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Keane: Nadas' Pediatric Cardiology, 2nd ed.

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SECTION VIII – Acquired Heart Disease

Chapter 22 – Innocent Murmurs, Syncope, and Chest Pain

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INNOCENT HEART MURMURS

Innocent heart murmurs occur in about half of all children. [1] [2] They occur in the absence of either anatomic or physiologic abnormalities of the heart and are not associated with subsequent cardiovascular disease. [3–5] The differentiation of innocent from organic murmurs for purposes of therapy, prognosis, and insurability is a leading cause for referral to a pediatric cardiologist (Exhibit 22-1). Discrimination of innocent from organic murmurs requires knowledge of the auscultatory findings in structural cardiac abnormalities, as well as of the characteristic findings of innocent murmurs. Innocent murmurs generally can be recognized using history, skilled physical examination including auscultation, and electrocardiography. [6–13]

EXHIBIT 22-1 -- Children's Hospital Boston Experience 1988-2002

Age First Seen (years) [□]	Congenital Heart Disease (n = 52,721)	No Significant Heart Disease (n = 6,902)	Mitral Valve Prolapse (n = 1,567)	Bicuspid Aortic Valve (n = 1,123)
	(%)	(%)	(%)	(%)
0–1	34	21	8	22
1–5	18	25	12	22
5–10	15	22	21	20
10–15	14	19	28	18
15–20	9	11	21	12
20+	10	2	10	6
% Male	50	56	42	71
% Female	50	44	58	39

* Age when patients were first seen by a cardiologist.

Prevalence

The reported prevalence of murmurs in the neonatal period varies widely, from 0.6% to 77.4%, with differing estimates probably attributable to differences in the frequency and timing of examinations, examining conditions, auscultatory skill, and the threshold for the inclusion of very soft murmurs. [14–18] The estimated likelihood of congenital heart disease among neonates with heart murmurs varies from about 1:2 to 1:12, with higher estimates occurring, not surprisingly, in studies in which residents or senior house officers detect murmurs under uncontrolled conditions. Echocardiography performed in newborn infants thought to have innocent heart murmurs reveals benign (physiologic) pulmonary branch stenosis in half, patent ductus

arteriosus in 60%, and patent foramen ovale in all.^[19] A heart murmur heard first at 6 months has been estimated to carry a 1:7 risk for structural heart disease, and one heard first at 12 months, only a 1:50 risk.^[15]

After infancy, the reported prevalence of innocent heart murmurs ranges between 17% and 66%, with most authors reporting between 40% and 60%.^{[1,] [2,] [20–23]} With exercise or with the use of phonocardiography, about 90% of children have murmurs.^{[22,] [24,] [25]} Even in reviews from cardiology referral centers, most children with newly referred murmurs have no significant heart disease.^{[13,] [22,] [26]}

Clinical Manifestations

General Characteristics

Innocent heart murmurs are always associated with normal heart sounds. The murmurs occur in systole, with the exception of the venous hum, which is continuous. Whereas organic murmurs may be of any length, innocent murmurs are usually brief, peaking in the first half of systole. Organic murmurs often have widespread transmission, with a pattern determined by the lesion, whereas innocent murmurs are often well localized, usually along the left sternal border. It is unusual for the grade of an innocent murmur to be greater than 3 (on a scale of 1 to 6). The murmur's intensity often changes with position and, occasionally, from examination to examination. With the exception of venous hums, there are no innocent thrills. Cyanosis should never accompany an innocent murmur. The quality of the innocent murmur is often vibratory and musical, or sometimes blowing, in contrast to the harsh quality of many organic murmurs. Independent predictors of structural heart disease during the first evaluation of children with heart murmurs at a tertiary pediatric cardiology center included specific features of the murmur (pansystolic timing, harsh quality, murmur intensity at least grade 3, and location at the left upper sternal border), as well as the presence of a click or abnormal second heart sound.^[13] In the future, screening of heart murmurs in children may be accomplished using artificial neural networks or automated spectral analysis.^{[27,] [28]}

The most common innocent heart murmurs are described below.

Still's Murmur

Still's murmur^{[3,] [29]} is most commonly heard in patients between the ages of 2 and 7 years. Characteristically, it is a grade 1 to 3, vibratory, buzzing, or twanging systolic ejection murmur, the quality of which is similar to that of a tuning fork. It is usually maximal between the third intercostal space, left lower sternal border, and apex; is much louder in the supine position than in the sitting position; and is characteristically louder with exercise, excitement, or fever. The intensity of ejection murmurs has been demonstrated by invasive phonocardiography to be greater above the aortic valve than above the pulmonary valve.^[30] The association of Still's murmur with false chordae tendineae in the left ventricle is controversial, with some authors finding a strong relationship^{[31,] [32]} and others finding a high prevalence of both Still's murmurs and false tendons in healthy hearts, but no association.^[33] The cardiac index of children with Still's murmur is similar to that of children without murmurs.^[34] However, individuals with Still's murmurs have been reported to have a significantly smaller mean ascending aortic diameter relative to body surface area, with higher average peak velocities in the ascending and descending aorta than are found in children and young adults without murmurs. These observations suggest that the origin of Still's murmur is in many cases related to a small aortic root and ascending aortic diameter with concomitant high-velocity flow across the left ventricular outflow tract and ascending aorta.^[35–38]

Physiologic Ejection Murmur

The physiologic ejection murmur, also called the *innocent pulmonic systolic murmur*, is identical in quality to the murmur of an atrial septal defect, comprising a murmur caused by flow through the normal pulmonic valve but associated with a normal second sound. Using phonocardiography, this murmur may be detected in most normal subjects.^[39] It is a grade 1 to 3, blowing, rather high-pitched, diamond-shaped murmur that always peaks in the first half of systole and is maximal in intensity in the second left intercostal space, without wide transmission. Like the Still's murmur, it is louder when the patient is in the supine position and is accentuated by exercise, fever, or excitement. The physiologic ejection murmur may be heard in children of any age and frequently occurs in children with asthenic builds who have narrow anteroposterior diameters or who have pectus excavatum. Studies with intracardiac phonocatheters have demonstrated that the physiologic ejection

murmur is located in the main pulmonary artery and is associated with the ejection of blood into the pulmonary artery.^[40] ^[41] The physiologic ejection murmur was the type of murmur most likely to be misdiagnosed by pediatric residents.^[42]

