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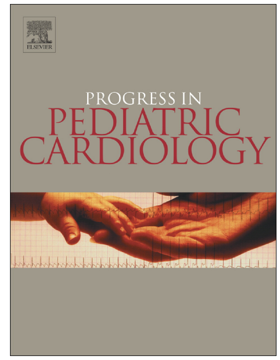

Pediatric stress echocardiography: A review

Alejandro Arevalo, Peace C. Madueme, Ronak Naik, Kate Ingebretsen, Bahram Kakavand, Bradley Robinson

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Title: Pediatric stress echocardiography: a review

Alejandro Arevalo[1,2], Peace C. Madueme[1,2], Ronak Naik[3], Kate Ingebretsen[1], Bahram Kakavand[1,2], Bradley Robinson[4,5]

[1]Nemours Cardiac Center, Nemours Children's Hospital, Orlando, FL

[2]Department of Pediatrics, University of Central Florida College of Medicine, Orlando, FL

[3]Department of Pediatrics, University of Tennessee Health Science Center, Memphis, TN

[4]Nemours/A.I. Dupont Hospital for Children, Wilmington, DE

[5]Department of Pediatrics, Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, PA

Corresponding Author:

Alejandro R. Arevalo, MD FACC

Nemours Cardiac Center

13535 Nemours Parkway

Orlando FL 32827

Office: 407-650-7470

Cell: 407-450-1645

Email: Alejandro.arevalo@nemours.org

Abstract

Stress echocardiography is a dynamic modality of evaluating the heart during pharmacologic or exercise stress. A basic understanding of exercise physiology and cardiac hemodynamics are essential to understand stress imaging. Stress echocardiography has proven to be overall safe with improved yield over standard exercise testing. The primary indication in adults is to discover evidence of inducible myocardial ischemia. Pediatric stress echocardiography is performed for two primary indications, evaluating cardiac hemodynamics as well as evidence of inducible myocardial ischemia. We performed a review of the current literature for pediatric stress echocardiography.

Keywords

pediatric, imaging, stress, echocardiography, review

1. Introduction

Stress echocardiography was first introduced in 1970 (1). It became clinically visible in the pediatric literature in 1980 by Alpert et al (2). Although a sizeable amount of information can be obtained from standard electrocardiogram (ECG) stress testing, the sensitivity and specificity of this exam leaves more to be desired. Ischemic cascade theory argues that wall motion abnormalities of the heart occur prior to ECG ischemic changes (3). The marriage of ECG stress testing with imaging modalities was inevitable to improve its accuracy. Stress echocardiography allows an insight into cardiovascular hemodynamic behavior during the active state which may help unmask myocardial compromise.

Therefore, the two fundamental questions of stress echocardiography evaluation are 1) is there inducible myocardial ischemia and 2) are there significant hemodynamic changes? Adult echo labs have become experts in identifying inducible myocardial ischemia based on the prevalence of adult coronary artery disease and the volume of studies in their labs. The pediatric population includes both coronary artery disease (Kawasaki disease/heart transplant) and as well as ventricular/valvular dysfunction where hemodynamics are important. The low prevalence of coronary artery disease, valve disease, and cardiomyopathy in pediatrics has led to a paucity of published data. This has made stress echocardiography a less popular imaging modality in the pediatric population. It also highlights the need for adult collaboration when reading pediatric stress echo studies to gain expertise. On the other hand, stress echocardiography competes with myocardial perfusion imaging and stress magnetic resonance imaging in regards to cost, expertise reproducibility, and information provided.

The true value of any test can only be realized when targeted toward a population with high disease prevalence. Stress echocardiography has been proven to be an important diagnostic modality in the adult population because coronary artery disease is prevalent. This allows meaningful but cautious extrapolation of test results to the pediatric population. In high volume pediatric centers where certain patient populations have a high prevalence of coronary artery ischemia, exercise stress echocardiography is often used. At Boston Children's Hospital, Kawasaki disease patients (with coronary artery aneurysms) and heart transplant recipients (to evaluate post-transplant coronary artery disease) are the most common indications for exercise stress echo studies (Fig. 1) (4). Toronto Children's Hospital reported 101 exercise stress echo studies (from 2011–2014), with the most common indication for stress echocardiography being heart transplant recipients to assess for post-transplant coronary artery disease (64/101 patients) (5).

This review will discuss common indications for exercise (as above) and dobutamine stress echocardiography in pediatrics. Basic physiology of exercise testing and, pathophysiology of ischemia (ischemic cascade) are reviewed. Exercise stress echo (ESE) using specific ergometers plus dobutamine stress echo (DSE) is presented . Finally, specific disease entities are reviewed to discover where ESE and DSE are most useful. ,

2. Physiology and hemodynamics of exercise

Understanding the integration of exercise physiology with cardiac hemodynamics is essential to interpret cardiac exercise stress testing. Evaluating the heart in an idle setting is as foolish as evaluating a Bugatti by reviewing a photograph or simply turning it on and saying it works well. When discussing the baseline cardiac hemodynamics, acknowledgement must be made of the environmental milieu such as dehydration, anxiety, relevant medications (beta blocker, anti-hypertensive), and history of anemia. If a recent hemoglobin level was obtained, it should be documented for the study.

Standard stress testing is usually performed with a treadmill or cycle ergometer, but also can be performed with rowing or arm ergometer. With aerobic exercise stress testing, the cardiac output can increase up to 3- to 5-fold due to an increase in stroke volume and heart rate.

The stroke volume can double compared with baseline, also referred to as myocardial or contractile reserve. The stroke volume in general increases in early- to mid-exercise and plateaus with minimal increase at peak/max exercise. In adults, the stroke volume can increase from 70 ml up to 130–140 ml per heartbeat. Trained endurance athletes and males can generate the greatest increase in stroke volume. Stoke volume is regulated by changes in end diastolic volume, mean arterial pressure, and contractile strength. Venous return increases during exercise due to venoconstriction, the skeletal muscle pump, and the respiratory pump. The heart rate response is linear to the amount of work, and therefore, most of the increase in cardiac output in late exercise is usually heart rate dependent. Heart rate response can be up to 2- to 3-fold at peak exercise.

Rhythm analysis should be noted at baseline and continually during the exercise stress test. Isolated premature ventricular contractions and premature atrial contractions with increased work are common and not pathologic unless in sequence (couplets, triplets). The PR interval and QTc interval should shorten with exercise.

With aerobic exercise, the systemic and pulmonary vascular resistance will decrease due to vasodilation. The increased cardiac output but decreasing total vascular resistance will create a mild to modest rise in the pulmonary and systemic blood pressure. The systolic blood pressure usually increases by 25% to 50% compared with baseline. The diastolic blood pressure response may remain constant or decrease slightly (Fig. 2) (6,7).

With exercise, blood flow is redirected from the internal organs to contracting skeletal muscles. However, the heart retains the same percentage of total cardiac output. Because of an increase in cardiac output, coronary blood flow usually increases 3- to 5-fold in healthy patients. Unfortunately, coronary blood flow only increases 1- to 2-fold in non-ischemic dilated or hypertrophic cardiomyopathy patients (8).

