The Remarkable 50 Years of Imaging in HCM and How it Has Changed Diagnosis and Management
From M-Mode Echocardiography to CMR

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ABSTRACT

The almost 50-year odyssey of cardiac imaging in hypertrophic cardiomyopathy (HCM), revisited and described here, has been remarkable, particularly when viewed in the timeline of advances that occurred during a single generation of investigators. At each step along the way, from M-mode to 2-dimensional echocardiography to Doppler imaging, and finally over the last 10 years with the emergence of high-resolution tomographic cardiac magnetic resonance (CMR), evolution of the images generated by each new technology constituted a paradigm change over what was previously available. Together, these advances have transformed the noninvasive diagnosis and management of HCM in a number of important clinical respects. These changes include a more complete definition of the phenotype, resulting in more reliable clinical identification of patients and family members, defining mechanisms (and magnitude) of left ventricular outflow obstruction, and novel myocardial tissue characterization (including in vivo detection of fibrosis/scarring); notably, these advances afford more precise recognition of at-risk patients who are potential candidates for life-saving primary prevention defibrillator therapy. This evolution in imaging as applied to HCM has indelibly changed cardiovascular practice for this morphologically and clinically complex genetic disease. (J Am Coll Cardiol Img 2016;9:858–72)

Since the initial description of hypertrophic cardiomyopathy (HCM) >50 years ago, most of our understanding of this complex and heterogeneous genetic heart disease has resulted from insights gained through advances in cardiovascular imaging techniques. Indeed, perhaps no other heart disease has been so uniquely suited to noninvasive imaging as HCM (1–10). In many respects, the development of cardiac imaging from M-mode echocardiography to cardiac magnetic resonance (CMR) transpiring over several decades has paralleled the evolving understanding of this clinically and morphologically diverse disease (Figures 1 and 2). Therefore, in this comprehensive historical review, we revisit the development of imaging technology to assess its impact on the diagnosis and management of HCM (10).

THE BEGINNING

In the early 1960s, Dr. Harvey Feigenbaum (Indianapolis, Indiana) was largely responsible for the clinical adaptation of cardiac ultrasound (which he
termed “echocardiography”) (11-15), due to his vision, energy and focus, and fervent belief in this new technology. Dr. Feigenbaum formulated a worldwide initiative that included publications, workshops, national/international conferences, a comprehensive textbook spanning 45 years, the National Institutes of Health investigators created the first available sector scanner, and a cadre of trainees who carried forth a new message to a skeptical establishment.

Early investigations from the Feigenbaum laboratory reported the capability of measuring left ventricular (LV) wall thickness and cavity dimensions, and recognition of the ventricular septum (12,14-16). These observations and those of other investigators (17,18) were instrumental in promoting the imaging revolution for cardiac diseases (prominently including HCM).

EARLY HISTORICAL PERSPECTIVES ON CARDIAC/HCM DIAGNOSES

The initial contemporary morphologic description of HCM was recorded in 1958 by Dr. Donald Teare, the Coroner of London (19). In 8 young patients who had died suddenly, Dr. Teare described the classic gross and histologic features of HCM, including the asymmetric pattern of left ventricular hypertrophy (LVH) that ultimately became a diagnostic marker in the imaging era (20). Although these findings were considered possibly those of a cardiac tumor, his report is remarkable because it described for the first time, in novel anatomic detail, the disease entity that became HCM.

In the decade that followed (1960 to 1970), clinical recognition and investigation of HCM began in earnest, dominated by the Braunwald group at the National Institutes of Health (Bethesda, Maryland) (1). Their findings were largely hemodynamic and angiographic observations (Central Illustration) in the cardiac catheterization laboratory but also involved electrocardiograms, history-taking, and precordial auscultation. In 1958, a young man with a subaortic gradient and malignant family history became the first patient clinically diagnosed with HCM (21).