Cervical Venous Hum

The cervical venous hum^[4] is a continuous murmur with diastolic accentuation that may be elicited almost universally in normal children. It is located in the low anterior part of the neck, more often on the right than the left. The murmur is loudest with the patient in the sitting position and disappears or diminishes in the supine position. Usually the venous hum is accentuated by turning the patient's head away from the side of the murmur and elevating the chin. The murmur may be obliterated by pressing lightly over the jugular vein with the stethoscope or a finger. The mechanism of the venous hum has not been definitively delineated, although it has been postulated to be secondary to turbulence of venous flow in the internal jugular veins and, occasionally, in the external jugular veins.^[26] ^[40] ^[43–48]

Physiologic Pulmonary Artery Branch Stenosis of the Newborn

Physiologic pulmonary artery branch stenosis or peripheral pulmonary artery stenosis is heard in the newborn period as a low-frequency systolic ejection murmur maximal in the lateral chest, axillae, and occasionally the back, but is heard less well over the precordium itself. This murmur generally wanes by age 3 months and is believed to be caused by turbulence from the relative discordance in size between the larger main pulmonary artery and smaller branch pulmonary arteries.

Supraclavicular Arterial Bruit

The supraclavicular arterial bruit is a crescendo–decrescendo systolic murmur heard best just above the clavicles, usually on the right side more than on the left. It radiates better to the neck than below the clavicles and, very occasionally, can generate a faint carotid thrill. The bruit may be accentuated by exercise but is not affected by posture and respiration. It can be distinguished from the murmur of aortic stenosis by the disappearance of the supraclavicular murmur with the maneuver of hyperextension of the shoulders^[9] or compression of the subclavian artery against the first rib. Supraclavicular systolic murmurs have been postulated to arise from the major brachiocephalic arteries near their aortic origins.^[40] ^[49–51]

Laboratory Findings

Diagnostic testing should be tailored to the clinical situation. Most children older than 1 year of age can be evaluated with history, physical examination, and an electrocardiogram (ECG) alone. The qualifications of the examiner have been shown to have a major bearing on the ability to distinguish innocent from organic murmurs in children.^[42] ^[52] ^[53] In patients newly referred for evaluation of a heart murmur, the results of echocardiography are unlikely to change the clinical diagnosis of no significant heart disease when a pediatric cardiologist is certain of this diagnosis before echocardiography.^[7] ^[12] ^[13] Perhaps for this reason, it is more cost-effective for pediatricians to refer patients with newly diagnosed heart murmurs to pediatric cardiologists than to order two-dimensional echocardiograms.^[54] Heart disease is seldom diagnosed when a pediatric cardiologist orders an echocardiogram because of a family's or referring physician's anxiety if patients are older than age 6 weeks with innocent-sounding murmurs and have no worrisome signs or symptoms.^[12] Conversely, the threshold for performing a two-dimensional echocardiogram should be low in patients with innocent-sounding heart murmurs on skilled auscultation when structural heart disease is suspected by a pediatric cardiologist because of young age or worrisome history, signs, symptoms, or abnormalities on electrocardiography or chest radiography.^[12] In general, echocardiography for evaluation of heart murmurs after infancy in the outpatient setting should be performed if, after skilled clinical assessment, the pediatric cardiologist believes echocardiography is useful because of uncertainty in the diagnosis or to delineate the nature of suspected heart disease.

Management

For children younger than 2 years old in whom the diagnosis of innocent murmur is first made, the authors recommend reevaluation after 2 or 3 years if the murmur persists. Children older than age 2 years do not require reevaluation unless some uncertainty exists (e.g., because of suboptimal patient cooperation or a

possible abnormality on a diagnostic test).

It is of the utmost importance to reassure the family of a child with an innocent murmur. The label of heart disease may have adverse effects on the child and the family. ^[55] ^[56] Even temporary mislabeling may increase the morbidity from cardiac nondisease. ^[57]

Prognosis

The reliability of the diagnosis of "innocent" heart murmur on initial evaluation by a pediatric cardiologist is supported by published follow-up and actuarial studies. Follow-up studies of series of patients diagnosed as having innocent murmurs have confirmed the original diagnosis in 97% to 100% of the patients. ^[58] ^[59] Furthermore, actuarial data on people with systolic murmurs thought to be innocent show no deviation from the expected mortality—a discovery that led to a decision to remove restrictions on insurance and employment for those with innocent murmurs. ^[60]

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SYNCOPE

Definition

Syncope is the transient and abrupt loss of consciousness resulting from a decrease in cerebral blood flow, resulting in collapse and relatively prompt recovery over a period of seconds. Syncope should be distinguished from cardiac arrest in which the collapse requires intervention or results in significant end-organ damage. *Presyncope* or *near syncope* has symptoms including dizziness and visual changes that suggest an impending faint, but that do not progress sufficiently to result in collapse. Although these definitions are clear in the abstract, frequently the history is sufficiently vague that the primary question is how to classify a spell.

Incidence

Syncope is common, with a peak incidence in adolescent girls and a lower but increased incidence in toddlers. Many faints, appropriately, are managed without seeking medical care and if those are included, as many as 25% of adults will have had at least a single episode of fainting during childhood and adolescence, and 10% to 40% of adolescents will either faint or have significant presyncopal symptoms with provocative testing.^{[61.] [62]} About 1 in 1000 seek care for syncope each year.^[63] In toddlers with pallid breath-holding spells, boys and girls are equally affected, with the incidence of at least some symptoms being as high as 5%.^[64] By school age and adolescence, there is a marked female predominance, which extends well into adult life. The incidence of syncope remains relatively steady in early adult life, before gradually and steadily increasing in older age.^[65] Syncope represents a common cause of referral for patients seen in the cardiology outpatient setting at Children's Hospital Boston, with 3820 clinic visits in 1923 patients over 13 years, or 5% of all new patients.

This high incidence of syncope contrasts with the exceptionally low incidence of sudden death and aborted sudden death (1 per 100,000 patient-years) in the pediatric and young adult population.^{[66.] [67]} The incidence of sudden cardiac death remains low (about 1 per 100 patient-years), even in most patients with significant heart disease. Nonetheless, *syncope with heart disease or syncope closely associated with exercise represents clear risk factors for sudden death and serious heart disease.*^{[63.] [68]} Resolving the overall low incidence of serious outcomes and the high incidence of potentially serious symptoms represents the primary challenge of evaluating these patients.

Physiology

The core physiology of any true syncopal event is abruptly ineffective cerebral blood flow resulting from ineffective cardiac output or cardiovascular control.

