# EDITORIAL COMMENT

# Gadolinium-Enhanced Magnetic Resonance Imaging in Hypertrophic Cardiomyopathy

## In Vivo Imaging of the Pathologic Substrate for Premature Cardiac Death?*

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In vivo magnetic resonance imaging (MRI) of the heart with gadolinium-based contrast agents has been performed since the mid-1980s (1). A major limitation of the initial techniques was insufficient image contrast between normal and infarcted myocardium. Recently, a number of studies have demonstrated the effectiveness of a new segmented inversion recovery MRI pulse sequence for differentiating normal from infarcted myocardium with signal intensity differences of nearly 500% (2,3). This new technique for gadolinium-enhanced MRI has been shown to be effective in identifying the presence, location, and extent of myocardial infarction in both the acute and chronic settings (3–5). Furthermore, this technique has been validated in animal models of ischemic injury (2,6,7), provides scar size measurements that are closely correlated with positron emission tomography in patients with ischemic cardiomyopathy (8), and provides results superior to single-photon emission computed tomography perfusion imaging in patients with small myocardial infarctions (9).

Both acute and chronic infarcts are visualized on contrast MRI as bright or "hyperenhanced" zones. Normal myocardium, as well as injured but viable myocardium, such as stunned or hibernating myocardium, does not display hyperenhancement (2,5,10). The mechanism of hyperenhancement is believed to be due to tissue accumulation of gadolinium, possibly because of differences in contrast distribution volume (7,11). Clinically used gadolinium contrast media are "inert" extracellular agents that cannot cross intact sarcolemmal membranes (12). Because tissue volume in normal myocardium is predominantly intracellular (~75% to 80% [13]), the distribution volume of gadolinium is normally quite low. In the setting of acute necrosis, gadolinium will be able to passively diffuse across ruptured

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myocyte membranes into the intracellular space, which will lead to significant increases in gadolinium concentration at the tissue level. In the setting of collagenous scar, the interstitial space is expanded compared with the interstitial space between densely packed living myocytes that is characteristic of normal myocardium. In this situation, there will also be increased gadolinium concentration at the tissue level. Concerning tissue substrates for myocardial hyperenhancement, it has been postulated that it is the *absence of viable myocytes* that leads to myocardial hyperenhancement rather than any inherent properties that are specific for acutely necrotic tissue, collagenous scar, or other forms of nonviable tissue (14).

**Does MRI hyperenhancement represent replacement scarring in hypertrophic cardiomyopathy (HCM)?** Recently, gadolinium-enhanced MRI was performed in 21 patients with HCM (15). In these patients the maximum left ventricular (LV) end-diastolic wall thickness averaged 25 ± 8 mm, and they had preserved LV ejection fraction (70 ± 11%). Hyperenhancement was found in the majority (81%) of patients, with hyperenhancement mass on average 8 ± 9% of LV mass. The pattern of hyperenhancement was peculiar. Hyperenhancement occurred only in hypertrophied regions, was patchy with multiple foci, and predominantly involved the middle third of the ventricular wall. Additionally, all patients with hyperenhancement had involvement at the junctions of the interventricular septum and the right ventricular free wall (Fig. 1A). The direct comparison of gadolinium MRI to histopathology has not yet been performed in HCM. However, given the MRI-histopathologic correlations described here, and the fact that these patients were predominantly asymptomatic without any recent cardiac events, hyperenhanced regions were thought to represent scarred myocardium. Several necropsy studies have demonstrated that myocardial scarring is common in HCM (16–21). Similar to the pattern of hyperenhancement, the pattern of scarring in these studies was distinct from that seen in ischemic heart disease. For instance, scarring did not correspond to any particular epicardial coronary artery distribution and was often limited to the mid-wall or subepicardium (16–19,21). Moreover, Kuribayashi and Roberts (21) demonstrated in a necropsy study of patients with HCM that the junctions of the interventricular septum and right ventricular free walls are the locations where myocardial scarring (along with myocardial disarray) is most prominent. The similarity between hyperenhancement by MRI and myocardial scarring by pathology is demonstrated in Figure 1. The locations of hyperenhancement in the two asymptomatic living patients (Fig. 1A) are remarkably similar to the locations of scarring in the reproduced pathology figures from two *different* HCM patients studied at necropsy after sudden death (Fig. 1B) (16,20).