ECHOCARDIOGRAPHY AND M-MODE IMAGING. Introduction of echocardiography to clinical practice in the early 1970s signaled an abrupt transition from invasive cardiac catheterization to the modern imaging era (4,6,9,22,23) (Central Illustration). M-mode, a time-motion technique (“M” for motion), provided a single-dimensional (“ice pick”) representation of the heart (3,11,12,22,23) directed blindly through narrow rib interspaces, dissecting the center of the LV cavity to avoid obliquity. Consequently, images of the LV wall were confined to a small portion of the basal anterior ventricular septum and posterior (inferior) LV free wall (Figure 3). Unlike 2-dimensional echocardiography (2DE), M-mode does not provide a true picture of the heart but rather a diagrammatic display showing changes in the position of structures during the cardiac cycle. Recordings were made initially on hard paper strips, or as Polaroid stop-frame snapshots.

In 1972, 2 HCM cohorts imaged with new M-mode technology were published in Circulation 3 months apart (one from the University of California at Los Angeles [22] and one from the National Institutes of Health [23]), quantitatively measuring LV wall thicknesses for the first time. This research represented a major milestone for HCM, providing the opportunity to achieve a reliable noninvasive diagnosis, while avoiding the risk and inconvenience of cardiac catheterization. In the process, a new era of clinical investigation was created (Central Illustration).

The asymmetrically hypertrophied ventricular septum was proposed as a diagnostic hallmark (20,23), and the capability for diagnosing HCM in the absence of a subaortic gradient was a major advance since obstruction was a diagnostic prerequisite in the decade before M-mode (1). This scenario is evident by the names used at that time: IHSS (idiopathic hypertrophic subaortic stenosis) and HOCM (hypertrophic obstructive cardiomyopathy) (24,25).

M-mode echocardiography made it possible to compare thicknesses of small portions of the ventricular septum and the LV free wall, and early National Institutes of Health investigators created the “septal-free wall ratio” (20,23). This ratio is usually abnormal in HCM because the anterior septum and posterior wall are generally the thickest and the thinnest portions of the LV chamber, respectively (Figure 3). Ratios \( \geq 1.3 \) were initially promoted as pathognomonic diagnostic markers for HCM, leading to a brief renaming of the disease as “ASH” (asymmetric septal hypertrophy) (20). Unfortunately, characterizing a complex pathological process solely by using a single disease feature only added confusion, given the many acronyms already in use describing the same disease (24,25). Ultimately, the septal-free wall ratio proved to have low diagnostic specificity (26) and soon became obsolete as a HCM marker.

LV OUTFLOW OBSTRUCTION AND IMAGING. Surgical relief of LV outflow tract obstruction (1,2) began
in the early 1960s (nearly a decade before echocardiography) and progressed at that time even though the true mechanism of subaortic obstruction had not yet been defined. LV outflow tract gradients in HCM were initially attributed to muscular obliteration of the basal outflow tract by the hypertrophied vigorously contracting septum (i.e., “contraction ring”), on the basis of observations made in the operating suite during early septal myectomies (1,27). This concept of obstruction was ultimately supplanted in 1967 by cineangiographers who described the mechanism as mid-systolic contact between the mitral valve and septum, with associated mitral regurgitation (28,29).

In 1969, M-mode echocardiography unequivocally demonstrated that mitral valve systolic anterior motion (SAM) caused subaortic obstruction in HCM (Figure 4). This was initially the observation of Dr. Pravin Shah (Rochester, New York), who advanced the use of the acronym “SAM” (30). Thereafter, Popp and Harrison (3) showed that SAM could be provoked with amyl nitrite and abolished with beta-blockers, and Pridie and Oakley (31) reported an “abnormal systolic opening motion of the mitral valve” to cause outflow gradients. Notably, early M-mode studies focused on mitral valve dynamics, with the assessment of hypertrophy evolving 2 to 3 years later as image quality improved.

