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Myocardial perfusion imaging in pediatric cardiology

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Myocardial perfusion imaging (MPI) is an important procedure in pediatric cardiology in terms of evaluating myocardial ischemia, infarction and damage associated with various congenital or acquired heart diseases, such as Kawasaki disease, anomalous origin of the left coronary artery from the pulmonary artery and complete transposition of the great arteries after arterial switch surgery. This type of imaging can detect myocardial damage in the morphological right ventricle when it functions as a systemic pumping chamber in patients with complex congenital heart diseases after intra-cardiac repair. Myocardial perfusion imaging can also evaluate myocardial damage associated with primary or secondary cardiomyopathy in children. The magnitude of increased right ventricular uptake on MPI is a useful noninvasive means of estimating right ventricular pressure overload due to congenital heart or pulmonary diseases. This article reviews myocardial perfusion tracers and pharmacological stress tests used to diagnose heart conditions in children, and the current clinical roles of MPI in pediatric cardiology.

Key words: radionuclide imaging; myocardial perfusion; Kawasaki disease; heart defects, congenital

INTRODUCTION

STRESS-INDUCED MYOCARDIAL ISCHEMIA, infarction and damage associated with various congenital or acquired heart diseases, as well as myocardial damage associated with primary or secondary cardiomyopathy in children can be evaluated by MPI. The magnitude of increased right ventricular uptake on MPI is a useful noninvasive means of estimating right ventricular pressure overload due to congenital heart or pulmonary diseases.

RADIOPHARMACEUTICALS FOR USE IN PEDIATRIC MPI

The radiopharmaceuticals used in MPI to diagnose children and adults include thallium-201 (^{201}Tl) and technetium-99m (^{99m}Tc)-labeled tracers, such as methoxy-isobutyl-isonitrile (MIBI) and tetrofosmin. Since ^{99m}Tc-labeled tracers have a relatively short half-life and emit photons of energy that are ideal for gamma camera imaging, ^{99m}Tc-labeled tracers for pediatric use confer advantages such as improved image quality and radiation dosimetry compared with ^{201}Tl.[1] Indeed, the reported absorbed radiation dose per equivalent injected dose of ^{99m}Tc-MIBI or ^{99m}Tc-tetrofosmin by the genitals in children is from 0.1–10% less than that of ^{201}Tl[2] (Table 1). Lower attenuation of photons from the left ventricular inferoposterior and posteroseptal walls in adults is another benefit of ^{99m}Tc-labeled tracers compared with ^{201}Tl. However, this advantage is not apparent in children, since the attenuation effects on left ventricular tracer activity are negligibly small in pediatric patients. The key disadvantages of ^{99m}Tc-labeled tracers in pediatric myocardial imaging might be associated with slow liver clearance and a subsequently significant amount of hepatic tracer accumulation (Fig. 1). Dipyridamole or adenosine further augments hepatic tracer accumulation in children undergoing MPI. Thus, after infants or young children are injected with ^{99m}Tc-labeled tracers, at least 60 and sometimes over 90 minutes must elapse before rest or pharmacological stress images can be acquired, to minimize hepatic activity. One hour is usually sufficient to avoid marked hepatic activity among children over 10 years of age.

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Table 1 Radiation dose to pediatric patients from radiopharmaceuticals for myocardial perfusion imaging

		Absorbed dose per unit activity administrated (mGy/MBq)			
		1 year	5 years	10 years	15 years
Tc-99m-MIBI	Heart	3.0E – 02	1.8E – 02	1.2E – 02	8.2E – 03
	Testes	2.1E – 02	1.1E – 02	7.5E – 03	5.0E – 03
	Ovaries	4.5E – 02	2.5E – 02	1.8E – 02	1.2E – 02
	Thyroid	4.5E – 02	2.4E – 02	1.2E – 02	7.9E – 03
	Kidney	1.5E – 01	8.5E – 02	5.9E – 02	4.3E – 02
	Effective dose (mSv/MBq)	5.3E – 02	2.8E – 02	1.8E – 02	1.2E – 02
Tc-99m-Tetrofosmin	Heart	2.3E – 02	1.3E – 02	8.4E – 03	5.6E – 03
	Testes	1.3E – 02	7.4E – 03	5.0E – 03	3.2E – 03
	Ovaries	3.7E – 02	2.2E – 02	1.5E – 02	1.0E – 02
	Thyroid	5.0E – 02	2.7E – 02	1.3E – 02	8.6E – 03
	Kidney	5.8E – 02	3.4E – 02	2.3E – 02	1.7E – 02
	Effective dose (mSv/MBq)	4.3E – 02	2.2E – 02	1.3E – 02	9.6E – 03
Tl-201	Heart	1.1E + 00	6.2E – 01	3.9E – 01	2.6E – 01
	Testes	1.3E + 01	9.6E + 00	8.3E + 00	1.1E + 00
	Ovaries	8.3E + 00	3.5E + 00	2.0E + 00	6.2E – 01
	Thyroid	2.3E + 00	1.2E + 00	5.4E – 01	3.5E – 01
	Kidney	2.2E + 00	1.2E + 00	8.2E – 01	5.8E – 01
	Effective dose (mSv/MBq)	2.8E – 01	1.7E + 00	1.2E + 00	3.0E – 01

According to ICRP publication 80, Radiation dose to patients from radiopharmaceuticals

