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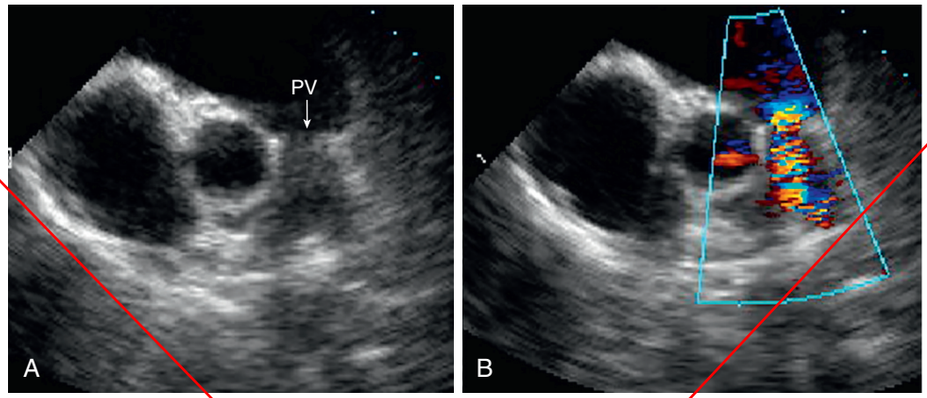
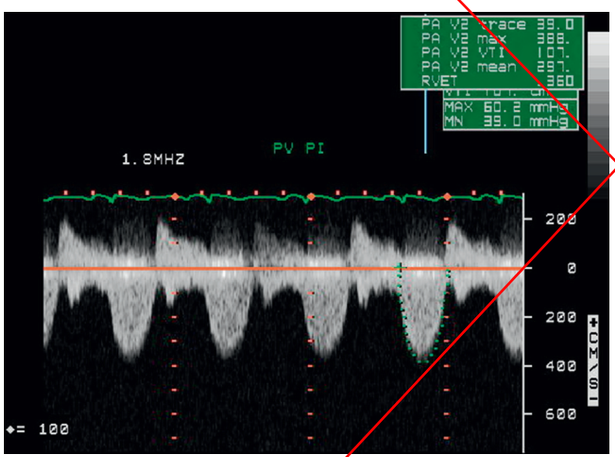


f0120 **Figure 177.4. A**, Thickened, retracted leaflets of the pulmonic valve. **B**, Pulmonic stenosis is demonstrated by color flow (see accompanying Video 177.4, *A* and *B*). *PV*, pulmonic valve.



f0125 **Figure 177.5.** Spectral Doppler signal demonstrating severe pulmonic stenosis.

and right-sided pressures. Balloon valvuloplasty has been reported to be successful in a handful of cases.[16,17]

p0955 Please visit ExpertConsult to view the corresponding videos for this chapter.

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sc0050 # 178 Amyloid

Au35 *Revathi Balakrishnan, MD, Muhamed Saric, MD, PhD*

s0315 INTRODUCTION

Au36 p0960 The term *amyloidosis* (from Greek ἄμυλον: starch) was popularized in the nineteenth century by the German pathologist Rudolf Virchow, because of amyloid's affinity for staining dyes with starch.[1] It is clearly a misnomer because amyloid deposits are made of protein and not starch. In general, amyloidosis entails typically extracellular infiltration by one of a variety of misfolded proteins, which all share the same β-pleated sheet configuration.[2] This misfolded protein configuration is visualized as apple-green birefringence under polarized light when tissue specimens are stained

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with Congo red.[3] At least 27 proteins have been shown to be amyloidogenic. Amyloidosis is a multiorgan disorder; the degree of myocardial involvement varies because amyloidogenic proteins are not equally cardiotropic.

