MINI-REVIEW

Apical Hypertrophic Cardiomyopathy: The Variant Less Known

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Hypertrophic cardiomyopathy (HCM) is an umbrella term for a heterogeneous heart muscle disease that was historically (and still is) defined by the detection of left ventricular (LV) hypertrophy (LVH) in the absence of abnormal cardiac loading conditions. Long after this morphological definition was established, the genetic basis of HCM was discovered, and we now know it is predominantly caused by autosomal dominant mutations in sarcomeric protein genes.[1] Several patterns of LVH have been described in HCM: asymmetric septal (here referred to as "classic" HCM), concentric, reverse septal, neutral, and apical (ApHCM),[2] as well as other, rarer LVH variants such as isolated lateral LVH and isolated inferoseptal LVH. Distinguishing between morphological HCM subtypes has conferred little in terms of personalized management strategies, with one distinctive exception: ApHCM. Compared with classic HCM, ApHCM is more sporadic, sarcomere mutations are detected less frequently, there is more atrial fibrillation (AF) and sudden cardiac death (SCD) risk factors differ. No authoritative ApHCM-specific recommendations to guide diagnosis, family screening, and patient risk stratification currently exist.

First described in Japan in 1976,[2] ApHCM is exemplified by "giant" negative precordial T-waves on electrocardiography and by "spadelike" configuration of its LV cavity in end diastole.[3] This review summarizes the epidemiology, clinical expression, genetics, and prognosis of ApHCM, while also highlighting knowledge gaps.

Pathophysiology and Clinical Characteristics

Epidemiology

ApHCM is not as rare as first thought, accounting for up to 25% of HCM in Asian populations and 1% to 10% in non-Asians.[4] Ethnic variation influences prevalence, natural history, and prognosis, and Western sufferers may exhibit a more malignant form.[1]

Genetics

Fewer ApHCM patients report a positive family history compared with classic HCM,[5] potentially suggesting differences in ascertainment screening and/or different etiological (genetic, environmental) factors. In this context, the applicability of conventional HCM risk stratification can be challenged given that family history of SCD is heavily weighted[6,7] (Table 1).[1,2,4,8–11]

In terms of identifiable sarcomere gene mutations, one study that used a 9-gene panel, 25% of 71 ApHCM versus 34% of 1053 all-cause HCM patients had detectable genetic defects[11]: *ACTC1* (cardiac α-actin 1), *MYBPC3* (myosin-binding protein C), *MYH7* (β-myosin heavy chain), *MYL2* (myosin regulatory light chain), *MYL3* (myosin essential light chain), *TNNT2* (cardiac troponin T2), *TNNI3* (cardiac troponin I3), *TNNC1* (troponin C1, slow skeletal and cardiac type), and *TPM1* (α-tropomyosin 1). The phenotype and clinical outcomes of these ApHCM patients did not differ between genotype-positive or -negative subjects.[11] Other studies confirm reduced mutation rates in ApHCM versus all-cause HCM (13% versus 40% with an 8-gene panel, plus 3 metabolic cardiomyopathy genes: *GLA* (α-galactosidase A) for Fabry disease; *LAMP2* (lysosomal associated membrane protein-2) for Danon disease; and *PRKAG2* (protein kinase, AMP-activated, noncatalytic, gamma-2) for PRKAG2 cardiomyopathy.[12]

As with classic HCM, identified genetic mutations in ApHCM are mainly sarcomeric, autosomal dominant, and influenced by environmental and ethnic/demographic factors including sex.[5] Specific data regarding genetic profiling in the different ApHCM morphologies or ethnicities are lacking. In a

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Table 1. Genetic and Phenotypic Differences and Similarities Between Classic HCM and ApHCM

	Classic (ASH) HCM	ApHCM
% Of all HCM cases	• 46[2]	• 8 [2]
Mean age at diagnosis, y	• 46 (all subtypes)	• 41.4[1]
ECG	• Voltage criteria for LVH • Nonspecific ST-segment and T-wave abnormalities • Deep, narrow Q-waves in the lateral and inferior leads	• Giant negative T-waves characteristic • Voltage criteria for LVH, T-wave inversion • AF relatively common; NSVT
Genetics	• Autosomal dominant sarcomere protein gene mutations • Identifiable pathogenic gene mutations in 34%–40% • Majority of gene mutations in MYBPC3 and MYH7	• Autosomal dominant sarcomere protein gene mutations • Identifiable pathogenic gene mutations in 13%–25% • Majority of gene mutations in MYBPC3 and MYH7[11]
Associated morbidity	• Atrial fibrillation[8] • LVOTO • Diastolic dysfunction • Chest pain • Pulmonary hypertension[9] • Ventricular arrhythmias	• Atrial fibrillation • Diastolic dysfunction • Chest pain • Pulmonary hypertension • Ventricular arrhythmias
All-cause mortality rate	• 1.3% (all subgroups combined)[10]	• 0.5%–4% (but much lower patient numbers)—likely equivalent[4]

ApHCM indicates apical hypertrophic cardiomyopathy; ASH, asymmetrical septal hypertrophy; HCM, hypertrophic cardiomyopathy; LVH, left ventricular hypertrophy; LVOTO, left ventricular outflow tract obstruction; MYBPC3, myosin-binding protein C; MYH7, β-myosin heavy chain; NSVT, nonsustained ventricular tachycardia.

study looking at genotype-phenotype correlations in ApHCM, those that carried a pathogenic sarcomere gene mutation had a stronger family history of HCM (39% versus 26%; P=0.4) but no phenotypic features were not significantly different.[11] European Society of Cardiology (ESC) and American College of Cardiology Foundation/American Heart Association HCM guidelines provide no ApHCM-specific genotyping or family screening recommendations.

Histopathology

Myocardial biopsies from the LV apex in ApHCM have been compared with those from the septum in classic HCM and show less myocyte disorganization (10% versus 86%, P<0.0001),[13] although severity and extent of interstitial fibrosis was equivalent (100% versus 93%; P=ns).[13]

Diagnostic Criteria and Subtypes

Characterized by lack of apical tapering and the presence of precordial T-wave inversion, the diagnostic criteria for ApHCM have evolved over time; originally contingent on left ventriculography demonstrating "unique spade-like configuration and marked apical obliteration" together with electrocardiographic "giant" negative T-waves and high QRS voltage.[14] With imaging advances, definition now relies on demonstrating LVH predominating in the LV apex, with wall thickness in the apex ≥15 mm and a ratio of maximal apical to posterior wall thickness ≥1.5, based on echocardiography or cardiovascular magnetic resonance (CMR).[1] Of note, this diagnostic criterion was not included in the 2014 ESC HCM guideline. The American Heart Association also lacks specific diagnostic criteria for ApHCM and similarly uses wall thickness of ≥15 mm as their threshold for diagnosis of HCM; however, a recent study assessing the reliability of sudden cardiac death recommendations used diagnostic criteria as unexplained hypertrophy in a nondilated LV with wall thickness ≥13 mm by CMR or transthoracic echocardiography,[10] highlighting an emerging trend toward using a lower diagnostic cutoff.

