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Seminars in
NUCLEAR
MEDICINE

Pediatric Nuclear Cardiology

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Echocardiography, magnetic resonance imaging and, more recently, multidetector computed tomography, have led to major advances in noninvasive image assessment of anatomy in pediatric cardiology. The radionuclide methods often lack sufficient resolution to precisely characterize complex morphology in congenital heart lesions. However, these methods provide an accurate and reproduceable quantitative assessment of the physiological consequences of structural heart disease. These unique capabilities will continue to assure ongoing clinical relevance of radionuclide methodology, as is the case in the assessment of heart disease in adult cardiology.
Semin Nucl Med 37:382-390

Cardiac catheterization and angiocardiography have long been the most definitive techniques for the anatomic and hemodynamic assessment of congenital heart disease. During the past decade, however, noninvasive imaging modalities such as 2-dimensional echocardiography, magnetic resonance imaging (MRI), and radionuclide scintigraphy have lead to a significant decrease in the necessity for invasive catheterization to evaluate congenital heart lesions. Echocardiography and MRI have emerged as the dominant methods for the morphologic assessment of congenital heart disease, whereas radionuclide imaging is used primarily for the assessment of cardiac physiology. Although rarely used today for the assessment of right and left ventricular function in pediatric patients, radionuclide studies continue to provide valuable information for the evaluation of intra- and extracardiac shunts, and assessment of myocardial perfusion.

Assessment of Left-to-Right Shunts

Echocardiography with Doppler is the most widely used method for assessment of the presence and magnitude of left-to-right shunts in congenital heart disease today. The radionuclide technique for left-to-right shunt quantification was established and validated more than 30 years ago.[1] However, more than of historical interest, these fundamentally sound principles remain valid and clinically useful today.

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The radionuclide method most often is used to assess the size of left-to-right shunts in 4 major congenital lesions: atrial septal defect, ventricular septal defect (VSD), patent ductus arteriosis, and partial anomalous pulmonary venous return. In uncomplicated atrial septal defect, the shunt is principally from the left atrium to the right atrium, leading to an increased volume load in the right ventricle, which becomes dilated (Fig. 1). The left ventricle does not participate in the shunt. Anomalous connections of pulmonary veins, generally to the right atrium, also result in left-to-right shunts where the right ventricle handles the increased volume.

In the typical perimembranous VSD, the shunt is principally from the left ventricle, across the ventricular septum, into the right ventricular outflow tract, and out the pulmonary trunk (Fig. 2). The left ventricle handles the increased volume load and dilates. Large left-to-right shunts associated with VSDs can lead to pulmonary hypertension and subsequent right ventricular hypertrophy.

In patent ductus arteriosus (PDA), the shunt occurs between the high pressure aortic trunk to the lower pressure pulmonary trunk (Fig. 3). The left ventricle handles the increased volume and dilates. As with large VSDs, large PDAs can lead to pulmonary hypertension and right ventricular hypertrophy. In each lesion, knowledge of the size of the shunt, expressed as pulmonary-to-systemic flow ratio (Qp/Qs) is essential for decisions regarding corrective surgery.

The scintigraphic technique involves the rapid injection of a bolus of radionuclide (usually ^{99m}Tc-DTPA), into the circulation while monitoring the transit through the heart and lungs with the gamma camera. For small infants (ie, premature newborn infants), a butterfly needle can be used in a temporal scalp vein to deliver a compact bolus of activity to the central circulation. In older children and adults, either a butterfly needle, or a small plastic catheter, can be inserted

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doi:10.1053/j.semnuclmed.2007.05.003

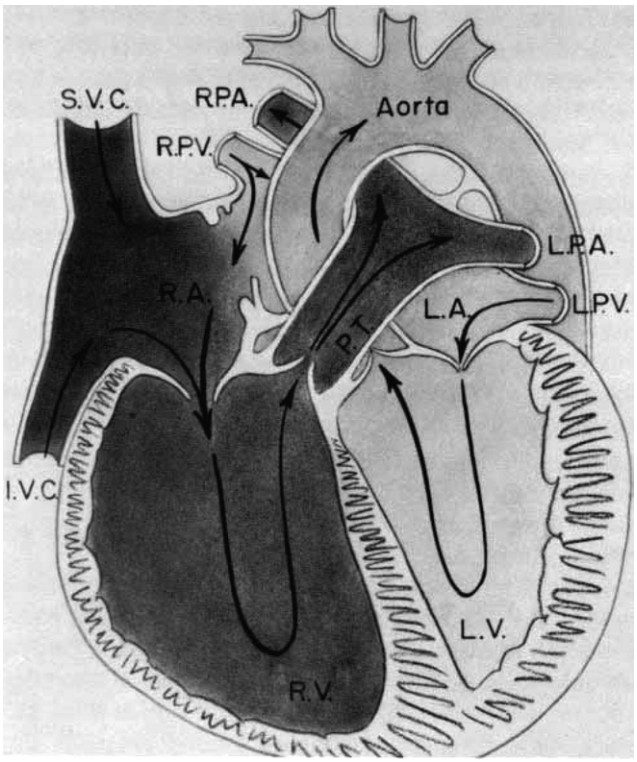

Figure 1 Uncomplicated atrial septal defect. (Reproduced with permission from Moller J, Amplatz K, Edwards J: Congenital Heart Disease. Kalamazoo, MI, Upjohn, 1971. © Association of Pathologic Chairs/Universities Associated for Research and Education in Pathology.)

preferably into an external jugular vein, although an antecubital vein can also be used. The delivery of a compact, nonfragmented bolus of activity is critical to allow accurate determination of the size of the shunt. With good technique, the success rate should be greater than 90%. It may be necessary to sedate infants and some children, since crying simulates a valsalva maneuver which can impede bolus entry into the thorax and lead to fragmentation of the bolus. As mentioned previously, ^{99m}Tc-DTPA is most commonly used for shunt studies. Doses are 200 uCi per kilogram of body weight, with a minimum dose of 2 mCi. The advantage of Tc-DTPA over other Tc-based agents is the fairly rapid renal excretion, which leads to prompt clearance of background activity. This becomes important if it is necessary to perform a second injection to improve the quality of the bolus. Generally, no more than two sequential injections are performed due to dosimetry limitations.

