Introduction

The term amyloidosis describes a series of disorders characterized by the extracellular deposition of insoluble amyloid protein fibrils in tissues throughout the body. Multiple organ systems may be involved, with cardiac involvement being associated with the worst prognosis and having the lowest survival rates. The classification of amyloidosis is based on the biochemical constitution of the amyloid fibrils, and consists of three major subtypes. Type AL, or primary systemic amyloidosis, is the most common form, and is a plasma cell dyscrasia in which the amyloid fibrils are composed of immunoglobulin light chains. A total of 85% of patients with systemic amyloidosis have primary AL type, with cardiac involvement occurring in up to 50% of patients, and congestive heart failure in as many as 25% [1]. Prognosis is highly dependent on the organ systems involved, with cardiac involvement conferring the worst prognosis with a median survival of 6 to 9 months [2]. Secondary amyloidosis, or type AS, is usually a complication of chronic inflammatory disorders such as rheumatoid arthritis and inflammatory bowel disease, and rarely causes cardiac disease; here the amyloid protein is typically serum amyloid A protein.
The third type consists of familial amyloidosis, caused by mutations in more than 20 different proteins; clinical manifestations and age of onset vary depending on the specific mutation. Familial amyloidosis is most often due to a single base-pair substitution in the gene coding for transthyretin found on chromosome 10 [3]. To date, more than 50 amyloidogenic transthyretin mutants have been identified. One particularly important variant, seen primarily in black individuals, results from a change in A to C on codon 122 leading to substitution of isoleucine for valine. The mutant transthyretin deposits primarily in the heart of elderly patients, causing a primary cardiac form of amyloidosis that is heritable [4]. When structurally normal transthyretin deposits in the hearts of aged individuals, the condition is known as senile cardiac amyloidosis, and may be an under-recognized cause of atrial fibrillation and heart failure in the elderly.

CARDIAC MANIFESTATIONS OF AMYLOIDOSIS
Amyloid causes disease by encroaching on normal tissues and disrupting normal tissue structure and function. Cardiac deposition of amyloid fibrils impairs myocardial function via three mechanisms: 1) impaired relaxation and diastolic dysfunction can occur with infiltration of the left ventricular myocardium with stiffened amyloid fibrils; 2) systolic dysfunction can occur when functional myocardial tissue is replaced with amyloid protein; and 3) the combination of severe restrictive filling pattern and reduced left ventricular contraction with marked amyloid infiltration can lead to the “stiff heart syndrome” [5–7].

Although systolic function would be expected to decrease with replacement of myocardium with stiff amyloid protein, preserved systolic function with cardiac amyloidosis commonly occurs, particularly early in the disease process. Studies by Swanton et al. [5] have demonstrated normal or near-normal systolic function in 60% to 80% of patients with documented cardiac amyloidosis. Impairment in diastolic dysfunction with amyloid deposition has been shown to produce a characteristic dip and plateau wave form in ventricular tracings, indicative of rapid early diastolic filling with cessation of filling in mid-diastole [5]. These features are characteristic of a restrictive cardiomyopathy, which may be difficult to distinguish from constrictive pericarditis. The clinical presentation of cardiac amyloidosis is disproportionately of right-sided heart failure symptoms, with venous congestion and frequently ascites. Atrial fibrillation is common.

PITFALLS IN DIAGNOSIS OF CARDIAC AMYLOIDOSIS
Amyloidosis is the most common diagnosis leading to restrictive cardiomyopathy in the United States. The diagnosis of cardiac amyloidosis may prove difficult, because it may mimic other infiltrative cardiomyopathies, hypertrophic cardiomyopathy, and constrictive pericarditis. Restrictive cardiomyopathy and constrictive pericarditis may present with similar clinical presentations, including right-sided heart failure symptoms with low voltage on electrocardiogram (ECG) and preserved systolic function. Several clues may help to distinguish the two disorders: 1) Hemodynamic studies tend to show higher left ventricular end-diastolic pressure than right ventricular end-diastolic pressure in patients with restrictive cardiomyopathy, whereas among those with constrictive pericarditis, pressures are similar in the two chambers [7]. 2) Imaging studies may show increased ventricular wall thickness with infiltrative disease and pericardial thickening or calcification with constrictive pericarditis [8]. 3) More recently, measurement of B-type natriuretic peptide levels has been proposed as another tool to distinguish the two entities: marked B-type natriuretic peptide elevation is typically seen in cardiac amyloidosis, whereas levels are usually normal or only modestly elevated in patients with constrictive pericarditis [9].

Findings on ECG and echocardiography may help point to the diagnosis of cardiac amyloidosis. The combined findings of low voltage and a pseudoinfarction pattern on ECG, in conjunction with increased myocardial thickness and a speckled appearing myocardium on echocardiogram, have been associated with biopsy-proven cardiac amyloidosis. Other common diagnostic echocardiographic findings include dilated and elongated atria, interatrial septal hypertrophy, valve thickening, and pericardial effusion [10]. However, echocardiographic findings may be difficult to distinguish from other myocardial disorders, such as hypertrophic cardiomyopathy, leading to the increased use of cardiac magnetic resonance imaging. Evidence of increased thickness of the interatrial septum and right atrial posterior wall, with evidence of pleural or pericardial effusions and decreased signal intensity of amyloid-infiltrated myocardium, have been shown to be specific magnetic resonance imaging findings for cardiac amyloid [11,12].

Despite advances in imaging tools, definitive diagnosis still requires biopsy, with abdominal fat pad aspiration and biopsy of rectal mucosa being the preferred screening tests for AL amyloidosis. These tests are limited by relatively high false-negative rates, and not infrequently, myocardial biopsy is required to establish a definitive diagnosis and characterization of the type of amyloid. In patients with primary cardiac amyloidosis, myocardial biopsy is required because systemic involvement is absent.