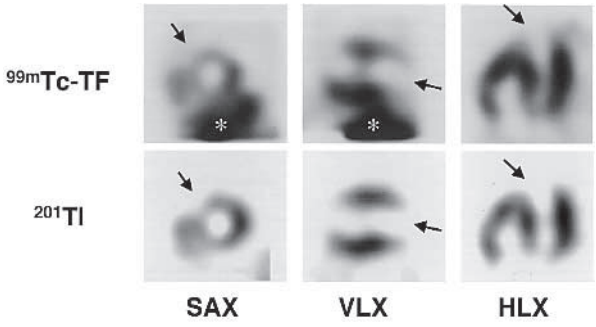

Fig. 1 Resting myocardial perfusion SPECT from a one-year-old patient with tetralogy of Fallot after Rastelli operation. Both ^{99m}Tc-tetrofosmin (TF, *upper panel*) and ^{201}Tl (*lower panel*) images show an apical and anteroseptal perfusion defect (*arrows*) due to total occlusion of the left anterior descending artery documented by coronary angiography. Note dense hepatic accumulation (*asterisk*) in ^{99m}Tc-tetrofosmin images acquired 60 minutes after injection of the tracer. Right ventricular uptake is abnormally increased due to right ventricular outflow tract obstruction. SAX, short axis; VLX, vertical long axis; HLX, horizontal long axis.

CARDIAC STRESS TEST FOR CHILDREN: METHODS AND SAFETY CONSIDERATIONS

Pediatric patients often undergo stress MPI by pharmacological, rather than exercise stress testing. The latter type of testing in this population is difficult to accomplish because instruments such as the bicycle ergometer, are not appropriately designed for children, and their ability to voluntarily cooperate in accomplishing maximal exercise is too limited to disclose abnormal coronary flow reserve. In addition, since exercise capacity significantly changes with physical growth during childhood, serial evaluation using exercise stress might prove difficult. Perfusion defects are more obviously induced by pharmacological stress than by exercise stress when compared in the same patients with Kawasaki disease.[3] Thus, pharmacological stress might be more appropriate than exercise stress in children when trying to identify coronary arterial stenosis,[3] or serial evaluation of the same child while observing the progression of coronary stenosis.[4] In contrast, exercise stress might be more suitable when evaluating patients with various exercise-related abnormalities, such as positive ischemic changes on exercise ECG, documented coronary arterial stenosis, or those under anti-ischemic medication to prevent exercise-induced myocardial ischemia. Exercise stress can be recommended for patients who have undergone coronary bypass surgery, since the false-positive rates of exercise MPI to identify bypass insufficiency are significantly lower than those obtained with pharmacologic stress in adults.[5] Consequently, stress methods for MPI in children should be individualized and adjusted according to the clinical purpose and conditions. Children can undergo the same type of pharmacological stress testing as adults, using dipyridamole, adenosine, or dobutamine.

Pharmacological stress for MPI in children has been accomplished by infusing 0.56 mg/kg of dipyridamole intravenously over four minutes,[6–8] or by adding 0.14 mg/kg/minute for one minute after the initial infusion is complete (total 0.70 mg/kg).[3,4,9–11] In both protocols,

Fig. 2 ^{99m}Tc-sestamibi myocardial SPECT images from a 20-year-old woman with Kawasaki disease. Exercise-induced reversible perfusion defects were observed at anteroseptal and inferoposterior walls. Subsequent selective coronary angiography indicated complete occlusion of the left anterior descending and right coronary arteries.

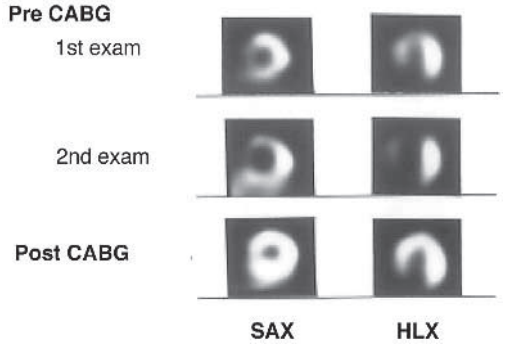

Fig. 3 Serial evaluations of a patient with Kawasaki disease by dipyridamole-stress ^{201}Tl myocardial SPECT. Images of the first examination (*upper panel*) indicate mild perfusion abnormalities at the septal and apical regions. On the second examination performed one year and 10 months later (*middle panel*), MPI documented worsening of the degree and extent of perfusion defects at in anteroseptal and apical regions. After the second examination, coronary arterial bypass graft surgery was performed, and myocardial perfusion became normal (*lower panel*).

heart rates after dipyridamole infusion significantly increase compared with those before stress, and systolic blood pressure either does not change or slightly decreases (maximally by 20 mmHg).[3,6,8,12–14] In contrast to the elderly, dipyridamole seldom induces extreme hypotension in children. Significant ST segment depression on ECG and anginal chest pain are sometimes experienced in patients with significant coronary arterial stenosis. Although other adverse effects of the dipyridamole test in children include abdominal pain, headache, flushing, nausea, and vomiting even in those without coronary stenosis, they are usually abolished soon after the administration of 3–5 mg/kg of aminophylline.[3,8,9] We routinely apply aminophylline for one minute after injecting myocardial perfusion tracers under dipyridamole stress, since possible prolonged myocardial ischemia after the end of the test might be difficult to identify, especially in infants and small children. An absolute contraindication for the dipyridamole test is children under treatment for active bronchial asthma. Patients with a history of bronchial asthma several years before who are not currently experiencing attacks and who are not taking medication can safely undergo this test. Other contraindications for the dipyridamole test might include symptomatic infants and young children with severe congenital abnormalities of the left main coronary artery that include anomalous origin of the left coronary artery from the pulmonary artery, and ostial atresia of the left coronary artery. Perfusion abnormalities are usually profound at rest in patients with angiographically documented, severe left main disease. Provoking myocardial ischemia in these patients might prove to be of minimal clinical value since the disease could deteriorate even as far as death. Myocardial viability determined by resting MPI might thus be more informative for such patients.

