaked curve being obtained only over the right side of the heart; there will not be a time-activity curve recorded over the left side of the heart because ^{133}Xe will be completely cleared by the lungs. The administration of ^{99m}Tc-sulfur colloid will produce sequential single-peaked curves over the right heart and left heart.

In right-to-left intracardiac shunts, ^{133}Xe in saline and ^{99m}Tc-sulfur colloid curve patterns are abnormal. With the injection of ^{133}Xe in saline, characteristic simultaneous single-peaked time-activity curves are shown over both the right and left side of the heart. This is due to shunting of some of the isotope from the right heart across a septal defect to the left side of the heart; the remainder of the radioactive xenon is cleared, as usual, by the lungs. With ^{99m}Tc-sulfur colloid, a single peak will be detected over the right heart, but a characteristic double-peaked curve will be obtained over the left heart. The first left heart peak appears abnormally early due to the right-to-left shunt and corresponds to the time of initial appearance of the bolus, shown as a single peaked curve, in the right heart. The second or normally timed left heart peak occurs after the passage of the remainder of the radioactive bolus through the lungs.

In left-to-right intracardiac shunts, the ^{133}Xe in saline time-activity curve will be normal, i.e., a single-peaked curve over the right side of the heart. The injection of ^{99m}Tc-sulfur colloid will show a characteristic double-peaked curve over the right heart; the initial peak represents normal filling of the right heart, whereas the second and abnormal peak occurs simultaneously with the normal filling and single peaked curve of the left heart. The abnormal right heart peak occurs due to shunting of some of the nuclide across the septal defect.

METHOD

A saline solution of radioactive ^{133}Xe is produced in this laboratory by a specially designed apparatus. The amount of radioactivity used is 5–7 mCi in 1.0–2.5-cc saline solution depending upon the age and size of the patient. The radiation dose from this radionuclide is well within tolerated limits due to its almost immediate disappearance through the lungs. For example, with the intravenous administration of 5 mCi of ^{133}Xe in saline in a 3-month-old infant, the absorbed dose to the lungs is 2.31 rads and the absorbed dose to the heart is 0.845 rads (*9*).

The amount of ^{99m}Tc (in sulfur colloid form) used is 2–4 mCi, again depending upon the age and size of the patient, in a volume of 0.7–1.3 cc. Technetium-99m-sulfur colloid is preferred over ^{99m}Tc-pertechnetate because the colloid does not diffuse into the extracellular space but remains within the vascular space, therefore permitting us to perform semiquantitative analysis of our data.

Two mCi of ^{99m}Tc-sulfur colloid administered intravenously to a 3-month-old infant will result in an absorbed dose to the liver of 4.41 rads; to the spleen, 3.25 rads; and to the red bone marrow, 0.40 rads (*9*). The whole-body radiation dose, calculated for a 70-kg ellipsoid, is 0.05 rads. Although this calculation of radiation dose is primarily applicable to adults, such an estimate indicates that even in small infants the radiation dose from this material is well within accepted limits (*10*).

An Anger gamma scintillation camera with a video tape data storage and playback system coupled with a dual-channel ratemeter strip-chart recorder system has been used for this study.

During the injection of the radioactive tracer the patient lies supine. Injection is made into an antecubital vein. The right arm has been found most suitable for injection due to positioning of the gamma camera over the left chest. Injection is performed by a three-way stop cock and by a peripheral 19–21-