3. Protocols

Based on practice guidelines from the American Society of Echocardiography (ASE), performing symptom-limited studies using a treadmill or cycle (upright or semi-supine) for evaluation is recommended. The study type (cycle vs treadmill) is chosen based on what data one is trying to obtain. For example, a treadmill protocol is chosen if one is looking for wall motion abnormalities and cycle ergometer for Doppler interrogation during the study. Baseline echocardiography should be obtained while supine and likely the physiologic state (position) in which it will be performed (upright vs semi-upright) (8). Independent of the protocol, critical echocardiographic imaging is obtained at peak and early in the recovery phase. The rapid decrease in a pediatric heart rates in the recovery period allow a short 1-2 minute window to capture adequate cine loops. Hemodynamic and ischemic changes persist into early recovery period, but coordinating with the pediatric sonographer is essential to obtain accurate information.

3.1. Cycle ergometer protocol

Using cycle ergometer, there is less motion artifact with more reliable ECG and blood pressure measurements. The disadvantage compared with treadmill testing is a decrease in the amount of cardiac stress achieved, noted by a lower peak heart rate and peak oxygen consumption. At Nemours Children's Specialty Care Clinic in Pensacola, FL, we perform cycle ergometer for hemodynamic stress echocardiograms; serial imaging is performed at baseline and during exercise at minute 1, 3, 5, 7, and 9 as well as at peak exercise. The watts are chosen by age and weight (kg). A basic sample cycle ramp protocol is shown (Fig. 3). The goal is to have a 10-minute stress test. The echocardiogram views are chosen based upon the indication of the study. For example, for a hypertrophic cardiomyopathy patient, a 5-chamber view would be the primary view since it would obtain a left ventricular outflow gradient, left ventricular function, and mitral insufficiency. Documentation of heart rate, blood pressure, electrocardiogram, oximetry, and symptoms are obtained. A max test is usually met when $\geq$ 85% of peak heart rate has been achieved. During the recovery period, the first 1–2 minutes is “the meat” of the stress echo. The sonographer should be guided to obtain the most pertinent information for the study.

3.2. Treadmill protocol

Performing a treadmill study, echocardiographic imaging primarily focuses on the baseline data and “early” recovery phase. We tend to use a standard Bruce protocol with a goal of 85% of peak heart rate but push patients to achieve as high a heart rate as possible. After the patient has reached peak exercise for a treadmill study, the patient is safely and quickly placed in a supine position and focused images are obtained within 60–90 seconds of peak exercise. In the pediatric age group, the heart rate decreases immediately after stopping exercise more quickly than adults. This means any delay in transferring the patient to the imaging bed will decrease the probability of achieving the stress images at maximal effort. The youngest age of pediatric patients for stress echocardiography will depend on their maturity level (5–8 years of age).

3.3. Semi-supine bike protocol

Ciliberti et al. described a semi-supine bike protocol that may effectively be used with exercise stress echocardiography. The advantage was that the stress echocardiography may be obtained in “real time” avoiding the drop in the heart rate normally seen post exercise in stress echo. They studied 42 patients (mean age 14±3 years) for a total of 50 studies. They showed the study was safe with reliable inter-observer agreement (9).

3.4. Dobutamine stress echo

Physiologic exercise stress testing should be the preferred method at all times when possible. The benefit of dobutamine is the ability to increase the heart rate and oxygen demand without physical effort by the patient, and at the same time, allowing a slower heart rate recovery. Dobutamine primarily works through beta-1 receptors, which leads to 2- to 3-fold increase in heart rate and a 1.2-fold increase in end diastolic volume resulting in a change in systolic blood pressure of 1.5- to 2-fold. There is a mild beta-2 receptor effect producing mild vasodilation. Myocardial contractility (elastance) can increase up to 4-fold.

Dobutamine compared with physiologic exercise stress testing has less preload (venous return) recruitment, which can be seen by echocardiography with a greater change in left ventricular end diastolic dimensions with physiologic exercise stress (4). The dobutamine stress echo protocol is described by Noto et al. (10-12).

4. Reporting

Reporting should merge the echo data at baseline, stress, and recovery phase with the correlating hemodynamic data. Prior echocardiograms should be reviewed for comprehensive evaluation. The baseline stress echocardiogram should be tailored to the key components, which are in question. From a reporting standpoint, the different environments should be clearly separated and discussed. The report should detail the story of the patient's hemodynamics and its integration with the echocardiogram data through the exercise stress test into the recovery period. The peak and recovery data tend to have the most robust impact and should detail peak heart rates, blood pressure, pulse oximetry, and symptoms as obtained. Table 1 shares some common cut off values reported in the adult literature (8).

The ASE guidelines recommend use of a 16–17 segment wall model. Each segment should be graded at rest and peak exercise as normal, hyperdynamic, akinetic, hypokinetic, or diskinetic/aneursymal. Note dyssynchrony of the segment may come from a right bundle branch block pattern or pacing so it should be mentioned in reporting. If a wall motion abnormality is recognized, it represents a pefusion abnormality in that coronary artery distribution. After segmental wall motion is scored, the overall left ventricular global function response to stress should be judged. Standard echo views are apical 4, apical 2, and long axis view (apical 3-chamber view) as well as parasternal long axis and short axis views (base, midpapillary, and apex). See Figure 4 for a graphic representation (4).

5. Safety

In general, most large studies in pediatrics have shown very safe outcomes of standard stress testing on the bike ergometer (13). There are no known adverse outcomes from ultrasound using current imaging frequencies. The risk for stress testing is mitigated by continuous heart rate, rhythm, blood pressure, symptom, and oximetry monitoring. Rare side effects have been reported in the pediatric population.

Larsen et al. reported hypertension in 11% of 72 heart transplant subjects (3–18 years old, median 5.7 years [12]). Kimball et al. report ventricular ectopy and headache with hypertension that resolved with stopping dobutamine (11).

The risk for life-threatening complications is very rare in adults in stress echocardiography (0.015%). Dobutamine stress testing is slightly higher with a risk of 0.18% in adults. About 3% of (adult) patients with a dobutamine stress test will experience minor symptoms such as nausea, anxiety, headache, tremor, and urinary urgency. Most diagnostic tests are terminated due to patients' symptoms, but can also be terminated due to achieving > 85% of predicted work load, marked ECG, or echo positivity (14).