Adenosine can be continuously infused into children i.v. at a dose of 0.14 mg/kg/min for four to six minutes (total amount of 0.56 to 0.84 mg/kg).[15–18] A similar amount of adenosine triphosphate is used in Japan, since adenosine itself has not yet been approved for clinical use.[19] Significant increases in heart rates are associated with adenosine infusion, but without obvious changes in blood pressure.[16–18,20] The major adverse effects include flushing in about 50% of patients, as well as shortness of breath and headache. These signs and symptoms disappear within one minute after the infusion is stopped, and adenosine can be used safely in pediatric patients.[20]

Dobutamine can be administered to children for MPI as well as multi-gated blood pool angiography, starting as a continuous drip of 5 μg/kg/min, with incremental increases of the same amount every three to five minutes, up to a maximum of 15 to 30 μg/kg/min.[21–23] Heart rates and blood pressure increase with dobutamine administration, which is sometimes associated with premature ventricular contraction or supra-ventricular tachycardia.[23]

DIAGNOSIS OF MYOCARDIAL ISCHEMIA BY STRESS MPI IN CHILDREN

The diagnostic accuracy of stress MPI in identifying myocardial ischemia in children has mainly been studied in patients with Kawasaki disease[3,4,7,9–11,24] (Fig. 2). Stress MPI can also monitor the appearance or aggravation of myocardial ischemia, and evaluate the effects of coronary arterial intervention (Fig. 3). Table 2 summarizes current reports describing the diagnostic accuracy of stress MPI in Kawasaki disease. The results indicated that pharmacological or exercise stress MPI can detect angiographically proven significant coronary stenosis at about 70% to 90% sensitivity. Stress MPI can identify single coronary vessel stenosis in Kawasaki disease more accurately than exercise stress ECG, which is only about 15% sensitive.[10] On the other hand, specificity varies from 33% to 100%

Table 2 Diagnostic accuracy of stress-myocardial perfusion imaging for identifying a coronary arterial stenosis due to Kawasaki disease

Tracer	Stress method	Interpretation	Subject number	Sensitivity (%)	Specificity (%)	Reference
Tl-201	dipyridamole	visual	38	80	100	10
Tc-99m tetrofosmin	dipyridamole	visual	86	90	100	11
Tl-201	dipyridamole	visual	49	91	60	3
		quantitative	49	88	93	3
Tl-201	dipyridamole	visual	54	79	—	9
Tl-201	exercise	visual	23	73	58	24
Tl-201	dipyridamole	visual	34	71	33	7

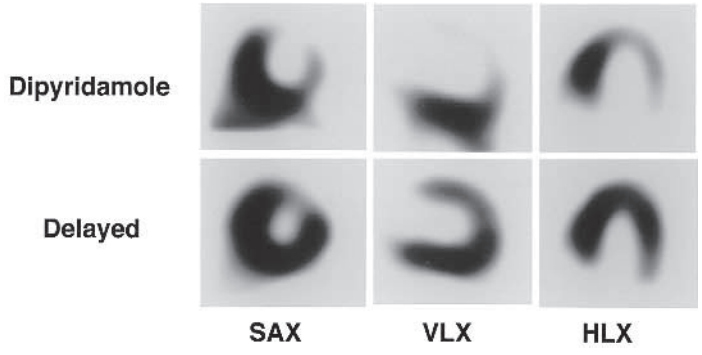

Fig. 4 Dipyridamole-stress ^{201}Tl myocardial SPECT of a 12-year-old boy with anomalous origin of the left coronary artery from the pulmonary artery. Stress-induced reversible perfusion defects are obvious at the anterior and lateral walls of the left ventricle. On delayed images, redistribution is complete at the anterior and lateral walls, but incomplete at the anterolateral wall.

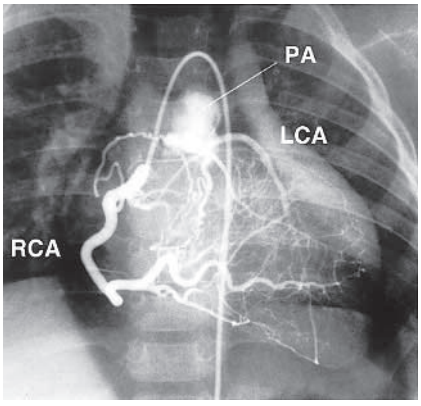

Fig. 5 Selective right coronary angiogram of a patient with anomalous origin of the left coronary artery from the pulmonary artery. Injection of contrast medium demonstrates the right coronary artery (RCA), collaterals, and retrograde filling of the left coronary artery (LCA) and main pulmonary artery (PA).

across studies. The approximately 60% median value of specificity determined from visual analyses of stress MPI suggests that the false positive rate is relatively high.

Several mechanisms might be related to the relatively high false positive rate in pediatric stress MPI. Artifacts due to unexpected patient motion during acquisition of MPI might be one of the factors generating false positive results. We routinely continuously watch the motion of pediatric patients during acquisition of images with the co-operation of their guardians. We also induce complete sedation by using intravenous administration of sedative drugs (such as midazolam and/or pentobarbital) for those under the age of 5 years. Another factor might be related to the fact that the normal distribution pattern of myocardial perfusion in the left ventricle is substantially different between children and adults. In children, the anterolateral wall shows the lowest activity in the left ventricle,[3] probably due to negligibly small attenuation effects on left ventricular inferoposterior and posteroseptal walls, and reversal effects of scattered photons from hepatic tracer activity on these walls. Effects of breast attenuation are quite obvious in adolescent females, which are sometimes found as mild or even moderate perfusion abnormalities at the antero-apical regions. Differentiation of these artifacts from true perfusion abnormalities can be accomplished by noticing reversibility of the abnormality between stress and resting images. Combined use of ECG-gated SPECT is also useful to distinguish true and false positive perfusion defects by analyzing left ventricular wall motion.

Another value of stress MPI might be related to the stratification of cardiac risk. A report by Miyagawa et al. has shown that the presence of reversible perfusion defect on dipyridamole-stress MPI is a powerful predictor of cardiac events during the chronic stage of Kawasaki disease.[8] Follow-up (mean, 8.8 ± 1.2 years; range, 8 to 14 years) of 90 patients under long-term aspirin therapy identified 15 cardiac events (1 death, 5 infarctions, 7 unstable anginas, and 2 coronary bypass surgeries). The event-free rate at 12 years after stress MPI was only about 40% in 27 patients with reversible defect, in contrast to 98% in 63 without reversible defects. The presence of a reversible defect was the best predictor of a late cardiac event in multivariate analyses of various clinical and scintigraphic variables, and the number of aneurysms on coronary angiography contributed minimally.[8] These

results indicated that reversible defects on stress MPI can stratify patients with Kawasaki disease according to the likelihood of future ischemic cardiac events (death, infarction and unstable angina).

We recently evaluated the effects of long-term beta-blocker therapy on ischemic cardiac events in patients with Kawasaki disease at high risk. We administered propranolol for 8.7 ± 4.8 years (range, 0.9–16.3 yrs) to 51 patients who had reversible defects on stress MPI. The severity of coronary artery obstructive disease (evaluated as the number of stenotic vessels per patient, and the ratio (%) of ischemic myocardium to the whole left ventricle) did not significantly differ from those under aspirin therapy in the study by Miyagawa referred to above. We found an 89% ischemic event-free rate at 15 years after initiating propranolol therapy, suggesting that the long-term administration of propranolol can minimize ischemic cardiac events associated with Kawasaki disease in high risk patients.

APPLICATION OF MPI FOR CONGENITAL HEART DISEASE

Anomalous origin of left coronary artery arising from the pulmonary artery (ALCAPA)

In this rare congenital anomaly, which usually appears as the only lesion, the right coronary artery arises normally while the left coronary artery arises from the pulmonary artery. This condition usually clinically manifests as angina-like episodes, acute myocardial infarction, mitral regurgitation and congestive heart failure during early to mid infancy. Very young children can be asymptomatic and the condition is uncovered in older children and adults only through abnormal ECG findings or other signs, including sudden death. Since ALCAPA can be diagnosed through echocardiography followed by selective coronary angiography, MPI can be performed at rest before surgical correction of myocardial damage to assess myocardial viability in infants, or to assess stress induced myocardial ischemia in older children and adults.

Myocardial perfusion abnormalities are mostly localized at the high lateral, anterior and lateral walls in ALCAPA (Fig. 4). Such distribution might be useful in distinguishing this disorder from congestive cardiomyopathy in infants.[25] In many infants with ALCAPA, extensive perfusion abnormalities are more frequent at the apical and inferior walls. These characteristic features reflect the pathophysiology of ALCAPA, in which the left main coronary territory is perfused in retrograde fashion via collateral circulation from the right coronary artery (Fig. 5). Thus, the myocardium becomes damaged at the part of the left coronary artery that receives unoxygenated blood at a low perfusion pressure, which is most severe around the proximal left main artery.

Reimplantation of the left coronary artery into the aorta is the current standard surgical procedure for correcting

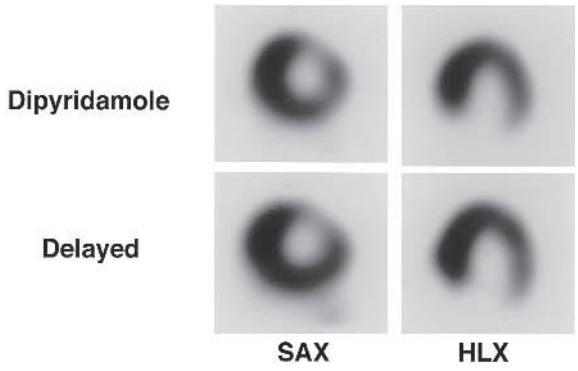

Fig. 6 Dipyridamole-stress ^{201}Tl myocardial SPECT from the same patient as in Figure 4, performed 18 days after reimplantation of the left coronary artery into the aorta. Reversible mild perfusion abnormality is found at the lateral wall. Of note, some degree of reverse-redistribution was observed at the anterolateral wall, suggesting viable but damaged myocardium under successful revascularization of left coronary territories. A following dipyridamole-SPECT study performed 10 years later showed only mild fixed perfusion abnormality at the anterolateral wall (figures not shown).

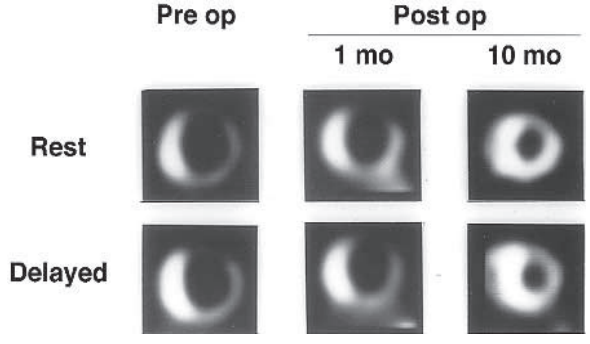

Fig. 7 Resting and delayed ^{201}Tl myocardial SPECT of an infant with anomalous origin of the left coronary artery from the pulmonary artery. Before operation, at six months of age, moderate to severe perfusion defects were observed at the anterior, lateral, and inferior walls on the initial image (*left upper*), and incomplete redistribution at the lateral and inferior walls on the delayed image (*left lower*), associated with severely depressed left ventricular ejection fraction of 31% determined by contrast ventriculography. One month after reimplantation of the left coronary artery into the aorta, myocardial perfusion improved at the lateral and inferior walls, associated with mild reverse-redistribution at the lateral wall (*middle panel*). Ten months after the surgery, myocardial perfusion improved dramatically at the anterior, lateral, and inferior walls, associated with significant reduction of the left ventricular cavity size (*right panel*). Left ventricular ejection fraction at this time was normalized to 66%.

ALCAPA. Other studies indicate that severe preoperative myocardial dysfunction continuously and obviously improves over 1 year after surgery.[26] Some degree of fixed or reversible perfusion abnormalities frequently persist even after successful coronary reimplantation. This might

be due to preoperative myocardial damage and persistent microvascular dysfunction after surgery (Fig. 6). Hurwitz et al. found that a preoperative left ventricular ejection fraction of 0.37 ± 0.16 increases to 0.67 ± 0.07 after surgery.[27] In this regard, myocardial viability determined by MPI might be useful when considering surgical indications for ALCAPA. Left ventricular function similarly improved in an infant with ALCAPA that we examined using thallium MPI at rest. The preoperative ejection fraction increased from 31% to 66% at five years after coronary reimplantation. We discovered a severe fixed perfusion defect at the anterior and anterolateral walls as well as a moderate perfusion abnormality with minimal redistribution at the lateral wall before surgery (Fig. 7). At one month after surgery, myocardial tracer uptake improved at the lateral wall, but the defect at the anterior wall did not improve significantly. Ten months later, myocardial perfusion further improved at both the lateral and anterior walls with a significantly reduced left ventricular cavity. These findings suggested that preoperative thallium MPI underestimates myocardial viability, presumably due to myocardial hibernation in the region of the left coronary artery that is perfused with unoxygenated blood after birth. Thus, the anomalous origin of the left coronary artery should be treated by reimplantation upon diagnosis even in those with severe permanent perfusion defects on MPI, since the condition can be surgically corrected during infancy.

Complete transposition of the great arteries after arterial switch

The arterial switch operation (ASO) is the current standard procedure for correcting transposition of the great arteries from early infancy and includes mobilization and reimplantation of the coronary arteries into the neo-aorta. Thus, the long-term success of this procedure depends on continued patency and adequate functioning of the coronary arteries, which can be compromised by kinking of the coronary artery or failed coronary arterial anastomosis. Several investigators have used MPI to identify myocardial perfusion in children after ASO.[28–30]

As in Kawasaki disease, proximal obstruction of the translocated coronary artery after ASO can be detected by stress induced perfusion defects on MPI (Fig. 8). In addition to the usual profile of stress induced, rest redistributed transient perfusion changes, Weindling et al. found reverse perfusion abnormalities in patients after ASO. These consisted of perfusion defects at rest that improved or disappeared after peak exercise stress.[30] They also noted that the most common location of perfusion defects was the apical lateral free wall of the left ventricle, which corresponded to the distal territories of the left coronary artery.[30] The grade of perfusion defects between rest and exercise was the same in 9.4%, and different at peak exercise in 17.7% of all left ventricular myocardial segments. Of segments with different grades

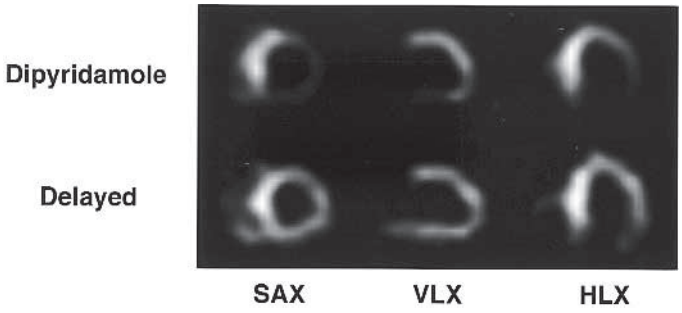

Fig. 8 Dipyridamole-stress ^{201}Tl myocardial SPECT of a 14-year-old male patient with complete transposition of the great arteries after arterial switch operation performed during the neonatal period. Reversible perfusion defects were observed at the lateral and inferoposterior walls, suggesting coronary arterial obstruction at the left circumflex and right coronary arteries.

between rest and exercise, perfusion improved in 79.2% and worsened in 20.8% with exercise.[30] Other studies have also indicated that perfusion abnormalities are less frequent in patients who underwent ASO as the primary type of repair in infancy than in those who underwent a two-staged repair with initial pulmonary arterial banding when they were older.[28,29] Hauser et al. also documented a perfusion abnormality at the myocardium supplied by the distal left coronary artery after ASO in a $^{13}NH_3$-PET study.[15] They found that adenosine induced perfusion defects at the anterior, anterolateral and lateral wall in 5 of 21 patients after ASO, with globally reduced coronary flow reserve in the left ventricle. None of the five patients had localized stenosis of the coronary artery on angiography. However, right coronary circulation perfusing the inferior, posteroseptal, and inferiorolateral left ventricular wall dominated in all patients, with a remarkably small contribution of the left anterior descending artery in the distal part.[15] We noted the same phenomenon using dipyridamole-stress thallium MPI in a patient after ASO (Fig. 9). Thus, perfusion scan abnormalities after ASO might reflect not only proximal coronary obstruction but also arteriolar or capillary pathophysiology with abnormal vasomotor tone at rest or in response to exercise or pharmacological stimuli. All of these effects might be exacerbated and apparent as perfusion defects at territories of the hypoplastic distal left coronary artery in patients after ASO.

Morphological right ventricle as systemic ventricle

In many patients with congenital heart diseases, the morphological right ventricle functions as a pumping chamber that maintains the systemic circulation after intracardiac repair. Survivors who underwent surgery two or three decades previously following atrial baffle repair for simple complete transposition of the great arteries are included in this category. Among patients with a functionally univentricular heart repaired by Fontan type

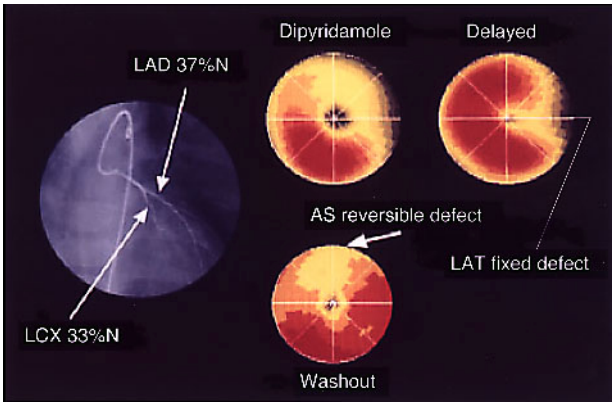

Fig. 9 Dipyridamole-stress ^{201}Tl myocardial SPECT of a 5-year-old male patient with complete transposition of the great arteries after arterial switch operation performed during the neonatal period. Reversible and fixed perfusion defects were found at the anteroseptal (AS) and lateral (LAT) walls, suggesting left coronary obstructive disease. Selective coronary angiography demonstrated diffusely hypoplastic left anterior descending (LAD) and circumflex (LCX) arteries, whose arterial diameters were quantified as 37% and 33% of age-matched normal values (N), respectively. No obvious localized stenoses were found in those arteries.

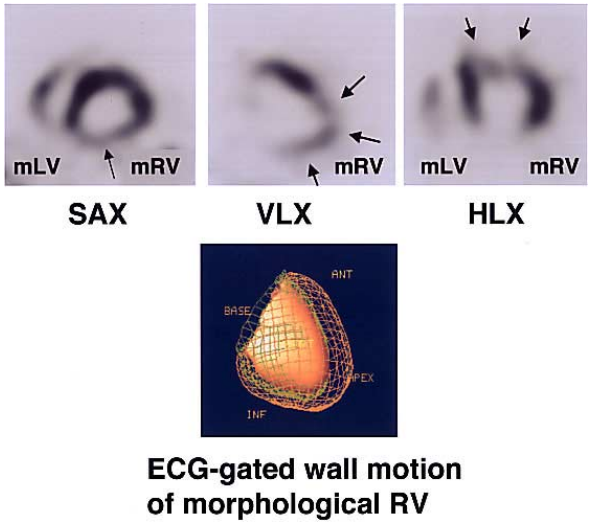

Fig. 10 Resting ^{99m}Tc-tetrofosmin myocardial SPECT from a 26-year-old male with congenitally corrected transposition of the great arteries surgically corrected with conventional Rastelli procedure. Perfusion abnormalities were found at the anterior, apical, and inferior walls of the morphological right ventricle (mRV) from which the aorta arose (*upper panel*). Wall motion was diffusely impaired, most severely at the anterior and apical walls, on ECG-gated myocardial SPECT studies (*lower panel*).

operations, the morphological right ventricle frequently functions as a systemic ventricle. Many patients with a morphological right ventricle in the systemic circulation gradually develop right ventricular dysfunction, leading to congestive heart failure, decreased functional capacity

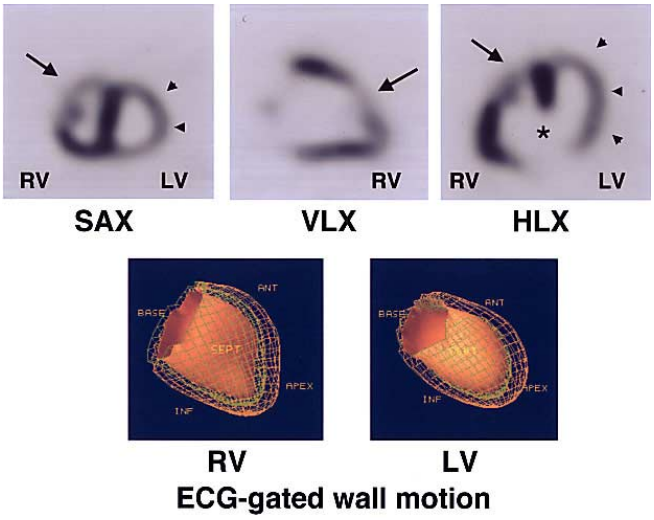

Fig. 11 Resting ^{99m}Tc-tetrofosmin myocardial SPECT from a 16-year-old female with asplenia and complete form of endocardial cushion defect after Fontan operation. Since the right and left ventricles (RV, LV) communicated with each other through a large ventricular septal defect (*asterisk*), myocardial uptake of both ventricular free walls would be equivalent, reflecting an equivalent pressure load on both chambers. However, particularly in this case, perfusion abnormalities were found at the LV free wall (*arrowhead*) and RV anterior and apical walls (*long arrow*), suggesting the presence of myocardial damage (*upper panel*). ECG-gated myocardial SPECT demonstrated severe wall motion abnormality of the whole LV and RV anterior, apical, and inferior walls (*lower panel*).

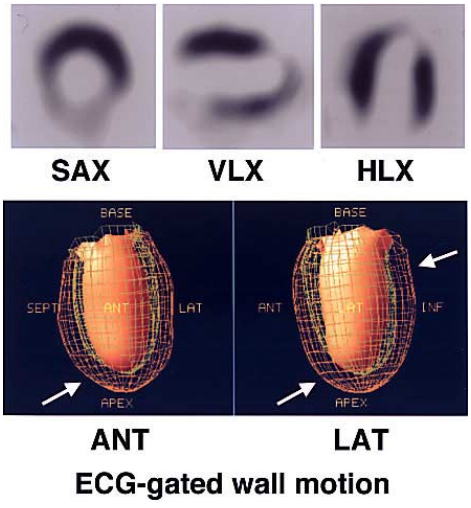

Fig. 12 Resting ^{99m}Tc-tetrofosmin myocardial SPECT from a 22-year-old male with Duchenne muscular dystrophy. Posterior, posterolateral, and anteroapical walls showed perfusion defects (*upper panel*) as well as wall motion abnormality (*lower panel, arrow*).

and early death. Systemic right ventricular function also undergoes such progressive deterioration even without a history of systemic hypoxemia or cardiac surgery using cardiopulmonary bypass in patients with congenitally corrected transposition of the great arteries. The mechanism of failure is unclear, but the inability to tolerate long term functioning at systemic pressure might result from the macroscopic and microscopic structure of the right ventricular myocardium.

Several investigators have suggested that myocardial perfusion plays a causative role in right ventricular dysfunction.[31–33] According to these studies, perfusion abnormalities are most frequent in the anterior and inferior walls and septum and less frequent in the free wall (Fig. 10). Reversible perfusion abnormalities are induced by exercise or pharmacologic stress, but constant defects also develop.[32] Such perfusion defects are associated with regional wall motion abnormalities,[33] and the extent of perfusion defects closely correlates with depressed global right ventricular function.[31] These findings suggest that inadequate perfusion of the myocardium relates to the pathogenesis of consequent contractile dysfunction in patients with a right ventricle that functions systemically.

The morphological right ventricle is supplied by a morphological right coronary artery system, which lacks a well-developed anterior descending artery in a left coronary system. The right coronary arterial system might provide inadequate flow in the presence of considerable hypertrophy when the right ventricle functions at systemic pressure for long periods. Gross hypertrophy of the right ventricle under systemic pressure is especially conspicuous towards the apex. Hypertrophy places substantial extra demand on the right coronary arterial supply, which is less extensive than that from a left coronary system. Our studies support this notion. We evaluated myocardial perfusion and fatty acid metabolism using ^{201}Tl and ^{123}I-BMIPP in patients with a single right ventricle, and showed that the myocardium is normally perfused, hypertrophied at rest but metabolically compromised at apico-anterior regions with regional contractile dysfunction.[34] Since one study indicated that significant fixed defects are invariably associated with wall motion abnormalities, stress-induced reversible defects are only occasionally associated with wall motion abnormalities at rest.[32] Therefore, reversibility might reflect ongoing microvascular and/or myocardial changes and thus provide an opportunity for intervention.

Estimation of right ventricular pressure overload by MPI

The right ventricular free wall is not normally visualized on MPI when the patient is at rest. However, myocardial uptake of perfusion tracers by the right ventricular wall is increased and obvious in patients under pathological conditions that cause pressure or volume overload of the right ventricle.[35–38]

The magnitude of the relative increase in myocardial uptake of the right to the left ventricle closely correlates with right ventricular peak systolic pressure as well as the ratio of right-to-left ventricular peak systolic pressure in patients with congenital heart disease.[35–37] Pure volume overload does not significantly increase right ventricular uptake.[36] According to Ravinovitch et al., visual grading of the right ventricular appearance on planar ^{201}Tl images with background subtraction can differentiate at least four categories of right ventricular pressure load.[35] The absence of an apparent right ventricle indicates that the right ventricular pressure is within normal limits. A minimal to definite image of the right ventricle that is less than that of the left ventricle, corresponds to a mild to moderate increase (30–70 mmHg) in the right ventricular pressure, and equally dense right and left ventricles to a moderate to severe (equal to the systemic level) increase (50–100 mmHg). Supra-systemic right ventricular hypertension appears as a more dense right than left ventricle on MPI.[35]

More precisely, quantitative approaches to measuring increased right ventricular uptake have been applied to planar and SPECT images. One method compares the right and left ventricles in terms of peak counts of the ventricular free wall.[37] A region of interest is defined as a crossing line perpendicular to the septum in a planar left anterior oblique image after background subtraction or in a short axial SPECT image. Thereafter, peak counts of both ventricular walls on the line are determined, and the ratio of the counts is calculated. Another method compares the average counts of the left and right ventricles.[36] A left ventricular region of interest is drawn on the left ventricle including the septum, and a right ventricular region of interest excluding the septum, is drawn on the left anterior oblique planar image after background subtraction or in summed short axis SPECT images encompassing the whole ventricle. Both approaches applied to planar or SPECT images generate similar estimates of right ventricular pressure overload. These results constantly indicate that similar uptake by both ventricular walls implies right ventricular hypertension equal to the systemic level.[36,37] According to Akiba et al. who used ^{201}Tl-SPECT and a peak count method, a ratio of right to left ventricular counts of $\geq$0.45 predicts right ventricular pressure overload with a sensitivity of 92%, and a specificity of 88%.[37] Theoretically, SPECT might more accurately estimate right ventricular pressure overload than planar imaging, since the latter method sometimes cannot clearly determine the optimal projection to visualize right and left ventricular walls, especially in patients with considerable variations in the position and rotation of the heart due to congenital heart disease. However, the correlation between the ventricular count ratio and right ventricular pressure overload in planar studies is similar or better than that obtained using SPECT.[36]

Right ventricular pressure overload is usually noninvasively estimated by echocardiography, and MPI is seldom performed primarily for this purpose. Thus,

increased right ventricular uptake and estimated right ventricular pressure overload are usually additional information generated during nuclear examinations for other purposes, such as stress MPI of the left ventricle. Regional or global perfusion defects on SPECT images with increased right ventricular uptake due to pressure overload of systemic or supra-systemic level might be more significant, since such findings could indicate myocardial damage and failure related to right ventricular dysfunction (Fig. 11).

APPLICATION OF MPI TO DETERMINE MYOCARDIAL DISEASE IN CHILDREN

Hypertrophic cardiomyopathy

Children with hypertrophic cardiomyopathy diagnosed between 1 and 14 years of age are at higher risk for sudden cardiac death than adult patients, and the mortality rate is approximately 50% within 9 years of diagnosis. Several potential mechanisms for cardiac arrest and syncope in patients with hypertrophic cardiomyopathy have been proposed. In adults, prevalent ventricular arrhythmias are believed to be the most important cause of sudden cardiac events in hypertrophic cardiomyopathy. However, in children with hypertrophic cardiomyopathy with prior cardiac arrest, ventricular arrhythmias are infrequent on ambulatory ECG, suggesting that the primary mechanisms of sudden death in children differ from that those in adults.

Several studies have indicated an important role of myocardial ischemia in the pathomechanisms of sudden cardiac death in children with hypertrophic cardiomyopathy. Dilsizian et al. used ambulatory ECG and exercise-stress ^{201}Tl-SPECT to evaluate 23 patients with hypertrophic cardiomyopathy aged 6 to 23 years who had previous cardiac arrest or syncope (n = 15) or a family history of sudden cardiac death (n = 8).[39] The results showed that 3 of the 15 patients with a history of cardiac arrest or syncope had ventricular tachycardia on ambulatory ECG. However, all 15 patients with either cardiac arrest or syncope had inducible ischemia according to MPI compared with only 3 (37%) of 8 patients with no such history. Exercise-stress MPI demonstrated perfusion abnormalities with a localized (usually in the anterior, septal, and apical regions) and/or diffuse distribution (reversible apparent left ventricular cavity dilation, suggesting subendocardial ischemia).[39]

The mechanisms of myocardial ischemia in hypertrophic cardiomyopathy might be intramural abnormalities of the small vessels, abnormal myocellular architecture, or massive hypertrophy. The role of myocardial bridging (systolic compression of epicardial coronary arteries) in ischemia and sudden death in children with hypertrophic cardiomyopathy is controversial. Yetman et al. report that bridging is an important cause of angina and myocardial ischemia, and that it is a significant risk factor for ventricular arrhythmias and sudden death.[40] However, Mohiddin et al. recently reported that exercise-induced perfusion abnormalities on ^{201}Tl-MPI are related to the severity of septal hypertrophy and septal perforator compression rather than bridging.[41] They also showed that bridging is more frequently associated with massive septal hypertrophy, which is a relatively common feature of hypertrophic cardiomyopathy in children.[41] The study of Tadamura et al. using dipyridamole-stress ^{13}NH-PET might reveal mechanisms of stress-induced myocardial ischemia in pediatric hypertrophic cardiomyopathy.[13] They demonstrated that hypertrophic cardiomyopathy in children is characterized by an absolute reduction of myocardial blood flow after pharmacological vasodilation in hypertrophied septal regions. The mechanisms might be related to significant regional heterogeneity of the coronary flow reserve in pediatric hypertrophic cardiomyopathy. Since coronary flow reserve is severely attenuated at the hypertrophied septal region while preserved normally at the non-hypertrophied lateral region in such pediatric patients, coronary steal might develop between the coronary arteries perfusing hypertrophied and non-hypertrophied regions.[13] In contrast, the coronary steal phenomenon is not obvious in adult patients with hypertrophic cardiomyopathy, because coronary flow reserve is also impaired at non-hypertrophied regions.[13] An absolute reduction of myocardial blood flow after vasodilatory stimuli could explain why ischemia is an important cause of cardiac events in children with hypertrophic cardiomyopathy.

Cardiomyopathy in Duchenne progressive muscular dystrophy

Duchenne muscular dystrophy (DMD) is frequently associated with myocardial degeneration and fibrosis. The distribution of myocardial lesions is unique, segmental and initially located throughout the basal inferior and contiguous lateral walls of the left ventricle.[42] In the later stages of DMD, the lesions spread to the middle inferior, apical, and anterior left ventricular walls. Approximately 15–20% of patients with DMD die of cardiac failure.

The extent of myocardial involvement in DMD evaluated by MPI has shown frequent perfusion defects in the posterolateral wall of the left ventricle (Fig. 12). Several nuclear studies have examined the myocardial tissue characteristics of perfusion defects. Nishimura et al. performed initial and delayed resting ^{201}Tl-MPI in 7 patients with DMD, and compared the location and extent of perfusion defects in terms of the post-mortem histopathological findings.[43] They found that fixed perfusion defects commonly corresponded to severe transmural fibrosis and severe fatty infiltration. They also found areas of redistribution on MPI, in which the degree of fibrosis was greater than in areas of normal perfusion, and more prominent interstitial edema than in patients with normal perfusion or fixed defects.[43] These results suggested that

perfusion defects on initial resting MPI do not directly indicate non-viable scar tissue, but rather include viable but partially damaged tissue under progressive myocardial fibrosis. In such progressively fibrotic areas, ventricular contraction might cause abnormal distortion between normal and abnormal myocardial fiber bundles, leading to hypoperfusion and interstitial edema due to compression of veins and lymphatic vessels,[43] as well as damage to myocytes with a fragile cell membrane due to a dystrophin deficiency in DMD. Such histopathological findings might be supported by studies using PET with ^{13}N-ammonia and ^{18}F-fluorodeoxyglucose. These investigations have indicated perfusion and metabolic mismatches at the posterobasal and posterolateral walls of the left ventricle in patients with DMD, where glucose utilization is selectively increased at hypoperfused areas.[42,44] Thus, myocardial ischemia might be involved in the myocardial changes and progression of cardiomyopathy in DMD.

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