In ApHCM, there is typically no LV outflow tract obstruction from systolic anterior motion of the anterior mitral valve leaflet and therefore no associated mitral regurgitation. ApHCM can exist with or without midventricular obstruction and cavity obliteration (MVOCO) and with or without apical aneurysm formation.[15] It can be subclassified into 3 forms: (1) "pure," with isolated apical hypertrophy; (2) "mixed," with both apical and septal hypertrophy[16] but with the apex thickest[1]; and (3) "relative" ApHCM, believed to be an early ApHCM phenotype. Individuals with relative ApHCM do not meet conventional diagnostic criteria for ApHCM but share imaging findings with the pure group. Relative ApHCM is diagnosed when electrocardiography shows characteristic precordial T-wave inversion and CMR shows loss of the usual apical wall thickness tapering due to apical wall thickness exceeding basal wall thickness, although failing to reach the ApHCM diagnostic cutoff of wall thickness ≥15 mm.[17] As the normal heart exhibits tapering of wall thickness towards the apex, loss of this is abnormal. One CMR study reported 22 subjects, 95% of whom had additional

cardiac structural abnormalities including left atrial (LA) dilatation, apical aneurysm, myocardial scar, and ≥20 mm apical systolic cavity obliteration.[17] In another study, relative apical hypertrophy appeared to be the only explanation for giant T-wave inversion, given the absence of other causes of this abnormality.[18]

Relative ApHCM was originally considered entirely benign, but recent data suggest associated pathology with LA dilatation, apical aneurysm, and myocardial scar[17] (Figure 1). Relative ApHCM may simply represent early disease that with time progresses to overt ApHCM, eventually meeting conventional criteria, as with other HCM variants where penetrance is age dependent.

Natural History and Prognosis

ApHCM is more prevalent in men than women, with male-to-female ratios typically 1.6 to 2.8:1.[1,4] The average age at presentation is 41.4±14.5 years,[1] with mixed ApHCM tending to be more symptomatic and have a greater likelihood of LA enlargement, increased LV filling pressures, and elevated blood cardiac protein biomarkers in the absence of acute coronary syndrome.[1]

ApHCM was originally thought to carry no increased mortality risk,[1] but recent data suggest annual cardiac death rates of 0.5% to 4%, approaching those for classic HCM.[4,11] Increased mortality in women was reported, possibly due to more AF and pulmonary hypertension[4] (Table 1). Patients with mixed ApHCM, younger age at presentation (<41 years),[1] complete end-systolic cavity obliteration at the level of the papillary muscles, paradoxical diastolic flow jet by echocardiography, and apical asynergy[16] have been shown to have higher cardiovascular morbidity. Malignant ventricular arrhythmias and mortality has been linked to apical aneurysms, but only in Western sufferers.[16]

In terms of small-vessel disease and microvascular obstruction, a feature recognized in HCM, there may be an increased role for ischemia in ApHCM from cavity obliteration and the persistence of apical contraction into early-mid diastole, resulting in dynamic small-vessel obstruction in the apical segments, regional myocardial perfusion defects, and chest pain.[19] Impaired myocyte relaxation and increased energetic cost of early hypercontractility may contribute, particularly in early disease.

Electrocardiography and Arrhythmias

Giant negative T-waves defined as negative voltage of ≥1 mV (≥10 mm)[1] are characteristic but not mandatory for diagnosis (Figure 2). In one ApHCM study of 105 patients, 94% had abnormal ECGs with voltage criteria for LVH (65%) and T-wave inversion (93%), but only 47% had giant negative T-waves.[1] Maximal T-wave negativity weakly correlated with apical wall thickness, and electrocardiography does not well differentiate mixed and pure ApHCM variants.[1] Giant negative T-waves have also been identified in other types of HCM and cardiac disease, including coronary artery disease, so are not a pathognomonic feature.

Holter monitoring in ApHCM detected asymptomatic and symptomatic nonsustained ventricular tachycardia (VT) in 18% and 5%, respectively[1]; AF in 12%; VT in 3%; and VF in 1%.[1] AF prevalence in other studies was higher, at 20% to 28%.[3] Monomorphic VT occurs in ApHCM with aneurysms, possibly related to reentry around the aneurysm. LA enlargement secondary to LV diastolic dysfunction at the time of first ApHCM presentation predicts later AF,[20] which is commoner in females and prognostically adverse.[4,20]

Serum Biomarkers

Comparing high-sensitivity cardiac troponin T levels between different HCM morphological subtypes found rates in ApHCM versus nonobstructive versus obstructive classical HCM of 14%, 47%, and 57%, respectively.[21] High-sensitivity cardiac troponin T correlated with age, LA area, and maximum LV wall thickness when considering all subtypes.[21] In another study, cardiac troponin I was significantly lower in ApHCM compared with classic HCM, and it correlated with maximum LV wall thickness, LV dysfunction, and male sex when considering all subtypes.[22]

Cavity Obliteration

Apical systolic cavity obliteration occurs in pure, and to a lesser extent, relative ApHCM. A measure of the degree of apical cavity obliteration is provided by the ratio of the end-systolic length of apical obliteration to the end-systolic length of the LV cavity.[23] A systolic obliteration-to-cavity ratio >0.5 is associated with increased incidence of AF, stroke, heart failure, and cardiovascular death.[24] Degree of obliteration rather than apical wall thickness influences prognosis.[23]

MVOCO may occur as a consequence of midapical lateral and septal hypertrophy[15] and therefore a complication of mixed rather than pure ApHCM. In severe cases, midventricular cavity obliteration persists in diastole and is often associated with a paradoxical midcavity diastolic flow jet, which indicates the associated presence of an apical aneurysm.[16] In contrast, the pathophysiology behind midventricular obstruction in classic HCM is attributable to the basal-to-midseptal hypertrophy coming into contact with a hypercontractile but nonhypertrophied LV free wall, often with the interposition of hypertrophied papillary muscle.

Apical Aneurysms

Apical aneurysms are defined as a discrete, thin-walled, dyskinetic/akinetic segment of the most distal portion of the