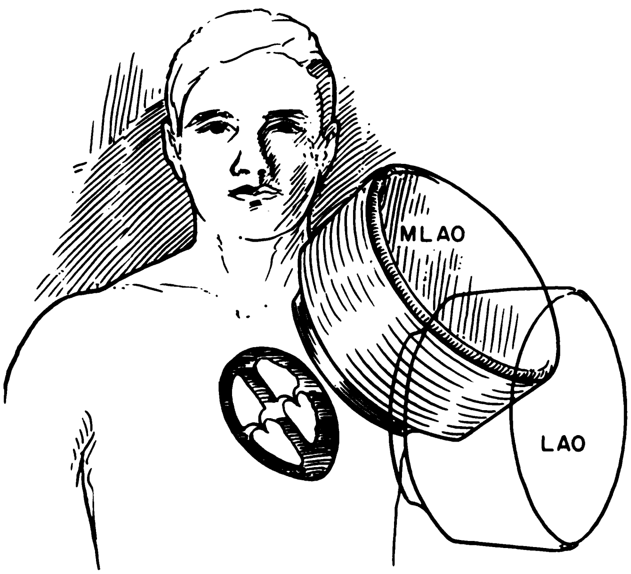


FIG. 2. Modified left anterior oblique position of camera detector used for optimum visualization of individual heart chambers.

gage butterfly needle. The ^{133}Xe in saline solution is injected first, followed 40–60 sec later by the injection of ^{99m}Tc-sulfur colloid. Both injections are performed by the same needle, and both radiotracers are rapidly flushed with 5–10-ml saline solution. The entire study is completed 2.0–2.5 min after the first injection.

The camera detector is placed in the modified left anterior oblique (MLAO) position (*11*) in preference to the left anterior oblique (LAO) position (Fig. 2). With the MLAO position, the longitudinal rotation axis of the detector is parallel to the interventricular septum. We have found the MLAO position advantageous over the LAO because it allows optimal resolution of the right and left sides of the heart and better separation of the atria from the ventricles. If this MLAO position is not used, accurate placement of regions of interest may not be possible resulting in either (A) inability to differentiate left and right atria and ventricles or (B) false-positive analysis in normal subjects. Although some authors prefer anterior views to avoid overlying lung activity, we have not found this to be a problem.

A low-energy parallel-hole multichannel collimator is used for both radionuclides. Sequential injection of both radionuclides is preferred to simultaneous injection to avoid saturation of the system from too large a number of counts and to avoid summation of the two volumes that would disadvantageously increase the size of the radioactive bolus. Each study is completely recorded, including verbal information, from the time of injection until the completion of the test on a highspeed video tape recorder.

The flow pattern of ^{99m}Tc-sulfur colloid gives visualization of all heart chambers and is therefore used for selecting and setting up of the regions of interest over the various heart chambers during the playback of the tape. Because there is no movement of the patient during the study, the settings for the ^{99m}Tc-sulfur colloid regions of interest are applied to the ^{133}Xe in saline flow for the venous side of the heart. The "empty" or "cold" space within the cardiac region on the ^{133}Xe in saline flow corresponds to the arterial side of the heart on the ^{99m}Tc-sulfur colloid flow. The time-activity curves from the region of interest settings are used to insure optimal timing when Polaroid or other pictures are obtained. If, for example, the right ventricular peak occurs 3 sec after injection, the optimal Polaroid picture of the right ventricle is taken from 2–4 sec after injection.

For the simultaneous display of the time-activity curves from two regions of interest, a dual-channel ratemeter and a dual-channel strip chart recorder are used.

TABLE 1. NORMAL PATTERN GROUP*

Patient no.	Sex	Age	Final clinical diagnosis	Accuracy of method	Comments
1	M	12	Normal heart	+	
2	M	3	ASD after surg. closure	+	
3	F	16	Pectus excavatum	+	
4	F	20	TOF after surg. closure of VSD	+	
5	M	33	Normal heart	+	No catheterization, clinically normal volunteer.
6	F	25	Normal heart	+	No catheterization, clinically normal volunteer.
7	F	21	Pulmonary valv. stenosis	+	

* ASD = atrial septal defect; TOF = tetralogy of Fallot; VSD = ventricular septal defect; and + = radioisotope angiography result in accordance with hemodynamic data.

TABLE 2. RIGHT-TO-LEFT SHUNT GROUP*

Patient no.	Sex	Age	Final clinical diagnosis	Qp:Qs	Accuracy of method	Comments
1	M	3	L-TGV, PA band, VSD	0.6:1	+	
2	F	12	AV canal, severe PS	0.5:1	+	
3	M	10	TOF, functioning L. Blalock anast.	0.5:1	+	
4	M	2	TOF	0.9:1	+	Atria and ventricles not resolved. Bidirectional shunting indicated.

* L-TGV = levotransposition of great vessels; PA = pulmonary artery; Qp:Qs = pulmonary to systemic flow ratio; TOF = tetralogy of Fallot; VSD = ventricular septal defect; AV = atrioventricular; PS = pulmonic stenosis; and + = radioisotope angiography result in accordance with hemodynamic data.

Thirty-one individuals have been studied. Six served primarily for the establishment of the technique—i.e., determination of the amount of radioactivity, specific concentration, method of application of the tracer, and positioning of the gamma camera. The remaining 25 patients were comprised of 12 men and 13 women. These patients ranged in age from 1 to 48 years, although most were pediatric cases.

Seven normal subjects were studied. Four of these were patients without evidence of heart disease; two were patients studied following successful surgical closure of atrial and ventricular septal defects; and one was a patient with pulmonary stenosis without an associated shunt lesion (Table 1).

Four patients had right-to-left intracardiac shunts. The first patient had ventricular inversion, levotransposition of the great vessels, ventricular septal defect, and pulmonary artery banding, whereas the second patient had atrioventricular canal with severe pulmonic stenosis. The third and fourth patients had tetralogy of Fallot with the third also having a functioning left Blalock anastomosis (Table 2).

Fourteen patients had left-to-right shunts. Five had atrial septal defects and seven had ventricular septal defects. One patient had a patent ductus arteriosus and one had acyanotic tetralogy of Fallot with left-to-right shunt (Table 3).

All patients underwent cardiac catheterization and contrast angiography with the exceptions of two normal subjects without evidence of heart disease.

RESULTS

Based on the final clinical diagnosis, the results are presented in three groups: normal (Table 1); right-to-left shunts (Table 2); and left-to-right shunts (Table 3).

Radioisotope angiography results in terms of accuracy of method were compared with the final clinical diagnosis, cardiac catheterization, and contrast angiographic results.

All seven patients with normal hemodynamic patterns had radioisotope angiography results consistent with the clinical and/or cardiac catheterization data (Table 1). No false-positive results were obtained.

Right-to-left shunts were correctly diagnosed by the present method in all four of the patients studied with a pulmonary-to-system flow ratio (Qp/Qs) as small as 0.9/1.0 being detected (Table 2). This method also correctly diagnosed shunts at the atrial or ventricular level except in the youngest patient, 2 years old, due to the small size of his heart.

Three of 14 patients with left-to-right shunts were not diagnosed by the present method. These showed normal patterns (Table 3). The false-negative study of Patient No. 10 was probably due to right ventricular outflow obstruction caused by hypertrophied muscle found at autopsy. The reason for the false-negative result of Patient No. 11 was probably technical. Patient No. 14, who had tetralogy of Fallot with a small left-to-right almost balanced shunt showed by catheterization oxymetry, also had a false-negative study.

In 9 of 11 patients in whom left-to-right shunts were detected by the radioisotope method, it was possible to visually distinguish the atria from the ventricles for positioning the regions of interest. This was not possible in the two youngest patients, 1 year and 2 years of age (Table 3), due to the small size of their hearts. On the other hand, in two patients (Nos. 4 and 8, Table 3), the present method was sensitive enough to show left-to-right shunts (documented by contrast angiography) in which oxymetry failed. One patient (No. 13, Table 3) with patent ductus arteriosus was also diagnosed by the present method as an extracardiac left-to-right shunt. With