Replacement scarring represents only one type of myocardial fibrosis. For example, "plexiform fibrosis" refers to a
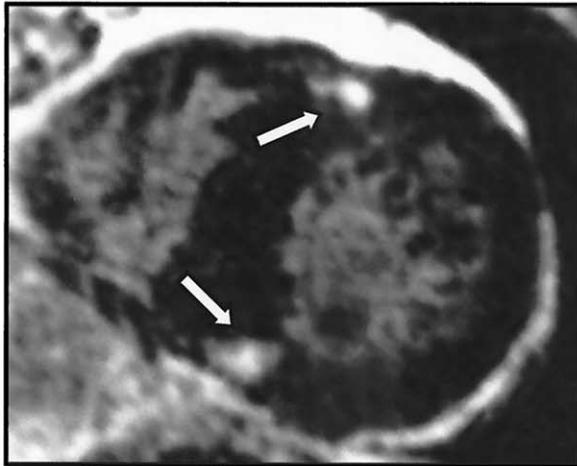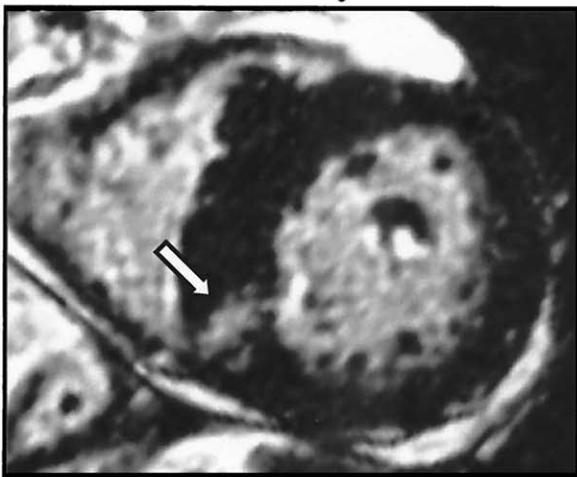
**Figure 1.** Comparison between in vivo gadolinium enhanced magnetic resonance images (MRI) in two patients from reference 15 **(A)** with reproduced pathology figures from two different patients with hypertrophic cardiomyopathy studied at necropsy after sudden death **(B)**. **Arrows** point to regions of hyperenhancement on magnetic resonance imaging or regions of scar on pathology. **Panel B** is reproduced with permission from Roberts CS, Roberts WC. Morphologic features. In: Zipes DP, Rowlands DJ, editors. Progress in Cardiology. Vol. 2/2. 1989:3–22; and Basso et al. Hum Pathol 2000;31:988–98.

unique type of interstitial fibrosis that is characteristic of myocardium exhibiting myocardial fiber disarray (22). Therefore, it is possible that myocardial hyperenhancement in HCM is not specific for replacement scarring since, theoretically, gadolinium distribution volume can be increased in the setting of all forms of myocardial fibrosis. This is unlikely for two reasons. First, it should be noted that contrast MRI is sensitive to *regional* differences in gadolinium accumulation rather than an overall increase because the technique depends on the ability to "null" signal from "remote" (presumably normal) myocardium. Therefore, cardiac disorders that lead to focal regions of fibrosis will hyperenhance, whereas disorders that lead to global changes such as diffuse interstitial fibrosis will not. As an example of this concept, we have found that patients with idiopathic dilated cardiomyopathy, a group in whom diffuse interstitial fibrosis is common but grossly visible scarring is rare (23), generally do not exhibit hyperenhancement (4). Second, it should be noted that the voxel resolution of contrast MRI is approximately 1.9 mm by 1.4 mm by 6 mm. The histopathologic analogue is fibrosis visible to the naked eye, which is, to paraphrase Anderson et al. (22), *"almost certainly the result of replacement of irreversibly damaged myocardium and can be termed a gross or macroscopic scar."* Although it is possible that partial or incomplete hyperenhancement may result from regions with increased interstitial fibrosis without replacement fibrosis, it is improbable that hyperenhancement of the quality or intensity seen in Figure 1 occurs without macroscopic scarring.