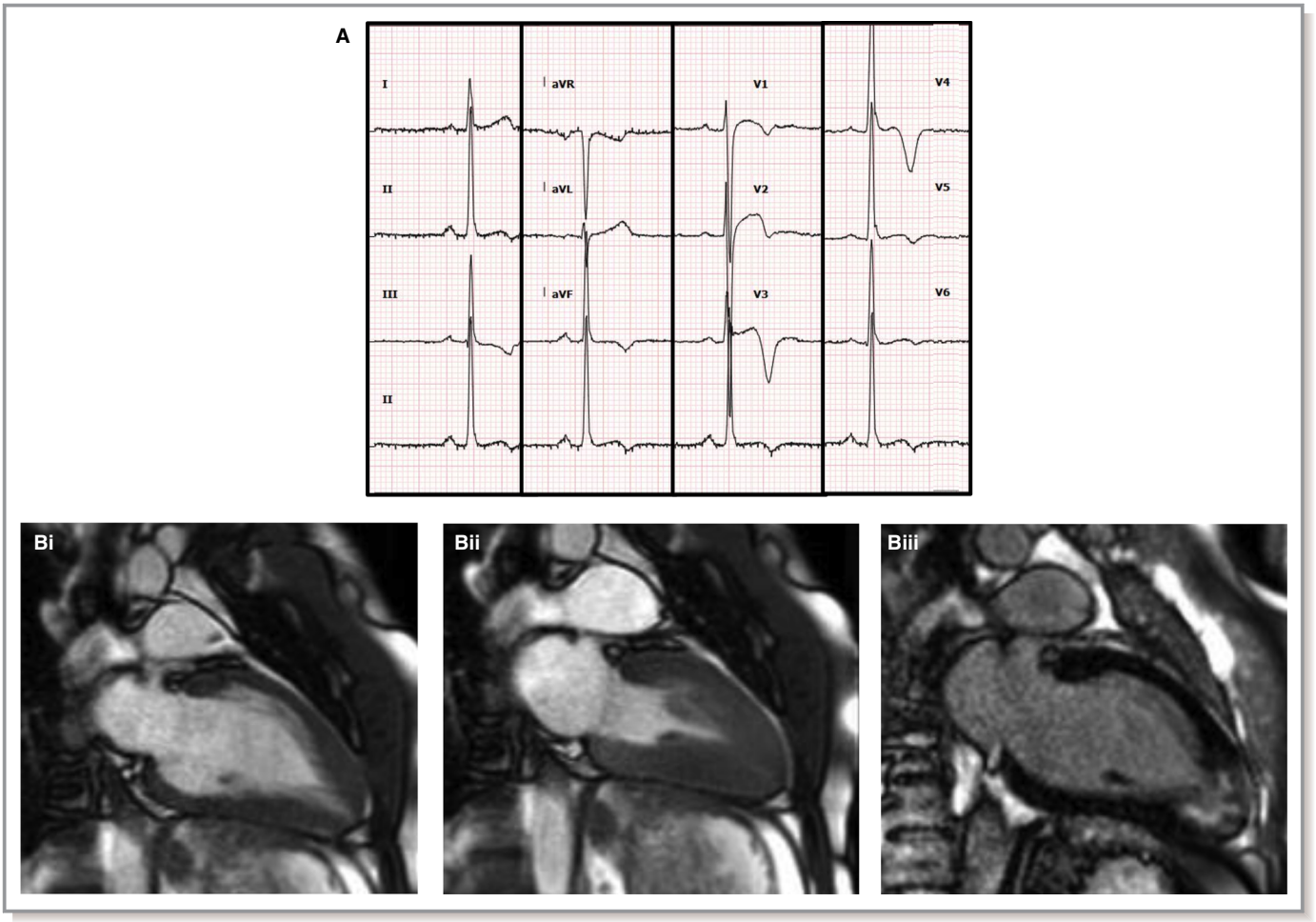

Figure 1. ECG and CMR in relative ApHCM. **A**, ECG demonstrates precordial T-wave inversion and voltage criteria for LVH. **B**, Two-chamber CMR demonstrates loss of apical tapering with relative but not absolute apical hypertrophy in diastole (**Bi**), systolic apical cavity obliteration (**Bii**) and LGE in the hypertrophied apex (**Biii**). ApHCM indicates apical hypertrophic cardiomyopathy; CMR, cardiovascular magnetic resonance; LGE, late gadolinium enhancement; LVH, left ventricular hypertrophy.

LV with a relatively wide communication to the main cavity in diastole.[16] They occur in 2% of patients with HCM and 13% to 15% with ApHCM[16,25] (Figure 3). A cue to their presence is the persistence of apical blood pooling distal to the point of apical systolic cavity obliteration[17] and/or a paradoxical diastolic jet. Small aneurysms are often overlooked on echocardiography and may be difficult to delineate without advanced imaging.[15] In ApHCM, it is hypothesized that apical aneurysms and obstructive physiology arise from regional myocardial scarring caused by repeatedly exposing the apical myocardium to increased LV wall stress and high systolic pressures, leading to pressure overload, increased oxygen demand, impaired coronary perfusion, and ischemia.[25] The dyskinetic/akinetic aneurysm confers risk of apical thrombus formation and thromboembolic stroke.[25] Apical aneurysms have been associated with LVH severity, SCD, monomorphic VT,[24] LV systolic dysfunction, and heart failure.[25]

It is important to distinguish apical aneurysms arising from ApHCM from those arising from midcavity obstruction in classic HCM. One study investigating outcomes in patients with apical aneurysms irrespective of the HCM morphological subtype, identified aneurysms in 4.8%.[26] Authors identified 2 distinct patterns of LVH in those with aneurysms: segmental thickening confined to the distal LV in 51%, and in the remaining 49% diffuse thickening of the septum and free wall, resulting in an "hourglass" configuration with midventricular muscular narrowing, creating discrete proximal and distal chambers.[26] Thromboembolic events were 2-fold more common (P=0.06) in those with apical aneurysms compared with those without, and this subgroup also experienced a 3-fold greater adverse event rate, at 6.4%/year.

Phenotypic Mimics

Fabry disease causes progressive LVH that potentially mimics ApHCM. Up to 23% of patients with Fabry disease with LVH have ApHCM pattern by CMR.[27]

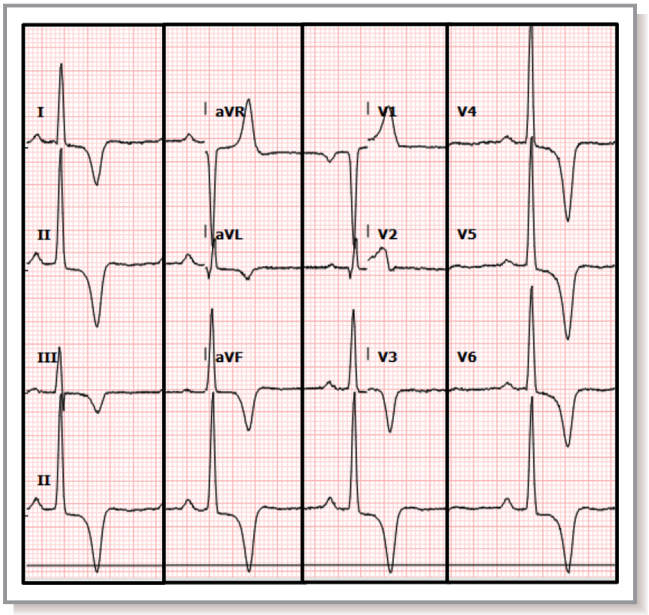

Figure 2. EKG in pure ApHCM. Voltage criteria for LVH and giant negative T-wave inversion in precordial and inferolateral leads. ApHCM indicates apical hypertrophic cardiomyopathy; LVH, left ventricular hypertrophy.

Long-term athletic training produces cardiac structural changes, namely, increased diastolic dimensions of the LV cavity, LVH, and increased LV mass.[28] In athletes with LVH, distinguishing the physiological "athlete's heart" from HCM may be challenging. An overlapping "gray zone" is described when absolute LV wall thickness is between 13 and 15 mm, observed in 2% of highly trained male athletes.[29] Highly trained female athletes rarely show >11 mm of LVH, suggesting that athletic females presenting within the "gray zone" are more likely to have HCM.[29] In one athletes study exploring LVH ≥13 mm on echocardiography, 3 had pure apical LVH (range 15–18 mm), and 2 had LVH basally, as well as in the apex.[28] Native T1 and extracellular volume values using CMR are lower in athletes than in HCM, which is a useful differentiator.[30] Furthermore, as LVH increases in athletes, extracellular volume continues to decrease, whereas in HCM it continues to increase.

Athletes with pure apical LVH had normal ECGs (no T-wave inversion[28]), and the phenotype was postulated to reflect athletic training, rather than true HCM. Another study demonstrated that athletes with HCM were 3 times likelier to exhibit ApHCM than their sedentary HCM counterparts (35.8% versus 11.9%).[31] It is difficult to distinguish apical LVH attributable to athletic remodeling from ApHCM; however, an ApHCM-pattern ECG is regarded as unequivocally abnormal.[31] The increased frequency of ApHCM in athletes may itself reflect an ascertainment bias resulting from screening programs, but as mentioned above, the difficulty in assessing SCD risk remains.

Imaging

Echocardiography

Transthoracic echocardiography can reveal apical hypertrophy, differentiate between pure and mixed forms, and identify additional prognostic features that could influence outcome such as the presence of diastolic dysfunction, MVOCO, or apical aneurysms.[23,32,33] However, imaging the apex remains a potential challenge, particularly for subtle prognostic features such as apical akinesis or sequestration caused by massive hypertrophy.[16] Early phenotypes and relative ApHCM could be missed by echocardiography; thus, those with deep T-wave inversion and noncontributory echocardiography should undergo additional imaging.[34]

Although global LV systolic function may appear normal or supranormal in ApHCM, LV peak systolic mitral annular velocity (S') is commonly reduced, more so in the mixed rather than in the pure form.[32] Interstitial fibrosis of the subendocardium (where muscle bundles aligned along the LV driving long-axis function), commonly seen in ApHCM, may partly account for this impairment. Furthermore, end-systolic MVOCO and paradoxical diastolic flow jets predict apical asynergy and apical aneurysms, and are associated with increased morbidity[16] (Figure 4).

