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Editorial Comment

The Expanding Prognostic Role of Late Gadolinium Enhanced Cardiac Magnetic Resonance*

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Identifying prognostic markers is of increasing importance in patients with congestive heart failure of either ischemic or nonischemic etiology. In nonischemic cardiomyopathies, the benefits of implantable cardioverter-defibrillators (1) and biventricular pacemakers (2) are well documented. These therapies have been shown to be cost-effective by modern standards (3,4) but represent an ever-increasing cost burden to the health care system. Therefore, identifying patients who would benefit most from these important therapies is an imperative (5).

See page 1977

The initial development of the technique of late gadolinium enhancement (LGE) in cardiac magnetic resonance (CMR) was to identify necrosis caused by myocardial infarction (6,7). However, all that enhances is not infarction. Late gadolinium enhancement is a marker of myocardial fibrosis of any etiology, and recent studies have documented its utility in nonischemic cardiomyopathies (8). For example, LGE has been shown in acute myocarditis, especially noted in the basal lateral wall in the midwall and epicardium (9). Patients with hypertrophic cardiomyopathy may have LGE, particularly at the right ventricular (RV) insertion sites (10), a common location of interstitial fibrosis on pathological studies. The presence of LGE correlates with wall thickness in this disorder. Infiltrative cardiomyopathies such as amyloidosis (11) and sarcoidosis (12) may be identified by LGE, the former often by diffuse subendocardial enhancement and the latter by more focal enhancement that may be reduced by steroid therapy. Other cardiomyopathies that can show LGE include the RV in arrhythmogenic RV cardiomyopathy (13) and areas of scar in Chagas disease (14).

Over the past few years, the group at the Royal Brompton Hospital in London has studied and followed up a cohort of patients with chronic congestive heart failure with LGE CMR. They initially showed that LGE is present in patients with known ischemic cardiomyopathy but also is present in patients with nonischemic cardiomyopathy, some in an infarct distribution (subendocardial progressing to transmural), but others in the midwall (15). This group then followed up 101 of the patients with nonischemic cardiomyopathy over nearly 2 years (16). Thirty-five percent of these 101 patients showed midwall fibrosis and had a higher incidence of a predefined primary composite end point of all-cause mortality and cardiovascular hospitalization than those without midwall fibrosis. Mortality alone was similar between groups. When corrected for between-group differences including LV size and function in a multivariate analysis, midwall LGE was the only significant predictor of the primary end point. In addition, the presence of midwall fibrosis predicted a higher risk of a secondary end point of sudden cardiac death and ventricular tachycardia.

The work of Assumoll et al. (16) in this issue of the *Journal* should be viewed as preliminary and as fodder for further study. The sample size was relatively small for an outcome study, hence the lack of significance in mortality and the requirement for composite end points. We do not know the prognostic implications of the LGE in an infarct pattern in patients without obstructive coronary disease because these were excluded from this particular outcome study. Further multicenter outcome studies of LGE will be important to define the ultimate utility of CMR in both nonischemic and ischemic cardiomyopathies. Patients with pacemakers and defibrillators are still contraindicated from undergoing CMR, a growing limitation in congestive heart failure. However, safety is being actively examined (17) and MR-compatible devices are in active development by device manufacturers. It may be that CMR has its most important role in defining which patients will benefit most from a device, although more study is needed.

The present study adds to our growing understanding of the prognostic importance of LGE in myocardial disease. Late gadolinium enhancement was recently shown to be the most important independent predictor of major cardiac adverse events over other clinical predictors, including ejection fraction (EF), in a cohort of 195 patients who underwent CMR for clinical reasons primarily to evaluate for ischemia in the setting of coronary artery disease (18). Even the smallest

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amount of LGE was predictive of an adverse outcome with no gradation by the amount of LGE. In contrast, in nonischemic cardiomyopathy in the study of Assomull et al. (16), receiver-operating characteristic analysis showed that more than 4.8% of LV mass with LGE differentiated patients with worse outcomes.

Thus, in both ischemic and nonischemic myocardial disease, fibrosis is a marker of poor outcome over and above standard clinical markers, including EF. Why might this be? In ischemic cardiomyopathies, it is likely a marker of the burden of coronary artery disease and its activity. The extent of infarct scar by CMR is also a better marker of inducible ventricular tachycardia than is EF (19). Although fibrosis is a hallmark of ischemic cardiomyopathies, a recent postmortem study shows that extracellular matrix proteins, including types 1, III, and IV collagen, laminin, and fibrinonectin, are expressed more frequently in human hearts with dilated cardiomyopathy than those with ischemic cardiomyopathy (20). Thus, fibrosis is more characteristic of nonischemic cardiomyopathies. In nonischemic cardiomyopathies, fibrosis is thought to be at the root of myocardial re-entry leading to ventricular tachycardia (21). This is especially true in the epicardium based on electrophysiological mapping studies (22). Prior studies using late gadolinium enhancement have shown that scar that subtends 25% to 75% of the wall thickness identifies patients that are at higher risk for inducible ventricular tachycardia on electrophysiological testing (23). Fibrosis may also involve the conduction system and lead to dyssynchrony and worsening congestive heart failure.

Risk stratification in patients with congestive heart failure is a growing necessity in cardiology. It is becoming increasingly apparent that fibrosis may be an important prognostic marker and may identify patients at higher risk of ventricular arrhythmias and cardiac death. A coalescence of the ability to image fibrosis by late gadolinium-enhanced CMR with an enhanced understanding of its etiology and prognostic implications will advance care of the patient with congestive heart failure in the years to come.

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