Abstract

Apical Hypertrophic Cardiomyopathy is an uncommon phenotype of hypertrophic cardiomyopathy. We present a review of best evidence on presentation, pathophysiology, diagnosis, outcomes and management for patients with apical hypertrophic cardiomyopathy.

Key Words: Apical Hypertrophic Cardiomyopathy, Mimics, Incidence, Natural Course, Diagnosis

Introduction:

Apical Hypertrophic Cardiomyopathy (AHCM) is characterized by hypertrophy of the myocardium predominantly in the left ventricular (LV) apex and has now been recognized as an uncommon phenotype of hypertrophic cardiomyopathy (HCM). The incidence of AHCM ranges from 3% of all HCM patients in North America to up to 15% and 16% in reports from Japan and China respectively. We review the latest evidence on epidemiology, pathophysiology, diagnostic modalities, management and natural course of AHCM.

Typical Presentation

In a cohort of 208 patients from China, the most common symptom was chest discomfort that was characterized as chest pain, chest tightness and palpitations. In another study 46% of the patients were asymptomatic. In another cohort of 105 patients, 16% complained of angina, 14% had atypical chest pain, 10% had palpitations, 6% complained of dyspnea, and 6% had pre-syncpe.

Diagnostic considerations and types of AHCM

The diagnosis is made on imaging studies. On transthoracic echocardiogram(TTE) AHCM is defined as LV wall thickening confined to the most distal region of the apex, below the papillary muscle level with the ratio of apical to basal LV thickness more than 1.3. Hypertrophy at this region is best visualized in apical views. In a cohort of 182 patients with AHCM 3 subtypes were identified based on the patterns of hypertrophy. These subtypes are pure, pure diffuse and mixed. AHCM is more commonly classified as “pure” when no concomitant septal hypertrophy is present, and “mixed” when evidence of septal hypertrophy is seen. In two studies no significant difference was found between cardiovascular mortality and morbidity between these variants of AHCM. Figure 1A and 1B show an illustration of the location of hypertrophy and differences between the two variants.

Echocardiography-strengths and limitations

TTE is usually the first line imaging modality in patients suspected to have AHCM, because of its widespread availability and relatively low cost. Figure 2 shows typical finding of pure variant of AHCM on TTE. Frequent inability to visualize the apical endocardium can limit diagnosis of AHCM by TTE. Furthermore the distribution of hypertrophy may be inaccurately measured on TTE and severity of wall thickening may be underestimated. In a study TTE only detected one in four cases of AHCM related LV aneurysms. Even in classic HCM patients TTE was only able to identify LV aneurysm in 57% of the patients. Hence additional imaging modalities are recommended in patients with suspicion of AHCM and initial TTE is non-diagnostic or with sub optimal visualization of the apex.

1. University of Nevada School of Medicine, Department of Internal Medicine, Las Vegas, Nevada, 89146
2. University of Nevada School of Medicine, Department of Cardiovascular Medicine, Las Vegas, Nevada, 89146
3. Aga Khan University Medical College, Karachi, Pakistan 74800
Apical hypertrophic cardiomyopathy mimics and the role of other imaging modalities

As mentioned a TTE although often the first line imaging modality can be non-diagnostic for AHCM especially if the apex is not fully visualized. Furthermore apical thrombus, Loefflers endocarditis, LV aneurysm, LV non compaction, and endomyocardial fibrosis may give a similar echocardiographic appearance on TTE to AHCM.\(^\text{15-17}\) Other common imaging modality options include TTE with contrast, trans-esophageal echocardiogram (TEE), cardiac multidetector computer tomography (MDCT) and cardiac magnetic resonance imaging (CMR).

Apical ballooning syndrome or Takotsubo cardiomyopathy can also mask underlying AHCM.\(^\text{18}\) In such cases TTE with contrast can be helpful.\(^\text{18}\) Figure 3A shows typical findings on TTE in Takotsubo cardiomyopathy. TTE with contrast can also help in differentiating LV thrombus and LV non-compaction from AHCM.\(^\text{18}\) Figure 3B and 3C show representative images of typical findings on TTE in LV thrombus and LV non compaction respectively.