Two-dimensional strain or speckle tracking demonstrate regional apical dyskinesis and reduced LV "twist," which can be attributable to cavity obliteration negating the effect of apical twist in systolic contraction.

Cardiovascular Magnetic Resonance

CMR may detect early ApHCM phenotypes better than echocardiography. Apical hypertrophy was missed by echocardiography in 40% of cases, later detected by CMR.[35] CMR is more sensitive at detecting apical aneurysms and can identify 25% to 43% of those missed by echocardiography.[25,36] CMR has advantages in confounding patient populations, such as athletes. Late gadolinium enhancement (LGE) is common in HCM; the presence and amount of LGE may be associated with the severity of hypertrophy as well as increased risk of heart failure and SCD.[37] LGE patterns in ApHCM are characteristically apical and subendocardial[37–39]–patterns that are uncommon in other HCM variants in the absence of coexisting coronary disease. This "MI pattern" of LGE adds credence to the hypothesis that apical myocardial ischemia is key in ApHCM. HCM registry data showed LGE in ApHCM in 45.8% of subjects.[40] Aneurysms are considered the arrhythmogenic substrate, but it may be the intra-aneurysm scar that matters most. Of note, extent/presence of (apical or any) LGE does not feature in the ESC HCM risk-stratification algorithm.

Despite heterogeneity in reported native T1 values (indicating diffuse myocardial fibrosis) in classic and ApHCM

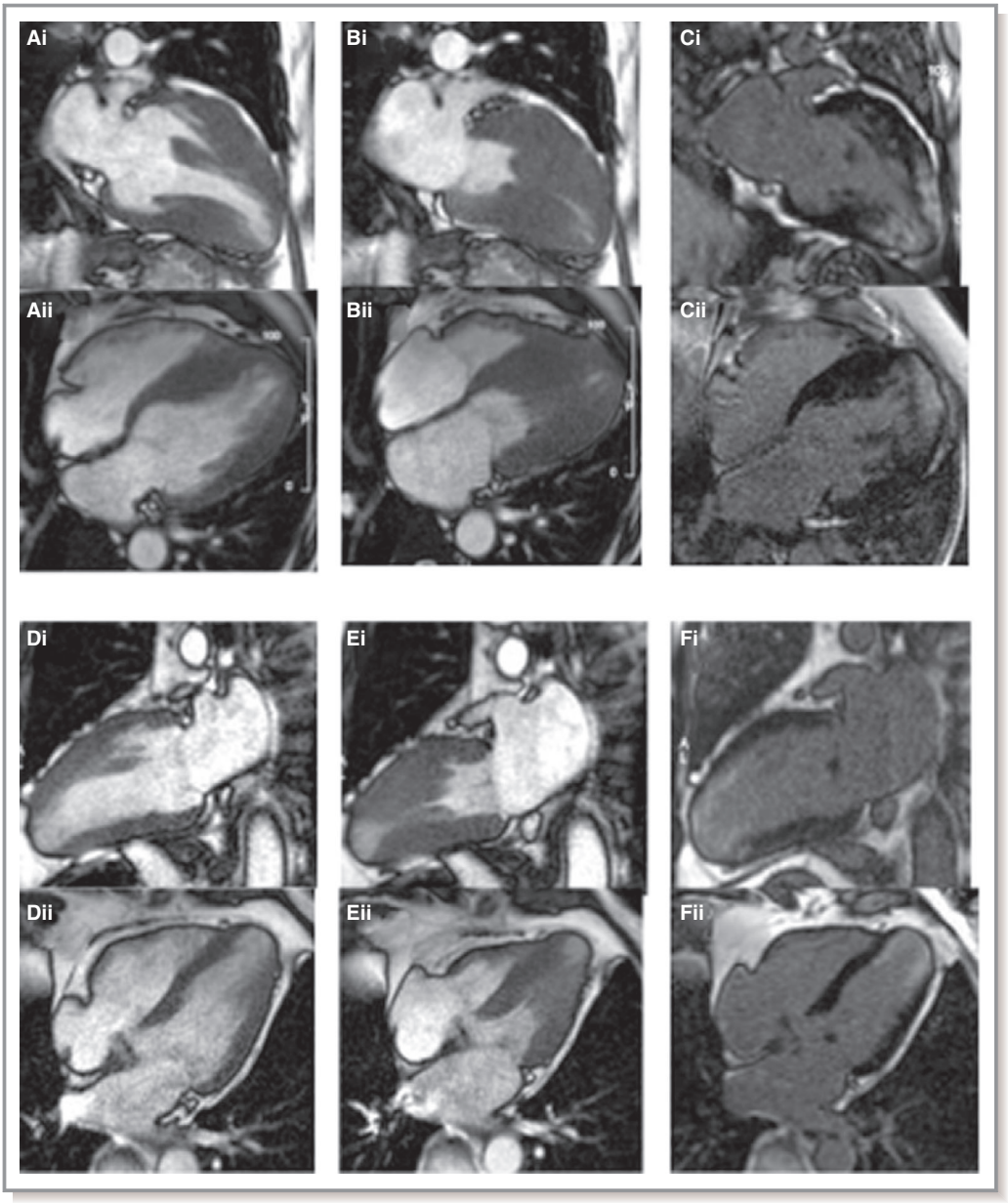

Figure 3. CMR comparison of mixed ApHCM (**A** through **C**) and pure ApHCM (**D** through **F**), both with apical aneurysm formation. Long-axis views of a patient with mixed ApHCM in diastole in 2-chamber (**Ai**) and 4-chamber (**Aii**), which in systole demonstrate midventricular obstruction but not total cavity obliteration due to persistence of apical chamber (**Bi**; **Bii**). The apical aneurysm contains LGE (**Ci**; **Cii**). A different patient with pure ApHCM has a thinned aneurysmal apex demonstrated in diastole on 2- (**Di**) and 4-chamber views (**Dii**). In systole, the apical aneurysm becomes apparent (**Ei**; **Eii**) and contains LGE (**Fi**; **Fii**). ApHCM indicates apical hypertrophic cardiomyopathy; LGE, late gadolinium enhancement.

versus healthy controls, values consistently correlate with wall thickness and LGE and can also be elevated in LGE-negative apical segments.[41] Areas of T2 elevation (indicating myocardial edema) are also seen in HCM.

Rest and stress perfusion data are missing for ApHCM (Figure 5). Rest perfusion abnormalities have been well described in classic HCM, correlating with severity of LGE, degree of hypertrophy and myocardial fibrosis.[42] The clinical significance of perfusion abnormalities is not yet explored.

Cardiac Computerized Tomography

Computerized tomography (CT) using iodine-based contrast detects late enhancement consistent with the presence of myocardial fibrosis. While the segment-based sensitivity of