6. Disease specific

6.1. Coronary anomalies

6.1.1. Kawasaki disease

Kawasaki disease is a vasculitis of small and medium arteries of unknown etiology. It is the most common cause of acquired pediatric heart disease in the United States. If untreated, 15%–25% of patients will have coronary artery involvement (15). Patients with coronary artery aneurysms are at risk for thrombosis and developing stenosis leading to myocardial ischemia. McCrindle et al., in the 2017 American Heart Association Scientific statement, recommends if patients have small aneurysms or greater (z value $\geq$ 2.5), it is reasonable to assess for inducible myocardial ischemia via stress echo, stress magnetic resonance imaging, nuclear stress, positron emission tomography every 2–3 years, or if the patient has symptoms suggestive of ischemia or signs suggestive of ventricular dysfunction (16). In Kawasaki disease, evaluation of induced myocardial ischemia evaluation by stress echocardiography is practical since the coronary pathology mimics adult coronary artery disease and follows the ischemic cascade (3).

Pahl et al. studied 28 patients (ages 6–16 years) with Kawasaki disease 1 to 10 years prior to study with coronary involvement (4/28 had aneurysms > 8 mm). Two patients had a wall motion abnormality at rest that resolved with exercise. Patients were exercised on a treadmill using a Bruce protocol with stress echo in recovery. Two of 28 patients had a positive wall motion artifact consistent with left anterior descending stenosis during exercise later confirmed by angiography. No patients had resting or exercised-induced ischemia on ECG during stress testing. Exercise stress echo was safe and identifies ischemia not seen on exercise ECGs (17).

Noto et al. used dobutamine stress echocardiography to study a total of 50 patients (ages 3–16 years; 26 with coronary artery involvement and 24 without coronary involvement). All had angiography to confirm coronary status. Left ventricle regional wall motion was divided into 16 segments and a positive test was a new or worsening wall motion abnormality. In the 26 patients with coronary artery involvement, 21 had coronary artery disease by angiogram (> 50% stenosis of major vessels). Dobutamine stress echo showed new or worsening wall motion abnormalities in 19 of 21 patients (sensitivity 90%), and there were no wall motion abnormalities in the control group (specificity 100%) (10).

A long-term (15-year) follow-up study by Noto et al. showed dobutamine stress echocardiography was an independent prognostic factor for patients with Kawasaki disease. Mean age was 13.6 years at the initial dobutamine stress echo. These patients were followed for major arterial coronary event. The grade of peak wall motion score indices at initial testing was the only independent predictor of major coronary events (relative risk: 3.28; 95% confidence interval: 1.73 to 6.20). They suggested dobutamine stress echocardiogram may be an alternative to coronary angiogram (Fig. 5) (18).

In patients with Kawasaki disease and significant coronary abnormalities, dobutamine stress echo may add clinical information to standard ECG stress testing and avoid the need for cardiac catheterization. Zilberman et al. studied 47 patients and showed dobutamine stress echo was able to detect 2 out of 4 patients with coronary abnormalities with class V American Heart Association coronary involvement. The positive dobutamine stress echo patients both had confirmation by coronary angiogram and the 2 negative-result patients were explained by extensive collaterals in 1 and coronary occlusion < 50% in the other. The authors conclude dobutamine stress echo may be a useful screening alternative to coronary angiograms in the patient with American Heart Association class V or above (19).

6.1.2. Pediatric heart transplant recipients

Transplant-induced coronary vasculopathy is a common cause of graft loss, cardiac re-transplantation, and late mortality. According to an angiographic multicenter study, the incidence of coronary vasculopathy would be 2%, 9%, and 17% at 1, 3, and 5 years (20). Thus, stress echo to detect coronary artery disease is a common indication in pediatric heart transplant centers.

Chen et al. studied 47 transplant recipients who had angiograms and exercise stress echo testing from 2007–2010 at Boston Children's Hospital. They reported 89% sensitivity and 92% specificity for detection of coronary artery disease with a 97% negative predictive value for the angiographic-detected coronary artery disease. The authors conclude exercise stress echo may lessen the need for coronary angiography in the post-transplant recipient population (21).

Larsen et al. studied 70 pediatric post-transplant patients in 1985–1986 who had both dobutamine stress echo and angiograms. They reported 72% sensitivity and 80% specificity for detection of coronary artery disease for dobutamine stress echo compared with the gold standard of coronary angiograms (12).

In summary, exercise stress echo and dobutamine stress echo are commonly used to assess post-transplant coronary disease in pediatric centers. Their sensitivity and specificity is good and may decrease the need for such frequent coronary angiograms in this patient population.

6.1.3. Anomalous aortic origin of coronary artery

The true incidence of anomalous arterial origin of the coronary artery remains unknown. Cheezum et al. reviewed 77 studies with more than 1 million patients and concluded an incidence of 0.03% of anomalous left coronary artery and 0.28% of anomalous right coronary artery (22). In the sudden cardiac death literature, anomalous coronaries have been reported to be as high as the second leading cause/etiology (23). Brothers et al. calculated a cumulative risk of death over a 20-year period in young adults with anomalous arterial origin of the coronary artery (ages 15–25 years) participating in competitive sports at 6.3% for anomalous left coronary artery and 0.2% with anomalous right coronary artery (24).

While often anomalous aortic origin of the coronary artery is suspected by transthoracic echocardiography other modalities are needed to confirm the diagnosis such as computed tomography, magnetic resonance imaging, and more rarely by angiography confirm the diagnosis (23). The 2015 American Heart Association/American College of Cardiology and 2017 Expert Consensus Guidelines recommend exercise restriction and surgery be offered if symptoms suggest myocardial induced ischemia (cardiac arrest, ventricular arrhythmias, or ischemic chest pain).

The mechanism of ischemia and sudden unexplained death is unknown. Two theories are 1) ostial stenosis of the coronary take off along with an oblique take off compromises oxygen delivery and 2) compression of the anomalous coronary intramurally and/or between the great arteries (24). These patients do not always follow the adult ischemic cascade or temporal sequence of ischemia (diastolic changes followed by wall motion changes and then ECG change) that allows one to detect the wall motion abnormalities in stress echocardiography prior to stress changes. Therefore, the role of stress imaging is unclear in the asymptomatic patient.

Molossi et al. presented a recent article on how to describe the anomalies. In the face of uncertainty, functional testing is often performed. Inducible ischemia during stress is reported to be 6%–22% preoperatively. They found incidence of inducible ischemia at 8% in their cohort (25).

Brothers et al. evaluated 24 postoperative anomalous coronary patients (16 anomalous right, 8 anomalous left) with stress echocardiogram. They found 9 patients with evidence of inducible ischemia on stress echocardiogram or myocardial perfusion scan. They conclude these patients should be followed serially to assess their ischemia changes (26).

In summary, anomalous arterial origin of the coronary artery is a rare but important cause of sudden unexplained death in children. Patients with an anomalous left coronary artery die more often than patients with an anomalous right coronary. The mechanism of death is not clear. If patients have ischemic symptoms, then they should be restricted from exercise or offered surgery. Functional assessment by stress echo is helpful if positive. One should exhibit caution in interpreting a negative exercise stress test/stress echocardiogram as reassuring in these patients.