The study is done in the anterior projection using a converging collimator (which provides magnification) in infants, and ideally a high sensitivity parallel collimator in older children and adults. A dynamic acquisition with a sampling rate of 2 to 4 frames per second is adequate for evaluation of shunts. If ejection fraction measurements are to be made by the first pass method, a rate of at least 25 frames per second should be used. The sequential flow study is reviewed to provide useful information regarding chamber orientation and vascular connections. In the presence of normal anatomic relationships, right heart structures will appear, followed by the main pulmonary artery, lungs, and subsequently, the left ventricle (levophase), and descending aorta. Persistent pulmonary activity, resulting in the absence of a distinct levophase is consistent with a moderate-to-large left to right shunt (Fig. 4). This appearance results from recirculation of activity from heart back to lungs and vice versa, across the shunt. This appearance has been called the "smudge sign," and generally indicates a pulmonary to systemic flow of at least 1.6/1.

For quantification, time versus radioactivity curves are generated from regions of interest over the superior vena cava, to assess the quality of the bolus; and the periphery of the right lung, for shunt detection and magnitude (Fig. 5). A separate curve may be generated from a region over the left lung if differential shunting is expected (as may occur with a patent ductus arteriosus). The normal pulmonary arterial curve has an ascending limb, reflecting the arrival of tracer in the pulmonary circulation, and a symmetric descending limb, reflecting the tracer exiting the lungs, and entering the left side of the heart. A late peak will appear, reflecting systemic recirculation. In the presence of a left to right shunt, a shoulder will be present on the downslope, indicating recirculation of activity back to the lungs across the shunt. For shunt quantification, the shape of the pulmonary portion of the curve is approximated by an algebraic expression called a gamma variate function (Fig. 6).[1] In practice, the computer is given the coordinates of the upslope and initial downslope of

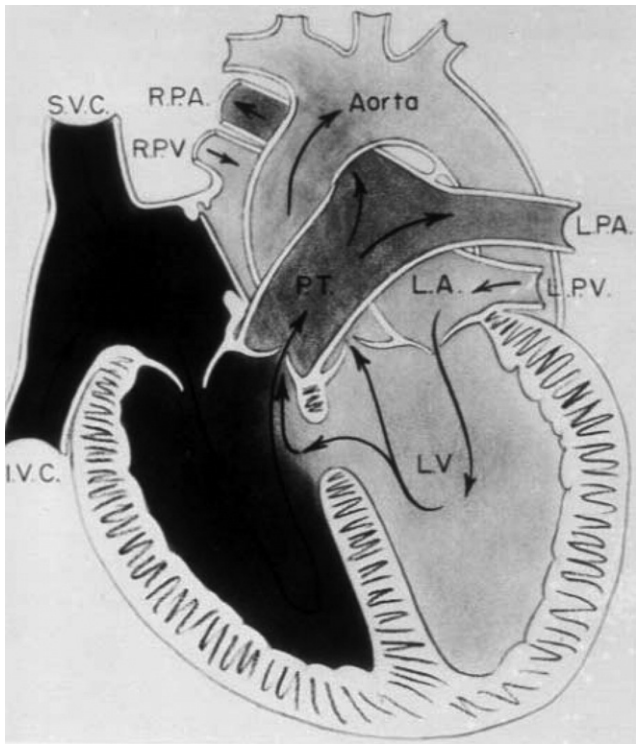

Figure 2 Ventricular septal defect. (Reproduced with permission from Moller J, Amplatz K, Edwards J: Congenital Heart Disease. Kalamazoo, MI, Upjohn, 1971. © Association of Pathologic Chairs/Universities Associated for Research and Education in Pathology.)

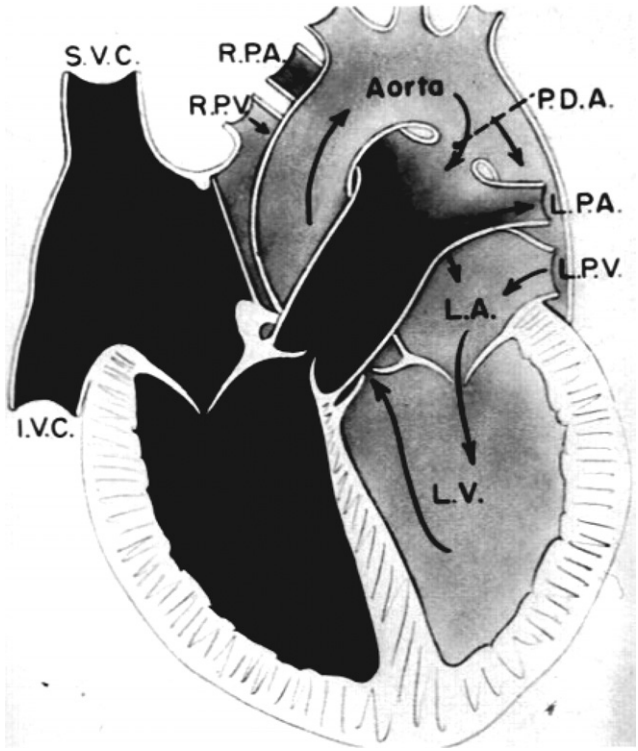

Figure 3 Patent ductus arteriosus. (Reproduced with permission from Moller J, Amplatz K, Edwards J: Congenital Heart Disease, Kalamazoo, MI, Upjohn, 1971. © Association of Pathologic Chairs/ Universities Associated for Research and Education in Pathology.)