TABLE 3. LEFT-TO-RIGHT SHUNT GROUP*

Patient no.	Sex	Age	Final clinical diagnosis	Qp:Qs	Accuracy of method	Comments
1	M	3	ASD	2.3:1	+	
2	F	48	ASD	1.7:1	+	
3	M	16	ASD	1.4:1	+	
4	M	3	ASD		+	Not documented by oxymetry.
5	F	43	ASD	2.8:1	+	
6	F	7	VSD	1.2:1	+	
7	F	5	VSD	1.5:1	+	
8	F	4	VSD		+	Not documented by oxymetry.
9	F	16	VSD	1.5:1	+	
10	M	14	VSD, severe AI	2.5:1	—	Missed.
11	M	5	VSD	1.5:1	—	Missed.
12	M	1	VSD	1.3:1	+	Atria and ventricles not resolved.
13	F	22	PDA	2.5:1	+	Extracardiac L-R shunt.
14	F	2	TOF, acyanotic	1.3:1	—	Missed; atria and ventricles not resolved.

* AI = aortic insufficiency; ASD = atrial septal defect; PDA = patent ductus arteriosus; Qp:Qs = pulmonary to systemic flow ratio; TOF = tetralogy of Fallot; VSD = ventricular septal defect; + = radioisotope angiography result in accordance with hemodynamic data; and — = radioisotope angiography result not in accordance with hemodynamic data.

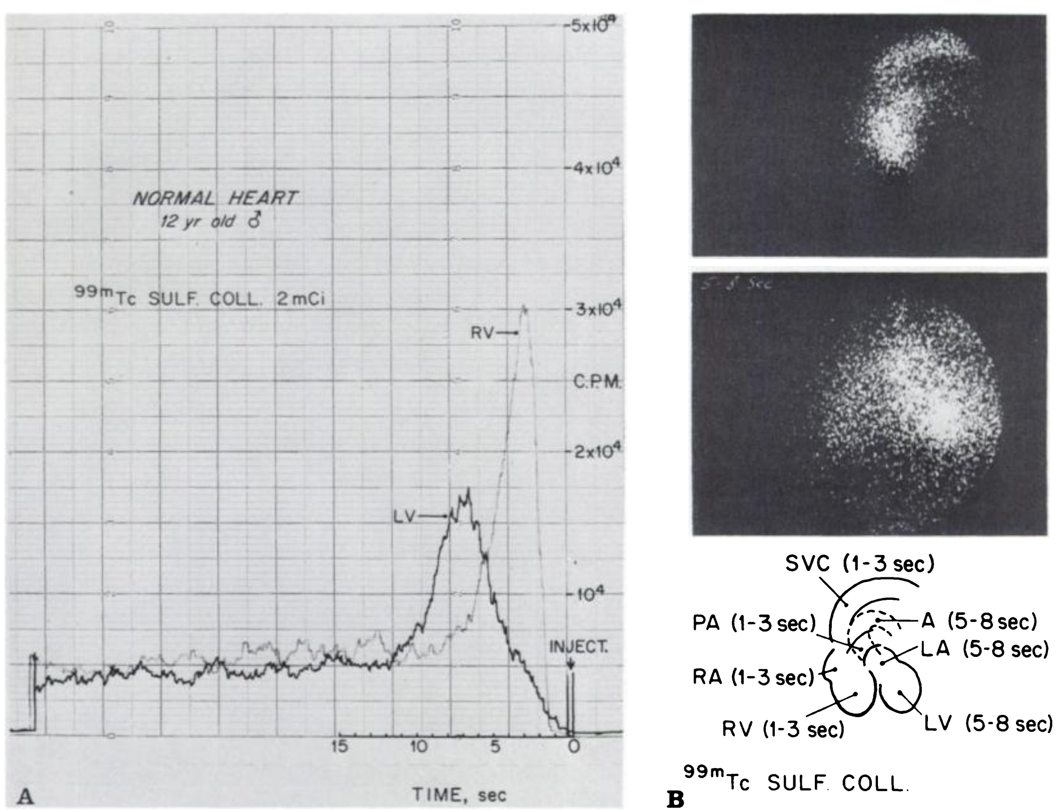


FIG. 3. (A) Normal pattern of ^{99m}Tc-sulfur colloid time-activity curves obtained simultaneously from regions of interest over right and left heart ventricles in 12-year-old boy. Curves show single peaks at time intervals corresponding to passage of bolus of radioactivity through right and left heart chambers. (B) Polaroid pictures taken at optimal time intervals to show right and left sides of heart, reveal clear separation of both sides of heart and thus possibility of setting up regions of interest over cardiac chambers.