**Is there a link between myocardial scarring and premature cardiac death?** The study by Moon et al. (24) in this issue of the *Journal* adds further information. The investi-

gators report on contrast MRI findings in 53 patients with HCM. Overall, hyperenhancement (scarring) was found in 79% of patients, a figure quite similar to that found by Choudhury et al. (15). This study, however, is the first to compare contrast MRI findings to known clinical risk factors for premature cardiac death. For instance, 18 patients had two or more clinical risk factors for sudden death and 9 patients had adverse LV remodeling with progressive wall thinning and cavity dilation. When the entire cohort was considered, the authors observed increased extent of hyperenhancement in patients with two or more risk factors for sudden death (15.7% vs. 8.6% of LV mass, p = 0.02). This finding remained significant when the patients with LV remodeling were removed from the analysis (n = 44, p = 0.02). Within the group of patients that had serial echocardiograms performed for five or more years (n = 34), the occurrence of LV remodeling was also associated with increased extent of hyperenhancement (28.5% vs. 8.7% of LV mass, p < 0.001). This finding remained significant when patients with two or more risk factors for sudden death were removed from the analysis (n = 20, p = 0.04).

These results in living patients are consistent with data from necropsy studies. Tanaka et al. (25), in a small study of 10 patients with HCM, observed that patients who died suddenly had a larger amount of myocardial fibrosis than those who died from noncardiac causes (13 ± 3% vs. 6 ± 3% of LV mass, p < 0.05). Basso et al. (16) evaluated 19 patients with HCM under the age of 36 years who died suddenly. Although only a single transverse (short-axis) section was evaluated for the presence and extent of scarring, septal scars were found in 11 patients (58%), and these were large, forming 10% to 28% of the septal area. Additionally, the extent of scarring was positively correlated with the magnitude of LV hypertrophy, one of the established clinical risk factors for sudden death (26). Varnava et al. (19) evaluated 72 patients with HCM who either died suddenly or progressed to end-stage heart failure (n = 22). This study focused primarily on microscopic evaluation of myocyte disarray, fibrosis, and small-vessel disease. Macroscopic evaluation was limited; nonetheless, the extent of replacement scarring was associated with LV hypertrophy and cavity dilation. The authors comment, *"As fibrosis but not disarray increases with increasing heart weight, it is likely that the mechanism of sudden death in these patients is related to marked fibrosis and scarring, rather than to disarray."*

It has recently been established that ventricular tachycardia (VT) or ventricular fibrillation (VF) is the principal mechanism of sudden death in patients with HCM (27). Ventricular tachyarrhythmias are also a predominant cause of sudden death in patients with chronic coronary artery disease (CAD) (28). Although scarred myocardium is an established anatomic and electrophysiologic substrate for the occurrence of ventricular tachyarrhythmias and sudden death in patients with CAD (28,29), its role in HCM is less clear. Scarred myocardium, of course, represents healed infarction in the setting of ischemic heart disease. In HCM,

even in the absence of significant epicardial coronary disease, scarred myocardium may still be the end result of ischemia, leading to myocardial necrosis. Several studies have reported increased numbers of structurally abnormal intramural coronary arteries within areas of scarred myocardium, and a causal role for these arteries in producing ischemia has been postulated (18).