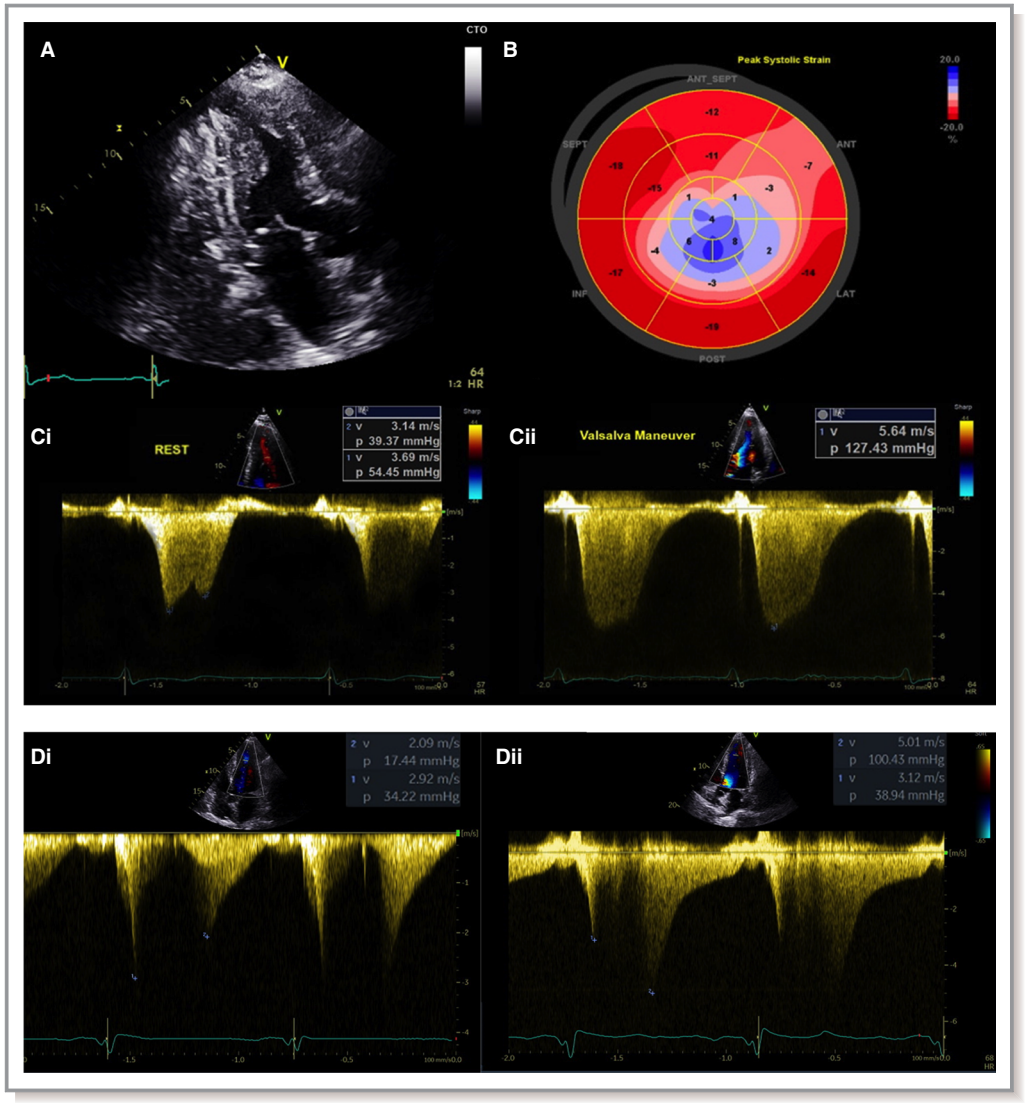

Figure 4. Transthoracic echocardiography in ApHCM. ApHCM with a small discrete apical chamber visible in the apical 3-chamber view (**A**) and corresponding polar plot showing loss of longitudinal strain apically (**B**). At rest, continuous wave Doppler across the point of distal ventricular obstruction demonstrates a midsystolic peaking jet, followed by a drop in velocity prior to second peak representing paradoxical early diastolic jet flow, with gradients of 54 and 39 mm Hg, respectively (**Ci**). During Valsalva, systolic and diastolic jets merge, with a systolic intracavity gradient of 127 mm Hg, and a lengthening of the diastolic "tail" toward late diastole (**Cii**). By contrast, (**D**) demonstrates continuous wave Doppler traces from a patient with ApHCM and midcavity obstruction. At rest, there is midsystolic loss of Doppler alignment due to cavity obliteration, with corresponding Doppler dropout before paradoxical diastolic jet (**Di**). During Valsalva, the measured systolic gradient is unchanged, but the paradoxical diastolic jet gradient now exceeds 100 mm Hg with extension in duration to the end of diastole (**Dii**). ApHCM indicates apical hypertrophic cardiomyopathy.

computerized tomography for HCM fibrosis detection is lower than for CMR, patient-based sensitivity is similar[43] offering a viable alternative for those unable to undergo CMR. As it is not uncommon for ApHCM to open clinically with chest pain and T-wave inversion, computerized tomography reporters should be alert to the possibility of discovering ApHCM in such referrals.

Nuclear Scintigraphy

Perfusion imaging using single photon emission computed tomography (SPECT) unveils the characteristic (but not pathognomonic) "solar polar" perfusion map of ApHCM: an intensely bright apical spot of counts surrounded by a circumferential ring of decreasing counts.[44] Other findings