M-mode also permitted noninvasive estimation of the magnitude of LV outflow obstruction. Investigators, including Dr. Douglas Wigle (Toronto, Ontario, Canada) (32–35), showed that magnitude of the LV outflow gradient was directly related to the duration of systolic contact between the mitral valve and septum, with a quantitative index proposed for estimating gradients (Figure 4) (33). Early on, echocardiographic imaging demonstrated that SAM (3,6,30) is abolished by myectomy (34); later, other clinical and imaging observations substantiated that outflow obstruction in HCM is of pathophysiological
significance and represents true impedance to LV outflow (2,36–38). Finally, outcome studies in obstructive HCM negated the now obsolete argument (originally based largely on angiography) that dynamic obstruction in HCM is of no clinical significance (36,37).

Subsequently, impedance to LV outflow was demonstrated with a drop in LV ejection velocities and flow, as well as reduced LV myocardial contraction velocities, all reversible after relief of outflow obstruction by myectomy (2,39–45). Echocardiographic imaging also showed that the dominant hydrodynamic force acting on the mitral valve is drag, the pushing force of flow (rather than Venturi forces) (39–45). Notably, this understanding has contributed to an evolution of the myectomy operation from the classic Morrow procedure (27,36) to the more extended myectomy (46,47). M-mode recordings derived from 2DE images are still used for measurement of chamber dimensions, as well as timing of SAM, due to its target sensitivity and high effective sampling rate.

2-dimensional imaging. Development of cross-sectional cine-imaging scanning dates to 1967, even before M-mode echocardiography (48–52). About 10 years after M-mode was introduced into cardiovascular practice, 2DE imaging became commercially available, first with mechanical sector scanners and then phased array technology providing “wide-angle” real-time images (53). This development expanded visualization of cardiac anatomy in contrast to the static pictures produced by single-dimensional M-mode (Figure 3), constituting another imaging paradigm for clinical researchers and practicing cardiologists. Early real-time 2DE images were considered striking when introduced but required accompanying artistic drawings for publication (Central Illustration); in retrospect, they are many generations in technology removed from present quality and resolution (4,53,54) (Central Illustration, Figures 1, 5, and 6).

2DE studies in HCM initially targeted SAM, subaortic obstruction, and mitral valve motion rather than LVH (53,55). A large 2DE analysis of 125 patients provided the first comprehensive quantitative characterization...
of the many LVH patterns within the broad HCM disease spectrum (4), followed by an expanded analysis of 600 patients (56). This research created an appreciation for HCM phenotypic heterogeneity and a morphologic classification (4) that is still used (57).

Specifically, the continuous short-axis scan showed that although LVH is often distributed diffusely, it may also reside segmentally in isolated sites remote from the anterior septum (4,5,56) (Figure 3), as first underscored in a 1981 2DE paper describing “unusual locations of LVH undetected by M-mode” (e.g., posterior septum, anterolateral free wall, and apex [54]).

2DE imaging clarified the diverse mechanisms and clinical implications of LV outflow gradients (58-64) (Figure 5); these included patterns of SAM and obstruction by the posterior mitral leaflet (60) or anomalous insertion of papillary muscle into the mitral valve (61), the importance of basal LV outflow tract area (64), as well as the septal LV outflow tract resection. With improved image resolution in the 1990s, a number of reliable quantitative observations were possible, including the linear relation between sudden death and LV thickness, and ≥30 mm as an independent sudden death risk marker (65).

Serial echocardiographic studies performed over extended periods of time established important principles; these included phenotype remodeling with increased LV thickness and mass, usually associated with growth during adolescence, but

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**CENTRAL ILLUSTRATION** Evolution in HCM Imaging Over 50 Years

(A) Angiogram of the left ventricle (LV) representative of the early 1960s showing mid-ventricular obstruction (arrows). (B) M-mode from 1970s showing a disproportionately thickened ventricular septum (VS) compared with a normal posterior wall (PW) thickness. (C) 2DE long-axis showing distally hypertrophied VS. (D) At the time, an accompanying drawing was usually required for publication. Reprinted with permission from Maron et al. (4). (D) CMR image of VS hypertrophy. (E) Contrast-enhanced CMR with extensive transmural late gadolinium enhancement (myocardial fibrosis) in VS (arrows) of a young, high-risk patient. Reprinted with permission from Maron et al. (124). (F) Short-axis CMR showing diffuse multiple focal areas of late gadolinium enhancement in the LV. AML = anterior mitral valve leaflet; Ao = aorta; CMR = cardiac magnetic resonance; HCM = hypertrophic cardiomyopathy; LA = left atrium; PML = posterior mitral valve leaflet; RV = right ventricle; 2DE = 2-dimensional echocardiography.

occasionally in adulthood (66,67). With 2DE visualization of the LV chamber, family screening became far more reliable than was possible with M-mode alone in obtaining the septal–free wall ratio (68).

DOPPLER IMAGING. From 1988, Doppler imaging with color flow imaging provided the opportunity to noninvasively estimate LV outflow tract gradients (using the Bernoulli equation) and the magnitude of mitral regurgitation. In 2 studies, Doppler-derived gradients were equivalent to those measured invasively (69,70), altering the long-standing practice of subjecting patients with HCM to serial cardiac catheterizations. Combining continuous wave Doppler imaging with treadmill (stress) exercise testing provided important insights into the clinical course and management of HCM (Figure 6) (71). Patients with severe drug-refractory symptoms due to physiologically provoked (exercise) gradients become candidates for heart failure reversal with myectomy (or selectively alcohol ablation)(2,7,71). With all of these advances in echocardiography emerging in <20 years, an imaging examination for HCM was assembled that within 30 min could comprehensively define LV morphology, physiology, and hemodynamic state.

Transesophageal echocardiography introduced in the early 1990s (72) has contributed to intraoperative imaging during myectomy to assess distribution and extent of septal hypertrophy, adequacy of muscular resection, and reduction in SAM. Hand-held miniaturized 2DE instruments are used in selected clinical settings, including intensive care units, emergency departments, ambulances, and outpatient departments (73).

CMR. The initial wave of CMR imaging emerged from the academic radiology community in 1983 (74,75). Case reports and small patient surveys highlighted the diagnostic potential of this new technology. Initially, a major obstacle was CMR images formatted in cross-sectional planes incompatible with standard 2DE, thereby contributing to initial resistance toward this technology on the part of clinical cardiologists. Remarkably, the second wave of advanced CMR did not become relevant to HCM practice for 25 years (76).

It is now evident that CMR technology is ideally suited to the diverse HCM phenotype, providing images with high spatial and temporal resolution, sharp contrast between myocardial borders and blood pool, and tomographic reconstruction of the heart with nonoblique visualization of all LV segments (Central Illustration, Figures 7 and 8) (76–85). CMR also harbors distinct advantages over 2DE, not encumbered by limited acoustic windows.

Over a decade of study, application of CMR to large HCM cohorts has enhanced diagnosis and clinical management, including recognition of patients not reliably identifiable with 2DE imaging (5,8,76–88). LV wall thickness measurements by CMR are in some patients more precise than with 2DE imaging (Figure 7), including improved recognition of the crista supraventricularis muscle that can over-estimate LV wall thickness.
Furthermore, just as 2DE imaging revealed large areas of the LV chamber that were not visualized by M-mode, CMR has a similar capability to identify hypertrophied areas “blind” to 2DE imaging, most commonly portions of the most distal (apical) region, posterior septum, and particularly the anterolateral LV free wall for which the epicardial interface can be obscured by pulmonary parenchyma (4,5,8,10,54,76,78,89) (Figure 8). Therefore, as HCM imaging evolved, a consistent principle was that incrementally greater portions of the LV chamber could be more reliably visualized.