the pulmonary curve, and a curve is generated that approximates the shape of the pulmonary curve. The area under this curve is proportional to pulmonary flow, Qp. This fitted curve is then subtracted from the initial time versus radioactivity curve, and another gamma variate fit is done on the remaining curve. The area under this second fitted curve is proportional to the shunt flow, Qsh. The difference between the 2 fitted curves is a measure of systemic flow, Qs. The resultant calculation of pulmonary to systemic flow, Qp/Qs, is performed as:

$$Qp/Qs = Qp/(Qp - Qsh)$$

Ratios less than 1.2:1 are consistent with the absence of left to right shunts. The Qp/Qs calculation, by the gamma variate method, has shown excellent correlation with shunt size determined at cardiac catheterization, over a clinically significant range of 1.2:1 to 3.0:1.[1] This relationship remains valid even in the presence of pulmonary hypertension, tricuspid regurgitation, and heart failure.[1,2] In these conditions, extensive dilution and slow flow lead to a slow downslope to the pulmonary curve. However, the upslope should be proportionately slowed and the curve fit method should generally apply. Nevertheless, caution should be exercised in these cases. Because the method is dependent on the full passage of the administered radionuclide through the lungs, left to right shunts will be overestimated in the presence of right to left shunts. Shunts greater than 3.0:1 are difficult to fit by the gamma variate method because of distortions in curve shape as a result of the large and torrential shunt flow. This is not a practical limitation, however, as any shunt greater than 3.0:1 is very large. In general, a shunt of 2.0 or greater is sufficient to warrant surgical correction.

With the anatomic detail provided by echocardiography, the hemodynamic correlates from Doppler examination, and the precise quantitation available from a radionuclide shunt study, it is sometimes possible to proceed directly to surgery without the necessity of preoperative cardiac catheterization. This is particularly true with uncomplicated patent ductus, and secundum atrial septal defect. In the situation of anomalous pulmonary venous return, the radionuclide determination of shunt size may be more accurate than that determined at catheterization by oximetric methods, due to the inability to obtain a good mixed venous blood sample at catheterization.[3] The radionuclide method has also been used to measure changes in shunt magnitude in response to oxygen therapy, to assess the reactivity of the pulmonary vascular bed, in patients with large shunts and pulmonary hypertension.[4] This is a very important consideration in determining operability in patients with moderate to large ventricular septal defects.

One of the leading indications for radionuclide shunt studies is the postoperative assessment of residual shunt size in patients with murmurs and echo Doppler evidence of persistent shunting after surgical correction of septal defects. Doppler quantification of shunt size is often not very reliable after patch closure of defects due to the turbulence generated

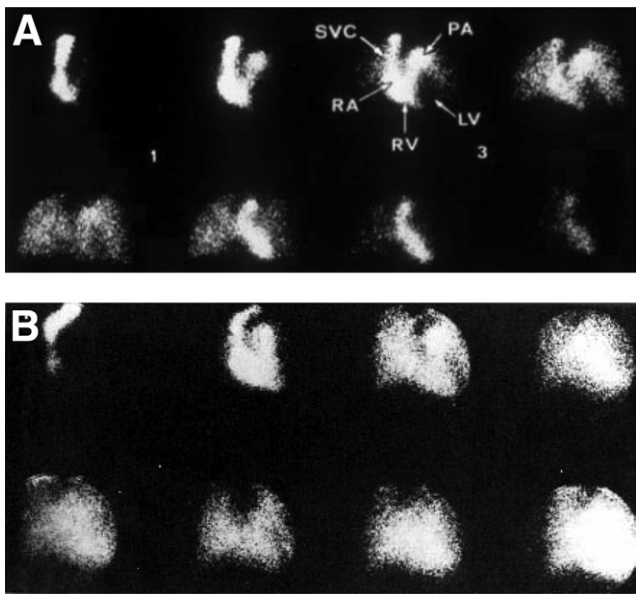

Figure 4 Radionuclide first-pass flow studies. Shown are radionuclide flow studies, progressing left to right in a patient without left-to-right shunt (A) and in a patient with left-to-right shunt (B). The absence of a levophase in the latter is consistent with a moderate-to-large shunt with a Qp/Qs >1.6. (Image A adapted from Treves S, Maltz D, Adelstein S: Intracardiac shunts, in James AE Jr, Wagner HN Jr, Cooke RE (eds): Pediatric Nuclear Medicine. Philadelphia, Saunders, 1974; image B adapted from Botvinick E, Schiller N, Shames D: The role of echocardiography and scintigraphy in the evaluation of adults with suspected left-to-right shunts. Circulation 62:1020, 1980.)

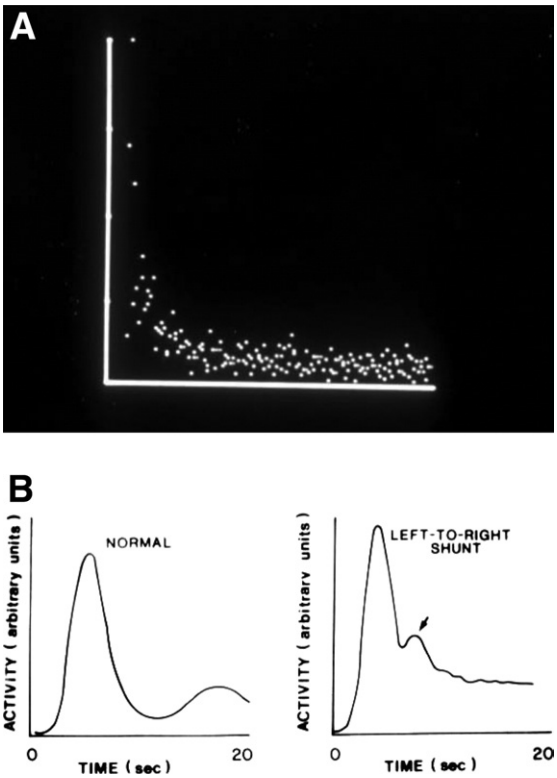

Figure 5 (A) Time–activity curve from a region over the superior vena cava. The bolus of radiotracer is adequate because it produced a single peak. (B) Pulmonary time–activity curves. Normal (left). Left-to-right shunt (right). (Reproduced with permission from Treves S, Royal H, Babchyck B: Pediatric nuclear cardiology, in Engle MA (ed): Pediatric Cardiovascular Disease. Philadelphia, PA, FA Davis, 1981, pp 247-274.)