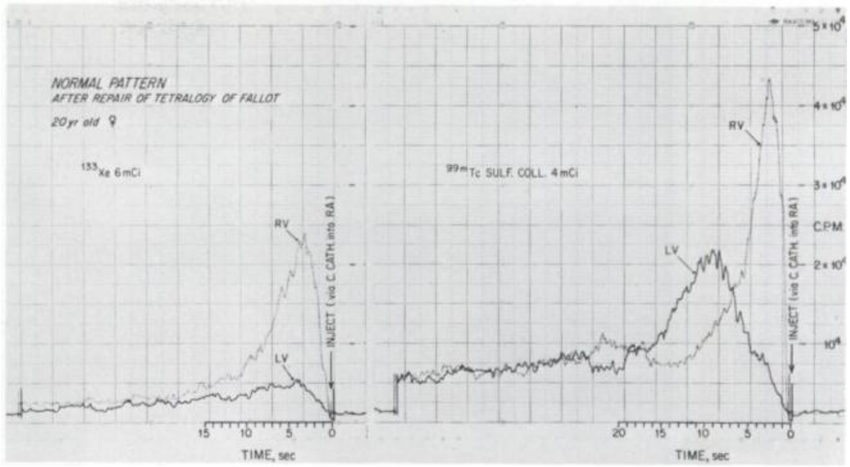


FIG. 4. Normal time-activity curves of ^{133}Xe in saline and ^{99m}Tc-sulfur colloid obtained after surgical closure of ventricular septal defect in 20-year-old woman with tetralogy of Fallot. Injection of radiotracers was made through cardiac catheter kept in situ after routine cardiac catheterization, which does not improve slope of curves when compared to all other cases done with peripheral injection.

the exceptions of the three false-negative studies, patients who had left-to-right shunts with a Qp/Qs ratio as small as 1.2/1.0 could be detected.

In summary, for the 18 patients with cardiac shunts, three false-negative results were obtained.

Typical cases illustrating the results obtained with this method are shown in Figs. 3–6. The original time-activity curves are presented with counting rates in counts per minute versus time in seconds from the moment of injection of the radiotracer.

DISCUSSION

A new method for diagnosing intracardiac shunts should offer distinct advantages in diagnostic accuracy, safety, patient comfort, cost, and ease of performance. At the present time, it would be inappropriate to claim that radioisotope angiography offers diagnostic accuracy equivalent to that of cardiac catheterization and selective contrast angiography. In two cases in which oxymetry failed to show small left-to-right ventricular shunts, radioisotope angiography confirmed contrast angiography findings.

Safety, patient comfort, and cost are significant advantages of the method. The entire procedure takes only a few minutes, entails no discomfort beyond that of a venipuncture, and does not require hospitalization. In addition, the radioisotopes give less radiation than the fluoroscopy used in conventional methods. In the patient with severe pulmonary hypertension or myocardiopathy, radioisotope angiography offers a safe and practical alternative to catheterization and contrast angiography.

Two radiotracers are used to assure the proper positioning of regions of interest by showing both sides of the heart and to make use of the characteristic hemodynamic patterns shown by time-activity-curves. Xenon-133 in saline very accurately shows right-to-left shunts, whereas ^{99m}Tc-sulfur colloid confirms the presence of right-to-left shunts shown by ^{133}Xe in saline and detects most left-to-right shunts.

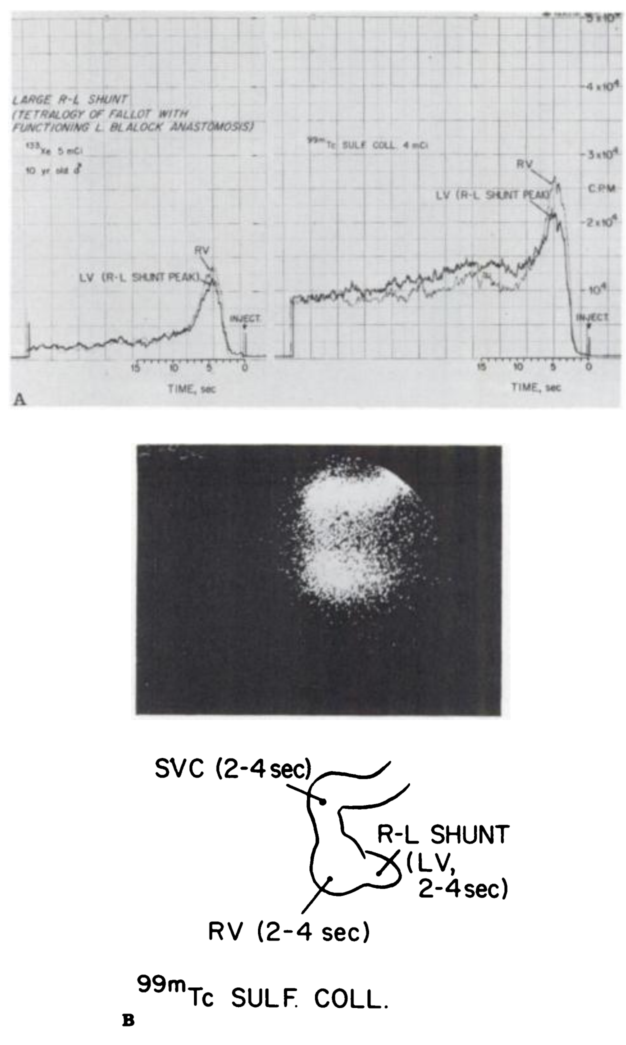
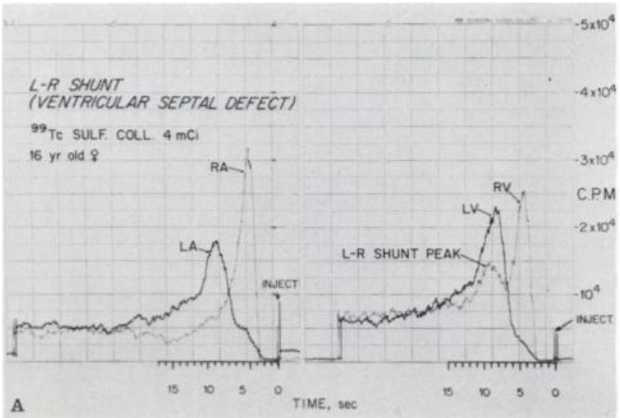
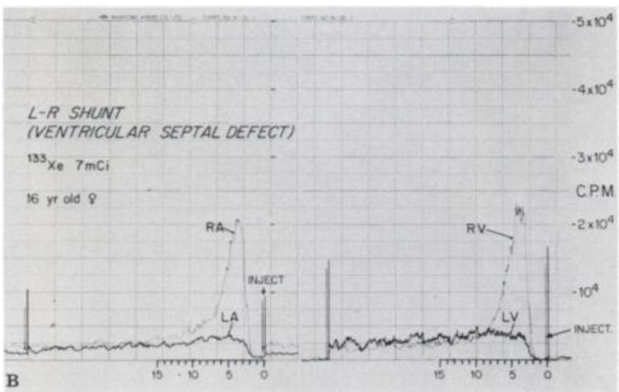


FIG. 5. (A) Abnormal ^{133}Xe in saline and ^{99m}Tc-sulfur colloid time-activity curves characteristic of right-to-left shunt in 10-year-old boy with tetralogy of Fallot (50% shunt) and functioning left Blalock anastomosis. Characteristic of both isotope curves is abnormal early peak over left ventricle, occurring simultaneously with normal right ventricle peak. The ^{99m}Tc-sulfur colloid curve also shows bidirectional shunting by simultaneous appearance of wide and low second peak over both ventricles, which is consistent with functioning left subclavian artery—left pulmonary artery anastomosis. (B) Polaroid picture shows filling of both ventricles simultaneously at 2–4 sec.





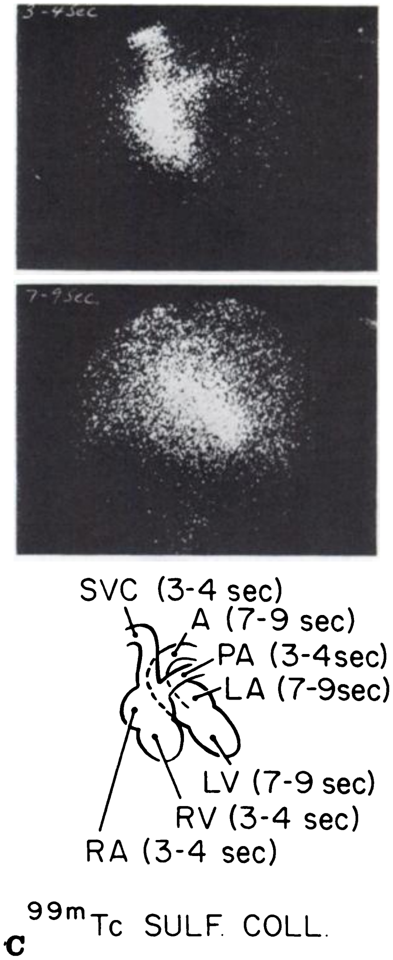


FIG. 6. (A) Abnormal ^{99m}Tc-sulfur colloid time-activity curves characteristic of left-to-right shunt in 16-year-old girl with ventricular septal defect (33% shunt). Characteristic of ^{99m}Tc-sulfur colloid curves is abnormal delayed second peak over right ventricle occurring simultaneously with normal left ventricle peak. Time-activity curves over both atria show expected normal pattern in case of VSD. (B) Normal ^{133}Xe in saline time-activity curves recorded simultaneously over both atria and ventricles are characteristic of left-to-right-shunts. (C) Polaroid pictures of ^{99m}Tc-sulfur colloid flow taken at optimal time intervals that show visual separation of each cardiac chamber with MLAO position of camera detector. Visualization of ^{99m}Tc-sulfur colloid flow through left heart does not reveal left-to-right shunt on black and white Polaroid picture or on time color-coded pictures made according to technique described by Patton (*12*).

Technetium-99m-sulfur colloid may also be used to show bidirectional shunts.

The modified left anterior oblique (MLAO) position of the gamma camera, used in preference to the conventional left anterior oblique, is also an important part of the procedure as it enables separation not only of the right and left sides of the heart but also of the atria and ventricles. If this MLAO position is not used, false-positive analysis in normal subjects may be obtained.

The value of recording data by time-activity curves is particularly emphasized by a 16-year-old girl with a small-to-moderate left-to-right ventricular shunt that had been diagnosed by cardiac catheterization data. The analog time-activity curves clearly show the presence of left-to-right shunts at the ventricular level (Fig. 6A, 6B, 6C). However, simple analysis of the Polaroid pictures, either black and white or time color-coded (*12*), failed to show the left-to-right shunt. This technique can be used to localize a left-to-right shunt at the atrial level as shown by Patients 1–5 (Table 2).

Our preliminary findings suggest that the method will permit reliable noninvasive screening for diagnosis of right-to-left intracardiac shunts as well as left-to-right shunts of hemodynamic and surgical significance. The present limited applicability of this method to small infants could probably be improved by use of a pinhole collimator for image amplification as has been suggested (*6,13,14*).

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