Cardiac syncope occurs secondary to combinations of obstruction to left ventricular filling (pulmonary hypertension, tachycardia), left ventricular ejection (aortic stenosis or hypertrophic cardiomyopathy), or ineffective contraction (profound bradycardia, dilated cardiomyopathy, pathologic tachyarrhythmia) with an underlying substrate of either structural, functional, or electrical heart disease. By definition, these episodes are transient.

Common fainting, or *neurally mediated syncope*, goes by many names, some of them emphasizing the dominant line of disordered cardiac and vascular regulation that results in symptoms. These include *vasovagal syncope*, *cardio-inhibitory syncope*, *pallid breath-holding spells (or reflex anoxic seizures)*, *vasodepressor syncope*, *postural orthostatic tachycardia syndrome*, and many others. Although there are clear distinctions between both the clinical manifestations and the patients who demonstrate each subtype of physiology, the summary terminology of neurally mediated or neurocardiogenic syncope emphasizes the inter-relationships between each kind of syncope.

The most classic form of syncope, often called *vasodepressor* or *vasovagal syncope*, is initiated by blood pooling in the extremities, typically with standing. That results in decreased right ventricular and, several heart beats later, left ventricular filling, which in turn triggers combinations of left ventricular sensory activation to the brain stem, combined with carotid body and carotid sinus activation. Each of these initially results in decreased vagal and parasympathetic activation and increased sympathetic and catecholamine activation to raise heart rate, increase venous and arteriolar tone, and enhance left ventricular contractility. When these are sufficient, there is a modest increase in heart rate and narrowing of pulse pressure with an effective transition to upright posture. When the initial homeostatic responses are either inadequate or exaggerated, the homeostatic control mechanisms increase their efforts to maintain adequate blood flow; however, these same mechanisms can produce paradoxical parasympathetic (vagal) stimulation, resulting in heart rate slowing, with or without sympathetic withdrawal resulting in decreased vascular tone and lower blood pressure. External influences, including anxiety and hyperventilation, can exacerbate these responses. Active use of the skeletal muscle pump (jogging, isometrics) can enhance venous return and raise systemic blood pressure, blunting the initial responses. Medications or concomitant medical disorders can also exacerbate or blunt the cyclic swings in cardiac and vascular control. Implicit in this summary is the view of cardiac physiology as a series of inter-related sensors and amplifiers, so that the specific clinical manifestations are the result of dynamic control, including but not limited to the baroreflex, not of simple action-reaction reflexes. [69]

Clinical Manifestations

Overview

Cardiac syncope is characterized by an abrupt onset of collapse with few premonitory symptoms. The typical history is one of acute collapse, often with activity or exercise, with nearly immediate recovery. Palpitations are sometimes noted, but are not diagnostic in any clear fashion. When there is significant residual of confusion, disorientation, or need for CPR the event is best classified as aborted sudden cardiac death. For transient events, recovery is similarly rapid. While symptoms of palpitations, occurrence with exercise, injury, urinary incontinence and an onset while sitting or supine all increase suspicions of a serious arrhythmia, none are diagnostic (Table 22-1). Indeed the responses to arrhythmias, and other transient impairments in cardiac output, are in part determined by the effectiveness of baroreflex controls. Hence the most critical distinction is whether there is historical or exam evidence of heart disease.

TABLE 22-1 – Relative Frequency of Premonitory Symptoms and Residual Findings in Patients with Common Neurally Mediated Syncope and those with More Serious Cardiac Syncope

	Neurally Mediated	Cardiac Syncope
Symptoms		
Premonitory Symptoms	+++	?
Lightheadedness	+++	+/?
Palpitations	+	++
Occurs while upright	+++	+
Occurs while sitting	+/?	+
Emotional Trigger	++	++
Exercise Trigger	+	++
Residual Findings		
Pallor	+++	+/?
Incontinence	–	+
Disorientation	–	+

Fatigue	++	?
Diaphoresis	++	?
Injury	+	++

+++ Very common (> □ 50%); ++ common (> □ 20%); + not rare (> □ 5%); ? uncommon (< 5%); - rare (< □ 1%).

Neurally Mediated Syncope

Typical adolescent syncope has a history that is almost pathognomonic. An adolescent girl, having been standing upright on a hot day, possibly at chorus or band practice, has pre-monitory symptoms of feeling warm, constriction of visual fields with the "world going dark" and nausea with a sense that her heart is pounding hard. She may attempt to move away from where she is standing and walk to the nurse's office but turns pale and falls, with only a brief period of unconsciousness. When she recovers, she continues to feel somewhat dizzy, remains pale for minutes and is typically exhausted, often is diaphoretic and clammy, sometimes with a headache. While she has occasional "head rushes" when she stands, she generally feels terrific, is active in school, and has minimal additional medical concerns. With that history, sufficient evaluation is comprised of a normal detailed physical examination, including orthostatic heart rate and blood pressure, dynamic cardiac auscultation, a normal ECG, a reassuring family history focusing on a sibling and parental history of adolescent syncope^[70] (common), and of sudden cardiac death (a worrisome finding). For single episodes, the only important reason for referral is parental or patient anxiety.

Convulsive Syncope

Acute pain, anxiety, or other less clear provocation can trigger acute vagal activation resulting in cardiac slowing and sometimes dramatic cardiac pauses captured on event monitoring or during head-up tilt (see Fig. 22-1). When induced during head-up tilt, there are often presyncopal findings of relative hypotension and cyclic heart rate accelerations. These dramatic events can result in opisthotonos that mimics a seizure, often triggering the rescue squad and emergency room evaluation. While these spells can be highly suggestive of cardiac syncope and deserve thoughtful consultation, many children will have no heart disease and a favorable prognosis. While prolonged pauses can be seen in as many as 5% of head-up tilts,^[71] but this finding is neither reliably reproduced nor predictive of clinical course in children and adolescents. The precise mechanisms of this dramatic response are complex, as patients have been observed with both sinus tachycardia and profound AV block. This variable rhythm, combined with the failure of pacemakers to completely eliminate symptoms in syncope,^[72-74] emphasizes both the dynamic nature of the physiology and the importance for careful symptom/rhythm correlation.