TTE with contrast can help in diagnosing AHCM in patients with high suspicion and a non-diagnostic TTE.\(^\text{10}\) TEE can also accurately measure wall thickness at the apex if TTE imaging is not adequate.\(^\text{12}\)

In recent years there has been a great increase in the use of CMR in the diagnosis of HCM including AHCM, because of its precise determination of myocardial anatomy and the depiction of myocardial fibrosis.\(^\text{15}\) CMR has also been shown to distinguish pure from mixed variant of AHCM.\(^\text{19}\) In a small cohort of ten patients with non-diagnostic TTE, AHCM was seen on CMR.\(^\text{20}\) CMR has shown better performance in detection AHCM compared to TTE, and in also detecting LV aneurysms related to AHCM.\(^\text{13}\)

**Fig.-1:** Pattern of hypertrophy A) pure variant of Apical Hypertrophic Cardiomyopathy (AHCM), B) mixed variant of AHCM

**Fig.-2:** Representative trans-thoracic echocardiogram image of pure variant of apical hypertrophic cardiomyopathy
Characteristic findings on single photon emission computed topography (SPECT) imaging can also aid in diagnosis. In a cohort of 20 patients with AHCM, 75% demonstrated an increased tracer uptake and characteristic spade-like deformity of the LV chamber.\textsuperscript{21} Evaluation of the LV cavity on ventriculogram can also show the spade-like configuration of LV in end diastole.\textsuperscript{21}

MDCT has been used with success to detect significant coronary artery stenosis and has also emerged as a novel technique to evaluate cardiac morphology. Due to its high spatial resolution MDCT enables accurate delineation of apical endocardial border and dynamic evaluations of myocardial thickness and global and regional LV function.\textsuperscript{22}

Table 1 shows the sensitivity of some of the imaging techniques from different studies.\textsuperscript{10, 12, 13, 20, 23} As only positive results from the modality being tested resulted in a confirmatory gold standard test being performed, specificities of imaging modalities could not be calculated. Although TTE has low sensitivity it has the advantage of having a low cost and widespread availability. A reasonable alternative could be TTE with contrast.

Fig.-3: A) Representative 2D transthoracic echocardiogram images of Takatsubo Cardiomyopathy B) Patient with left ventricle (LV) thrombus, C) LV non compaction
Electrocardiography

The electrocardiogram (EKG) findings that have been associated with AHCM include deep inverted T waves in precordial leads, and presence of notched QRS in more than one lead.23-25 T wave inversions can disappear during long term follow-up.26 Figure 4A shows an EKG with characteristic T wave inversions in precordial leads associated with AHCM.

Presence of notched QRS without bundle branch block (BBB) is associated with impaired apical contraction and late gadolinium enhancement (LGE) on CMR, and is associated with higher prevalence of ventricular tachycardia.25 Reports have shown the association of a notched QRS in inferior leads with an apical aneurysm.27,28 Hence notched QRS without BBB may be a useful indicator of morbidity and risk of aneurysm formation in patients with AHCM. Figure 4B shows an EKG with notched QRS in inferior leads.

Pathophysiology

Cellular mechanism and role of gene mutations

Decades of intense investigation has identified more than 11 genes and 1400 mutations implicated in HCM.29 In AHCM the most common gene mutations are MYH7, MYBPC3, ACTC1 and TPM1.1,30,31 The protein coded by these genes plays an important role in the contraction of the sarcomere.32

The key histological feature of HCM is myocyte and myofibrillar disarray.33 Myocyte hypertrophy with nuclear enlargement and hyperchromasia is also seen.34 Dysplasia of small arteries seen as medial and intimal smooth muscle proliferation with luminal narrowing can also develop.35 The mechanism by which genetic mutations cause these changes is poorly understood.32

Prevalence of mutations does not correlate with phenotypic features. In the largest studied cohort of patients with AHCM only 18/71 (25%) of the patients were genotype positive with majority of mutations found in MYH7 and MYBPC3.1 In another cohort of 61 patients gene mutations were found only in 8/61 (13%) of the patients.31 Furthermore genotype positive patients did not have any significant differences in outcomes.