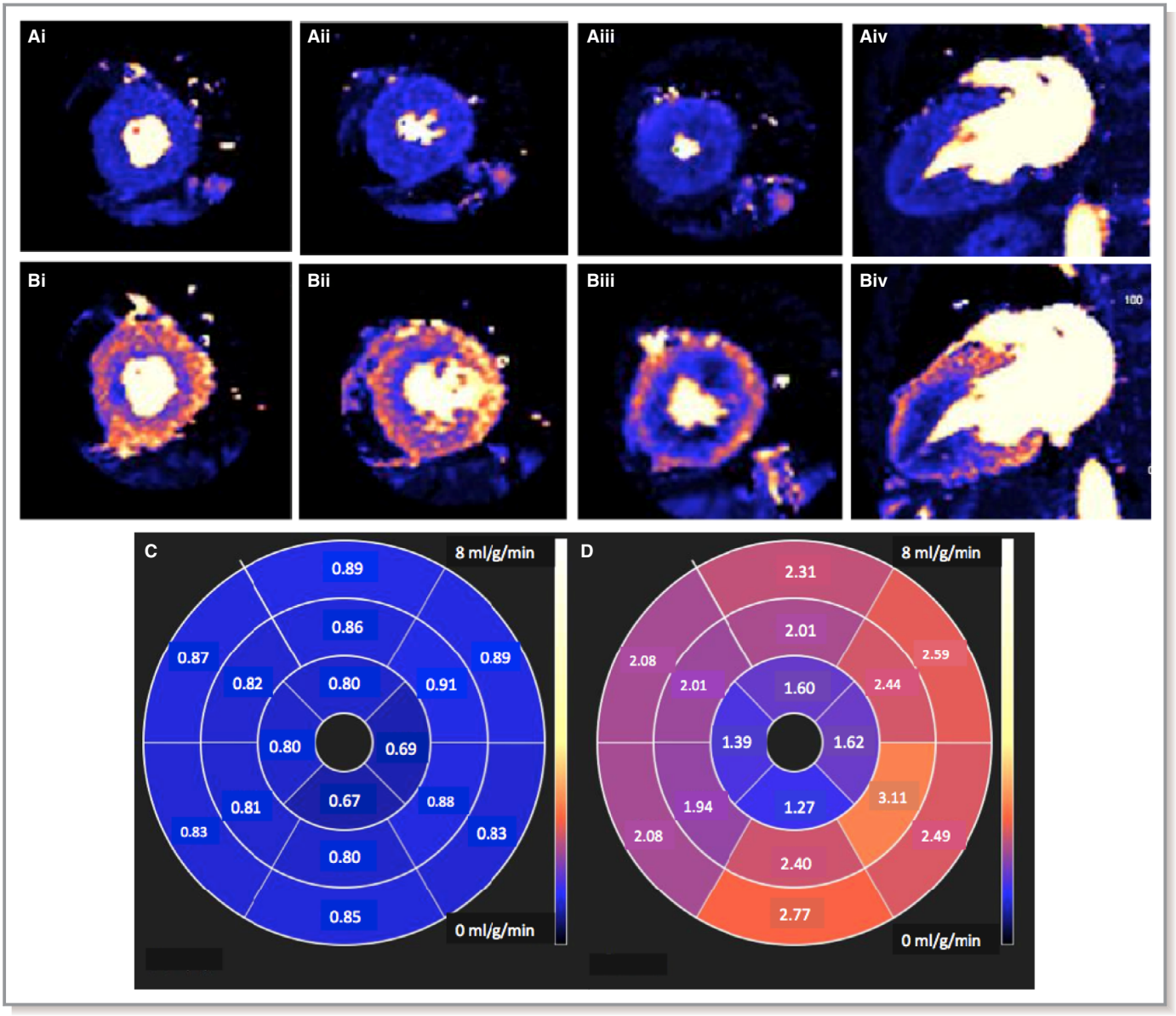

Figure 5. Quantitative perfusion mapping in ApHCM. CMR pixelwise inline perfusion maps at rest (**A**), stress (**B**) in (**i**) basal, (**ii**) mid, (**iii**) apical short axis and (**iv**) 2-chamber views in a patient with ApHCM and MVOCO. Stress perfusion defects are seen in the hypertrophied apex. Bull's-eye plots are shown (rest **C**, stress **D**). There is 37% MBF reduction at stress (**D**) apically (1.47 mL/g per minute) vs 2.35 mL/g per minute in remote, non-hypertrophied segments. Rest MBF(**C**) is 0.74 and 0.85 mL/g per minute, respectively. MPR is 1.99 in the apex and 2.76 in remote myocardium, indicating microvascular disease in the hypertrophied apex. Healthy volunteer stress MBF is 2 to 4 mL/g per minute. ApHCM indicates apical hypertrophic cardiomyopathy; CMR, cardiovascular magnetic resonance; MBF, myocardial blood flow; MPR, myocardial perfusion reserve; MVOCO, midventricular obstruction and cavity obliteration.

include increased apical tracer uptake at rest and the spadelike configuration of the LV.[45] Fixed and reversible stress perfusion defects are reported in the context of unobstructed epicardial coronary arteries,[45] but again, the significance of these findings is unexplored. Single photon emission computed tomography can miss ApHCM because dense apical fibrosis normalizes apical tracer counts so single photon emission computed tomography and other findings (ECG, wall thickness) do not correlate.[1,45]

Angiography

Left ventriculography identifies the characteristic "ace of spades" LV cavity configuration in end diastole in 69% of cases[1] and aids the detection of apical aneurysms.[16]

Management Strategies

Management in HCM involves symptom assessment and determination of likely mechanisms of symptoms, risk

Table 2. Management Differences and Similarities Between Classic HCM and ApHCM

	Classical (ASH) HCM	ApHCM
Medical	• β-Blockers–first line treatment (aim to reduce LVOTO and burden of ventricular arrhythmias) • Nondihydropyridine calcium channel blockers–second line • Atrial fibrillation and thromboembolism less common than in ApHCM but if present, anticoagulant indicated	• β-blockers also first line (symptom improvement in MVOCO and reduce burden of ventricular arrhythmias) • Nondihydropyridine calcium channel blockers also second line • Anticoagulants in the case of atrial fibrillation or thromboembolism
Ablation	• Alcohol septal ablation of hypertrophied basal septum in symptomatic LVOTO • VT ablation considered	• Potential role of alcohol ablation in symptomatic ApHCM with MVOCO (no randomized control data) • No role for alcohol septal ablation • VT ablation in rare cases
Devices	• ICD implantation (ESC 5-y HCM SCD risk score tailored more specifically to ASH risk factors than other morphological variants) • AHA guidance on ICD implantation broader	• ICDs may be underutilized because of current scoring criteria if using ESC algorithm • Current prospective trial of distal ventricular pacing for ApHCM with drug refractory symptoms and MVOCO
Surgical	• Septal myectomy (reduces symptoms and risks associated with LVOTO)	• Few case reports detailing symptomatic improvement following apical myectomy. No randomized control data

AHA indicates American Heart Association; ApHCM, apical hypertrophic cardiomyopathy; ESC, European Society of Cardiology; ICD, implantable cardiac defibrillator; LVOTO, left ventricular outflow tract obstruction; MVOCO, midventricular obstruction and cavity obliteration; SCD, sudden cardiac death; VT, ventricular tachycardia.

assessment and its mitigation, family screening, and chronic symptom/risk management. Treatment options for ApHCM are based on classic HCM approaches aiming to minimize any heart failure, AF, or MVOCO symptoms and reduce/mitigate ventricular arrhythmias and sudden death. Therapy is medical or electrophysiological (device/ablation), but as LV outflow tract obstruction is typically absent in ApHCM, therapeutic benefits may be lower than in classic HCM, and myectomy-type approaches are exploratory rather than routine (Table 2).

Medical

β-Blockers reduce rest and exercise-induced LV outflow tract obstruction in classic HCM,[46] and the negative inotropic and chronotropic effects of nondihydropiridine calcium channel blockers prolong LV filling, reduce gradients, and improve subendocardial blood flow in classic HCM,[46] but data for ApHCM are missing.

Catheter Ablation

Although sustained monomorphic VT is uncommon in classic HCM, a case series reported monomorphic VT in ApHCM from reentry in a region of apical scar. Circuits were varied (endocardial, epicardial, intramural) and successfully ablated using endocardial/epicardial/transcoronary approaches.[47]

Devices

There are currently no trials or predictive models to guide implantable cardiac defibrillator (ICD) insertion specifically for ApHCM. The ESC 5-year HCM SCD risk score[6,7] was based on all HCM morphological subtypes without breakdown for ApHCM.[6] Potential risk markers for SCD in ApHCM (apical aneurysm, MVOCO, midcavity gradient, paradoxical diastolic flow jet) were not shortlisted predictors. ApHCM patients tend to score negative for family history of SCD, and there is concern that risk may be underestimated. For intermediate-risk patients, the ESC guideline suggests that the presence of "other" potentially relevant associated adverse markers like apical aneurysms (alluding to ApHCM) may also be taken into account when planning implantable cardiac defibrillators.[48] In contrast, Maron's group have recently sought to evolve the American Heart Association guidance for implanting cardiac defibrillators by proposing new criteria for HCM patients fulfilling one or more major risk factors for SCD. These include novel high-risk markers such as CMR LGE demonstration of extensive fibrosis comprising ≥15% of LV mass by quantification or "extensive and diffuse" by visual estimation, and also the presence of LV apical aneurysm, independent of size, with associated regional scarring.[10] This risk stratification is more sensitive at predicting those at risk of SCD than the ESC guidance[10,40] and demonstrates progression toward understanding more individualized risk factors.

Dual-chamber pacing with short atrioventricular delay has been proposed as a treatment for symptomatic HCM with apical LVH where there are detectable midapical LV

obstructive gradients.[49] This is thought to work by reducing the extent of regional LV cavity obliteration through the introduction of contractile dyssynchrony. Our group is currently conducting a randomized placebo-controlled trial of distal ventricular pacing in patients with drug-refractory symptoms and MVOCO (Clinicaltrials.gov NCT03450252).

Alcohol Septal Ablation and Apical Myectomy

The absence of overt septal hypertrophy causing LV outflow tract obstruction may render septal ablation/myectomy in ApHCM unwarranted, but single case studies have highlighted a potential role in those with symptomatic MVOCO, as it may reduce gradients and improve heart failure symptoms. Additionally, apical myectomy has been reported to increase end-diastolic dimensions and improve symptoms.

Conclusions

ApHCM poses specific etiological, diagnostic, prognostic, and therapeutic challenges compared with more commonly detected and better understood morphological HCM variants. The phenotypic spectrum and natural history of ApHCM ("pure," "mixed," and "relative") is being clarified, as is the impact of sarcomere gene mutations, sex, and other clinical and environmental factors on phenotype expression. Further research is needed to understand why some patients develop mixed ApHCM with a higher risk of arrhythmias, heart failure, and SCD, while others go on to manifest the pure form with a relatively more benign course. ApHCM-specific treatments are needed to halt or regress the LV mid-to-apical hypertrophy and its ensuing complications and multicenter longitudinal outcome data needed to robustly inform on an SCD risk stratification tool appropriate for ApHCM.

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None.

