amyloidosis represents a diverse group of diseases characterized by the common factor of deposition of twisted β-pleated sheet fibrils (amyloid) formed as a result of the misfolding of various proteins produced in several different pathological states. The different forms of amyloidosis are classified by the composition of the amyloid fibril. AL amyloidosis (previously designated as primary amyloidosis) is derived from light-chain immunoglobulin produced by monoclonal plasma cells. It is the most severe and probably, at least in the United States, the most common form of amyloidosis. The accumulation of amyloid disrupts the tissue architecture and, possibly in conjunction with a toxic effect from the light chains, leads to severe organ damage that may involve the kidneys, heart, liver, or peripheral nerves. Familial amyloidosis is an uncommon, autosomal dominant disease with a high degree of penetrance. Most cases result from the production of an unstable variant of the serum protein transthyretin (ATTR amyloidosis). More than 80 point mutations have been identified for ATTR amyloidosis, which predominantly result in neurological or cardiac dysfunction or both. A particularly common mutant transthyretin resulting from the substitution of isoleucine for valine at position 122 is found in ≈4% of the African American population, with an unknown penetrance. This mutation results in a cardiomyopathy that has been suggested to be one of the most common types of cardiomyopathy in older adult African American patients. Senile systemic amyloidosis is the result of the deposition of wild-type transthyretin and is almost exclusively limited to the heart. This disease may be becoming more prevalent because of the increasing age of the general population. Reactive systemic amyloidosis is the result of an overproduction of a nonimmunoglobulin protein AA and is rarely associated with any cardiac involvement.

In AL amyloidosis, cardiac involvement is common and is the cause of death in most of these patients. Effective treatments for AL amyloidosis exist, but treatment options are limited once cardiac disease becomes clinically apparent. Recently, the use of high-dose melphalan with rescue autologous peripheral blood stem cell transplantation has resulted in reversal of the clinical manifestations of AL amyloidosis in a significant proportion of patients who survived the procedure. Cardiac involvement not only indicates a poor prognosis in most forms of amyloidosis but also predicts poor tolerance to high-dose chemotherapy and stem cell transplantation. Although cardiac biopsy can reliably diagnose cardiac amyloidosis, its procedural risks and uncertainty about sampling error limit its applications in monitoring the clinical course of the disease. Therefore, noninvasive diagnostic techniques that can stage cardiac amyloidosis should have important prognostic and treatment implications.

Echocardiography is considered the noninvasive test of choice to diagnose cardiac amyloidosis. Typical abnormalities seen on echocardiography include a small left ventricular size, biventricular and atrial septal thickening, atrial enlargement, and, in the late stages, a restrictive left ventricular filling pattern. Imaging of the structural and morphological changes, however, is often insufficient in addressing the spectrum of disease in cardiac amyloidosis. Whereas a combination of ECG and echocardiographic features may raise the suspicion of cardiac amyloidosis with a high accuracy in selected subsets of patients presenting with heart failure, advanced patient age and common comorbidities such as hypertension render ventricular hypertrophy nonspecific to the underlying disease process. Substantial echocardiographic evidence of cardiac amyloid such as hypertrophied ventricles and restrictive filling pattern is a late finding that is associated with a median survival of only 6 months. Therefore, it has limited impact in guiding treatment decisions, and a noninvasive technique to detect earlier changes in the disease would be of great value. Furthermore, after effective treatments such as intravenous melphalan and autologous stem cell transplantation, echocardiographic monitoring is problematic because regression of abnormalities often is not observed despite a favorable clinical or hematologic response to the treatment. This may be a result of the difficulty of obtaining precisely reproducible echocardiographic measurements in individual patients. Recent advances in longitudinal myocardial strain and peak systolic strain rate hold promise for early diagnosis and treatment monitoring of cardiac amyloidosis. These advanced echocardiographic modalities are minimally affected by passive motion and may detect the effects of cardiac amyloidosis at an early stage of the disease, when ejection fraction is normal. They do not function as diagnostic tools but, rather, they reflect the early functional abnormalities produced by amyloid infiltration. Nuclear scintigraphy with 99Tc pyrophosphate or indium-labeled antimyosin antibody has been reported to detect extensive cardiac involvement of cardiac amyloidosis. Detection of the less extensive or early disease in the heart appears to be less reliable, however, and needs to be studied further.
In this issue of Circulation, Maceira et al. studied 29 patients with systemic amyloidosis and 16 hypertensive controls using gadolinium-enhanced cardiac MRI. The study aimed to explore the pattern of abnormal myocardial characteristics in patients with biopsy-proven amyloidosis and echocardiographic evidence of cardiac amyloidosis. Although echocardiography was used to select patients with probable cardiac amyloidosis, this was not a comparative study of echocardiography versus cardiac MRI for distinguishing amyloidosis from true hypertrophy, because the data Maceira et al. provide in their table imply that control patients did not undergo echocardiography. Thus, no conclusions about the superiority of cardiac MRI over echocardiography should be drawn. The MRI data did, however, show some interesting features in cardiac amyloid patients. With the high spatial resolution (≈2 mm) and tissue contrast differentiation of cardiac MRI, amyloidosis patients were noted to have qualitative global and subendocardial gadolinium enhancement of the myocardium. Myocardial enhancement was associated with increased ventricular mass and impaired left ventricular systolic function. Shortly after intravenous administration of gadolinium contrast, amyloidosis patients had faster gadolinium clearance from the blood pool marked by a blood T1 value over time that was higher than that in controls. This resulted in a diminished T1 difference between the myocardium and blood in amyloid patients as compared with that observed in control patients.