The setting of healed infarction leads to *"... areas of abnormal conduction and refractoriness, heterogeneity of conduction and refractoriness, enhanced automaticity, and areas of inexcitability, all of which are potentially arrhythmogenic"* (28). Evidence for slowed and fragmented intraventricular conduction as seen in patients with ischemic heart disease has also been observed in patients with HCM, and these observations have been associated with risk for sudden death (30,31). Slowed conduction in HCM, although attributed to potential electrophysiologic effects of myocardial disarray, may simply reflect the substrate of myocardial scarring as in ischemic heart disease.

However, programmed ventricular stimulation performed in patients with HCM only rarely induces monomorphic VT (32). Other rhythms such as polymorphic VT and VF are induced more frequently, but are thought to be nonspecific (33). In this regard, it is interesting to note that patients with CAD who present with sudden death are less likely to have inducible monomorphic VT than those that present with hemodynamically tolerated VT. Additionally, patients who present with sudden death generally have less extensive infarction, less frequent incidence of LV aneurysm, higher ejection fractions, and fewer abnormal electrograms than those who present with tolerated VT (29). It is believed that patients who present with sudden death have an anatomic substrate that is qualitatively similar but quantitatively smaller than those who present with tolerated VT (28). This "intermediate substrate" is sufficient to produce rapid malignant ventricular arrhythmias but is not extensive enough to support sustained uniform VT (28). In an analogous fashion, one could speculate that various subgroups of patients with HCM also represent different points in the continuum of abnormal electrophysiologic substrates. In the majority of patients with HCM, those with normal to supranormal LV ejection fraction and minimal or no scarring (15), there will be insufficient abnormal substrate to produce malignant ventricular arrhythmias. A small percentage of patients with normal ejection fraction, however, will have sufficient scarring, albeit in a patchy, multifocal fashion (15), to support smaller re-entrant circuits and thus be at risk for rapid malignant arrhythmias. Conversely, these patients will have insufficient abnormal substrate to reproducibly develop sustained uniform VT during programmed stimulation. Finally, in the very few patients with adverse LV remodeling and systolic dysfunction, these patients will have sufficient scarring to develop both spontaneous malignant ventricular arrhythmias and sustained uniform VT during programmed stimulation.

The results of Moon et al. (24) demonstrate that patients

with adverse remodeling had the greatest amount of hyperenhancement (scarring). In fact, the patient with least amount of hyperenhancement in this group had hyperenhancement of over 15% of the LV myocardium. It is perhaps not surprising that significant hyperenhancement was found in both patients with risk factors for sudden death as well as those with adverse remodeling. Continuing our analogy with CAD, scarring of course is often found in those with CAD that die suddenly as well as those that die from progressive heart failure. In both HCM and CAD, it is probable that appropriate triggers (systemic hypotension, physical exertion, and so on) are required in addition to the electrophysiologic substrate for the occurrence of malignant ventricular tachyarrhythmias.

The associations between hyperenhancement and clinical risk factors for premature cardiac death demonstrated by Moon et al. (24) represent an important first step. However, it is apparent that there is a wide range in the extent of hyperenhancement within patient subgroups and there is clearly overlap between groups. With this in mind, it is important to note that using two or more clinical risk factors as a marker of sudden death provides a sensitivity of only 45% and a positive predictive accuracy of 23% (34). Ultimately, of course, the independent prognostic value of gadolinium-enhanced MRI in assessing premature cardiac death will need to be determined. Given the relatively rare occurrence of HCM in the general population and the relatively benign nature of this disease, a prospective study in a sufficient patient population may initially appear prohibitive. Conversely, gadolinium-enhanced MRI is a simple, reproducible technique (35), and the number of centers able to perform this technique is growing exponentially. The important data by Moon et al. (24) indicate that assessment of the prognostic value of gadolinium-enhanced MRI in HCM is warranted.

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