6.1.4. Transposition of the great arteries

Residual or acquired coronary pathology occurs in about 5%–8% of patients after repair for transposition of the great arteries in the post Jatene era. It can lead to sudden death. In postoperative patients with transposition of the great arteries, inducible myocardial ischemia by stress imaging has an incidence range of 25%–75%. Hui et al. studied 31 patients after repair for transposition of the great arteries with dobutamine stress echocardiography and showed 74% positivity despite all having normal baseline angiograms. They concluded that coronary pathology was global (microvascular) vs regional involvement (27).

Tsuda et al. have shown a 7% coronary artery obstruction rate in their retrospective review of 97 patients with transposition s/p Jatene procedure. Seven patients had significant coronary artery obstruction. Of these 7, 5 had exercise testing. Only 2 of these 5 patients had positive ECG changes. The mechanism hypothesized was narrowing of the suture line at the coronary artery button anastomosis, kinking and stretching of the transplanted coronaries, and reactive inflammation to the surgery. They showed that exercise testing and myocardial perfusion are not always helpful in detecting coronary artery stenosis in this patient population. Our diagnostic test of choice is coronary artery angiogram postoperatively (28). We speculate that the mechanism of sudden unexplained death may not follow the ischemic cascade with gradual narrowing of the coronary artery lumen, which would present with wall motion changes prior to ECG changes.

6.1.5. Stress echo vs nuclear perfusion scan

The sensitivity and specificity varies but overall are very similar in the centers that have experience with them. Most centers adopt one stress modality as their preference. In general, stress echocardiography has a similar accuracy to other stress imaging modalities. It does have a slightly lower sensitivity than single-photon emission computed tomography, but a higher specificity. Stress echocardiography has an average sensitivity of 85% and a specificity of 77% in a meta-analysis for evaluation of adult coronary artery stenosis compared with exercise single-photon emission computed tomography, which has 87% sensitivity and 64% specificity (29). Chen et al. showed a sensitivity of 89% and specificity of 92% in pediatric heart transplant patients for stress echo compared with angiography (30). Higher specificity allows stress echocardiogram to better discriminate between patients with or without disease.

Myocardial imaging is limited as it is only helpful in evaluating left ventricular ischemia. The tagged radio isotope will primarily opacify the left ventricle and not the right ventricle so it would not be helpful in identifying an anomalous right coronary artery (31). It is also important to remember that myocardial perfusion scan involves radiation and has more false positive cases.

6.2. Valve disorders

Evaluation of dynamic valve dysfunction with correlation to symptoms/hemodynamics is another common indication for stress echocardiography. In adult patients, valve stenosis severity is discussed as an area indexed to body surface area compared with pediatric patients where severity is discussed as a gradient. A gradient is only interpretable if a baseline normal stroke volume is crossing the valve. The stroke volume can be altered in two major ways in pediatrics resulting in a pseudo low gradient. The first reason is depressed systolic ventricular function. For example, if a patient has critical aortic stenosis but is unable to generate any output, the aortic valve gradient will be 0 mmHg. The second reason is a “pop off” prior to the valve. An example of this phenomenon can be seen in older patients with aortic coarctation who develop collaterals proximal to the coarctation site. Other examples are a ventricular septal defect with aortic stenosis or an atrial septal defect with mitral stenosis. In a similar fashion, if the patient is anxious, anemic, or hyper-dynamic function, then the gradient will be over-estimated. The goal of stress echocardiography is to evaluate changes in valvular stenosis with increasing stroke volume, which in essence is testing the valve compliance. (Fig. 6).

Specific recommendations are made from adult 2020 ASE guidelines evaluating change in gradients. For the aortic and the mitral valve, a significant increase in gradient suggests two principles. The first principle is the concept of myocardial reserve and the second principle is that the valve has poor compliance and cannot be forced open. In general, a mean transaortic gradient of > 18–20 mmHg during exercise suggests a poorly compliant aortic valve (in aortic stenosis). A mean transmitral gradient of 15 mmHg seen in mitral stenosis during exercise and 18 mmHg during dobutamine stress echo is considered significant.

Lancellotti et al. studied 69 adult patients with asymptomatic severe aortic stenosis. In this study, patients who achieved a mean gradient greater than 18 mmHg had a statistically higher chance of having a cardiac event in the next 15 months (32). In 135 adult patients with aortic stenosis, Marechaux et al. showed that an increase in the exercise-induced mean gradient of more than 20 mmHg had a hazard ratio of 3.83 (33). In 98 pediatric patients with asymptomatic aortic stenosis, Naik et al. concluded that wall motion abnormalities and ST depression noted on stress echocardiogram may be helpful in detecting inducible myocardial ischemia and risk stratifying this population (hazard ratio of 12.0) (34).

6.3. Cardiomyopathy

Stress imaging has been used to evaluate the ventricular performance in systole and diastole with changes in preload, systemic, and pulmonary vascular resistance. The goal is to unmask dysfunction. This can be performed for all phenotypic forms of cardiomyopathy (hypertrophic, dilated, restrictive, and right ventricular).

6.3.1. Systology/cardiac reserve/contractility reserve

In evaluating systolic function, different echo parameters varying from the gold standard of ejection fraction to more advanced forms of tissue Doppler imaging/strain have been used. Strain is defined as local deformation of cardiac muscle compared with baseline (strain=change length/baseline length). When evaluating systole, the goal is to improve the stroke volume during exercise. Changes greater than 20% have been reported as normal. Stroke volume calculated by quantitative Doppler techniques (i.e. velocity time integral in cm of left ventricular outflow tract multiplied by its cross sectional area in cm^2) has been reported. If the stroke volume will not improve by 20%, it is considered an abnormal response. Changes of > 2% in global longitudinal strain are considered normal. If strain is less than 2% in primary mitral regurgitation, then this is considered abnormal. Myocardial contractility can also be evaluated by observing changes in muscle movement compared with calculated stroke volume changes. Systolic reserve was studied by radial strain analysis in 20 dilated cardiomyopathy adult patients with simultaneous catheterization data and dobutamine stress echocardiography. Minoshima et al. concluded that stress echo may provide insight to left ventricular systolic dysfunction (35).

6.3.2. Diastology

Diastology is a volume/pressure relationship that cannot be assessed in a static environment. The central venous pressure in a patient with right heart disease and volume depletion can be very low even in the setting of a “stiff” right ventricle. Evaluating the baseline diastolic mechanics compared with increasing the preload can unmask poor dynamic diastolic properties. This can be valuable in possible abnormal hypertrophic remodeling vs an athletic adaption (36).

This type of study is performed on a cycle ergometer. Baseline supine and upright diastolic parameters are obtained, specifically E/e’ (E=early trans-mitral diastolic velocity, e’=early tissue Doppler imaging velocity of the mitral valve annulus). In diseased patients, the mitral E velocity tends to increase with a disproportionate increase of the e’, resulting in an increase of the ratio. A ratio greater than 14 is suggestive of impaired dynamic diastolic dysfunction. Ryerson et al. studied 80 pediatric cancer survivors and risk stratified them based on anthracycline dosing. There was a baseline difference in diastology in the high risk group, which normalized compared with other groups with exercise (37). Although not performed with stress echo, this has been evaluated by stress magnetic resonance imaging in anthracycline exposure survivors by Kaneko et al. They concluded that impaired left ventricular contractility and functional reserve played a role in decreased exercise capacity (38).