CMR has also expanded the definition of the complex HCM cardiomyopathic process in several respects (Figure 7): quantitative assessment of LV mass (not possible reliably with 2DE imaging) (79); extension of hypertrophy into the right ventricular wall (80); noncontiguous segmental hypertrophy (5,8); elongated mitral valve leaflets responsible for outflow obstruction (82); aberrant LV muscle bundles relevant to strategic planning for surgical myectomy (84,85); and de novo onset of LVH in adults (67,86). In addition, CMR was responsible for identifying a new subset of patients; that is, those with LV apical aneurysms and scarring, often associated with mid-cavity muscular obstruction, and with high event rates that may justify the use of primary prevention implantable
cardioverter-defibrillators (81,90,91). Some aneurysms (and apical hypertrophy) can also be imaged with the combination of transthoracic echocardiography and the intravenous administration of contrast, effective for LV opacification and defining endocardial borders.

Furthermore, in association with commercial genetic testing, CMR imaging (as well as echocardiography) have been instrumental in defining the novel gene-positive/phenotype-negative subset, by unequivocally demonstrating the absence of LV wall thickening in all segments of the chamber (92).

In addition, early structural and functional markers of affected status have been identified in nonhypertrophied muscle, including diastolic dysfunction, mitral leaflet elongation, myocardial scarring, and narrow blood-filled myocardial crypts (87,88,92,93). Such imaging markers may impact management strategies because the identification of one or more of these structural abnormalities could serve as evidence of positive genetic status in family members in whom genotyping results are negative or ambiguous, or in family members for whom genetic testing has not yet occurred.

Finally, contrast CMR with gadolinium affords the unique capability for in vivo myocardial tissue characterization. In HCM, extensive late gadolinium enhancement (LGE), which is often evidence of myocardial fibrosis and replacement scarring (94-104), is a source of ventricular tachyarrhythmias (104) and an independent prognostic marker for sudden death or appropriate implantable cardioverter-defibrillator discharges (94). LGE ≥15% of LV mass conveys a 2-fold increase in risk and raises consideration for the primary prevention of sudden death with the implantable defibrillator in young patients with, as well as without, other conventional risk markers (94). Absence of LGE is associated with lower risk.

Diffuse transmural high signal intensity LGE is characteristic of end-stage heart failure and systolic dysfunction. Although the initial 2DE description of HCM suggested that multiple speckled echoes ("ground glass texture") in the thickened septum could represent fibrosis (53), contrast CMR showed that this finding is more likely an ultrasound artifact (105).

Contrast CMR has a role in differentiating sarcomeric HCM from phenocopies with LVH. Similar septal and LV free wall thicknesses combined with global subendocardial LGE is highly specific for cardiac amyloidosis (106). Symmetric LVH patterns associated with posterolateral LGE are reported in Fabry disease...
Massive LVH and extensive LGE may suggest lysosome-associated membrane protein2 in young patients. Distinguishing LV noncompaction from apical HCM can be aided by identifying the deep trabeculations characteristic of noncompaction.

OTHER CONSIDERATIONS

Computed tomography (CT) angiography, useful for noninvasively excluding atherosclerotic coronary artery disease in patients with HCM presenting with chest pain, has achieved only selective application for characterizing the HCM phenotype, and is used primarily in those patients ineligible for CMR. Nevertheless, CT imaging possesses superior spatial resolution and may be considered an alternative to CMR for measurement of LV wall thickness and identification of abnormal intraventricular structures.

Positron emission tomography has been periodically promoted in HCM to assess abnormalities of myocardial blood flow due to impaired coronary microvascular function, to determine the etiology of chest pain, or as a marker of increased risk for adverse events. However, the limited accessibility of

(A) Apical 2DE and (B) continuous-wave Doppler showing absence of SAM and obstruction at rest. (C and D) Intense exercise provokes SAM-septal contact (arrow) and outflow velocity of 5 m/s (100 mm Hg gradient). Reprinted with permission from Maron et al. (71). (E) Changes in left ventricular outflow gradient from rest to post-exercise showing physiologically provoked gradients in large consecutive cohort (by mechanism shown in C and D). (F) Abolition of subaortic gradient by surgical myectomy is associated with long-term (all-cause) survival similar to the general U.S. population. Reprinted with permission from Ommen et al. (125). (G and H) End-stage HCM. Two patients with extensive late gadolinium enhancement (myocardial fibrosis) (arrows) responsible for systolic dysfunction and progressive heart failure, leading to transplant. RA = right atrium; other abbreviations as in Figures 1 and 2.
Positron emission tomography for cardiac imaging has made its integration into clinical practice challenging.

Echocardiography has been used extensively in the noninvasive assessment of diastolic function with transmitral or pulmonary venous pulsed Doppler, tissue Doppler imaging, and (more recently) longitudinal and radial systolic strain imaging and speckle tracking (111-118). These techniques have been of considerable interest for assessing myocardial function, mechanics, and performance, and have provided a variety of insights into HCM disease mechanisms, including: estimation of left-sided filling pressures (111,115), differential diagnoses of physiological versus pathological LVH (112,119), determinants of heart failure (113,120), and diastolic dysfunction preceding LVH in relatives genetically affected with HCM (92,93,116).

Real-time 3-dimensional echocardiography provides a complete cardiac volume rendition with some potential advantages in calculating LV chamber volume and assessing valve structure (121). This technique has been applied to HCM primarily to characterize LV outflow tract anatomy and the mechanism of obstruction. However, the incremental value of 3-dimensional echocardiography over CMR (or 2DE) for clinical management is uncertain, and it remains primarily a research tool.

Genotyping in HCM over the past 30 years has resulted in identification of at least 11 genes encoding proteins of the cardiac sarcomere, and almost 2,000 mutations among these genes, many of which...
are pathogenic for HCM (92). More recently, the MOGE(S) nosology system classification has clarified genotype-phenotype associations by relating imaging-defined cardiac phenotypes (including HCM) to organ(s) involvement, genetic inheritance pattern, etiology/genetic defect, underlying disease/substrate, and functional status (122). However, the enormous diversity in patterns of LVH noted among related family members with HCM, as well as phenotypes as heterogeneous as apical aneurysms, end-stage remodeling, and massive LVH, show that specific genotypes cannot be used to predict clinical phenotypes.
(or outcome) in HCM. Conversely, these observations support the notion that HCM is not composed of many unrelated conditions but is rather a unified (albeit diverse) disease of the sarcomere.

FUTURE DIRECTIONS

Due to the remarkable advances in echocardiography and CMR imaging over 5 decades, appreciation for the vast morphologic expression of HCM can be considered highly advanced, at least in terms of clinical diagnosis and investigation. However, the overall HCM imaging story is likely far from over.

We can speculate that the future imaging era for HCM will be focused on emerging techniques defining the myocardial substrate with greater precision, including insights into heart muscle metabolism and biochemistry, as well as more robust tissue characterization, all of which would have been unimaginable to the early pioneers of M-mode and 2DE. For example, CMR-based T1 mapping is a potential noninvasive imaging marker for the extent of expanded extracellular space within the myocardium (presumably, the combination of interstitial and replacement fibrosis). We expect greater insights into the power of T1 mapping in HCM with outcome data from the ongoing HCMR (Hypertrophic Cardiomyopathy Registry) study (123).

Such studies will also determine whether T1 is superior to LGE in differentiating HCM from its phenocopies, including Fabry disease and amyloid or physiological athlete’s heart, as well as potentially improving recognition of affected family members at risk for developing HCM with LVH. Incorporating such emerging technology into future clinical trials could possibly determine the efficacy of novel drug or device therapy. T2-weighted imaging could clarify the clinical significance of edema that may occur as part of the HCM phenotypic expression. Finally, CT scanning with contemporary sequences providing lower radiation exposure, high temporal resolution, and faster acquisition times, as well as its 3-dimensional imaging capability, will have expanded application to HCM.

Incorporating such techniques into clinical studies performed over extended periods of time will also enhance the understanding of phenotypic remodeling and its impact on clinical course. Furthermore, novel contrast agents may emerge capable of differentiating structural components of the myocardium (e.g., interstitial vs. replacement fibrosis). All these advances will contribute clarity to the clinical profile, management, and natural history of patients with HCM.

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