Natural course, morbidity and mortality

Relative to HCM, patients with AHCM have more benign outcomes. Incidence of sudden cardiac death (SCD),

Table-I

Sensitivity of different imaging modalities in diagnosing AHCM

<table>
<thead>
<tr>
<th>Author</th>
<th>Imaging Modality Studied</th>
<th>Sample Size</th>
<th>Gold Standard</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crowley JJ</td>
<td>TEE</td>
<td>6</td>
<td>Previous Diagnosis</td>
<td>100%</td>
</tr>
<tr>
<td>Crowley JJ</td>
<td>TEE</td>
<td>6</td>
<td>Previous Diagnosis</td>
<td>83%</td>
</tr>
<tr>
<td>Fatori R</td>
<td>TEE</td>
<td>13</td>
<td>CMR</td>
<td>69%</td>
</tr>
<tr>
<td>Moon JC</td>
<td>TEE</td>
<td>10</td>
<td>CMR</td>
<td>0</td>
</tr>
<tr>
<td>Ward RP</td>
<td>TTE</td>
<td>26</td>
<td>TTE with contrast</td>
<td>0</td>
</tr>
<tr>
<td>Chen CC</td>
<td>MDCT</td>
<td>14</td>
<td>Previous diagnosis</td>
<td>100%</td>
</tr>
</tbody>
</table>

Fig.-4: A) Electrocardiogram showing characteristic GiantT wave inversions B) notched QRS associated with Apical Hypertrophic Cardiomyopathy
cardiac dysrhythmias and heart failure is less frequent than HCM. However, common causes of cardiovascular mortality still include myocardial infarction, congestive heart failure, dysrhythmias and left ventricular apical aneurysms. To our knowledge only 10 studies, looking at long term outcomes in AHCM, with a sample size greater than 30, have been published. Symptoms at presentation were not specified in majority of the studies. Mortality and morbidity outcomes from these studies are summarized in Table 2 and Table 3. Most studies did not report MI unrelated to pre-existing coronary artery disease.

AHCM patients have a relatively small burden of myocardial fibrosis and less severe diastolic dysfunction, hence have a better prognosis than HCM patients. Some of the common causes of long term cardiovascular morbidity in patients with AHCM include atrial fibrillation, stroke, transient ischemic attack, syncope, pre-syncope and myocardial infarction. In several of the major outcome studies, atrial fibrillation was the most common, followed by stroke. The incidence of atrial fibrillation is higher in mixed type. However another report showed a higher incidence of atrial fibrillation in patients with pure variant. The prognosis is worse in women with a higher

### Table-II

**Mortality rates in major studies for AHCM.**

<table>
<thead>
<tr>
<th>Author</th>
<th>Region</th>
<th>N</th>
<th>Mean age at presentation (years)</th>
<th>Mean Follow-up (years)</th>
<th>All-Cause mortality</th>
<th>Cardiovascular mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sukamoto T et al (1986)</td>
<td>China</td>
<td>31</td>
<td>47</td>
<td>2-13</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Erickson MJ et al (2002)</td>
<td>Canada</td>
<td>105</td>
<td>41.4</td>
<td>13.6 ± 8.3</td>
<td>11/105</td>
<td>2/105 (1.9%)</td>
</tr>
<tr>
<td>Lee CH et al (2006)</td>
<td>Taiwan</td>
<td>40</td>
<td>60</td>
<td>6 ± 5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Chen CC et al (2011)</td>
<td>Taiwan</td>
<td>47</td>
<td>60</td>
<td>2.95 ± 1.97</td>
<td>4/47</td>
<td>3/47 (6.4%)</td>
</tr>
<tr>
<td>Yan L et al (2012)</td>
<td>China</td>
<td>208</td>
<td>52</td>
<td>**</td>
<td>3/193</td>
<td>2/193 (1.0%)</td>
</tr>
<tr>
<td>Klarich KW et al (2013)</td>
<td>USA</td>
<td>193</td>
<td>58</td>
<td>**</td>
<td>55/187</td>
<td>7/187 (3.7%)</td>
</tr>
<tr>
<td>Kim EK et al (2015)</td>
<td>Korea</td>
<td>85</td>
<td>56</td>
<td>37 months*</td>
<td>**</td>
<td>0</td>
</tr>
</tbody>
</table>