6.3.3. Exercise induced left ventricular outflow obstruction

Evaluating exercise inducible left ventricular outflow obstruction is primarily performed in the symptomatic patient with hypertrophic cardiomyopathy. A test is considered positive in adults if a peak instantaneous gradient > 50 mmHg is induced (ASE guidelines, [8]).

Shah et al. studied 87 adult symptomatic patients with hypertrophic cardiomyopathy without left ventricular outflow obstruction (defined as a gradient > 30 mmHg). They were able to induce a left ventricular outflow gradient (> 30 mmHg) in about two-thirds of the patients with exercise. The concept was that the treatment goal to reduce the exercise induced gradient resulted in improved functional class and less syncope/presyncope (39).

Assaad et al. studied 91 pediatric patients with hypertrophic cardiomyopathy. The patients without inducible left ventricular outflow tract obstruction had better outcomes at 3 years of follow up. The patients with a high gradient at rest (≥ 30 mmHg) and with exercise (> 30 mmHg) had a 5-fold increased risk of developing symptoms or serious clinical outcomes (40).

6.4. Right ventricle/pulmonary hypertension

The response of the pulmonary vasculature to increasing pulmonary blood flow is a dynamic relationship. This was well illustrated in adult patients with normal versus pulmonary hypertension. Stress testing with or without imaging can aid in the longitudinal follow up of pulmonary hypertension. Lewis et al. showed the expected normal relationship to pulmonary arterial pressure with increasing cardiac output as well as the abnormal relationship seen in adult connective tissue patients with a steeper slope (Fig. 7) (41). Stress assessment in pediatric pulmonary hypertension is not indicated for diagnosis. It has not been shown to be a strong independent prognostic factor in pediatrics. Although 6-minute walk tests are primarily done/recommended for longitudinal follow up of patients with pulmonary hypertension, stress echocardiography can unmask an abnormal pulmonary vascular response (42).

A large study using stress echocardiography evaluated 4068 consecutive stress echocardiograms in symptomatic adults (chest pain/shortness of breath). They found a prevalence of 11.7% meeting echo criteria (tricuspid regurgitation > 50 mmHg), which correlated to 65% of those patients having abnormal hemodynamics in the catheterization lab. (43)

Moller et al. found 33% of patients with ventricular or atrial septal defects (ages 13-25 years) studied had an abnormal right ventricular pressure response (> 50 mmHg) (44). Grunig et al. has shown an abnormal response in patients at risk for high altitude pulmonary edema in 9 patients (45).

Evaluation of the right ventricular function has been performed in adults stress echocardiography for the primary indication of coronary artery disease. Different parameters have been reported in adults for the evaluation of the right ventricle including wall motion score index (WMSI), tricuspid annular plane systolic excursion (TAPSE), and fractional area of change (FAC) (4). In the pediatric literature, stress echocardiography of the right ventricle has been evaluated in Tetralogy of Fallot and heart transplant patients using tricuspid annular plane systolic excursion (TAPSE), fractional area of change, and right ventricular global strain (5).

7. Future directions

When evaluating complex pediatric patients for hemodynamics or inducible ischemia, standard exercise testing remains the work horse of testing. Standard stress testing replicates the most natural physiologic exercise state. The marriage of functional imaging modalities in past decades continues to be an evolving process. Strain rate (strain=change in length of muscle/baseline; strain rate is how the delta strain/over time) imaging in stress echocardiography has found its footing in the adult population. Conceptually, strain is not affected by global cardiac displacement or adjacent adhering fibrous structures like mitral annulus. Strain is shown to be a more accurate marker than tissue Doppler indices for detecting systolic regional myocardial dysfunction (46). Strain rate analysis with dobutamine stress echo can provide accurate assessment of myocardial viability (47).

Stress cardiac magnetic resonance imaging is the newest modality on the block and is likely superior but less available, requires more technical expertise, and is more expensive. Adenosine stress magnetic resonance imaging has been used in adults to assess risk stratification of coronary artery stenosis.

Noel et al. at Texas Children's have been using stress magnetic resonance imaging with pharmacologic agents in anomalous aortic origin of the coronary artery to assess inducible myocardial ischemia. In their opinion, stress magnetic resonance imaging is well tolerated and safe in pediatric patients and is reliably able to detect perfusion defects and wall motion abnormalities (48).

Stress magnetic resonance imaging has also been used in patients with Kawasaki disease. In 1 case series, 14 asymptomatic patients with Kawasaki disease were assessed with adenosine administration (coronary artery vasodilator resulting in coronary artery steal from diseased portions of the coronary arteries). Stress magnetic resonance imaging and gadolinium were performed. They found 1 patient with inducible ischemia and 1 patient with myocardial scarring. It should be noted that 8 patients had anesthesia (49).

In a larger study from the Netherlands, comprehensive magnetic resonance imaging with adenosine was performed on 63 patients with Kawasaki disease. They found 15 patients with aneurysms, 6 of whom with no prior evidence of aneurysms by echo. They found 4 patients with ischemia and 5 with scar. They concluded that comprehensive magnetic resonance imaging is a superior, non-invasive, and radiation-free modality that should be considered for long-term surveillance of patients with Kawasaki disease (50).

8. Conclusion

Stress echocardiography permits functional evaluation in dynamic settings, which may help unmask compromised myocardium. Although it is an adjuvant test, it can be a robust modality if driven by sufficient data and adequate training. A better understanding of the dynamic cardiovascular physiology can help in optimizing patient care and risk stratifying for sports participation in pediatric patients. Current stress echocardiogram guidelines are primarily oriented toward the adult population. Its meaningful extrapolation can be helpful only if we are able to pivot and adjust the available data to our heterogeneous pediatric population with varied disease processes.

Credit authorship contribution statement

Alejandro Arevalo: conceptualization, methodology, formal analysis, investigation, writing—original draft, writing—review & editing, visualization, supervision; **Peace C. Madueme:** Writing—review & editing; **Ronak Naik:** Writing—review and editing; **Kate Ingebretsen:** writing—review & editing; **Bahram Kakavand:** writing—review & editing; **Bradley Robinson:** methodology, formal analysis, investigation, writing—review & editing, supervision.

Declaration of competing interest

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Figure Legends

Fig. 1. Pediatric indications for stress echo in children and young adults at Boston Children's Hospital for evaluation of ischemia from 2006-2017 (n=924). Adapted with permission from Pellikka PA, Arruda-Olson, A, Chaudhry FA, et al. Guidelines for performance, interpretation, and application of stress echocardiography in ischemic heart disease. J Am Soc Echocardiogr. 2020;33:1-41. AAOCA, anomalous aortic origin of a coronary artery; ASO, arterial switch operation; FH, familial hypercholesterolemia; RT, radiation therapy to the chest; TGA, transposition of the great arteries

Fig. 2. Hemodynamic response to exercise (6,7). Top left panel: Systolic and diastolic blood pressure relationship with increasing aerobic exercise. Top right panel: Stroke volume relationship with increasing aerobic exercise. Bottom left panel: Total vascular resistance (Systemic and pulmonary vascular resistance) relationship with increasing aerobic exercise. Bottom right panel: Heart rate relationship with increasing aerobic exercise.

