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IV.I

Myocardial crypts in hypertrophic cardiomyopathy: the new gang in town

Ethan J. Rowin and Martin S. Maron

Editorial to 'Multiple myocardial crypts
on modified long-axis view are a specific finding in prehypertrophic
HCM mutation carriers'

Eur Heart J Cardiovasc Imaging. 2012;13:281-3

Since the initial description of hypertrophic cardiomyopathy (HCM) over 50 years ago, the majority of our understanding of this complex and heterogeneous genetic heart disease has been the result of insights gained through advances in cardiovascular imaging techniques [1–5]. In the pre-echocardiographic era, the haemodynamic laboratory provided the sole method of diagnosis for HCM by demonstrating a pressure gradient between the left ventricular cavity and the aorta [1,2]. The introduction of echocardiographic imaging in the early 1970s led to a greatly expanded appreciation for the vast heterogeneity of phenotypic expression in this disease, including the first non-invasive demonstration of the characteristic asymmetric pattern of LV hypertrophy, as well as defining the non-obstructive form as an important subset of the HCM disease spectrum [1,2].

More recently, advanced imaging techniques such as cardiovascular magnetic resonance (CMR) have emerged, ushering in a new era of cardiac imaging [3–5]. CMR provides three-dimensional tomographic images with high spatial resolution, with sharp contrast between the blood pool and the myocardium. These unique imaging strengths make it particularly well suited to characterize the diverse morphological expression of HCM [3]. Indeed, CMR has now been applied to large cohorts of HCM patients resulting in a number of clinically relevant observations, further expanding our appreciation and understanding of HCM disease expression beyond traditional imaging modalities [3-7].

CMR improves diagnosis of HCM, by detecting LV hypertrophy unrecognized (or not well seen) by echocardiography, particularly when confined to the anterolateral free wall (or apex) [3–5]. Furthermore, in some HCM patients, the magnitude of wall thickening may be underestimated by echocardiography, which may have important management implications when massive LV hypertrophy is detected by CMR (wall

thickness ≥ 30 mm is an independent risk factor for sudden death) [4]. Other HCM patient subgroups identified with CMR include those with thin-walled scarred LV apical aneurysms (which prior to CMR imaging in HCM remained largely undetected) [6] and end-stage systolic dysfunction (EF, 50%), in whom identification may raise additional management options including implantable cardioverter defibrillators for primary prevention and anticoagulation for stroke prophylaxis [1,6]. CMR has also broadened our understanding of HCM disease expression to now include hypertrophy of the right ventricle, and morphological abnormalities of the papillary muscles and the mitral valve [1,4–7]. Contrast-enhanced CMR with late gadolinium enhancement (LGE) has generated tremendous enthusiasm by providing the opportunity to identify the abnormal myocardial substrate of fibrosis, a potential novel marker of risk.

Over the last two decades, the availability of genetic testing in routine clinical cardiovascular practice has resulted in the identification of HCM family members who carry a diseasecausing sarcomere mutation (and therefore at risk of developing phenotypic HCM) but who are without LV hypertrophy, i.e. genotype positive–phenotype negative (G+P2) patients [8]. This led to the observation with echocardiography that abnormalities of myocardial function are present in G+P2 patients, [9] and the emerging principle that even in the absence of increased LV wall thickness, these hearts may be abnormal. CMR has added to these insights by demonstrating that a number of additional morphological abnormalities may be present in G+P2 patients, including LGE (i.e. fibrosis) [10] and elongated mitral valve leaflets [7].

This sets the stage for the Brouwer et al. [11] paper. In this investigation, the authors have characterized a unique structural abnormality consisting of narrow,

deep blood-filled invaginations within the LV myocardium of predominantly G+P2 HCM patients, termed myocardial crypts (or clefts). Crypts were detected only by CMR in the majority (70%) of G+P2 patients and in a much smaller number (12%) of control patients with other forms of congenital heart disease [11]. Based on these initial observations, a number of questions have arisen, including: (i) why only recently have these structural abnormalities of the LV wall been appreciated; (ii) is this morphological feature specific to HCM; (iii) are crypts just part of LV non-compaction; (iv) what is the clinical significance of this structural finding.