Although the descriptive findings of this study represent structural myocardial changes from amyloid infiltration, several limitations must be considered in the noninvasive diagnosis of cardiac amyloidosis via the MRI techniques presented in this study. The patient sample consisted of a group of 29 amyloidosis patients and 16 “matched” hypertensive controls. All 29 amyloid patients had biopsy-proven amyloidosis and were considered to have cardiac amyloidosis on the basis of the presence of morphological and diastolic filling changes on echocardiography. Only 2 of the 29 patients had endomyocardial biopsy confirmation of cardiac amyloid infiltration. Because amyloidosis patients without clearly abnormal changes on echocardiography were not part of the study sample, it is unlikely that the amyloidosis patients included in this study sample adequately represented the spectrum of early cardiac involvement. The authors conclude that the combined assessment of myocardial T1 with demonstration of global subendocardial late gadolinium enhancement yielded an 87% accuracy for the detection of cardiac amyloidosis and that this improved to 97% with the more complicated parameter of the difference in T1 between subendocardium and blood. There are several problems with this seemingly highly accurate method for distinguishing amyloid infiltration from true cardiac hypertrophy. The 2 groups are said to have statistically insignificant difference in left ventricular mass, but the amyloid patients did have greater mean mass, which reaches statistical significance (P = 0.03) if calculated by 1-tailed analysis. Furthermore, although the mean ejection fraction did not differ between the groups, 40% of the amyloid patients with late enhancement are described as having “impaired systolic function,” and late enhancement was associated with more severe cardiac amyloid, characterized by greater left and right ventricular mass.

As the prevalence of cardiac amyloidosis in the general population is a minute fraction of the population with true left ventricular hypertrophy, it is important to recognize that this will dramatically decrease the predictive accuracy of any individual noninvasive test that does not have a virtually 100% sensitivity and specificity for cardiac amyloidosis. We therefore cannot draw any conclusions about the clinical utility of gadolinium enhancement and kinetics for the diagnosis of cardiac amyloidosis in patients with increased left ventricular mass on cardiac MRI, nor can the staging of the extent of cardiac involvement in patients with systemic amyloidosis be fully addressed with the present results. These practical issues, as well as the prognostic value of the contrast-enhanced MRI technique, need to be investigated by a prospective study. As yet, the mechanism of the altered gadolinium kinetics in amyloidosis remains unclear. Although the authors speculated that a faster gadolinium washout from blood and myocardium among amyloid patients represented gadolinium distribution into the total body amyloid load, there was no correlation between the blood and myocardial gadolinium clearance and measures of total body amyloid load. This may represent a limitation of serum amyloid P component scintigraphy for accurately assessing total body amyloid load or it may suggest another as yet unknown mechanism.

How, then, does the present study help us? Gadolinium-enhanced MRI techniques have proven clinical value in characterizing myocardial infarction and fibrosis in other cardiac disorders; however, the histological basis of gadolinium delayed enhancement remains incompletely understood. Current evidence suggests that it is related to a combination of delayed washout kinetics and an increased volume of distribution of gadolinium in the interstitial space of abnormal myocardium. The pathological result presented by Maceira et al. from the sole cardiac amyloidosis patient who died shortly after MRI extends our current understanding of the histological basis of delayed enhancement. Regions of delayed enhancement have been reported to correlate with the increased collagen content of myocardial fibrosis in hypertrophic cardiomyopathy. In contrast, and similar to previous pathological reports of cardiac amyloidosis, histological assessment of this patient indicated little local tissue reaction invoked by amyloid infiltration with minimal myocardial fibrosis, yet extensive delayed enhancement was demonstrated in matched regions where >40% of the subendocardial volume was infiltrated by amyloid. This finding suggested that interstitial expansion from amyloid infiltration without interstitial fibrosis could also cause delayed enhancement detectable by MRI. Therefore, the present study may provide insights into the histological basis of MRI gadolinium-related abnormalities in patients with amyloidosis and other infiltrative processes.

Despite the described limitations, abnormal myocardial characteristics and gadolinium washout kinetics, as presented by Maceira et al. may be valuable in advancing our knowledge of cardiac amyloidosis. If further studies show that this noninvasive method can allow serial quantification
of the extent of myocardial infiltration, then we may gain further insight into the natural history of cardiac amyloidosis. Noninvasive imaging with highly reproducible and quantifiable results such as can be obtained by cardiac MRI also may help to estimate the prevalence of cardiac involvement in systemic amyloidosis when cardiac morphological changes are not apparent by echocardiography. Screening of subclinical early cardiac involvement may become possible should delayed enhancement prove to have adequate sensitivity in detecting amyloid infiltration. Better knowledge of the disease process and improved noninvasive surveillance may, as the authors suggest, also aid in the evaluation of current and novel chemotherapeutic agents. With advances in imaging technology, the future direction in the diagnosis or surveillance (or both) of this disease may be further improved by the development of specific contrast agents that target sites of the amyloid proteins. Hand in hand with improvements in treatment, advances in imaging may offer the patients who battle amyloidosis an improved outlook in the future.

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Cardiovascular Magnetic Resonance in Cardiac Amyloidosis
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