References

1. Eriksson MJ, Sonnenberg B, Woo A, Rakowski P, Parker TG, Wigle ED, Rakowski H, Douglas Wigle E, Rakowski H, Toronto F. Long-term outcome in patients with apical hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2002;39:638–645.
2. Sakamoto T, Tei C, Murayama M, Ichiyasu H, Hada Y. Giant T wave inversion as a manifestation of asymmetrical apical hypertrophy (AAH) of the left ventricle. Echocardiographic and ultrasono-cardiotomographic study. *Jpn Heart J*. 1976;17:611–629.
3. Kubo T, Kitaoka H, Okawa M, Hirota THE. Clinical profiles of hypertrophic cardiomyopathy with apical phenotype. *Circulation*. 2009;73:2330–2336.
4. Klarich KW, Jost CHA, Binder J, Connolly HM, Scott CG, Freeman WK, Ackerman MJ, Nishimura RA, Tajik AJ, Ommen SR. Risk of death in long-term follow-up of patients with apical hypertrophic cardiomyopathy. *Am J Cardiol*. 2013;111:1784–1791.
5. Arad M, Penas-Lado M, Monserrat L, Maron BJ, Sherrid M, Ho CY, Barr S, Karim A, Olson TM, Kamisago M, Seidman JG, Seidman CE. Gene mutations in apical hypertrophic cardiomyopathy. *Circulation*. 2005;112:2805–2811.
6. O'Mahony C, Jichi F, Pavlou M, Monserrat L, Anastasakis A, Rapezzi C, Biagini E, Gimeno JR, Limongelli G, McKenna WJ, Omar RZ, Elliott PM; Hypertrophic Cardiomyopathy Outcomes Investigators. A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM risk-SCD). *Eur Heart J*. 2014;35:2010–2020.
7. O'Mahony C, Jichi F, Ommen SR, Christiaans I, Arbustini E, Garcia-Pavia P, Cecchi F, Olivotto I, Kitaoka H, Gotsman I, Carr-White G, Mogensen J, Antoniades L, Mohiddin SA, Maurer MS, Tang HC, Geske JB, Siontis KC, Mahmoud KD, Vermeer A, Wilde A, Favalli V, Guttmann OP, Gallego-Delgado M, Dominguez F, Tanini I, Kubo T, Keren A, Bueser T, Waters S, Issa IF, Malcolmson J, Burns T, Sekhri N, Hoeger CW, Omar RZ, Elliott PM. International external validation study of the 2014 European Society of Cardiology guidelines on sudden cardiac death prevention in hypertrophic cardiomyopathy (EVIDENCE-HCM). *Circulation*. 2018;137:1015–1023.
8. Patten M, Pecha S, Aydin A. Atrial fibrillation in hypertrophic cardiomyopathy: diagnosis and considerations for management. *J Atr Fibrillation*. 2018;10:1–6.
9. Spirito P, Ferrazzi P. Pulmonary hypertension in hypertrophic cardiomyopathy: a forgotten marker in the identification of candidates to surgical myectomy? *Eur Heart J Cardiovasc Imaging*. 2016;17:611–612.
10. Maron MS, Rowin EJ, Wessler BS, Mooney PJ, Fatima A, Patel P, Koethe BC, Romashko M, Link MS, Maron BJ. Enhanced American College of Cardiology/American Heart Association strategy for prevention of sudden cardiac death in high-risk patients with hypertrophic cardiomyopathy. *JAMA Cardiol*. 2019;4:644–657.
11. Towe EC, Bos JM, Ommen SR, Gersh BJ, Ackerman MJ. Genotype-phenotype correlations in apical variant hypertrophic cardiomyopathy. *Congenit Heart Dis*. 2015;10:E139–E145.
12. Gruner C, Care M, Siminovitch K, Moravsky G, Wigle ED, Woo A, Rakowski H. Sarcomere protein gene mutations in patients with apical hypertrophic cardiomyopathy. *Circ Cardiovasc Genet*. 2011;4:288–295.
13. Morimoto S, Sekiguchi M, Uemura A, Hiramitsu S, Kimura K, Ohtsuki M, Ishii J, Kato S, Kasanuki H, Hishida H. Cardiac muscle cell disorganization in apical hypertrophic cardiomyopathy a cardiac biopsy study. *Jpn Heart J*. 2003;44:506–513.
14. Yamaguchi H, Ishimura T, Nishiyama S, Nagasaki F, Nakanishi S, Takatsu F, Nishijo T, Umeda T, Machii K. Hypertrophic nonobstructive cardiomyopathy with giant negative T waves (apical hypertrophy): ventriculographic and echocardiographic features in 30 patients. *Am J Cardiol*. 1979;44:401–412.
15. Jan MF, Todaro MC, Oreto L, Tajik AJ. Apical hypertrophic cardiomyopathy: present status. *Int J Cardiol*. 2016;222:745–759.
16. Chen CC, Lei MH, Hsu YC, Chung SL, Sung YJ. Apical hypertrophic cardiomyopathy: correlations between echocardiographic parameters, angiographic left ventricular morphology, and clinical outcomes. *Clin Cardiol*. 2011;34:233–238.
17. Flett AS, Maestrini V, Milliken D, Fontana M, Treibel TA, Harb R, Sado DM, Quarta G, Herrey A, Sneddon J, Elliott P, McKenna W, Moon JC. Diagnosis of apical hypertrophic cardiomyopathy: T-wave inversion and relative but not absolute apical left ventricular hypertrophy. *Int J Cardiol*. 2015;183:143–148.
18. Wu B, Lu M, Zhang Y, Song B, Ling J, Huang J, Yin G, Lan T, Dai L, Song L, Jiang Y, Wang H, He Z, Lee J, Yong HS, Patel MB, Zhao S. CMR assessment of the left ventricle apical morphology in subjects with unexplainable giant T-wave inversion and without apical wall thickness >/=15 mm. *Eur Heart J Cardiovasc Imaging*. 2016;18:186–194.
19. Stephenson E, Monney P, Pugliese F, Malcolmson J, Petersen SE, Knight C, Mills P, Wragg A, O'Mahony C, Sekhri N, Mohiddin SA. Ineffective and prolonged apical contraction is associated with chest pain and ischaemia in apical hypertrophic cardiomyopathy. *Int J Cardiol*. 2018;251:65–70.