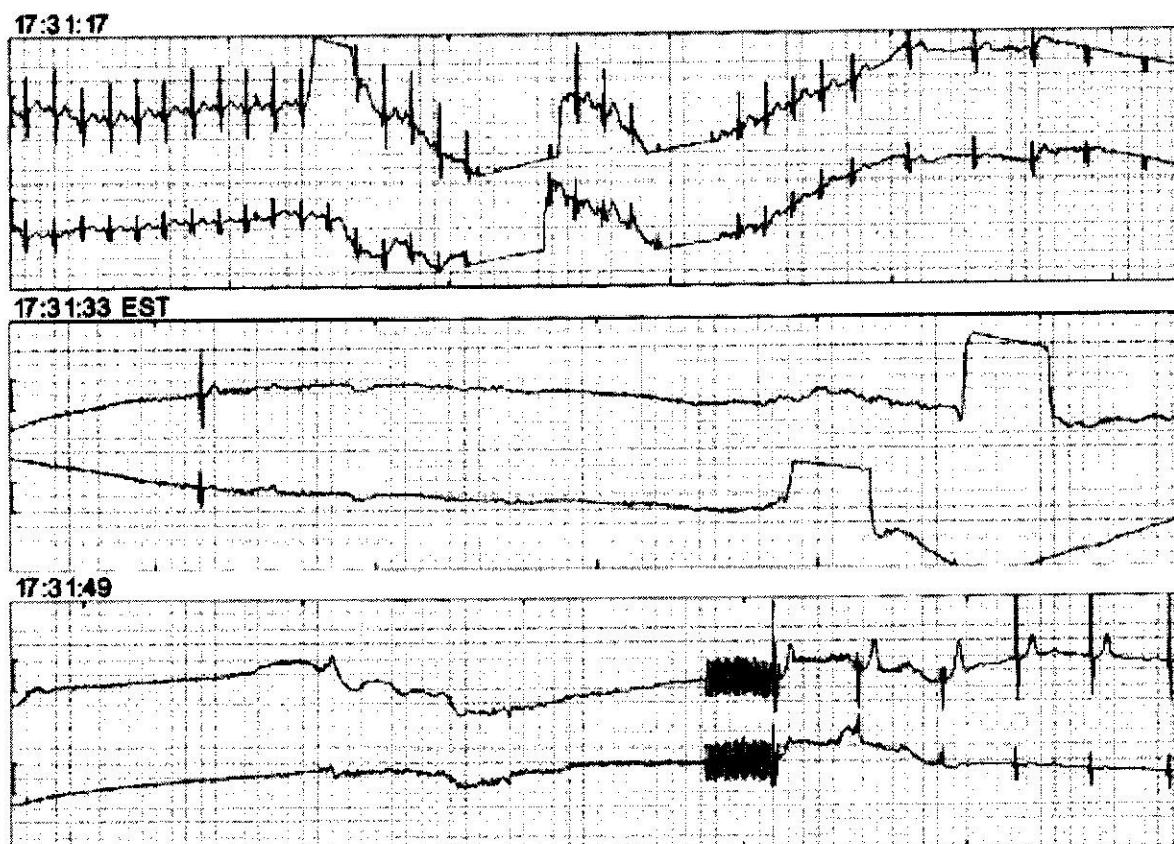


FIGURE 22-1 Recording from a memory looping event monitor of a toddler with recurrent spells with negative neurology evaluation. There is brief sinus acceleration before dramatic sinus slowing with associated motion artifact. The second panel demonstrates a 2-second pause, a single escape beat, and a second 23-second pause before gradual recovery that includes continued sinus bradycardia with a junctional escape rhythm. This pattern is repeated on subsequent spells, confirming the diagnosis of pallid breath-holding spells.

Postural Orthostatic Tachycardia and Recurrent Symptoms

A syndrome of recurrent postural orthostatic tachycardia, characterized by a greater than a 30 to 40 beat/minute heart rate increase with a 6-minute stand test, similar findings on head-up tilt, and multiple symptoms, is well described in young adults^[75] and has been observed in adolescents, some of whom are quite disabled by their symptoms and may be determined to have chronic fatigue syndrome.^{[76.] [77]} Although many of these patients have minimal actual syncope, they have recurrent presyncopal symptoms that may be manifest as palpitations or exercise intolerance. Like other syncope patients, they have an adolescent female dominance. Typically, the referring physicians already have excluded thyroid disease, anemia, and the other obvious causes of this chronic disorder. Recognition can allow some focus to subsequent diagnostic and therapy choices.

Exercise-Induced or Exercise-Associated Syncope

The rare deaths that have been reported in adolescents with syncope invariably highlight that *syncope with exercise is a worrisome finding*.^{[63.] [68]} Hypertrophic, dilated, and electrical myopathies all can present with exercise-associated syncope with no prior symptoms. All patients with syncope associated with exercise deserve prompt cardiac referral and additional testing with at least an echocardiogram if no diagnosis is apparent on initial evaluation.

Exercise also represents an almost optimal trigger for neurally mediated syncope. Particularly with highly dynamic sports like distance running, the cardiovascular response to exercise is to vasodilate, increase sympathetic output, and shift blood flow to the legs. During running, the skeletal muscle pump action of the

leg muscles enhances venous return, facilitating increased cardiac output. Immediately after exertion, that pump function is decreased or absent and can permit the same reflex responses seen in any other example of venous pooling. When an initial evaluation does not identify clear heart disease, most cases of exercise-induced syncope can eventually be demonstrated to be some form of neurally mediated syncope. [68.] [78.] [79.]

Psychogenic Syncope and Situational Syncope

The relationship between fainting and "nerves" is not always as obvious as it eventually becomes. There are numerous examples of convulsive events and faints triggered by acute anxiety and resulting in prolonged cardiac pauses. In those cases, the emotional trigger (e.g., the sight of blood) results in the physiologic event of profound bradycardia.

More problematic are patients in whom some of the events seem to be typical neurally mediated syncope, but over time, there is acceleration and potential embellishment of the symptoms, so that some events seem to result from panic or anxiety. The history in this setting does not make sense; physical examination, laboratory testing, and monitoring are neither consistent nor diagnostic of clear pathology. In young adults, measures of anxiety are a better predictor of future faints than syncope during head-up tilt. [80.] In practice, this interaction is often easy to recognize, but may be difficult to prove.

Toddler Syncope

Variously called *pallid breath-holding spells*, *white syncope*, *reflex anoxic seizures*, and *toddler syncope*, there is a well-recognized, generally stereotypical syndrome of paroxysmal collapse in toddlers. [64.] [81.] Repeated spells are often referred to cardiologists or neurologists for further evaluation. In the typical spell, a trivial physical or emotional trauma triggers an aborted cry, opisthotonic stiffening, and pallor that resolves over about a minute and is often followed by sleep. Rarely, such spells trigger true seizures. They contrast and overlap with classic breath-holding spells, with ongoing crying with cyanosis, breath-holding, and then symptoms. Onset is typically between age 6 months and 3 years, with termination in more than 65% of cases by age 5 years and in the vast majority by age 8 years, after which they would generally be classified as convulsive syncope. Nearly 20% of toddlers with breath-holding spells have some syncope as adolescents.

When isolated and typical, toddler syncope is generally managed by the primary care physician with little formal investigation. When recurrent, evaluation for anemia, [82.] [83.] arrhythmia, and epilepsy is appropriate. Iron therapy may be useful, but efficacy has been more impressive in developing countries than in recent U.S. experience. Although the level of bradycardia can be quite impressive, most toddlers have infrequent episodes that resolve without specific therapy.

Diagnostic Evaluation

Similar to the experience in evaluating heart murmurs in the minimally symptomatic child, the diagnosis of neurally mediated syncope can be confidently made in most children with a detailed history, physical examination, and ECG. In 480 patients referred to a pediatric cardiology practice for syncope, 22 (5%) had cardiac syncope. Of those, 21 were identified either by the historical linkage to exercise (10 of 153, 6%), abnormal ECG, [16.] [69.] a concerning family history of arrhythmia, or abnormal physical examination.

The history is the critical test and focuses on triggers, presyncopal symptoms that can serve as both clues to the physiology and a proxy for therapy efforts, and some assessment of the severity of symptoms. A 10-point visual analogue scale (0, no symptoms, 10 constant dizziness and recurrent syncope) allows rapid self-assessment and a quick way to track symptoms over time. Family history focuses on a history of sudden unexpected death before age 40, congenital deafness, or cardiomyopathy, all of which are worrisome, and the common history of recurrent adolescent or toddler syncope that was outgrown.

Physical examination should include orthostatic vital signs, repeating heart rate and blood pressure supine, then having the patient move directly to standing and repeating the heart rate and blood pressure at 1 and 3 minutes. A brief neurologic examination is appropriate, as is a detailed cardiac examination in several positions, examining for transient murmurs from dynamic subaortic stenosis and mitral valve prolapse. Focused history and examination should explore signs and symptoms of systemic disease, connective tissue disorders like Marfan syndrome, and underlying eating disorders.

Electrocardiography

The ECG is examined for left ventricular hypertrophy, Wolff-Parkinson-White syndrome, atrioventricular and interventricular conduction defects, and electrical myopathies, most notably long QT syndrome. The ECG is an imperfect screen for hypertrophic cardiomyopathy and has no value in screening for most coronary anomalies that present after the first year of life. It is not surprising to see somewhat prominent respiratory sinus arrhythmia. For patients with combinations of borderline ECGs or worrisome family histories, ECGs on siblings and parents are useful tools. Ambulatory ECG monitoring, including 24-hour Holter monitors, portable event monitoring,^[84] and rarely implantable loop recorders,^[85] can each be useful in correlating clinical symptoms with arrhythmias, although, like echocardiograms, the primary yield is demonstrating the absence of serious disease.

Echocardiography

Routine echo screening with syncope referred to pediatric cardiology has a low yield, 5% in those with normal screening examinations, with most of those findings representing minor valvular findings that are unrelated to the syncope.^[68] A careful echocardiographic examination, including examination of the coronary origins,^[86] is indicated when the history, physical, ECG, or family history is suggestive of cardiac disease or cardiac syncope, or when the frequency of the episodes is becoming worrisome.

Cardiac Catheterization

For patients with structurally and functionally normal hearts by echocardiogram, nondiagnostic or normal ECGs, and unrevealing ambulatory monitoring, there is little to no yield in cardiac catheterization, even if it includes programmed electrical stimulation. Most pediatric echo laboratories can adequately image the coronaries to exclude anomalous coronaries. Other diagnoses are effectively excluded by echo or may require drug challenges.

For patients with congenital heart disease, particularly those with combinations of syncope, palpitations, nonsustained ventricular tachycardia, or other arrhythmias, cardiac catheterization, including programmed atrial and ventricular stimulation and appropriate hemodynamic evaluation, is indicated.^[87] The role of catheterization in evaluating arrhythmia risk in patients with cardiomyopathy remains poorly defined.

Other Studies

Head-up tilt testing is an effective way to recreate neurally mediated syncope and can be effectively performed in adolescents.^[88] Unfortunately, these same maneuvers can induce syncope in completely asymptomatic adolescent volunteers,^{[61,] [62]} of whom up to 40% will have presyncopal symptoms with a 70-degree tilt.

Because of the high incidence of false-positive results, head-up tilt testing cannot be viewed as a diagnostic test. Rather, it should be used as confirmatory test or a physiologic probe. At Children's Hospital Boston, the test has evolved as a way of exploring challenging and recurrent symptoms.

Treadmill exercise testing has a poorly defined role in evaluating patients with syncope. It has advantages of being relatively nonthreatening, easy to obtain, and a reasonable screen for a number of occult arrhythmias. In some series, as many as 15% to 20% of syncope patients recreated their symptoms during or immediately after exercise. At Children's Hospital Boston, exercise testing is obtained more frequently than head-up tilt testing in patients with problematic syncope, although it is still performed in less than 5% of syncope patients.

Management

For cardiac syncope, therapy is directed at the underlying disorder. For neurally mediated syncope, the episodic, self-resolving nature of the disorder contributes to inadequate double-blind, placebo-controlled data regarding therapeutic choices in adults and even fewer data in children. Therapy recommendations are based on limited series, more limited trials, and rational planning based on the clinical physiology.

Nonpharmacologic, Nondevice Therapy

Education regarding the nature of syncopal events and ways to either prevent or abort spells represents the cornerstone of therapy. Most patients will have significant relief with a combination of *overhydration*, including increased fluid, decreased caffeine, and increased sodium intake, and *antigravity maneuvers*, including isometric leg or arm contractions, staged shifts from supine to upright, squatting or lying down with onset of presyncopal symptoms, and possibly use of compression stockings. In difficult cases, "tilt training" with supervised upright time leaning against a wall^[89] can be beneficial. Upright, weight-bearing aerobic exercise may also be beneficial.^[90] Education on these techniques can also be diagnostic because symptoms caused by arrhythmia will not be reliably eliminated by these maneuvers.

For many cases of situational syncope and certainly for hysterical or psychogenic fits, behavioral therapy is critical. When patients will not accept a purely behavioral approach, many accept a combined approach of modest medical therapy along with a cognitive-behavioral approach through psychiatry.

Drug Therapy

Pharmacologic management focuses on volume enhancement, limiting excessive catecholamine drive, blood pressure augmentation, and rarely anticholinergic therapy. In refractory cases, the effects of these agents appear at least additive, and many have been used in combination.^[91]

Volume enhancement using fludrocortisone represents a mainstay in therapy.^[92] An essentially pure mineralocorticoid, fludrocortisone appears to work by increasing blood volume by enhancing sodium renal reabsorption. Advantages include rare side effects, once-daily dosing, and low cost. Disadvantages include slow onset of action and, particularly with higher doses, the potential for chronic hypokalemia or chronic hypertension, although the incidence of those side effects is low.^[93] Low doses, by themselves, are ineffective for severe postural tachycardia symptoms.^[94]

Use of β blockers has a long history of apparent success in pediatric syncope,^[95] and atenolol is neither superior nor inferior to fludrocortisone in a small pediatric series.^[92] The use of β blockers for syncope aims at decreasing excessive catecholamine stimulation and hence blunting catecholamine-mediated vasodilation and potentially cardiac sensory triggers associated with a hyperdynamic, underfilled left ventricle. Several recent randomized trials in adults have shown no benefit^[96, 97] to nonselective β blockers. Pindolol, a unique agent with intrinsic sympathomimetic activity, may have some clinical advantages.

Midodrine hydrochloride is a unique prodrug that is metabolized into a peripherally active direct α_1 agonist. It has been useful in repeated trials of adults with neurally mediated hypotension.^[98, 99] Side effects are related to its direct drug effects and include piloerection, scalp itching, and rarely urinary symptoms. Advantages of midodrine include its direct and rapid action, allowing titration when required, and the very narrow therapeutic effect. Disadvantages include a short duration of action (3 to 5 hours) and high cost, limiting its use to highly symptomatic and highly motivated patients.

Limited case series, almost always in highly symptomatic patients, have used selective serotonin reuptake inhibitors, erythropoietin, and disopyramide.

For highly refractory syncope with documented, clinical pauses, both ventricular and dual-chamber pacing have been effective at decreasing, but not eliminating, symptoms. The published pediatric experience is very limited, and at Children's Hospital Boston, this indication for pacing was present in 12 of 497 patients treated with permanent pacemakers. When focusing on the specific indication for pacing of toddlers with pallid breath-holding spells, either ventricular or dual-chamber pacemakers can eliminate the seizure-like events in most severe cases, limiting them in the remainder.^[74, 100] Although highly effective in the most difficult cases, it is critical to note that the Mayo clinic implants about one pacemaker a year for this indication.^[101]

Course

Neurally mediated syncope is not associated with increased risk for mortality. Toddlers with breath-holding spells are more likely to have neurally mediated syncope than adolescents, but symptoms resolve in most by age 4.^[64] Most adolescents, even those most disabled, appear to outgrow their episodes over several years. For teens, improvement may result from effective use of behavioral and physical approaches to their symptoms. The episodic nature of syncope, its benign natural history, and the lack of perfect drug therapy

lead to an initial nonpharmacologic approach. When drug therapy is needed, therapy is typically continued for about 1 year, followed by trials of decreasing therapy.

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CHEST PAIN

After murmurs, chest pain in children and adolescents is the most frequent complaint leading to referral to a pediatric cardiologist.^[102] In most cases, the pain is not related to a serious underlying cause, and cardiac origins of chest pain are infrequent^[103]; however, accurate assessment of the clinical presentation is essential so that pathology is not overlooked. By the time a patient reaches the cardiologist, the anxiety level of the family is high, reinforced by knowledge that cardiac causes of chest pain in older individuals can be life threatening. Therefore, appropriate care for this group of patients must address not only the etiology but also reassurance about the nature of what is often a self-limited condition.

Epidemiology

Depending on the point of entry to the medical system, the epidemiology of chest pain varies in children. Estimates suggest that chest pain is the primary complaint in 650,000 pediatric encounters yearly,^{[104,] [105]} with such complaints accounting for 5% to 15% of patients referred to a pediatric cardiology clinic.^{[106,] [107]} Cardiac causes of chest pain in younger patients presenting to emergency rooms are sparse, constituting only 1% of patients evaluated in one review with idiopathic (21%) or musculoskeletal (5%) etiologies far more common.^[108–110]

Etiology

Noncardiac Causes of Chest Pain

Chest Wall. Pain attributable to the chest wall is the most common explanation in the pediatric age range, seen in as many as 31% of patients,^{[109,] [111]} and may involve connective, bony, or muscular tissue. The underlying cause can be traumatic or atraumatic. Costochondritis related to inflammation at the costochondral junction is a common explanation for chest pain, particularly in adolescents, and can be traced to traumatic strain in athletes or lifting of relatively heavy objects.^[112–114] Precordial catch syndrome is generally sharp pain of short duration and unclear etiology isolated to the left lower sternal border or apex that is sometimes exercise induced and may recur.^[115–117] Some patients are able to relieve the pain with deep inspiration. Slipping rib syndrome is pain caused by trauma or tension on the fibrous connections to the 8th, 9th, or 10th ribs. These ribs are not attached to the sternum but to each other, and with unrestrained motion of a rib, pain is produced by irritation of the intercostal nerves.^[118–120] The pain can be sharp or dull and is sometimes reproducible. The sternum itself can be the source of chest pain with a uncommon condition known as *hypersensitive xiphoid* that improves spontaneously.^[121] Pectus deformities of the chest wall can be associated with occasional pain that may be accentuated by exercise.^{[122,] [123]} Sickle cell disease is associated with acute chest syndrome, an important cause of death in this group of patients and frequently responsible for hospital admissions.^{[124,] [125]} The etiology of the pain remains unclear, with episodes attributed to fat embolism, infection, or bony infarction.^[126] Aggressive therapy with prophylactic transfusion and hydroxyurea has been used successfully to reduce frequency of these episodes.^{[127,] [128]} Breast conditions may produce pain in both males and females, although far more commonly in the latter. Causes include infection, pubertal or menstrual change, and pregnancy. Traumatic chest pain is very common in adolescents related to muscular strain or tears, rib fractures, or spasm. Such pain is almost always self-limited.