p0965 AL amyloid is the most common form of amyloidosis. It results from accumulation of clonal immunoglobulin light chain deposits in multiple myeloma and from similar disorders.[4] Only 10% to 15% of patients with multiple myeloma develop AL amyloidosis.[5] Cardiac involvement occurs in up to one half of the patients with AL amyloidosis, and half of these patients will develop restrictive, nondilated cardiomyopathy.[6] Only 5% of patients with AL amyloidosis present with isolated cardiac disease without other signs of systemic involvement.[7]

p0970 AA amyloid is the result of deposition of serum amyloid A protein in patients with chronic inflammatory disorders, such as rheumatoid arthritis or inflammatory bowel disease. It primarily affects the kidneys, and rarely, the heart.[8]

p0975 Amyloidosis related to transthyretin (TTR) deposits takes two forms: hereditary familial systemic amyloidosis and senile systemic amyloidosis.

p0980 Hereditary familial systemic amyloidosis is caused by autosomal dominant mutations in the TTR gene.[9] Predominant features are peripheral neuropathy and autonomic dysfunction; cardiac involvement is less aggressive than that in AL disease. Isolated cardiac involvement of familial amyloidosis is associated with a mutation in the isoleucine 122 location.[10]

p0985 Senile systemic amyloidosis is an age-related, slowly progressive form caused by deposition of amyloid derived from wild-type TTR. It primarily manifests as cardiac amyloidosis, but can also occur in multiple organ systems, including the brain, lung, liver, and kidney. It is less aggressive than AL amyloid.[11]

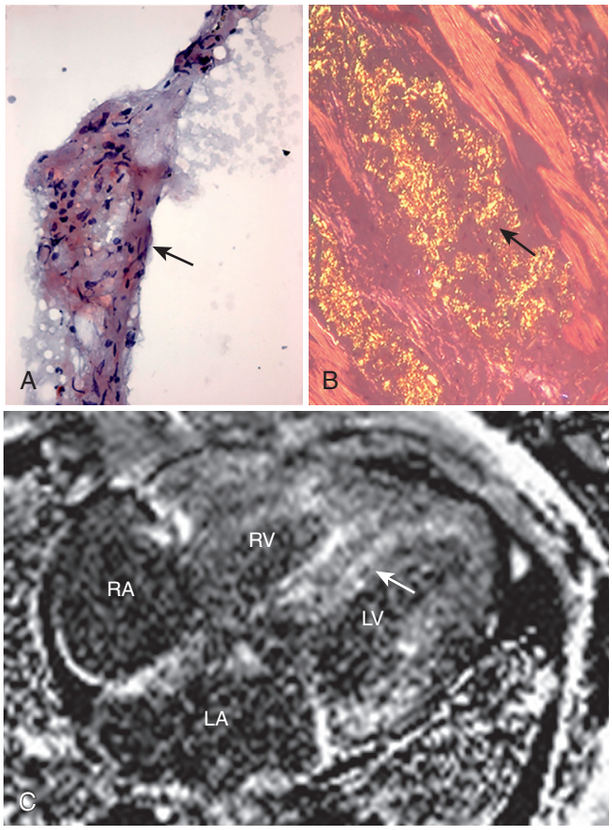
s0320 OTHER AMYLOIDOGENIC PROTEINS

p0990 Other forms of cardiac amyloidosis include isolated atrial amyloidosis, which is caused by endocardial deposition of atrial natriuretic peptide,[4] and hemodialysis-related amyloidosis, which is caused by the accumulation of β2-microglobulin in the setting of chronic uremia.[12]

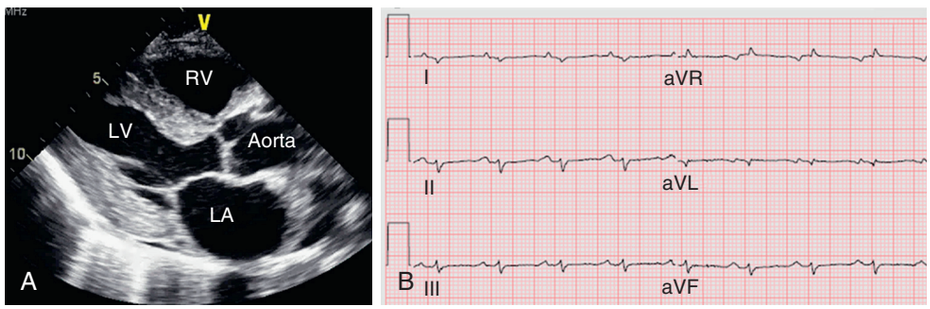
s0325 CLINICAL PRESENTATION

p0995 Clinically, cardiac amyloidosis is often first suspected as a discordant combination of a markedly increased left ventricular wall thickness on cardiac imaging (such as echocardiography) and the absence of electrocardiographic voltage criteria for left ventricular hypertrophy (Fig. 178.1). In advanced amyloidosis, the electrocardiogram may even demonstrate low QRS voltage ($\leq$0.5 mV in limb leads and $\leq$1.0 mV in precordial leads).

p1000 Cardiac magnetic resonance imaging demonstrates characteristic diffuse, predominantly subendocardial enhancement on delayed images. This late enhancement may reflect fibrosis rather than amyloid deposition per se.[13] The diagnosis of amyloidosis is confirmed by tissue biopsy, which is typically fat pad or endomyocardial biopsy (Fig. 178.2).



f0135 **Figure 178.2.** Histopathology and magnetic resonance imaging of amyloidosis. Congo red stained tissue samples demonstrating amyloid deposits *(arrow)* in a fat pad biopsy specimen (**A**) and the myocardium (**B**). Note in (**B**) the extracellur location of amyloid deposits between myofibrils. **C,** Cardiac magnetic resonance–delayed images demonstrate diffuse late gadolinium enhancement throughout the left and right ventricles consistent with amyloidosis. The deposits are predominantly subendocardial *(arrow)*. *LA*, left atrium; *LV*, left ventricle; *RA*, right atrium; *RV*, right ventricle. *(Courtesy of Dr. Robert Donnino, New York University Division of Cardiology and Veterans Administration New York Harbor Healthcare System.)*



f0130 **Figure 178.1.** Echocardiographic and electrocardiographic appearance of amyloidosis. Note the apparent discordance between marked thickening of the left ventricular (LV) walls on transthoracic echocardiogram in the parasternal long-axis view (A) and the low QRS voltage on the electrocardiogram (**B**) (see accompanying Video 178.1, *A*). *LA*, left atrium; RV, right ventricle.

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s0330 ## ECHOCARDIOGRAPHIC FEATURES

s0335 ### Structural Changes

p1005 Concentric wall thickening of a nondilated left ventricle in the absence of hypertension, aortic stenosis, or other known causes of apparent left ventricular hypertrophy is the hallmark of cardiac amyloidosis.[14,15] In the early era of two-dimensional (2D) echocardiography, when only fundamental (nonharmonic) imaging was available, granular sparkling of the myocardium was reported to be suggestive of cardiac amyloidosis.[16] Modern harmonic 2D imaging often gives a speckled appearance to the myocardium, even if amyloid is not present. Switching from harmonic to fundamental imaging can help avoid overdiagnosis of amyloidosis. An increase in the thickness of the right ventricular wall, interatrial septum, and the atria, bi-atrial enlargement, thickened valves, and pericardial and pleural effusions are also common findings.

s0340 ### Functional Changes

p1010 Cardiac amyloidosis typically presents as heart failure with a preserved left ventricular ejection fraction (LVEF). Left ventricular diastolic dysfunction is the predominant feature and eventually progresses to restrictive cardiomyopathy (Fig. 178.3). Although LVEF is preserved until terminal stages of the disease, subtle systolic dysfunction is detectable early on by strain imaging (Fig. 178.4).