### Table-III

**Percentage of Patients in Major Studies with Symptoms at Presentation and Major Morbid Clinical Outcomes**

<table>
<thead>
<tr>
<th>Author</th>
<th>At Presentation Asymptomatic</th>
<th>Chest Pain/ Dypnea</th>
<th>Giant Vtach &gt;10mm</th>
<th>Vfibr/ Vtach</th>
<th>Deep inverted t waves</th>
<th>Afib</th>
<th>CHF</th>
<th>stroke</th>
<th>Syncope/ Pre-syncpe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sukamoto T et al (1986)</td>
<td>*</td>
<td>3.2</td>
<td>*</td>
<td>*</td>
<td>100</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Erickson MJ et al (2002)</td>
<td>46</td>
<td>30</td>
<td>47</td>
<td>3.8</td>
<td>93</td>
<td>12.4</td>
<td>4.8</td>
<td>2.9</td>
<td>*</td>
</tr>
<tr>
<td>Lee CH et al (2006)</td>
<td>*</td>
<td>80</td>
<td>52.5</td>
<td>0</td>
<td>7.5</td>
<td>1</td>
<td>15</td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td>Chung T et al (2011)</td>
<td>*</td>
<td>*</td>
<td>46.8</td>
<td>*</td>
<td>*</td>
<td>31.2</td>
<td>9.3</td>
<td>6.3</td>
<td>6.3</td>
</tr>
<tr>
<td>Chen CC et al (2012)</td>
<td>*</td>
<td>*</td>
<td>59.6</td>
<td>4.2</td>
<td>*</td>
<td>14.8</td>
<td>25.5</td>
<td>10.6</td>
<td>10.6</td>
</tr>
<tr>
<td>Moon J et al (2014)</td>
<td>78</td>
<td>7</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>16</td>
<td>15</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Yan L et al (2015)</td>
<td>91.8</td>
<td>28.8</td>
<td>2.6</td>
<td>91.3</td>
<td>9.9</td>
<td>7.2**</td>
<td>1.6</td>
<td>7.2</td>
<td></td>
</tr>
<tr>
<td>Kim SH et al (2016)</td>
<td>*</td>
<td>*</td>
<td>36</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td></td>
<td>*</td>
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<tr>
<td>Kim EK et al (2015)</td>
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<td>*</td>
<td>1.2</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>3.5</td>
<td>2.4</td>
<td></td>
</tr>
</tbody>
</table>
incidence of heart failure and atrial fibrillation. The prognosis of AHCM becomes very poor with the development of apical aneurysms. It is not clear if myocardial infarction in the apex leads to aneurysm formation in these patients.

Management Considerations
The most recent guidelines, for management of patients with HCM, by the American College of Cardiology and American Heart Association (ACC/AHA) were published in 2011. Risk stratification of AHCM patients, based on history of SCD, syncope, family history of SCD and ventricular tachycardia (VT) is reasonable. In such instances an intra-cardiac defibrillator (ICD) is recommended for the patient. However the ACC/AHA guidelines do not separately address AHCM.

Future Directions for Research
AHCM is still a poorly understood disease. There is a dearth of significant multi-center studies looking at long term follow-up in patients with AHCM. The outcome studies either have a very small sample size or short follow-up period. No significant study has been done to look at natural course specifically in the young population. The mechanisms underlying the differences in incidence and outcomes in patients from different ethnicities and gender are also unclear.

More basic science research is needed to understand the genetic and molecular interactions causing disease, at the cellular level. Little is known about the mechanism by which gene mutations result in myocyte disarray and hypertrophy. A better understanding regarding these complex mechanisms is necessary to improve treatment and outcomes.

In order to develop a more evidence based approach, there exists a need for more large scale population based studies to evaluate the most effective strategy for imaging known or suspected AHCM. More outcome based research is needed to evaluate the role of ICDs for primary prevention in patients with AHCM. Having a central registry to document all cases of AHCM will lead to a better understanding about the pathophysiology and natural course of the disease.

References:


