Stress Echocardiography in Children

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The rationale for applying stress echocardiography in children is not different from application of the technique in adults [1]. Sick children may need cardiac stress imaging, and stress echocardiography is becoming more common in the pediatric population [2]. Obviously, to perform these procedures in the most adequate way, proper training of personnel and staffing of the pediatric stress laboratory are required to ensure the safety of patients and that the desired testing information is obtained. For these reasons, and as recommended by a recent 2006 statement of the American Heart Association (AHA), pediatric testing should remain an integral part of pediatric cardiology training [3]. A focused competence for the pediatric population should ideally be an integral part of the high-volume stress echocardiography laboratory. Diagnostic questions raised by children are extremely variable, and require a versatile approach of highly trained personnel. In our experience, pediatric stress echocardiography is performed in teamwork – between an adult cardiologist trained in stress echocardiography with a pediatric cardiologist directly involved in the treatment of the patient. Together, the two cardiologists discuss the indications, perform the examination, and use the results in light of the clinical context (Table 37.1). In this way, inappropriateness is minimized and the diagnostic yield is optimized.

37.1 Pediatric Coronary Artery Disease

There are several patient populations for whom stress echocardiography can be used to detect ischemia-producing coronary artery stenosis in children. Kawasaki disease (KD) is an acute self-limited vasculitis of childhood that is characterized by fever, bilateral non-exudative conjunctivitis, erythema of the lips and oral mucosa, changes in the extremities, rash, and cervical lymphoadenopathy. Advances in clinical therapies (with intravenous immune globulin and aspirin) have reduced, but not eliminated, the incidence of coronary artery abnormalities in affected children. Today, KD is the most common cause of acquired cardiovascular disease in children in the USA. Coronary artery aneurysms or ectasia develop in 20% of untreated children and may lead to ischemic heart disease or sudden

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Table 37.1 Application of pediatric stress echocardiography

	Target	Method	Stress	Disease
CAD detection	Regional wall motion abnormalities	2D	Ex (dob, dip)	Kawasaki, transplant CAD, Arterial switch
Valve stenosis	Transvalvular gradients	CW Doppler	Ex (dob)	Native aortic stenosis, native pulmonary stenosis, Prosthetic valves
Pulmonary hemodynamics	PASP	CW Doppler (TR jet)	Ex (dob)	Right ventricular overload
Contractile reserve	Normal baseline function, depressed baseline function	2D	Ex (dob)	Thalassemia
Coronary flow reserve	Coronary macro- and microcirculation	Pulsed Doppler CFR	Dip, ado, cold	Kawasaki, switch, right and left ventricular overload

CAD coronary artery disease, *Ex* exercise, *dob* dobutamine, *dip* dipyridamole, *CW* continuous wave, *PASP* pulmonary artery systolic pressure, *TR* tricuspid regurgitation, *CFR* coronary flow reserve

death [4]. According to 2004 AHA guidelines on KD, cardiac stress testing for reversible ischemia is indicated to assess the existence and functional consequences of coronary artery abnormalities in children with KD and coronary aneurysms (evidence level A). Whichever the chosen stress, diagnostic accuracy for identifying angiographically assessed coronary artery disease is high and comparable, with stress-induced wall motion abnormalities representing a highly specific, and sensitive, marker of coronary artery involvement. More than 100 cases have been published to date with exercise or pharmacological echocardiography, with excellent overall diagnostic accuracy [5–8], comparable to stress scintigraphy. Guidelines conclude that "*the choice of stress modality should be guided by institutional expertise with particular techniques, as well as by the age of the child (e.g., pharmacological stress should be used in young children in whom traditional exercise protocols are not feasible*" [4]. The acute diagnostic benefit is similar between these techniques, but the long-term risk is disproportionately high with ionizing techniques. Therefore, the use of methods such as myocardial scintigraphy [9], computed tomography [10], and systematic coronary angiography [11] should be drastically minimized in these patients [12, 13].

A national survey in Japan on the pediatric cardiologist's clinical approach for patients with KD showed that for high-risk patients, as early as in 2002, more responders favored stress echocardiography when compared with nuclear imaging. For high-risk levels, 60% of pediatric cardiologists perform coronary angiography not on a regular basis but only when coronary symptoms are present or when stress imaging suggests myocardial ischemia [14].

Clearly, more data are needed in this field, but stress echocardiography based on visual assessment of regional wall motion abnormalities will play a key role in surveillance and management of patients with coronary artery residua. To date, alternative echocardiographic approaches based on other, more quantitative markers of ischemia, are available. These include longitudinal function assessment with mitral annulus plane systolic excursion [15], cyclic backscatter variation with tissue characterization techniques [16], and perfusion changes with myocardial contrast echocardiography [17]. Each of these markers has an interesting rationale. Long-axis function can detect minor forms of ischemia, unable to affect radial function and regional systolic thickening, since longitudinal fibers run in the subendocardial layer, thus abnormalities accurately reflect subendocardial ischemic dysfunction. Longitudinal function can be impaired when radial motion is normal or even supernormal [15]. Cyclic backscatter variation is proportional to intramural contractility, and higher in the subendocardium than in the subepicardium, mirroring the well-known intramural contractility gradient. Therefore, minor forms of subendocardial hypoperfusion may impair subendocardial function and blunt cyclic backscatter variation without a detectable impairment in regional systolic thickening [16]. Finally, myocardial contrast echocardiography evaluates myocardial perfusion heterogeneity, which is more sensitive (albeit less specific) than regional wall motion abnormalities as a marker of myocardial ischemia [17]. None of these markers should be exclusively considered for clinically driven applications due to inadequate validation to date. At present, it appears reasonable to propose a very simple diagnostic algorithm in these patients, who must be screened with resting transthoracic echocardiography to detect coronary artery morphological anomalies, which are the cornerstone of diagnosis and risk stratification (from class I, low risk, to V, high risk). A positive stress echocardiography finding is frequently found in the high-risk class, therefore, it appears appropriate to use it in class V patients [8] (Fig. 37.1).

37.2 Transplant Coronary Artery Disease

The leading cause of death after the first year of cardiac transplant is transplant coronary artery disease, occurring in up to 43% of patients at 3 years following transplant [18]. This form of coronary disease, also known as graft coronary disease, differs from classical atherosclerosis in both histologic and angiographic features and it progresses much more rapidly. Because the disease is diffuse and usually involves small vessels it makes coronary arteriography an unreliable diagnostic technique — a matter that turned physicians to other modalities, such as stress echocardiography. A total of five dobutamine echocardiographic studies, including over 100 patients, showed excellent diagnostic value [19–21] and prognostic capability, since patients with positive test results had a sixfold higher risk of subsequent cardiac events [22, 23].

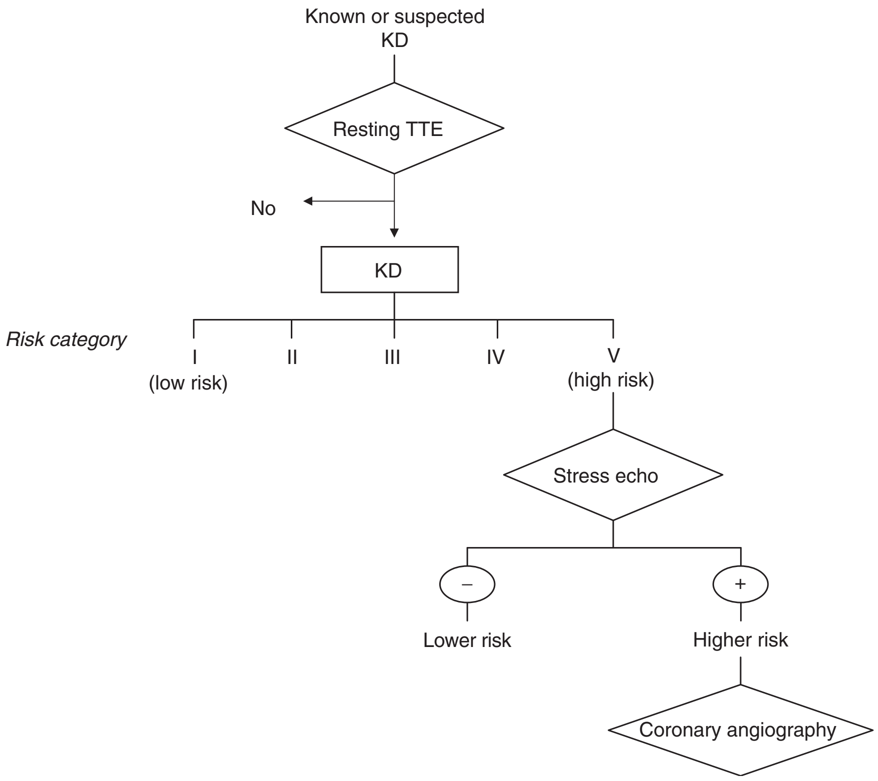

Fig. 37.1 A proposed algorithm in a young patient with known or suspected Kawasaki disease (*KD*). Resting transthoracic echocardiography is essential for the diagnosis and for risk assessment. In patients with high-risk class (AHA grade V), stress echocardiography is warranted. Patients with a positive response belong to a higher risk group warranting further investigation with coronary angiography with the perspective of an ischemia-driven revascularization

37.3 Transposition of Great Arteries After Surgical Repair

The long-term problems that are associated with repaired transposition of the great arteries depend on the type of repair. The oldest patients have intraatrial repair, either Mustard or Senning type, in which venous return is directed to the contralateral left ventricle by means of an atrial baffle. As a consequence, the right ventricle supports the systemic circulation. Relatively young patients undergo an arterial switch operation, to allow the left ventricle to function as the systemic pump through removal of the Mustard/Senning atrial baffles and reconstructing of an atrial septum in patients with complete transposition [24].

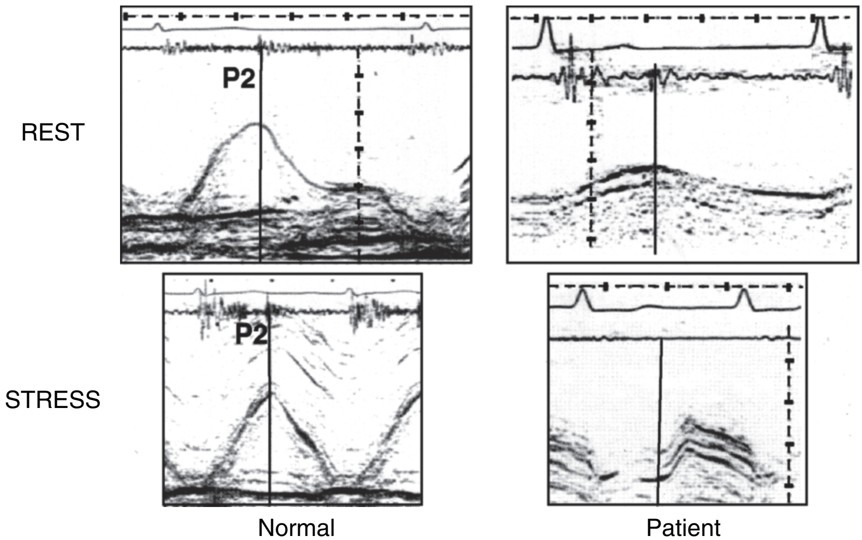

Fig. 37.2 Right ventricular free wall *M*-mode at rest (*top*) and stress (*bottom*) from a normal control and a patient after Mustard repair showing stress-induced incoordination of the patient (*right*) suggesting underlying ischemia. (Modified from [25])

In patients with Mustard or Senning repair, right ventricular dysfunction and pulmonary hypertension are a possible complication. Patients with exertional symptoms, angina-like chest discomfort, or breathlessness could be physiologically assessed by stress echocardiography. There is a close relationship between right ventricular function in these patients and exercise tolerance assessed by cardiopulmonary exercise testing. Furthermore, in these patients, the right ventricular function becomes very abnormal at fast heart rate, demonstrating disturbances similar to those seen in patients with coronary artery disease, suggesting a possible underlying ischemic dysfunction [25]. These findings are consistent with those found in dilated cardiomyopathy (Fig. 37.2).

The arterial switch operation, which includes coronary artery transfer, is the surgical procedure of choice for transposition of the great arteries. Mortality and clinical long-term outcome largely depend on adequate perfusion through the transferred coronary arteries. Late deaths can be related to coronary occlusion, and intravascular ultrasound assessment late after arterial switch operation revealed proximal eccentric intimal thickening in most coronary arteries, suggesting the development of early atherosclerosis in reimplanted coronary arteries [26]. These patients tend to have a consistently reduced coronary flow reserve [27]. Only anecdotal reports present in the literature on a total of 34 patients from two studies – one with dobutamine [28], the other with transesophageal atrial pacing [29] – suggest that a stress-induced regional wall motion abnormality or reduced left ventricular long-axis function portends a negative prognosis.

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37.4 Valve and Intraventricular Gradients

Several studies have been performed in native stenotic aortic, pulmonary, and prosthetic valves during high-flow states to unmask an abnormally high increase in gradients. In fact, the transvalvular gradient increases with increasing flow rates, the higher the transvalvular flow, the higher the pressure gradient. A moderately and a severely diseased native valve, and a normal or abnormally functioning prosthesis, may display similar gradients at rest, but the marked rise in mean gradients during stress in the latter is to be distinguished from the fairly flat gradient response of the moderately diseased native or normally functioning prosthetic valves. The rationale of this application is very strong, but systematic data, especially in children, are still conspicuously lacking to date [30]. A similar application evaluates the development of intracardiac gradients in young athletes or patients with hypertrophic cardiomyopathies, in whom dobutamine or exercise can unmask an intraventricular obstruction unapparent at rest and which may have prognostic and therapeutic implications [31].

37.5 Contractile Reserve

Patients with normal ejection fraction at rest can indeed have subtle alteration in left ventricular function. This initial impairment can be detected as a reduction in long-axis function detected by mitral annular plane systolic excursion or tissue Doppler imaging, both in experimental models [32] and in patients [33]. Alternatively, an initial myocardial damage can be detected as a blunted contractile response to an inotropic stress, such as dobutamine or exercise. This pattern has been described in anthracycline-treated long-term survivors of childhood cancer [34–37] or in thalassemic patients at an early stage of disease [38]. At a more advanced stage, left ventricular function can be depressed and the inotropic challenge can restore a normal function in patients who will have less perioperative risk in the case of intervention and better natural history if left on medical therapy [4] (Fig. 37.3).

The assessment of contractile reserve of the right ventricle is of great importance [25]. In patients with Mustard repair for transposition of the great arteries or repaired tetralogy of Fallot [39], impaired exercise tolerance can be predicted by right ventricular long-axis function at baseline and during stress. The lower the contractile reserve of the right ventricle, the lower the exercise capability and the right ventricular stroke volume. Longitudinal function can be assessed by simple long-axis amplitude of motion (from TAPSE for right and MAPSE for left ventricle, 25), or from peak systolic velocity of basal left ventricular segments by tissue Doppler imaging [39]. In patients with repaired tetralogy of Fallot, exercise stress echocardiography unmasks a substantial heterogeneity in right ventricular contractile reserve, pulmonary artery systolic pressure, and right ventricular volume (Fig. 37.4). Those patients with reduced right ventricular contractile reserve also have lower exercise tolerance, higher cardiac peptides plasma levels, and more dilated right ventricle with cardiovascular magnetic resonance [40].

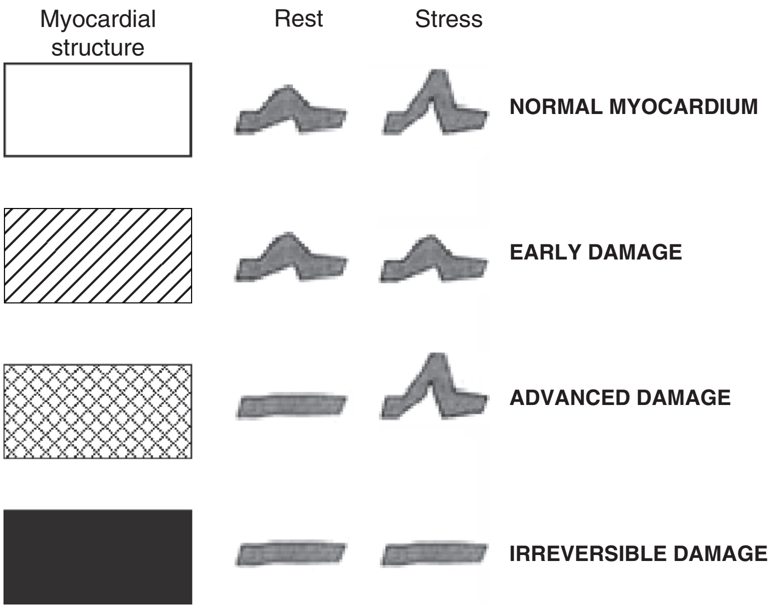

Fig. 37.3 Different stages of severity of myocardial damage in cardiomyopathy, due to, for instance, thalassemia or cardiotoxic chemotherapy

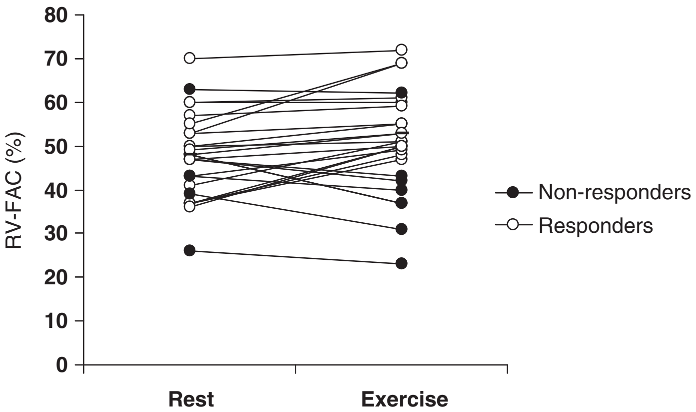

Fig. 37.4 Exercise stress echocardiography results in grown-up congenital heart disease patients with repaired tetralogy of Fallot. There is an obvious heterogeneity in right ventricular fractional area change during exercise. Patients with depressed right ventricular contractile reserve (nonresponders) also show higher BNP values and lower exercise tolerance. BNP, brain natriuretic peptides. (By courtesy of G. Festa et al. [39])

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37.6 Coronary Flow Reserve

Coronary flow reserve can be reduced in children with congenital heart disease as a consequence of epicardial coronary artery anomalies due to primary coronary microcirculatory damage or ventricular hypertrophy [41]. Pulsed Doppler transthoracic echocardiography is ideally suited for assessing coronary flow reserve in these patients, both in the mid-distal left anterior descending coronary artery (with >90% feasibility) and in the right coronary posterior descending arteries (with >70% feasibility). High-frequency transducers with second harmonic technology greatly enhance the success rate of the technique in expert hands, often not requiring contrast injection. The employed stressor is usually adenosine or dipyridamole, but the cold pressor test has also been fruitfully proposed in children. The normal increase in coronary flow reserve is about 250% following adenosine (or dipyridamole, which accumulates endogenous adenosine) and about 200% after cold, which mainly acts through a hemodynamically mediated increase in heart rate and blood pressure [42]. Coronary flow reserve could be impaired – even in the absence of anatomic epicardial coronary artery disease – in children 5–8 years after the switch operation, which is mirrored by reduced vasodilation following nitrates, an endothelium-independent vasodilator stimulus [27]. In KD, the impairment in coronary flow reserve is largely independent of epicardial coronary artery lesions and aneurysms, again suggesting primary coronary microcirculation impairment [43]. The reduction of coronary flow reserve can be either diffuse or branch-specific [43–49]. The impairment of coronary flow reserve is an integrated index of epicardial vessel status, myocardial hypertrophy, and coronary microcirculation structural and functional conditions [47, 48]: Fig. 37.5. In adults, the reduction in coronary flow reserve has a clinically relevant prognostic value, above and beyond regional wall motion [49, 50]. Whether this is true also for children remains to be established in future studies.

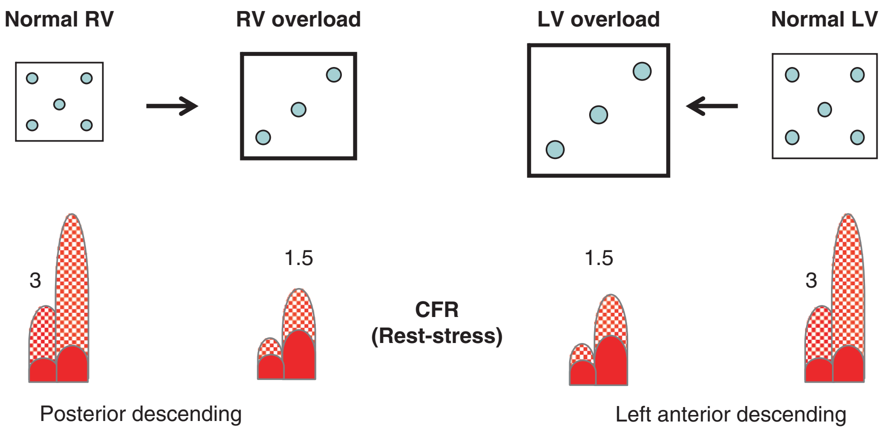

Fig. 37.5 The coronary flow reserve (*CFR*) pattern, as can be visualized by transthoracic vasodilator stress echocardiography, in patients with left ventricular (*right panel*) or right ventricular (*left panel*) overload

37.7 Conclusions

Stress echocardiography should be considered an extension of traditional resting cardiac assessment. The need and value of understanding myocardial function, valvular physiology, and pulmonary hemodynamics in children during stress will promote a growth of this specific field, especially in view of the increasing radiological exposure of children with congenital heart disease from aggressive use of computed tomography and scintigraphy [51–53] (Table 37.2). At the age of 15–20 years, grown-up congenital heart (GUCH) disease patients have already cumulated a dose exposure corresponding to 2,000 chest X-rays [54], with an estimated lifetime extra-risk of cancer of 1 in 10 to 1 in 100, and with a measured 200% increase in micronuclei and chromosome aberrations in circulating lymphocytes [55]. These data are worrying, but not surprising, since it is well known that the radiation damage for any given dose is three- to fourfold higher in children than in adults [56–58]. In spite of this, 30% of stress imaging in children is still done with perfusion imaging [3], which gives a radiation exposure of 500–1,700 chest X-rays (with a risk of cancer greater than 1 in 100 for a 1-year-old girl). This inconvenient situation is perpetuated by the lack of information of specialty guidelines – not even mentioning radiation dose and risk – and by the current very suboptimal awareness of doses and risks by patients [59, 60], pediatricians [59], cardiologists [61], and radiologists [62]. Notwithstanding this escalating radiation exposure, there has been remarkably little public discussion of the need for fundamental changes in our current imaging practice in adults and especially in children [3, 4]. Although we can debate the multiple reasons for this silence, there is no question that with the restoration of radiological awareness, stress echocardiography will become the technique of choice, even more than in adults (Table 37.3), and – when used in tandem with magnetic resonance – will help heart patients to achieve the benefits of the highest diagnostic standards without the long-term oncogenic risks of radiation exposure [63]. This

Table 37.2 Exposure and risks of imaging techniques in children younger than 1 year

	Dose (mSv)	Dose equivalent (chest X-rays)	Cancer risk
64-slice MSCT (with ECG modulation)	15	750	~1 in 100
64-slice MSCT (without ECG modulation)	29	1,450	~1 in 50
Cardiac stress scintigraphy (201-Thallium)	27	1,350	~1 in 50
Cardiac stress scintigraphy (99 m sestamibi)	10	500	~1 in 200
Coronary angiography	5	250	~1 in 500
Cardiovascular magnetic resonance	0	0	0
Echocardiography	0	0	0

MSCT multislice computed tomography

Table 37.3 Stress echocardiography in children vs. adults

	Adults	Children
Stress	Exercise>Pharmacologic	Pharmacologic>Exercise
Evidence available	Established	Initial
Safety concerns	+	+++
Vulnerability to radiation damage	+	++++
Use of cardiac scintigraphy	Declining	Disappearing
Complementary technique	CMR	CMR

CMR cardiovascular magnetic resonance

is important in all patients [64], and should be our dominant thought in planning diagnostic strategies in children.

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