Fig. 3. Sample bicycle protocol used in our Pensacola lab. Watt ramp bicycle ergometer protocol chosen by age.

Fig. 4. Coronary artery distribution. Used with permission from Pellikka PA, Arruda-Olson, A, Chaudhry FA, et al. Guidelines for performance, interpretation, and application of stress echocardiography in ischemic heart disease. J Am Soc Echocardiogr. 2020;33:1-41.

Fig. 5. Stress echocardiogram of patient with coronary artery aneurysm secondary to Kawasaki disease. Top left panel. Normal resting apical 4-chamber views during systole. Top right panel. Peak exercise apical 4-chamber view during systole with arrows indicating severe hypokinetic LV segments. Bottom left panel. Normal resting apical 2-chamber views during systole. Bottom right panel. Peak exercise apical 2-chamber view during systole with arrows indicating severe hypokinetic LV segments (Image courtesy of Dr. Ronak Naik).

Fig. 6. Mixed aortic valve disease. Top panels – resting aortic valve peak systolic pressure gradient of 26 mmHg with mild aortic insufficiency. Bottom panel – at peak exercise aortic valve peak systolic pressure gradient increased up to 49 mmHg and aortic insufficiency became severe (Image courtesy of Dr. Ronak Naik).

Fig. 7. Pulmonary pressure response to exercise. Pulmonary arterial pressure (PAP) estimated by echo. Flow relationships based on serial measurements of mean PAP and cardiac output during incremental exercise. Normal subjects (□), patients with scleroderma with PAP in the lower normal range (◊) and upper normal range (♦), and patients with resting pulmonary arterial hypertension (PAH) (•) demonstrate approximately linear pressure-flow responses during exercise. Higher ΔPAP/Δ cardiac output (CO) than normal may be indicative of early pulmonary vasculopathy in the scleroderma groups. Data from (□) Reeves et al. (51), (◊,♦) Kovacs et al. (52), and (•) Janicki et al. (53). Used with permission from Lewis GD, Bossone E, Naeije R, et al. Pulmonary vascular hemodynamic response to exercise in cardiopulmonary disease. Circulation. 2013;128:1470-79.

Table 1. Stress echo hemodynamic cut off values (8).

Systolic function (flow reserve)	Stroke volume < 20%
Systolic function (contractile reserve)	ΔLVEF < 4–5% in MR/AR
	ΔGlobal Longitudinal strain < 2% in primary MR
	ΔWMSI< 0.25 in dilated CMP
Diastolic function	Average E/e' of >14 and TR velocity>2.8 m/s
Valve compliance	Change of > 18–20 mmHg (AS)
Systolic pulmonary hypertension	Systolic PAP > 50 mmHg
Intraventricular obstruction	LVOT gradient > 50 mmHg

AS, aortic stenosis; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; PAP, pulmonary arterial pressure; TR, tricuspid regurgitation; WMSI, wall motion score index; MR, mitral regurgitation; AR, aortic regurgitation; CMP, cardiomyopathy

Figure 1.

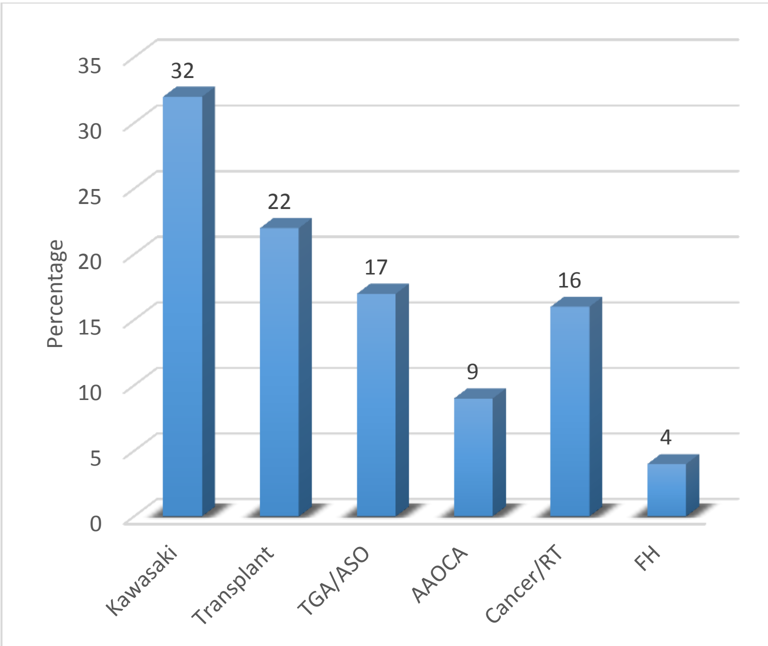

35
30
25
20
15
10
5
0
Percentage
32
22
17
9
16
4
Kawasaki
Transplant
TGA/ASO
AAOCA
Cancer/RT
FH

Figure 2.

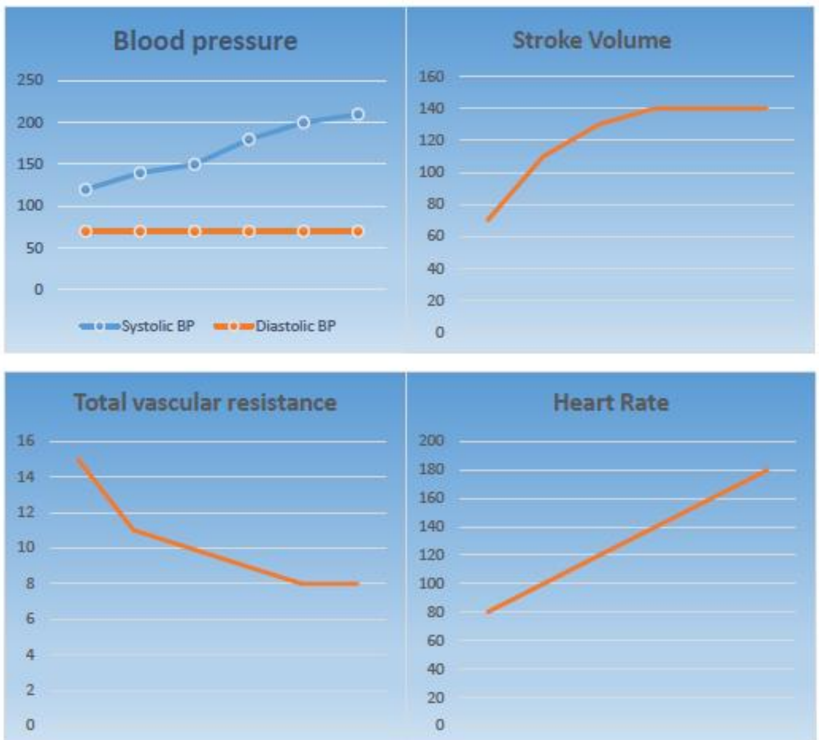

Blood pressure
250
200
150
100
50
0
Systolic BP
Diastolic BP
Stroke Volume
160
140
120
100
80
60
40
20
0
Total vascular resistance
16
14
12
10
8
6
4
2
0
Heart Rate
200
180
160
140
120
100
80
60
40
20
0

Figure 3.

Bicycle Protocol (Upright)										
STAGE	1	2	3	4	5	6	7	8	9	10
Watts (< 10 years)	5	10	15	20	25	30	35	40	45	50
Watts (> 10 years)	10	20	30	40	50	60	70	80	90	100
Minute	1	2	3	4	5	6	7	8	9	10
Maintain a rate per minute between 60–100 cycles.										

Figure 4.

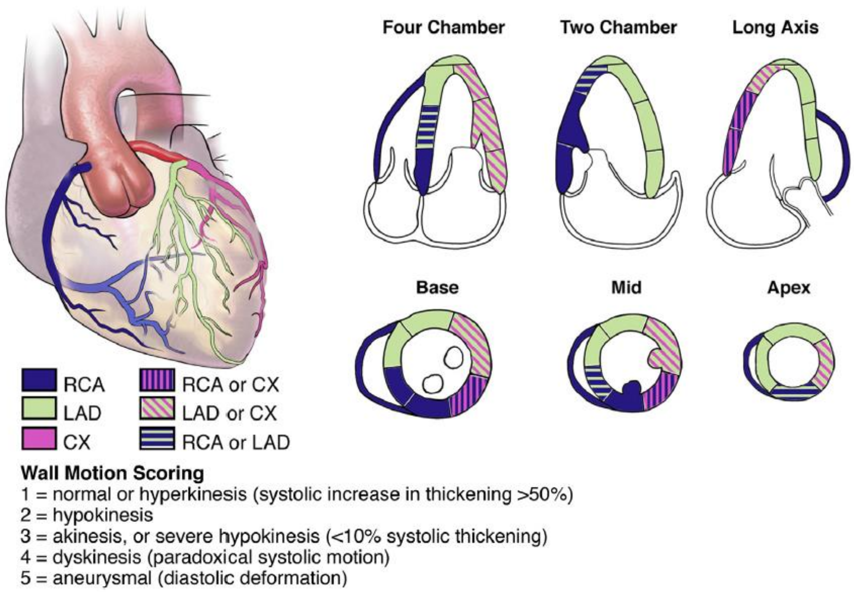

Four Chamber
Two Chamber
Long Axis
Base
Mid
Apex
RCA
LAD
CX
RCA or CX
LAD or CX
RCA or LAD
Wall Motion Scoring
1 = normal or hyperkinesis (systolic increase in thickening >50%)
2 = hypokinesis
3 = akinesis, or severe hypokinesis (<10% systolic thickening)
4 = dyskinesis (paradoxical systolic motion)
5 = aneurysmal (diastolic deformation)