in the vicinity of the patch. In this situation, the radionuclide technique has been helpful for assessing the need for repeat catherization and possibly reoperation.

It is possible to calculate the extent of left to right shunts using the equilibrium blood pool method. Stroke volume or

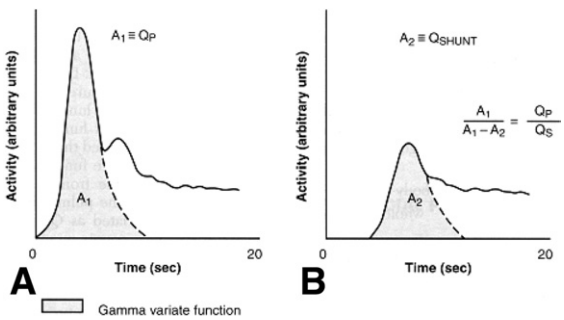

Figure 6 Calculation of pulmonary-to-systemic flow ratio (Qp:Qs) using pulmonary time–activity curves and the gamma variate model. (A) Area under the first pass of tracer through the lungs as defined by a gamma variate extrapolation. Qp, pulmonary flow. (B) Area under the portion of the curve corresponding to radiolabeled blood returning prematurely to the lung by the left-to-right shunt. Q shunt, shunt flow. A − B = Qs = systemic flow. (Reproduced with permission from Treves ST: Pediatric Nuclear Medicine. New York, Springer–Verlag, 1985.)

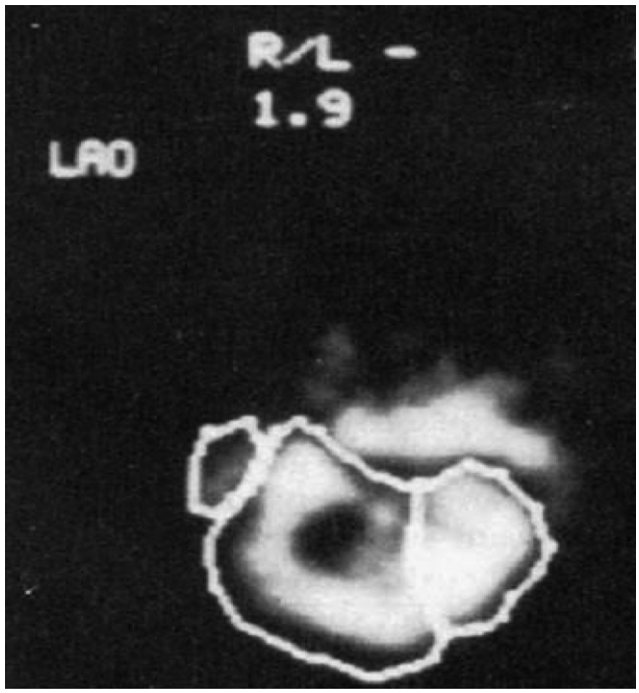

Figure 7 Amplitude images from the LAO projection from a patient with atrial septal defect. Note the increased amplitude (stroke volume) in the right ventricular region in the LAO projection. The amplitude ratio of the right ventricle to left ventricle, corrected for right atrial overlap with the right ventricle, is 1.9, similar to the measured Qp:Qs of 1.9.

amplitude images can be used to measure the difference in stroke volume between the ventricles, as is commonly performed for the evaluation of regurgitant lesions (Fig. 7).[5] With a ventricular septal defect or a patent ductus arteriosus, the left ventricle handles the excess volume of the shunt flow. The left ventricular stroke volume is proportional to the pulmonary blood flow, and the right ventricular stroke volume is proportional to the systemic blood flow. The pulmonary to systemic flow ration can be calculated as:

$$Qp/Qs = \text{LV stroke volume}/\text{RV stroke volume}$$

where, LV stroke volume equals LV end-diastolic volume minus end systolic volume, and RV stroke volume equals RV end-diastolic volume minus end systolic volume.

For an atrial septal defect, or anamolous pulmonary venous return, the right ventricle carries the excess shunt flow. The Qp/Qs can be calculated as:

$$Qp/Qs = \text{RV stroke volume}/\text{LV stroke volume}$$

A good correlation ($r = 0.79$) has been noted between the shunt Qp/Qs ratio calculated from stroke volume ratios and oximetry.[6] This approach may be particularly useful in situations where attempts at a good bolus injection were unsuccessful.

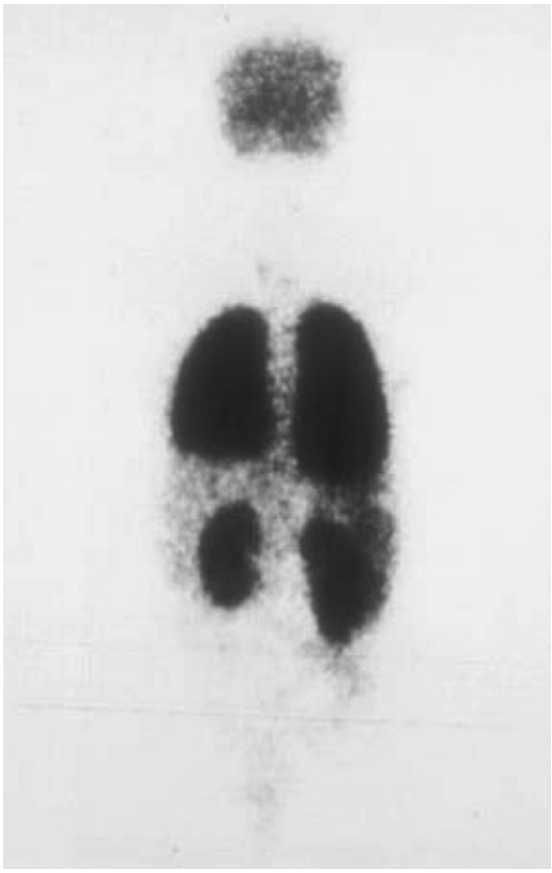

Figure 8 Shown is a posterior whole body image. Technetium-labeled MAA particles were injected intravenously and show localization to lungs, kidneys, and brain, indicating a right to left shunt.

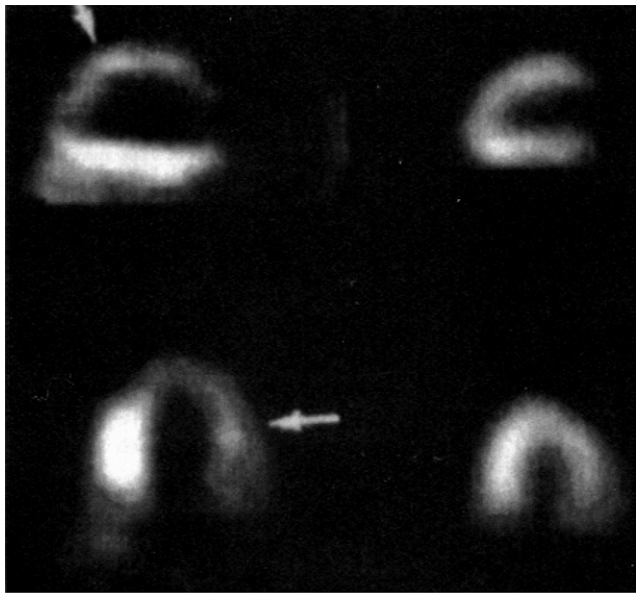

Figure 10 Shown are rest myocardial single-photon emission computed tomography thallium images from a 2-month-old infant presenting with a left coronary artery originating from the pulmonary artery. On the left are preoperative images showing markedly decreased perfusion to the anterior and lateral walls (arrows) and dilation of the left ventricle. Postoperative images on the right show almost complete normalization of perfusion and a dramatic reduction in the chamber size. (Reproduced with permission from Fernandes J, Rutkowshi M, Sanger JJ: Anomalous origin of the left coronary artery. Use of thallium perfusion scans in the evaluation of successful revascularization. Clin Nucl Med 17:177-199, 1992.)

Right-to-Left Shunt Evaluation

Right-to-left shunts can be detected by inspection of the first-pass radionuclide angiogram, which reveals a premature appearance of radioactivity in the left sided chambers or aorta. Time versus radioactivity curves generated from regions of interest over the carotid artery can be analyzed by curve fitting methods to quantify shunt size.[7] Intravenous injections of an inert radioactive gas, such as ^{133}Xe or krypton-81 month also can be used for detecting right-to-left shunts.[8] Significant systemic activity of these agents, which should be totally extracted by the lungs and exhaled in the alveolar gas, indicates shunting.

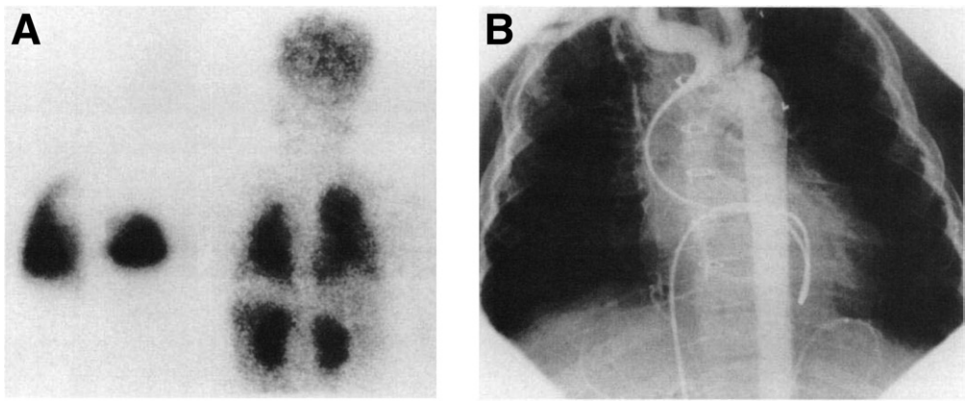

Figure 9 (A) Posterior view (after injection into arm vein on left, after injection into foot vein on right) of 8-year-old girl with dextrocardial after Glenn shunt and right Blalock-Taussig shunt. There is missing perfusion of the right upper lobe after tracer application into the right antecubital vein and hyperperfused right upper lobe after application into a foot vein. Right-to-left shunt volume from the inferior caval system was 61%. (B) Angiogram shows arterial collateral vessel originating from the descending aorta leading to the right upper lobe. (Adapted from Pruckmayer et al.[11])

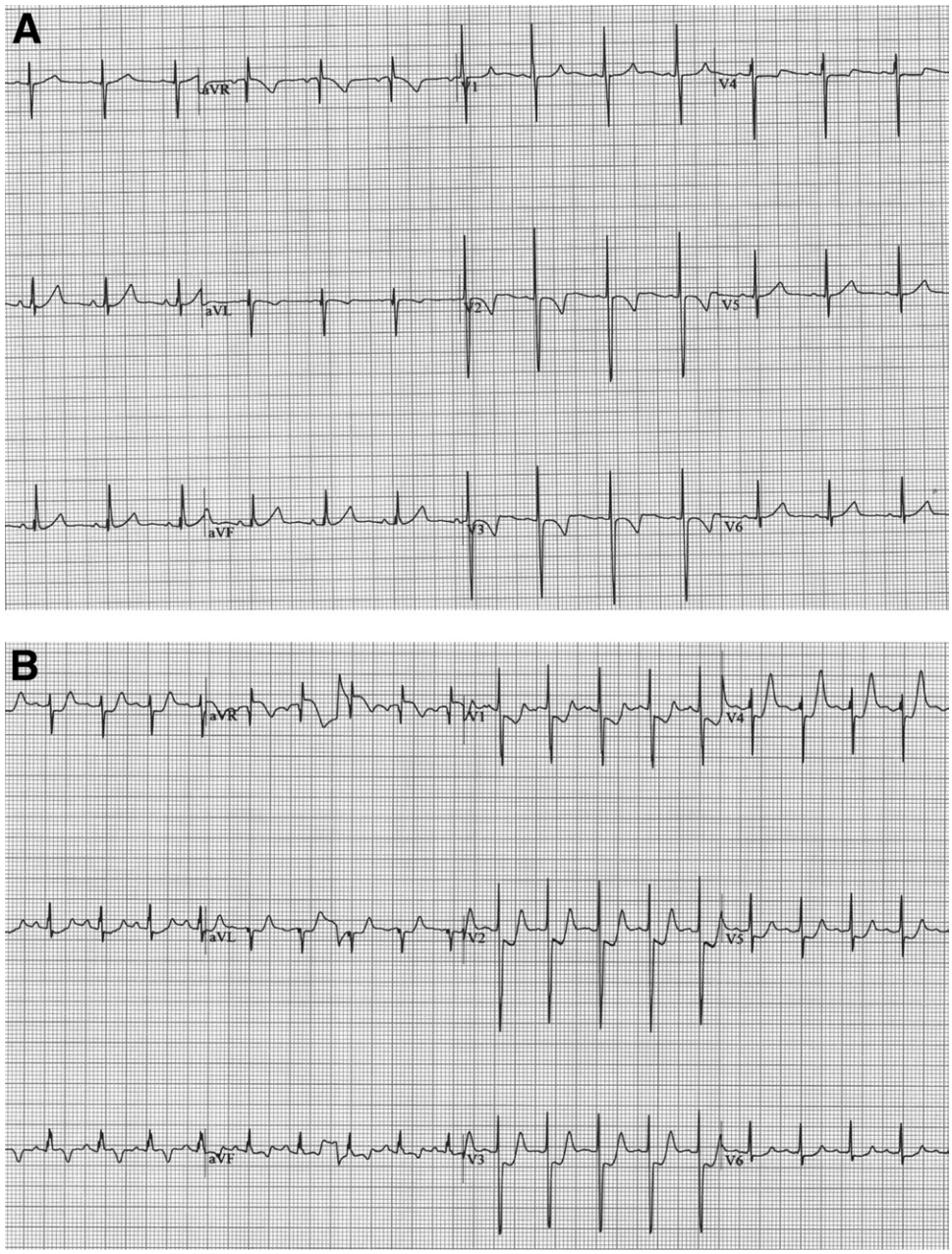

Figure 11 A 22-month-old s/p arterial switch procedure for D-transposition of the great vessels during the neonatal period. Recent catheterization showed possible stenosis of the left anterior descending coronary artery. A persantine myocardial perfusion was performed to assess myocardial perfusion. (A) Baseline ECG shows right ventricular hypertrophy with normal ST and T waves. (B) Postpersantine ECG shows marked ST-segment changes consistent with ischemia. (C) Stress images show severe reduction in myocardial perfusion at the anterior and apical regions of the myocardium, with normal perfusion at rest, consistent with ischemia in the left anterior descending artery territory. The right ventricle shows prominent activity consistent with right ventricular hypertrophy. The patient underwent patch plasty of the stenosed left anterior descending artery with subsequent clinical improvement. (ECGs provided by Kathy Lenihan, NP, University of California at San Francisco.)

The easiest and most commonly used method is the intravenous injection of ^{99m}Tc-labeled macroaggregated albumin (MAA) particles, similar to those used for the assessment of pulmonary perfusion.[9] In the absence of right-to-left shunting, all of the particles are trapped in the lungs. When right-to-left shunting occurs at any level, particles will enter the systemic circulation in proportion to the shunt flow, lodging in the capillary and precapillary beds of systemic organs (Fig. 8). A series of whole-body images are taken to determine the percentage of right-to-left shunt as:

$$(\text{whole body counts} - \text{lung counts})/\text{whole body counts}$$

Pulmonary to systemic flow ratio can be calculated as:

$$Qp/Qs = \text{lung counts}/\text{whole body counts}$$

A variation of this method is useful for assessing Qp/Qs in admixture lesions, where complete mixing of pulmonary and systemic blood occurs in one cardiac chamber. Images in Figure 8 were obtained from a 16-year-old cyanotic patient who presented with a history of pulmonary atresia with intact ventricular septum, and hypoplastic tricuspid valve. He received a Waterston aortic to right pulmonary artery shunt as a child. In addition, a left subclavian to central pulmonary shunt (Blalock-Taussig) was done, with flow primarily to the left lung. The procedure was done to assess the patency of the shunts.

Although technically there is a left-to-right shunt of blood from the aorta to pulmonary artery, the major hemodynamic abnormality in this cyanotic lesion is complete admixture of systemic venous and pulmonary venous blood at the level of the left atrium. Both pulmonary and systemic blood arise from the aorta. Note the presence of brain and kidney uptake, which is

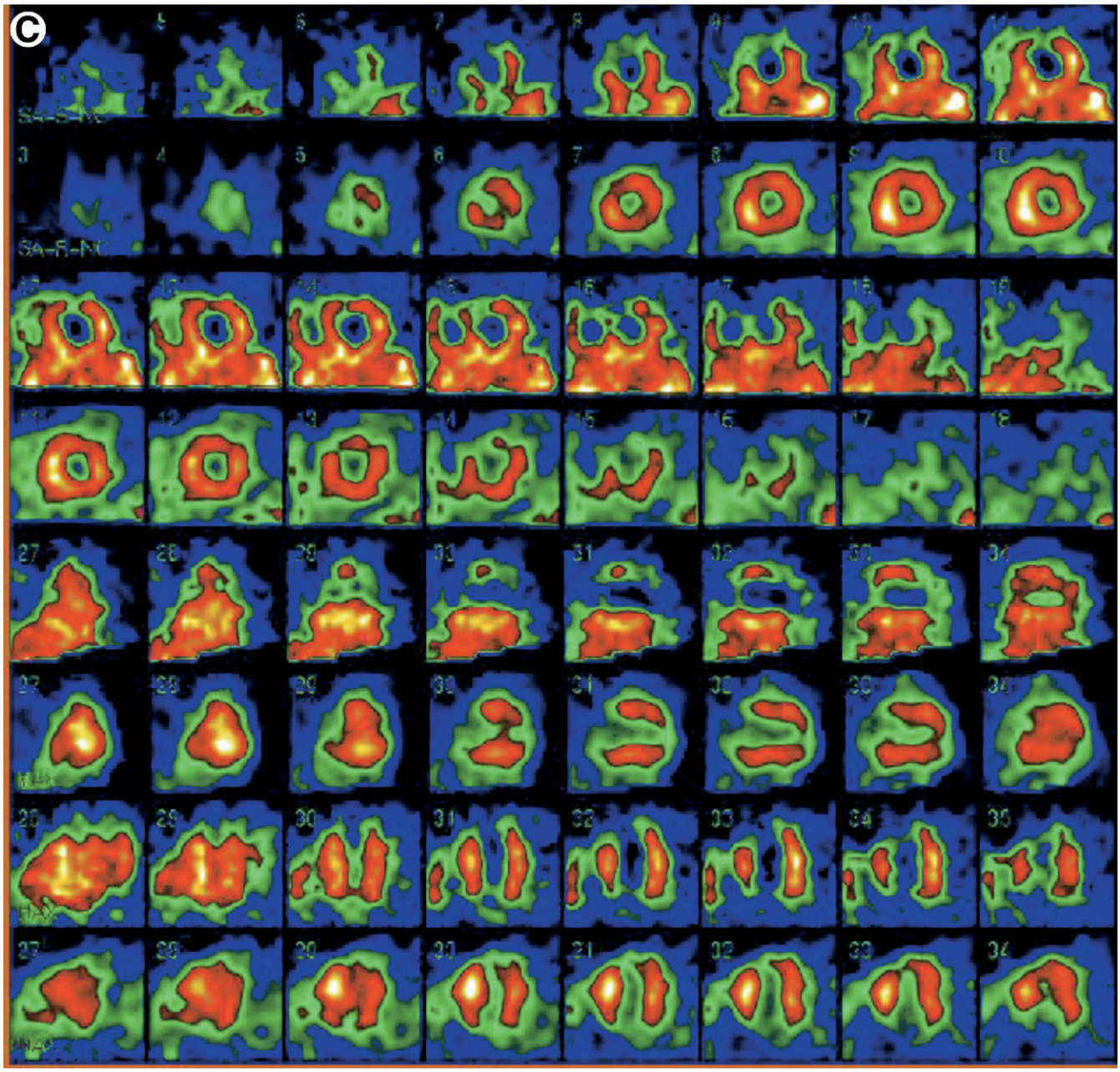

Figure 11 (continued)

consistent with right-to-left shunt. In this example, differential pulmonary perfusion was measured by determining relative counts in both lungs. Left lung activity represented 45% of total lung activity, whereas right lung activity was 55% of total. These findings suggested that both the Waterston and Blalock-Taussig shunts were functioning. Additional important data were obtainable from this MAA study. The pulmonary to systemic flow ratio, Qp/Qs, was calculated as: Qp = lung counts, Qs = whole body counts minus lung counts. This formula is applicable because the patient has an admixture lesion. There is complete mixing of the particles by the time the injected dose reaches the aorta. The particles are subsequently distributed in proportion to regional blood flow to the lungs and the body. The pulmonary/systemic flow ratio, Qp/Qs, is a very important determinant of systemic arterial oxygen saturation in patients with admixture lesions.[10] In the example shown above, the Qp/Qs was 1.6. This modest ratio suggested that pulmonary flow was not excessive, and increased systemic saturation would likely result with a slightly larger degree of pulmonary blood flow, ie, a larger Qp/Qs.

Despite the general reluctance to administer particles to patients with known right-to-left shunts, the method has proven to be safe, accurate, and very easy to perform.[9] The particle number should be kept <50,000 in pediatric patients.

The microparticle study is very useful for visualizing maldistribution of pulmonary blood flow after surgery for con-

genital heart disease. Pruckmayer and coworkers[11] studied 46 patients (mean age 8.2 yrs) with complex cardiac anomalies who had undergone either a Glenn shunt, or Fontan Procedure. Glenn Shunt and Fontan procedures may be associated with abnormal pulmonary flow patterns and the development of pulmonary AV fistula.[11] Imaging was done after sequential injections of ^{99m}Tc-microspheres into upper and lower limb veins. In 31 of 46 patients, blood flow from the superior vena cava (arm injection) drained preferentially to the right lung, whereas blood flow from the inferior vena cava (foot injection) drained equally to both lungs (Fig. 9). Lung perfusion scintigraphy after upper- and lower-extremity injections detected more abnormal pulmonary flow patterns than contrast echo. In addition, the technique was able to quantify right-to-left shunt volumes individually from the superior and inferior vena cava, a unique attribute compared with any other imaging method. Quantitative assessment of relative pulmonary perfusion before and after percutaneous intervention for peripheral pulmonary artery stenosis[12] has become one of the most commonly ordered scintigraphic procedures for cardiovascular assessment in pediatric patients in our practice.