20. Roh S-Y, Kim D-H, Ahn J, Lee KN, Lee DI, Shim J, Choi J-I, Park S-W, Kim Y-H. Long-term outcome of catheter ablation for atrial fibrillation in patients with apical hypertrophic cardiomyopathy. *J Cardiovasc Electrophysiol*. 2016;27:788–795.
21. Jenab Y, Pourjafari M, Darabi F, Boroumand MA, Zoroufian A, Jalali A. Prevalence and determinants of elevated high-sensitivity cardiac troponin T in hypertrophic cardiomyopathy. *J Cardiol*. 2014;63:140–144.
22. Kubo T, Kitaoka H, Okawa M, Yamanaka S, Hirota T, Hoshikawa E, Hayato K, Yamasaki N, Matsumura Y, Yasuda N, Sugiura T, Doi YL. Serum cardiac troponin I is related to increased left ventricular wall thickness, left ventricular dysfunction, and male gender in hypertrophic cardiomyopathy. *Clin Cardiol*. 2010;33:E1–E7.
23. Kim H, Park J-H, Won K-B, Yoon H-J, Park H-S, Cho Y-K, Nam C-W, Han S, Hur S-H, Kim Y-N, Kim K-B. Significance of apical cavity obliteration in apical hypertrophic cardiomyopathy. *Heart*. 2016;102:1215–1220.
24. Wilson P, Marks A, Rastegar H, Manous AS, Mark Estes NA. Apical hypertrophic cardiomyopathy presenting with sustained monomorphic ventricular tachycardia and electrocardiographic changes simulating coronary artery disease and left ventricular aneurysm. *Clin Cardiol*. 1990;13:885–887.
25. Maron MS, Finley JJ, Bos JM, Hauser TH, Manning WJ, Haas TS, Lesser JR, Udelson JE, Ackerman MJ, Maron BJ. Prevalence, clinical significance, and natural history of left ventricular apical aneurysms in hypertrophic cardiomyopathy. *Circulation*. 2008;118:1541–1549.
26. Rowin EJ, Maron BJ, Haas TS, Garberich RF, Wang W, Link MS, Maron MS. Hypertrophic cardiomyopathy with left ventricular apical aneurysm: implications for risk stratification and management. *J Am Coll Cardiol*. 2017;69:761–773.
27. Deva DP, Hanneman K, Li Q, Ng MY, Wasim S, Morel C, Iwanochko RM, Thavendiranathan P, Crean AM. Cardiovascular magnetic resonance demonstration of the spectrum of morphological phenotypes and patterns of myocardial scarring in Anderson-Fabry disease. *J Cardiovasc Magn Reson*. 2016;18:14.
28. Pelliccia A, Maron BJ, Spataro A, Proschan MA, Spirito P. The upper limit of physiologic cardiac hypertrophy in highly trained elite athletes. *N Engl J Med*. 1991;324:295–301.
29. Maron BJ. Distinguishing hypertrophic cardiomyopathy from athlete's heart: a clinical problem of increasing magnitude and significance. *Heart*. 2005;91:1380–1382.
30. Swoboda PP, McDiarmid AK, Erhayiem B, Broadbent DA, Dobson LE, Garg P, Ferguson C, Page SP, Greenwood JP, Plein S. Assessing myocardial extracellular volume by T1 mapping to distinguish hypertrophic cardiomyopathy from athlete's heart. *J Am Coll Cardiol*. 2016;67:2189–2190.
31. Sheikh N, Papadakis M, Schnell F, Panoulas V, Malhotra A, Wilson M, Carré F, Sharma S. Clinical profile of athletes with hypertrophic cardiomyopathy. *Circ Cardiovasc Imaging*. 2015;8:e003454.
32. Choi EY, Rim SJ, Ha J-W, Kim YJ, Lee SC, Kang DH, Park SW, Song JK, Sohn DW, Chung N. Phenotypic spectrum and clinical characteristics of apical hypertrophic cardiomyopathy: multicenter echo-Doppler study. *Cardiology*. 2008;110:53–61.
33. Moon J, Shim CY, Ha J-W, Cho IJ, Kang MK, Yang W-I, Jang Y, Chung N, Cho S-Y. Clinical and echocardiographic predictors of outcomes in patients with apical hypertrophic cardiomyopathy. *Am J Cardiol*. 2011;108:1614–1619.
34. Moon JCC, Fisher NG, Mckenna WJ, Pennell DJ, Pennell DJ. Detection of apical hypertrophic cardiomyopathy by cardiovascular magnetic resonance in patients with non-diagnostic echocardiography. *Heart*. 2004;90:645–649.
35. Pons-Lladó G, Carreras F, Borrás X, Palmer J, Llauger J, Bayés De Luna A. Comparison of morphologic assessment of hypertrophic cardiomyopathy by magnetic resonance versus echocardiographic imaging. *Am J Cardiol*. 1997;79:1651–1656.
36. Fattori R, Biagini E, Lorenzini M, Buttazzi K, Lovato L, Rapezzi C. Significance of magnetic resonance imaging in apical hypertrophic cardiomyopathy. *Am J Cardiol*. 2010;105:1592–1596.
37. Yamada M, Teraoka K, Kawade M, Hirano M, Yamashina A. Frequency and distribution of late gadolinium enhancement in magnetic resonance imaging of patients with apical hypertrophic cardiomyopathy and patients with asymmetrical hypertrophic cardiomyopathy: a comparative study. *Int J Cardiovasc Imaging*. 2009;25:131–138.
38. Choudhury L, Mahrholdt H, Wagner A, Choi KM, Elliott MD, Klocke FJ, Bonow RO, Judd RM, Kim RJ. Myocardial scarring in asymptomatic or mildly symptomatic patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2002;40:2156–2164.
39. Kebed KY, Al Adham RI, Bishu K, Askew JW, Klarich KW, Araoz PA, Foley TA, Glockner JF, Nishimura RA, Anavekar NS. Evaluation of apical subtype of hypertrophic cardiomyopathy using cardiac magnetic resonance imaging with gadolinium enhancement. *Am J Cardiol*. 2014;114:777–782.
40. Neubauer S, Kolm P, Ho CY, Kwong RY, Desai MY, Dolman SF, Appelbaum E, Desvigne-Nickens P, DiMarco JP, Friedrich MG, Geller N, Harper AR, Jarolim P, Jerosch-Herold M, Kim DY, Maron MS, Schulz-Menger J, Piechnik SK, Thomson K, Zhang C, Watkins H, Weintraub WS, Kramer CM; HCMR Investigators. Distinct subgroups in hypertrophic cardiomyopathy in the NHLBI HCM Registry. *J Am Coll Cardiol*. 2019;74:2333–2345.
41. Kato S, Nakamori S, Bellm S, Jang J, Basha T, Maron M, Manning WJ, Nezafat R. Myocardial native T1 time in patients with hypertrophic cardiomyopathy. *Am J Cardiol*. 2016;118:1057–1062.
42. Chiribiri A, Leuzzi S, Conte MR, Bongioanni S, Bratis K, Olivotti L, De Rosa C, Lardone E, Di Donna P, Villa ADM, Cesarani F, Nagel E, Gaita F, Bonamini R. Rest perfusion abnormalities in hypertrophic cardiomyopathy: correlation with myocardial fibrosis and risk factors for sudden cardiac death. *Clin Radiol*. 2015;70:495–501.
43. Langer C, Lutz M, Eden M, Lüdde M, Hohnhorst M, Gierloff C, Both M, Burchert W, Faber L, Horstkotte D, Frey N, Prinz C. Hypertrophic cardiomyopathy in cardiac CT: a validation study on the detection of intramyocardial fibrosis in consecutive patients. *Int J Cardiovasc Imaging*. 2014;30:659–667.
44. Parker Ward R, Hemlata MD, Pokharna K, Lang RM, Williams KA. Resting "Solar Polar" map pattern and reduced apical flow reserve: characteristics of apical hypertrophic cardiomyopathy on SPECT myocardial perfusion imaging. *J Nucl Cardiol*. 2003;10:506–512.
45. Cianciulli TF, Saccheri MC, Masoli OH, Redruello MF, Lax JA, Morita LA, Gagliardi JA, Dorelle AN, Prezioso HA, Vidal LA. Myocardial perfusion SPECT in the diagnosis of apical hypertrophic cardiomyopathy. *J Nucl Cardiol*. 2009;16:391–395.
46. Spoladore R, Maron MS, D'Amato R, Camici PG, Olivotto I. Pharmacological treatment options for hypertrophic cardiomyopathy: high time for evidence. *Eur Heart J*. 2012;33:1724–1733.
47. Inada K, Seiler J, Roberts-Thomson KC, Steven D, Rosman J, John RM, Sobieszczyk P, Stevenson WG, Tedrow UB. Substrate characterization and catheter ablation for monomorphic ventricular tachycardia in patients with apical hypertrophic cardiomyopathy. *J Cardiovasc Electrophysiol*. 2011;22:41–48.
48. Elliott PM, Anastasakis A, Borger M, Borggrefe M, Cecchi F, Charron P, Hagege A, Lafont A. 2014 ESC guidelines on diagnosis and management of hypertrophic cardiomyopathy. *Eur Heart J*. 2014;35:2733–2779.
49. Begley D, Mohiddin S, Fananapazir L. Dual chamber pacemaker therapy for mid-cavity obstructive hypertrophic cardiomyopathy. *Pacing Clin Electrophysiol*. 2001;24:1639–1644.

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