Figure. 5

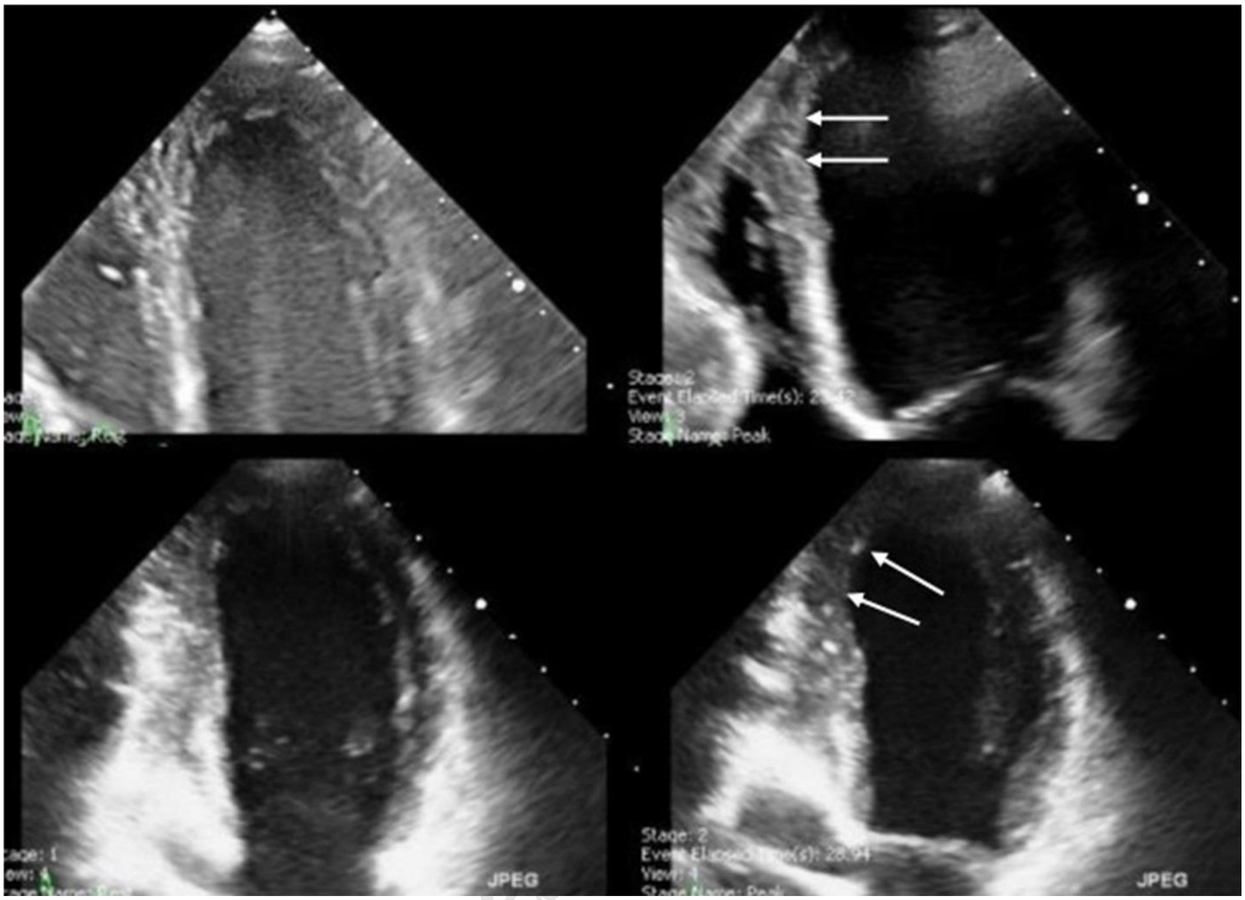

Stage: 2
View: 3
Stage Name: Peak
JPEG
Stage: 2
View: 4
Stage Name: Peak
JPEG

Figure. 6

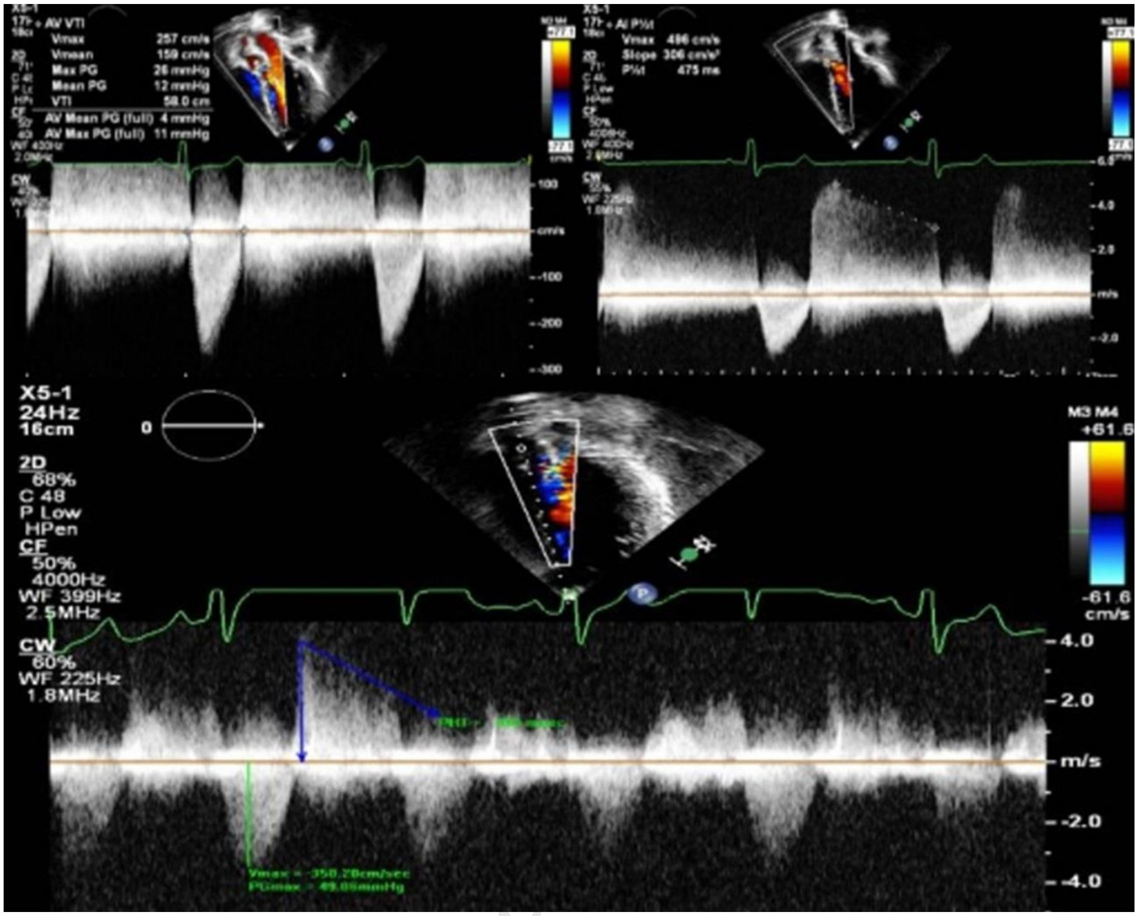
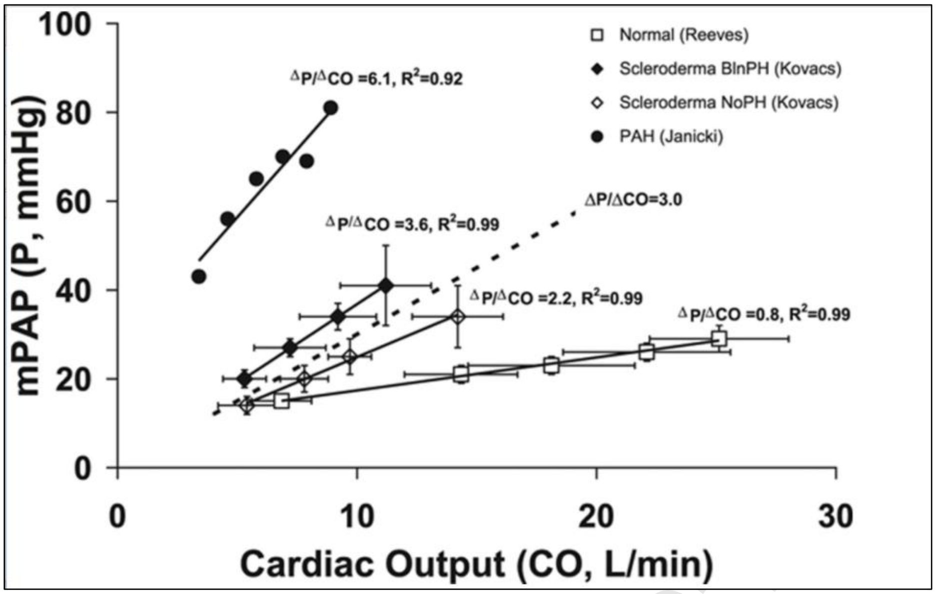

X5-1
24Hz
16cm
2D
68%
C 48
P Low
HPen
CF
50%
4000Hz
WF 399Hz
2.5MHz
CW
60%
WF 225Hz
1.8MHz
M3 M4
+61.6
-61.6
cm/s
4.0
2.0
m/s
-2.0
-4.0
Vmax 257 cm/s
Vmean 159 cm/s
Max PG 26 mmHg
Mean PG 12 mmHg
VTI 58.0 cm
AV Mean PG (full) 4 mmHg
AV Max PG (full) 11 mmHg
Vmax 496 cm/s
Slope 306 cm/s²
P½t 475 ms

Figure. 7


100
80
60
40
20
0
mPAP (P, mmHg)
0
10
20
30
Cardiac Output (CO, L/min)
Normal (Reeves)
Scleroderma BlnPH (Kovacs)
Scleroderma NoPH (Kovacs)
PAH (Janicki)
ΔP/ΔCO =6.1, R2=0.92
ΔP/ΔCO=3.0
ΔP/ΔCO =3.6, R2=0.99
ΔP/ΔCO =2.2, R2=0.99
ΔP/ΔCO =0.8, R2=0.99

Highlights

- Stress echocardiography is used to evaluate inducible ischemia and hemodynamics in pediatrics.
- Pediatric stress echocardiography is a safe and noninvasive modality.
- Pediatric stress echocardiography can help manage Kawasaki and heart transplant patients.
- Pediatric literature is scant and our review will give guidance to stress echocardiography.