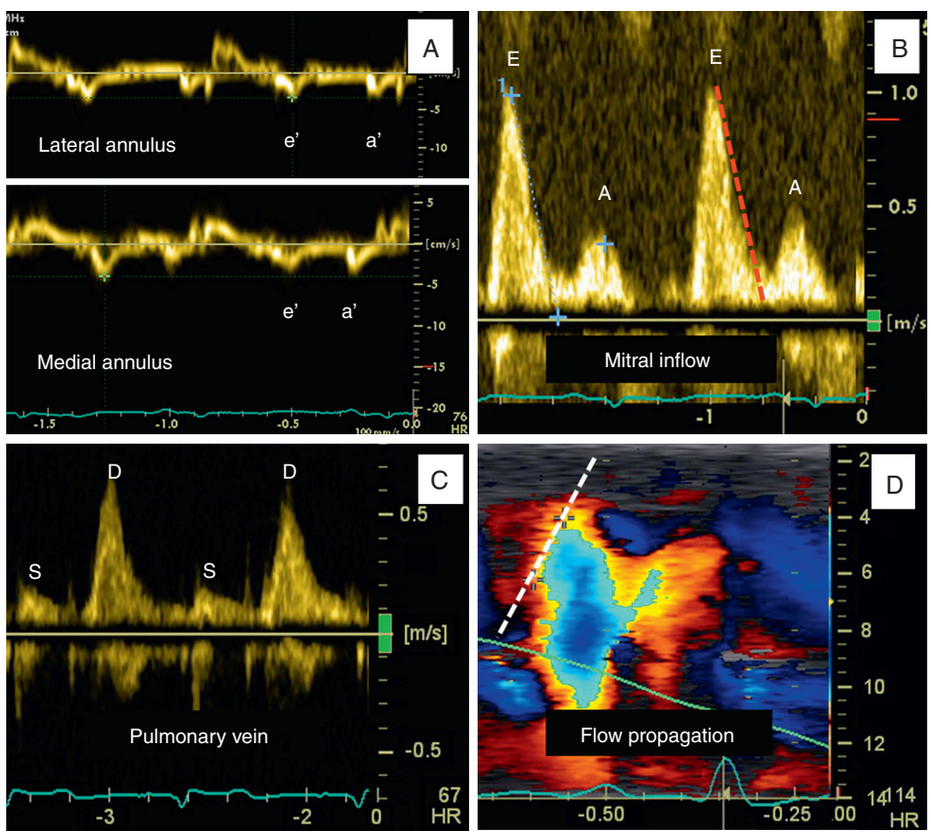
s0345 ### MITRAL TISSUE DOPPLER

178

p1015 Pulsed wave tissue Doppler velocity measured at the septal annulus and lateral mitral annulus in the apical views reflects the longitudinal excursion of the mitral annulus in systole and diastole, and can provide evidence of systolic and diastolic impairment in the presence of a preserved ejection fraction.[13] Normal values of tissue Doppler velocity at the septal and lateral mitral annulus typically decrease with age. For instance, at 60 years of age or older, normal early diastolic (e′) wave values are 10.4 ± 2.1 cm/sec at the septal annulus and 12.9 ± 3.5 cm/sec at the lateral annulus.[13] In cardiac amyloidosis, very low e′ velocities are frequently seen; these velocities are typically less than 8 cm/sec (see Fig. 178.3, *A*). Furthermore, the ratio of early diastolic (e′) to late diastolic (a′) mitral annular tissue Doppler velocity (e′/a′ ratio) progressively diminishes as cardiac amyloidosis advances.

s0350 ### MITRAL INFLOW PATTERN

p1020 With disease progression, the mitral inflow filling pattern progresses from impaired relaxation early on to the pseudonormal and restrictive filling pattern seen in advanced disease. Initially, isovolumic relaxation is impaired with an increased dependence on atrial contraction, which results in an impaired relaxation pattern with a decreased early diastolic flow across the mitral valve (E wave) relative to the atrial (A) wave (E/A ratio <1 and e′/a′ <1).



