

CORRESPONDENCE

Letters to the Editor

Late Gadolinium Enhancement and Higher Risk of Arrhythmias Fibrosis or Increased Ventricular Wall Stress?

Current criteria indicating implantable cardioverter-defibrillator (ICD) therapy for primary prevention of sudden cardiac death are poor, and non-evidence-based ICD implantations are more likely to have worse outcomes. Therefore, Iles et al. (1) examined late gadolinium enhancement (LGE) by using cardiac magnetic resonance imaging to predict appropriate device therapy in patients with ischemic and nonischemic cardiomyopathy. The study relies on the assumptions that myocardial fibrosis is the substrate of LGE and that fibrosis is associated with arrhythmias.

Well-documented links between fibrosis and LGE exist in patients who have experienced myocardial infarction in whom nonviable cardiomyocytes are replaced by collagen. This contiguous subendocardial or transmural area can be detected by a bright LGE pattern. Histological changes are very different in patients with dilative cardiomyopathies. Histopathological studies have shown that the myocardial remodeling can be associated with an increased collagen volume fraction, and in transmural left ventricular sections, the extent of fibrosis increased from epicardium to endocardium and from the right to the left side of the septum (2). LGE occurs as midwall (septal) streak (1) or is irregularly diffuse. Thus, in dilative cardiomyopathies, causes beyond fibrosis should be taken into account for LGE.

In the study by Iles et al. (1), all patients with ischemic cardiomyopathy exhibited LGE, and the ICD discharge rate was 14%, whereas it was 29% in patients with nonischemic cardiomyopathy and LGE. Also, based on the absence of differences in left ventricular ejection fraction and end-diastolic volume index, it was concluded that fibrosis predicts appropriate ICD therapy. However, it remains to be assessed whether indeed fibrosis or an increased wall stress was responsible for LGE and ICD therapy. Using echocardiography-based ventricular mass and geometry data, we suggest calculating wall stress and examining the contention that patients with ICD therapy exhibit increased wall stress.

In accordance with a role of wall stress for LGE, our recent study on 300 patients with dilative cardiomyopathy showed that a rise in wall stress (3) was associated with LGE (4). Most likely, higher wall stress is associated with an increased capillary leakage, and thus favors contrast medium emission into the interstitial space. Also, its venous clearance can be prolonged by an impaired redistribution. The link of LGE with arrhythmias would follow from experimental studies in which myocardial stretch and neuro-humoral reactions predispose patients to arrhythmias involving, for example, stretch-activated cation channels.

The proposed subanalysis also could clarify whether LGE per se is an independent prognostic predictor or a dependent surrogate

marker. Thus, in a study of 141 patients with dilated cardiomyopathy, the prognostic value of LGE regarding survival was found only by univariate, but not by multivariate, analysis (5). Increased wall stress thus could be the underlying mechanism of a worse prognosis and should be evaluated also as indicator for ICD therapy.

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Reply

Drs. Alter and Rupp propose that late gadolinium enhancement (LGE) in nonischemic cardiomyopathy may be the result of increased myocardial wall stress with resultant increased capillary permeability and reduced venous return.

In our study (1), patients without LGE did not experience implantable cardioverter-defibrillator discharges, suggesting that this group may be at lower risk for malignant ventricular arrhythmia. LGE previously was demonstrated to correlate well with ischemic regional fibrosis (2) and also in limited human studies in nonischemic pathological conditions (3). Therefore, we postulated the likely mechanism for implantable cardioverter-defibrillator discharges in advanced cardiomyopathy to be the presence of regional scar acting as an arrhythmogenic substrate. However, regardless of the mechanism, a lack of LGE was associated with a

favorable prognosis with respect to malignant arrhythmia, a finding supported by other studies (4,5). As wall stress also is increased in advanced cardiomyopathy, the association between LGE and wall stress referred to by the authors is not surprising, because LGE also is a feature of advanced cardiomyopathy (4,5).

One would expect that if increased wall stress is the underlying mechanism of myocardial contrast enhancement, it is likely to be diffuse rather than the focal process observed with LGE. Diffuse contrast enhancement cannot be detected with the technique of LGE, because this method requires the presence of apparently normal adjacent myocardium without contrast enhancement. However, because shortened post-contrast myocardial T1 times have been shown to correlate with histological fibrosis (6) in patients with cardiomyopathy, wall stress as the underlying mechanism of contrast enhancement seems unlikely. Interestingly, recent research in hypertensive patients revealed an absence of LGE despite increased wall stress compared with controls (7).

To determine conclusively that wall stress contributes to the presence of LGE in nonischemic cardiomyopathy independently of regional fibrosis would require contemporaneous measurement of LGE and wall stress coupled with histological examination of areas of myocardium in which LGE is present. To our knowledge, this has not been performed, and given the lack of invasive pressure measurement along with the unavailability of histological samples, such analysis is not possible from our study population.

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Dynamic Left Ventricular Outflow Tract Obstruction and Acute Heart Failure in Tako-Tsubo Cardiomyopathy

Given the relative paucity of data regarding tako-tsubo cardiomyopathy (TC) and the risk of heart failure, Madhavan et al. (1) are to be commended for their work recently published in the *Journal*.

However, we wish to raise one issue not mentioned in their paper. It is recognized that TC can be complicated by reversible systolic anterior motion (SAM) of the mitral valve (MV) with dynamic left ventricular outflow tract obstruction (LVOTO) (2). This can be associated with significant mitral regurgitation (MR). The pathophysiological basis of this complication remains unknown. Two studies, both including more than 100 patients, each reported an incidence of SAM and LVOTO in more than 10% of TC cases (3,4). Thus, dynamic LVOTO is certainly not a rare phenomenon in association with TC.

Hypotension may develop in patients with TC first due to left ventricular systolic dysfunction, second due to significant MR secondary to SAM of the MV, third due to dynamic LVOTO, or fourth a combination of these factors (5). Alternatively, hypotensive patients presenting with chest pain and ischemic electrocardiographic changes may, of course, have cardiogenic shock due to acute coronary syndrome. It is clinically important to differentiate the cause of hypotension in such patients because the immediate management varies depending on the underlying etiology.

In patients with acute coronary syndrome, intra-aortic balloon pump (IABP) counterpulsation improves coronary perfusion (during diastolic balloon inflation) and reduces systemic afterload (during systolic balloon deflation). The use of positive inotropes can also improve the hemodynamic status. In the patient with suspected TC who is hypotensive, these same therapies can be used if there is no SAM with LVOTO. By contrast, if there is significant LVOTO, both IABP placement and inotropes are relatively contraindicated because they would worsen the dynamic gradient and thereby further jeopardize cardiac function (6). Therefore, patients with predominant pump failure can safely receive IABP counterpulsation and inotropes, whereas those with significant LVOTO should instead be managed more conservatively with cautious fluids (if no pulmonary edema) and beta-blockers (to increase diastolic filling time and thus end-diastolic volume) (7).

We congratulate the authors on their retrospectively developed and prospectively validated risk scoring system. However, we believe that their final sentence “the use of intra-aortic balloon pump counterpulsation may be the preferred treatment strategy for moderate or severe hemodynamic compromise” would be further enhanced by the addition of the important clinical caveat “assuming there is no echocardiographic evidence of LVOTO.” We wonder whether the authors encountered cases of LVOTO in their series, and, if so, what percentage of these patients had acute heart