Almost certainly, the emerging visibility of myocardial crypts is a result of the high spatial resolution imaging of CMR combined with the sharp contrast generated between the bright blood pool (of the crypt) and the adjacent myocardium [11–14]. This is similar to CMR identification of regional hypertrophy confined to the anterolateral LV free wall or apex, regions of the chamber less reliably imaged by echocardiography [3–5]. Notably, recognition of myocardial crypts in HCM has not been confined to contemporary imaging methodologies, as early post-mortem studies reported the presence of deep invaginations within the LV wall of HCM patients, including the initial pathological description by Teare [15].

Based on the high prevalence of myocardial crypts reported among G+P2 HCM patients, crypts do appear to represent a distinct morphological component of HCM expression. However, in the current study (and in other series), crypts were also identified in a small proportion of patients with other forms of congenital heart disease [11,13]. Therefore, it seems reasonable to conclude at this time that crypts may not be specific for HCM. Indeed, one of the points emphasized by the authors is the number of crypts may be a more clinically relevant finding than just presence, as

the specificity for gene positive HCM status increased substantially in patients with two or more crypts.

However, determining a more precise assessment of the prevalence of myocardial crypts will require large, prospectively selected cohorts with HCM and other forms of heart disease studied with CMR. Other limitations will also need to be addressed, including agreement on a uniform, widely accepted morphological definition for crypts. Currently, a number of different criteria have been used by investigators, [11–14] created confusion for clinicians regarding what precisely defines a morphologically abnormal crypt. For example, should we consider minor invaginations of the LV wall that penetrate less than half the myocardial thickness as a crypt or reserve that designation only when these structures involve the majority of wall thickness? However, as the authors emphasize, crypts should not be confused with the trabeculations (i.e. sinusoids) characteristic of LV non-compaction, which are situated solely in the distal portion of the chamber (while crypts are predominantly localized to the basal or mid-LV level) and unlike crypts do not penetrate the wall of normal (i.e. compact) myocardium [11,14].

In addition, Brouwer et al. [11] illustrate the need to acquire nontraditional long-axis imaging planes in order to reliably detect crypts in some G+P2 HCM patients. Crypts can be small, occupying a focal area of the LV myocardium and therefore could be missed using routine cross-sectional imaging planes. One potential clue that a crypt may be present, even if not seen with standard imaging, is the presence on the short-axis image of a 'bright' triangular area at the insertion area of the right ventricular wall with posterior septum (i.e. this 'bright' area is due to partial volume effects of a crypt) [11,12,14]. Prescribing a non-standard imaging plane perpendicular through this 'bright' area will allow detection of crypts on the resulting two-

chamber image. Therefore, consideration should be given to altering current CMR protocols for G+P2 HCM patients to include the need for additional views based on inspection of the short-axis images.

These CMR-based observations with respect to G+P2 patients expand our current appreciation of the diversity of HCM phenotypic expression and underscore the emerging principle that even non-hypertrophied LV myocardium in HCM may be structurally abnormal [7–14]. Although myocardial crypts are the ‘new gang in town’, they should be considered along with a number of other clinical and cardiac morphological abnormalities previously reported in G+P2 patients which support this concept, including: 12-lead electrocardiographic abnormalities,[8] elongated mitral valve leaflets, [7] LGE, [10] and echocardiographic indices of diastolic dysfunction [9].

Although the precise clinical implications of crypts remain uncertain, they represent a morphological marker associated with genetically affected status with potentially important implications for management strategies, including an expanded role for CMR in earlier diagnosis of relatives within HCM families [11,12,14]. For example, identification of myocardial crypts by CMR in relatives for whom genetic testing is impractical due to cost or other considerations (or when the mutation remains undefined or of unknown significance after testing) should prompt continued surveillance with imaging studies. Likewise, identification of a crypt in an HCM family member raises consideration to obtaining genotyping to achieve a potentially definitive HCM diagnosis [14].

These observations continue to emphasize the important contribution of CMR in expanding our appreciation for the diversity of the HCM phenotype, including the principle that nonhypertrophied LV myocardium may be otherwise structurally

abnormal. Although, additional studies are needed to more precisely determine the prevalence and clinical significance of crypts, CMR continues to have a growing role in the contemporary evaluation of patients with this complex genetic heart disease.

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