Pulmonary. Underlying pulmonary pathology leads to chest pain in a variety of settings. Reactive airway disease causes pain related to strain from persistent cough, dyspnea, or pneumothorax. In particular, exercise-induced bronchospasm is present in many children and adolescents, limiting their ability to participate in sports. Pretreatment with bronchodilator therapy may avert recurrent episodes.^{[129,] [130]} Pneumonia is associated with chest pain in many patients in the setting of acute febrile illness. Chest pain is a frequent presenting symptom after a pulmonary embolus. Although uncommon, a family history of

hypercoagulability may provide insight into the diagnosis. Pleural disease is associated with chest pain that may be acute in onset, accentuated by inspiration and prolonged in duration. Pleural effusion is most frequently of infectious origin but can also be produced by systemic inflammatory conditions or malignancy. Pleural irritation can also result from pneumothorax producing inspiratory pain; however, the pain can also be referred to the shoulder from diaphragmatic irritation. Pneumothorax can present spontaneously in Marfan syndrome^[131] and cystic fibrosis,^[132] or it may follow trauma.

Gastrointestinal. Chest pain may derive from a number of common gastrointestinal conditions.

Gastroesophageal reflux with esophagitis produces a burning sensation in the retrosternal area, sometimes exacerbated by supine positioning.^[133]^[134] Signs of reflux in infants include arching of the back with feeding, spitting or recurrent vomiting, and respiratory changes related to aspiration, including wheezing and rhonchi. Peptic ulcer disease most frequently associated with *Helicobacter pylori* infection can be an important source of pain localized to the epigastric region or lower chest.^[135] Spasm of the esophagus can produce marked chest pain.^[133] When a possible gastrointestinal source of pain is suspected, evaluation of both motility and tissue involvement is warranted using manometry and endoscopy with biopsy.

Psychogenic. Among pediatric patients presenting to a cardiology clinic with chest pain, a substantial number have symptoms that are psychogenic in origin.^[108]^[109] The history can pinpoint a preceding event that can act as a trigger for the pain, including death of a friend or family member, divorce or separation, illness or trauma in a family member, or depression.^[136]^[137] Chest pain can present as a symptom in hyperventilation syndrome. Despite the inclination to ascribe the complaint to a nonorganic cause, the provider must consider the social setting. Family members are generally very anxious about the possibility of underlying organ pathology and may not be ready to accept an alternate explanation. Often, reassurance about the anticipated benign outcome is helpful. Adolescents with chest pain frequently believe they have heart disease and tend to change their lifestyle as a result.^[138] In some cases, it may be necessary to obtain some noninvasive testing to provide support for the absence of underlying disease. Several encounters may allow the development of trust and rapport, so that the family is more amenable to a diagnosis of psychogenic origin and likely to seek further counseling if necessary.^[139]

Cardiac Causes of Chest Pain

Myocardial. Cardiomyopathy, either hypertrophic or dilated, is associated with chest pain. The pain is the result of imbalance between myocardial demand and cardiac output. In the former case, marked increase in myocardial oxygen demand exceeds coronary flow during exercise, resulting in angina. Mid-cavitary obstruction exacerbates the imbalance, leading to increased myocardial work and myocardial oxygen consumption. In addition, coronary artery compression produced by myocardial bridging may cause myocardial ischemia and angina.^[140] In dilated cardiomyopathy, the muscle mass is decreased, but the capacity of the heart to deliver adequate coronary blood flow is impaired by diminished stroke volume. Acute myocarditis generally of viral origin may present with chest pain, usually the result of concomitant pericarditis.

Valvular. Severe aortic valve or subaortic obstruction produces chest pain due to limitation of cardiac output during exercise in the setting of left ventricular hypertrophy. The supply-demand mismatch is similar to that of hypertrophic cardiomyopathy. Mitral regurgitation can be the source of chest pain when severe, related to volume overload of the left ventricle producing increased myocardial work with output limited by the large regurgitant fraction of blood. Although more likely to occur as a chronic condition, the onset of mitral regurgitation can be acute after ruptured chordae tendineae in individuals with mitral valve prolapse or connective tissue disease. Less acute and poorly understood is the pain that has been associated in a small percentage of patients with mitral valve prolapse, which may in fact be unrelated to this condition.^[141]^[142]

Pericardial. Acute inflammation of the pericardium is frequently accompanied by chest pain thought to result from opposition of the inflamed parietal and visceral pericardial surfaces. The underlying cause can be viral, bacterial, autoimmune, or related to operative procedures in which the pericardium is entered. In the presence of effusion, the pericardial surfaces are separated, so that the pain is diminished or absent.

Coronary. Kawasaki disease results in the formation of coronary abnormalities in 20% to 25% of those not treated early in the course with intravenous γ -globulin and in 2% to 4% of those receiving treatment before 10 days from the onset of fever. Giant aneurysm (> 8 mm diameter) formation puts patients at risk for late progressive stenosis at the distal or proximal ends of the aneurysm. Exercise produces chest pain in those

with critical narrowing.^[143] Uncommonly, coronary artery abnormalities of congenital origin produce chest pain during exercise, which is thought related to compression of an artery between the aortic and pulmonic roots or insufficient coronary flow through a kinked acute-angle takeoff of the artery or spasm of the artery.^[144] Rarely, the left coronary artery may arise from the pulmonary artery, a condition that presents in infancy with heart failure after left ventricular infarction, but it can remain silent until later in childhood when symptoms of pain with exercise may prevail.

Aortic. Dissection of the aorta in Marfan syndrome, other connective tissue disorders, Turner's syndrome, and familial aneurysmal diseases causes acute severe chest pain that may radiate to the back. A sinus of Valsalva aneurysm can rupture unexpectedly into the right atrium or ventricle.

Rhythm Abnormalities. Children with supraventricular tachycardia may complain of chest pain during acute events. The pain may be the result of coronary ischemia related to diminished ventricular diastolic filling and low cardiac output. Some patients describe chest discomfort rather than pain. Ventricular tachycardia producing chest pain is most commonly seen in patients who have undergone repair or palliation of congenital lesions, as well as individuals with cardiomyopathy, long QTc syndrome, or severe electrolyte disturbances.

Clinical Evaluation

History

More than any other component of the clinical assessment, the history is most critical because careful exploration of the present illness can often identify the cause of chest pain. If possible, the history should be obtained from the patient rather than the parents, who may be prone to overinterpretation, exaggeration, or inaccuracy related to their personal experiences or anxiety. The patient should establish total duration of the symptom from the first episode. In most circumstances, chest pain is present for many months if not years before parents seek input, supporting a noncardiac cause. The manner of onset, whether acute or chronic, gradual or sudden, may suggest an etiology, with cardiac causes more acute in nature. Precipitating and predisposing factors provide insight, such as pain occurring with physical exertion (cardiac or musculoskeletal), injury or strain (musculo-skeletal), response to rest or analgesics (musculoskeletal), emotional circumstances related to family disruption, school difficulties, illness of a friend or relative, or depression (psychogenic). The characteristics of the symptom should be detailed first with a subjective description of the pain (i.e., squeezing, sharp, dull, aching, cramping), and the patient should locate the pain by pointing directly to the site of greatest intensity and then areas of possible radiation. Cardiac chest pain is generally mid-precordial and can radiate to the left arm. Severe crushing pain radiating to the back is experienced with aortic tears. Subcostal pain is generally chest wall related. The intensity of the pain should be estimated using a scale of 1 to 10, with the lower and upper ranges defined for reference. The temporal nature of the episode should be identified as continuous, constant, intermittent, or recurrent. Aggravating and relieving factors may provide insight about the nature of the cause with respect to exertion, position, meals, or breathing. The course of the symptoms since initial presentation may indicate that the process is improving or progressing. It is often helpful to ask patients if they are worried about the pain, and if so, why—a line of questioning that can help to disclose emotional factors influencing the symptoms. Associated symptoms may be helpful clues, including palpitations, dizziness, syncope, epigastric pain, nausea, vomiting, fatigue, fever, cough, coryza, shortness of breath, and orthopnea or dyspnea on exertion. The family history can identify other individuals with possible connective tissue disease.

Physical Examination

The appearance of the patient may suggest a connective tissue disorder in a tall individual with dolichocephaly and pectus excavatum or carinatum. The costochondral junctions should be palpated to elicit tenderness. Auscultation may identify wheezing associated with reactive airway disease or rales found with pneumonia or congestive failure. The cardiac assessment may suggest underlying heart disease by its hyperdynamic quality and displacement of the point of maximal intensity in patients with volume-overloaded lesions. A palpable thrill along the left sternal border, at the base bilaterally, and the suprasternal notch supports left ventricular outflow tract obstruction. An apical or parasternal heave is associated with right or left ventricular hypertrophy, respectively. On auscultation, underlying cardiac disease may be heralded by the presence of a loud S₂ associated with pulmonary hypertension, whereas muffled heart sounds are found in

moderate to large pericardial effusions. Systolic clicks are noted with bicuspid aortic valves or mitral valve prolapse. The harsh systolic ejection murmur of valvar or subvalvar aortic stenosis is heard along the left sternal border with radiation to the base and neck. Mitral regurgitation is heard at the apex with radiation to the left axilla, although murmurs associated with posterior mitral leaflet abnormalities may be heard at the left mid to upper sternal border, related to a more anteriorly and superiorly directed regurgitant jet. Aortic regurgitation of at least mild to moderate degree produces a regurgitant murmur radiating from the right base, down the left lower sternal border toward the apex. S_3 gallops are heard in the presence of at least moderate mitral regurgitation or dilated cardiomyopathy, whereas S_4 gallops, although far less common, are noted in hypertrophic cardiomyopathy or severe aortic stenosis. A friction rub is present with acute pericarditis.

Electrocardiogram

The ECG is of occasional benefit in the assessment of the patient with chest pain. A short PR interval and delta wave on ECG identifies the presence of an accessory bypass tract that can support supraventricular tachycardia in the patient who complains of chest pain with fast heart rate. Left ventricular hypertrophy is sometimes seen in patients with hypertrophic cardiomyopathy, moderate to severe aortic valve stenosis, subaortic stenosis, or aortic regurgitation and dilated cardiomyopathy. Long QTc interval may suggest the possibility of ventricular tachyarrhythmia. An infarct pattern can be present in anomalous left coronary artery from the pulmonary artery or rarely in Kawasaki disease. In pericarditis, diffuse T-wave abnormalities are common.

Chest X-ray

As with the ECG, chest x-rays are helpful in a limited number of those presenting with chest pain and therefore can be used selectively. In the patient with myocarditis, pericarditis, dilated cardiomyopathy, or aortic regurgitation of at least moderate degree, the x-ray may show cardiac chamber enlargement. A dilated ascending aorta can be present in those with Marfan syndrome. Reactive airway disease produces air trapping with hyperexpansion of the lung fields and flattened diaphragms. Pleural effusions or infiltrates are noted in infectious processes, and peripheral lung field abnormalities may be suggestive of pulmonary embolus. Spontaneous pneumothorax producing chest pain is readily recognized by radiograph.

Echocardiography

The echocardiogram is a useful modality if applied prudently in the assessment of the patient with chest pain because most patients do not have underlying heart disease. Echo can make the diagnosis of hypertrophic cardiomyopathy with or without left ventricular outflow tract obstruction. The left ventricular function is reduced in dilated cardiomyopathy or myocarditis with reduced ventricular function. Pericardial fluid is easily identified, and in the setting of large effusions, tamponade physiology is marked by atrial wall collapse and variability of the Doppler flow velocity across the mitral valve or in the descending thoracic aorta. In Marfan syndrome, the aortic dimensions can be markedly increased; associated findings include mitral valve prolapse with or without mitral regurgitation and aortic regurgitation related to a dilated aortic root. Coronary artery dilation or aneurysm formation is virtually pathognomonic for Kawasaki disease in a patient with a history of a prolonged febrile illness. Patients with giant aneurysms are at particular risk for stenotic lesions. Although echo identification of these stenoses is difficult, chest pain in the presence of giant aneurysms should prompt further workup for coronary ischemia. The course and distribution of rare coronary abnormalities predisposing to chest pain can be visualized by echo including single right or left coronary arteries.

Exercise Testing

In most patients with chest pain, exercise testing is not necessary. In some cases, rhythm abnormalities such as supraventricular tachycardia are unmasked during exercise testing. Ventricular arrhythmias can either suppress with exercise (generally thought to have benign implications) or degenerate during testing, potentially correlating with the patient's symptoms. When ischemia is suggested by history, upright treadmill exercise testing is a useful first step. Sesta-MIBI stress testing provides additional sensitivity by identifying regions of abnormal coronary perfusion. Such evaluation is helpful in patients with large aneurysms after Kawasaki disease and in those with congenital coronary artery anomalies identified by echo. In some cases, although the clinician is convinced that chest pain is unrelated to underlying heart disease or exercise-

induced bronchospasm, exercise testing may be necessary to reassure an anxious family about the benign nature of the pain.

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