f0140 **Figure 178.3.** Diastolic dysfunction in amyloidosis. **A**, Tissue Doppler imaging at both the lateral and medial (septal) annulus demonstrates very low e′ velocities (<5 cm/sec). **B**, Mitral inflow demonstrates a restrictive filling pattern: E/A greater than 2 and rapid E-wave deceleration (<150 msec; *dashed line*). **C**, Pulmonary vein flow velocity pattern demonstrates an S/D less than 1 pattern, which is indicative of elevated left atrial pressure. **D**, In this patient, mitral flow propagation velocity recording demonstrates paradoxically normal slope of the first aliasing velocity *(dashed line)* of 55 cm/sec. A normal slope of the first aliasing velocity does not exclude the diagnosis of amyloidosis.

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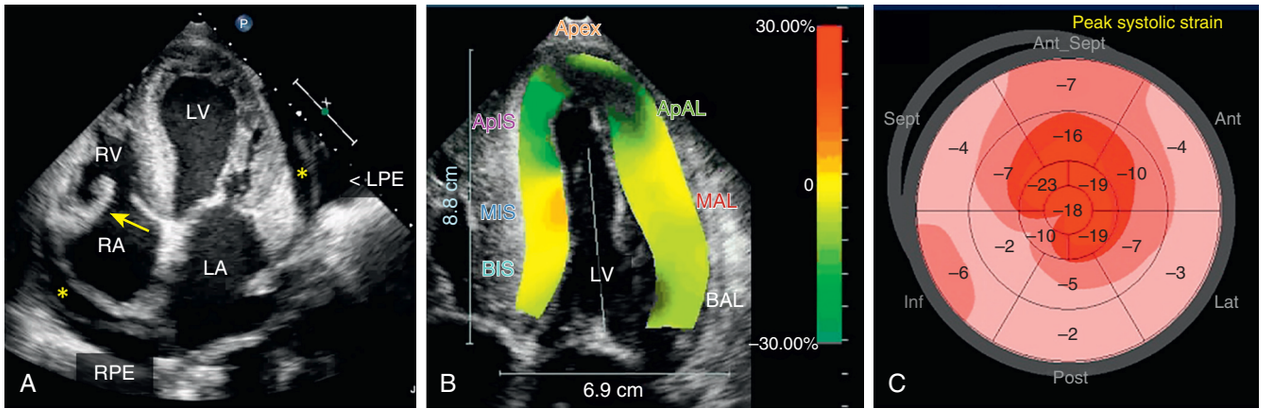

f0145 **Figure 178.4.** Two-dimensional echocardiography and strain imaging of amyloidosis. **A,** Transthoracic echocardiogram in the apical 4-chamber view demonstrates typical features of amyloidosis: increased left ventricular (LV) and right ventricular (RV) wall thickness, bi-atrial enlargement, thickened valves *(arrow)*, pericardial effusion *(asterisk)*, and pleural effusions. **B** and **C,** Speckle-based longitudinal strain imaging demonstrates the phenomenon of apical sparing (relative preservation of apical longitudinal strain in the setting of otherwise decreased LV longitudinal strain). Global longitudinal strain in this patient was diminished to −10% (see corresponding Video 178.4, *A* and *B*). *LA,* left atrium; *LPE*, left pleural effusion; *RA*, right atrium; *RPE,* right pleural effusion.

p1025 As myocardial infiltration progresses, left ventricular wall compliance decreases and left atrial pressures increases; this initially leads to a pseudonormal inflow pattern (1 <E/A <2 with e′/a′ <1) and then to a restrictive inflow pattern with E/A greater than 2, E-wave deceleration time less than 150 msec, and a very low e′ (see Fig. 178-3, *B*).[17] Elevated mid-diastolic flow (>20 cm/sec) can also be indicative of elevated left atrial pressure and advanced diastolic dysfunction.[18] In contrast to constrictive pericarditis, there are no marked respiratory variations in peak mitral E-wave velocities in patients with cardiac amyloidosis.

s0355 PULMONARY VEIN PATTERN

p1030 In a patient with sinus rhythm, pulmonary venous flow demonstrates two anterograde (systolic [S] and diastolic [D]) and 1 retrograde (atrial reversal [AR]) waves. In general, the peak velocity of the S wave is influenced by changes in left atrial pressure, contraction, and relaxation, whereas the D wave is influenced by changes in left ventricular compliance; D wave changes occur in parallel with the mitral E wave.[16] As filling pressures rise with progression of cardiac amyloidosis, the S velocity decreases and the D velocity increases, which results in a S/D ratio less than 1 (see Fig. 178.3, *C*). As left ventricular diastolic pressure increases, peak velocity and duration of the AR wave tend to increase. Left ventricular diastolic pressure is likely elevated whenever the AR wave outlasts the mitral A wave by at least 30 msec.[19] In atrial fibrillation, which frequently accompanies cardiac amyloidosis, there is a loss of the AR wave, and the peak velocity of the S wave diminishes even if the left atrial pressure is normal.

s0365 Mitral flow propagation

p1035 Early diastolic flow propagation velocity from the mitral valve to the cardiac apex reflects the relaxing properties of the left ventricle, especially when the left ventricle is dilated. Color M-mode images are acquired in the apical 4-chamber view, with the M-mode scan through the center of the left ventricle and the color Nyquist limit set to approximately 40 cm/sec. The slope of the first aliasing velocity (Vp) in early diastole is then measured.[16] The normal Vp is more than 50 cm/sec. Because of the presence of abnormal relaxation in cardiac amyloidosis, it is expected that the Vp would be diminished. Nonetheless, patients with amyloidosis often have a normal Vp, likely because the left ventricular cavity size is normal (see Fig. 178.3, *D*).

LEFT VENTRICULAR STRAIN IMAGING s0370

p1040 On strain imaging, amyloidosis is characterized by diminished longitudinal strain in basal and mid-left ventricular segments with characteristic apical sparing (see Fig. 178.4). The loss of global longitudinal function occurs because amyloid fibrils deposit predominantly in the subendocardial region, which is primarily responsible for longitudinal deformation. The normal range of global longitudinal peak systolic strain[20] is greater than $-18 \pm 2\%$; patients with amyloidosis typically have peak longitudinal strain values less than −12%. The loss of longitudinal function occurs early in the course of amyloidosis and reflects systolic dysfunction despite preserved LVEF and fractional shortening.[2]

p1045 The exact mechanism for apical sparing is yet to be fully elucidated. Nonetheless, apical sparing has been shown to be both sensitive (93%) and specific (82%) for the diagnosis of amyloidosis compared with other disorders with increased left ventricular wall thickness, such as hypertrophic cardiomyopathy and aortic stenosis.[21]

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179 Sarcoidosis

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p1055 Sarcoidosis is a multiorgan, inflammatory disorder characterized by noncaseating granulomatous infiltration. Sarcoidosis affects people of all racial and ethnic groups, and occurs at all ages; however, it is more likely to be chronic and fatal in black Americans.[1,2] The incidence of sarcoidosis varies by ethnicity and region, occurring in up to 2 per 10,000 white individuals and 8 per 10,000 black individuals.[3] The etiology and molecular mechanisms that cause sarcoidosis are not well understood, but genetic, environmental, infectious, and autoimmune mechanisms have all been implicated. Although it most commonly involves skin, eyes, and lungs, autopsy series suggest that a major cause of death in individuals with sarcoidosis is arrhythmia and heart failure due to cardiac infiltration.[4] Manifestations of cardiac sarcoidosis (CS) can range from being clinically silent to advanced heart failure that requires heart transplantation to sudden cardiac death. Granulomatous infiltration into the basal interventricular septum can result in conduction abnormalities, such as advanced atrioventricular block and bundle branch block. Similarly, regions of previous infiltration are thought to evolve into scar formation that serves as a substrate for reentrant ventricular tachycardia[5] and atrial arrhythmias.[6] The primary and secondary prevention annualized implantable cardioverter defibrillator (ICD) therapy rates in patients with CS have been reported by one group to be 10.7% and 21%, respectively.[7] Others have also shown similarly high rates of appropriate ICD therapies in patients with CS.[8,9] Current guidelines published by the American Heart Association consider cardiac sarcoidosis to be a class IIA indication for ICD insertion.[10]

p1060 Although cardiac involvement is an important cause of morbidity and mortality in patients with sarcoidosis, a recent Delphi study suggested that there is only a low to moderate agreement among sarcoidosis experts with regard to appropriate cardiac testing strategies for the evaluation of these patients.[11] Unfortunately, because CS is a patchy disorder that often involves only small amounts of the myocardium without causing obvious abnormalities in left ventricular (LV) function, commonly used cardiac tests do not reliably detect CS.[12] Previous studies have suggested that electrocardiography has a sensitivity ranging from 33% to 58% and a specificity of 22% to 71%.[13,14] Ambulatory Holter monitoring had a sensitivity of 50% to 67% and a specificity of 80% to 97% in other studies.[15,16] Even endomyocardial biopsy has a poor sensitivity for detecting CS due to myocardial sampling errors related to the patchy pattern of granuloma infiltration into the myocardium.[17] Cardiovascular magnetic resonance (CMR) and cardiac F(18)-fluorodeoxyglucose positron emission tomography (FDG-PET) are becoming the preferred imaging modalities for detecting CS. FDG-PET has been reported to have 85% to 100% sensitivity and 38.5% to 90.9% specificity.[18–20] CMR possesses the ability to accurately identify even small areas of myocardial damage, based on the presence of late gadolinium enhancement, making it a valuable tool for the detection and risk stratification of CS.[21–25] Approximately 20% of individuals with sarcoidosis have cardiac involvement based on CMR.

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p1065 Despite the increased utilization of imaging modalities such as CMR and PET, echocardiography remains central to the evaluation and management of individuals with suspected or known CS, because it is widely available and relatively inexpensive. In addition, it can be readily performed and helpful in patients with cardiac devices.[26] Echocardiography is typically thought to have a high specificity for the detection of CS (as high as 95% in one series[15]), but some have recently suggested that the specificity may be as low as 29%.[12] In patients who are highly suspected of having CS or who have known CS, the prevalence of LV systolic dysfunction (ejection fraction [EF] <50%) as detected on echocardiography may be high, with estimates ranging from 54% to 87%.[27] However, with the increased utilization of more sensitive tests, such as CMR and PET for the detection of CS, it is becoming increasingly evident that the prevalence of LV systolic dysfunction in patients with CS may be significantly lower. Similarly, others have shown that individuals with symptomatic CS (i.e., those with congestive heart failure or palpitations) often have abnormalities evident on echocardiography.[28] However, it must be recognized that one of the limitations of echocardiography for the assessment of CS is its low sensitivity (25%-62%).[15,25,29] In one series of CS patients who presented with significant atrioventricular block or ventricular tachycardia, an echocardiographic abnormality was present in only 10 of 20 patients.[30] Despite its limited sensitivity, echocardiography is an important component of the Japanese Ministry of Health and Welfare Criteria, which are traditionally used to diagnose CS (Box 179.1).

p1070 CS can affect the heart in several different ways, and echocardiography plays an important role in detecting many of these abnormalities.[31,32] Regions of the heart most commonly involved by CS are the interventricular septum, particularly the basal portion, as well as the basal LV posterior wall, the LV free wall, and the papillary muscles.[29] Atrial involvement has also been reported to be present in 20% of cases. Other echocardiographic manifestations

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