Assessment of Ventricular Function

Although radionuclide methods are well suited for the assessment of ventricular size and function in congenital heart lesions, these methods have been largely replaced by echocardiography in current clinical practice. Both first-pass and gated equilibrium methods for the determination of ejection fraction have been validated in the pediatric age group.[13,14] Quantitative assessment of absolute ventricular volumes[15] and determination of regurgitant fraction have been reported in children as well.[16,17] For infants, the imaging is optimized with the use of a converging collimator to improve spatial resolution and increase the sensitivity. It is feasible to measure ejection fraction even in tiny premature infants with the use of the pinhole collimator.[18] Ventricular size and function evaluation is useful at rest and with dynamic stress in a variety of congenital lesions, both before and after surgical correction.[19,20] Residual structural and functional abnormalities are very common and careful, long-term follow-up is important.

Assessment of Myocardial Perfusion

Myocardial perfusion scintigraphy has been used for clinical assessment in children for a number of years.[21,22] In the pediatric patient, perfusion imaging has been most widely used for the noninvasive identification of anomalous left coronary artery.[23-26] To evaluate patients for possible anomalous left coronary artery, a perfusion tracer is injected intravenously, at rest, and images are acquired in multiple planar projections, or single-photon emission computed tomography imaging is done. The usual anatomy in this rather rare disease is for the left main coronary artery to arise from the main pulmonary artery. This situation can lead to regional ischemia and infarction of the left ventricle as the result of low perfusion pressure from the pulmonary artery, which can create a coronary steal. Perfusion scintigraphy typically reveals a segmental perfusion abnormality at rest (Fig. 10). This pattern is useful for identifying anomalous left coronary as opposed to myocarditis or cardiomyopathy as the etiology for poor ventricular function in infants. The condition is often associated with Q-waves on the electrocardiogram. Echocardiography is sometimes able to identify the aberrant origin of the left coronary; however, catheterization is required for confirmation. Multidetector computed tomography (CT) has shown promise for the noninvasive detection of anomalous origins of coronary arteries.[27,28] Direct aortic implantation of the anomalous coronary artery is the preferred approach to surgical correction.[29,30]

Another clinical condition for which perfusion scintigraphy may be useful is Kawasaki disease, or the mucocutaneous lymph node syndrome.[31] This syndrome is associated initially with persistent fevers, rash, adenopathy, and mucus membrane abnormalities. Before the introduction of intravenous gamma globulin therapy, as many as 20% of these patients developed aneurysms of the coronary arteries. Treatment with gamma globulin within 10 days of the onset of the illness reduces the frequency of coronary aneurysms to approximately 4%. Approximately 30% to 50% of such aneurysms will spontaneously regress within the first 2 years of illness. The remaining aneurysms may later thrombose and cause myocardial ischemia and infarction.[32,33] Bypass surgery has been advocated for some patients with objective evidence of ischemia.[34]

Assessment of myocardial perfusion is important in the evaluation and follow-up of patients with transposition of the great vessels that have undergone the arterial switch procedure.[35,36] Transposition of the great arteries is a lethal congenital malformation and represents the most common cardiac cause of cyanosis in the neonate. Historically, left untreated, as many as 90% of infants with the condition died within the first year of life.[37] The prognosis for these infants, however, has been remarkably improved with the introduction of palliative and corrective surgical techniques. Among the earliest and most successful surgical procedures is a physiological correction of the circulation by redirecting the pulmonary and systemic venous returns to the appropriate ventricles using intra-atrial baffles (Mustard or Senning Procedure).[37] This atrial switch operation has met with great success in the early operative period, and survival rates at 10 and 20 years postoperatively of 90% and 80%, respectively.[37] Enthusiasm for this approach has been dampened somewhat because of concerns that the right ventricle may be unable to function successfully as the systemic ventricle for long periods of time.

Anatomic correction of transposition is now commonly performed.[38] The procedure consists of switching the great vessels to the proper ventricles and reimplantation of the coronary arteries to the newly formed aorta. The morphologic left ventricle then becomes the systemic pumping chamber for which it is better suited. Although technically demanding, the procedure is best performed during the neonatal period, before the regression of left ventricular mass as a result of the progressive decrease in pulmonary vascular

resistance that occurs after birth. Alternatively, the left ventricle can be conditioned to accept the high systemic vascular resistance by performing pulmonary banding as an initial procedure. Concerns have been raised since the inception of the arterial switch procedure about the possibility that distortion or growth failure of the newly implanted coronary arteries may result in myocardial ischemia and possibly infarction.

Some studies suggest that coronary artery manipulation and reimplantation do not result in late myocardial perfusion abnormalities, at least in those infants with successful initial results.[38] However, large perfusion abnormalities have been seen in the territories of stenosed coronary arteries after the switch procedure (Fig. 11).

Conclusion

Echocardiography, MRI and, more recently, multidetector CT, have lead to major advances in noninvasive image assessment of anatomy in pediatric cardiology. The radionuclide methods often lack sufficient resolution to precisely characterize complex morphology in congenital heart lesions. However, these methods provide accurate and reproducible quantitative assessment of the physiological consequences of structural heart disease. These unique capabilities will continue to assure ongoing clinical relevance of radionuclide methodology, as is the case in the assessment of heart disease in adult cardiology.

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