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CASE REPORT

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Apical hypertrophic cardiomyopathy, the ace of spades: detection by contrast tuned imaging echocardiography

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ABSTRACT

Apical hypertrophic cardiomyopathy (AHCM) is a known entity since its first introduction by Sakamoto and Yamaguchi. However, unlike classical hypertrophic cardiomyopathy (HCM), it is less explored in terms of its associated diagnosis and long-term outcomes. Given the increased availability and utilization of ultra-sophisticated cardiac imaging modalities, AHCM will be increasingly recognized as a distinct, clinically significant variant of classical HCM. It is associated with a wide spectrum of presentations ranging from asymptomatic course with incidental findings on imaging to rarely being associated with ventricular arrhythmias, syncope and sudden cardiac death (SCD). Contrast echocardiography is the most effective and diagnostic study when performed in the right setting with high suspicion on clinical and typical electrocardiogram (ECG) findings. Cardiac magnetic resonance imaging (CMR) has an equal diagnostic yield as a contrast echocardiogram. We are presenting a unique case report of a 57-year-old gentleman with asymptomatic AHCM, which was distinctly delineated after utilizing contrast tuned imaging (CnTI) echocardiography sans administration of intravenous contrast agents. This is the first case report of AHCM portrayed by this ingenious technology.

KEYWORDS

Apical hypertrophic cardiomyopathy; Left ventricular contrast echocardiography; Contrast tuned imaging; 4-dimensional XStrain echocardiography

ARTICLE HISTORY

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Introduction

AHCM typically has an autosomal dominant inheritance tern but can also be sporadic. Contemporary literature indicates the association of AHCM with genetic mutations in ACTC1, TPM1, MYBPC3, and MYH7 [1]. Detected first in Japan in 1976 [2], AHCM is characterized by "giant" negative precordial T-waves on ECG and by "spade like" configuration of its left ventricular cavity in the end diastole on left ventricular angiography [3]. AHCM accounts for up to 25% of HCM in Asian populations and 1% to 10% in non-Asians [4]. A more malignant course is found in the Western population [5]. There are numerous imaging modalities to distinctly identify and illustrate this rare entity of an advance healthcare directive (AHCD): echocardiography, cardiovascular magnetic resonance, cardiac computerized tomography, nuclear scintigraphy, left ventricular angiography and left ventricular contrast study employing intravenous contrast agents (Figure 1).

Transthoracic Echocardiography (TTE) is a versatile, easy to use tool, relatively cheap and available at the bedside. Hence, it is a preferred modality for imaging in AHCM. TTE can reveal apical hypertrophy and identify additional prognostic features that could influence outcome, such as the presence of diastolic dysfunction, mid ventricular obstruction, cavity obliteration or apical aneurysms [6-8]. Notwithstanding, imaging the apex always remains challenging because of frequent foreshortening of left ventricular apex and difficulty in detecting apical akinesis or sequestration caused by the massive hypertrophy [9]. Such phenotypes of AHCM could be missed by echocardiography; thus, those with deep T-wave inversion and noncontributory echocardiography findings should undergo additional imaging [10].

AHCM may not be detected by standard 2-dimensional echocardiography because of indiscrete visualization of the apical endocardial border [11]. When apical hypertrophic cardiomyopathy is suspected but not clearly documented contrast studies should be contemplated. If AHCM is present, the characteristic spade like appearance of the left ventricular cavity, with severe apical myocardial wall thickening, is vividly identified on contrast-enhanced images [12]. A number of earlier studies have reported intravenous microbubble contrast agents improving the diagnostic sensitivity of echocardiography [13-15].

Cardiac magnetic resonance (CMR) the most outstanding and unparalleled modality for AHCM characterization, may create additional risks, time delays, and costs [16]. In particular a major drawback of CMR is that it has got genotoxic effects as demonstrated by the significantly higher level of DNA double-strand breaks measured in human lymphocytes after exposure even with a 1.5T machine [17]. This cancerogenic effect is compounded by the possible gadolinium induced nephrogenic systemic fibrosis [18]. Contrast echocardiography on the other hand is totally safe, easily repeatable,

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showing the same diagnostic potential as CMR to evaluate left ventricular wall thickness and function and is extremely cost-effective [16]. Hence, it is a preferable test for assessing AHCM and in general, left ventricular function and left ventricular wall thickness in patients with poor visualization of left ventricular apex.

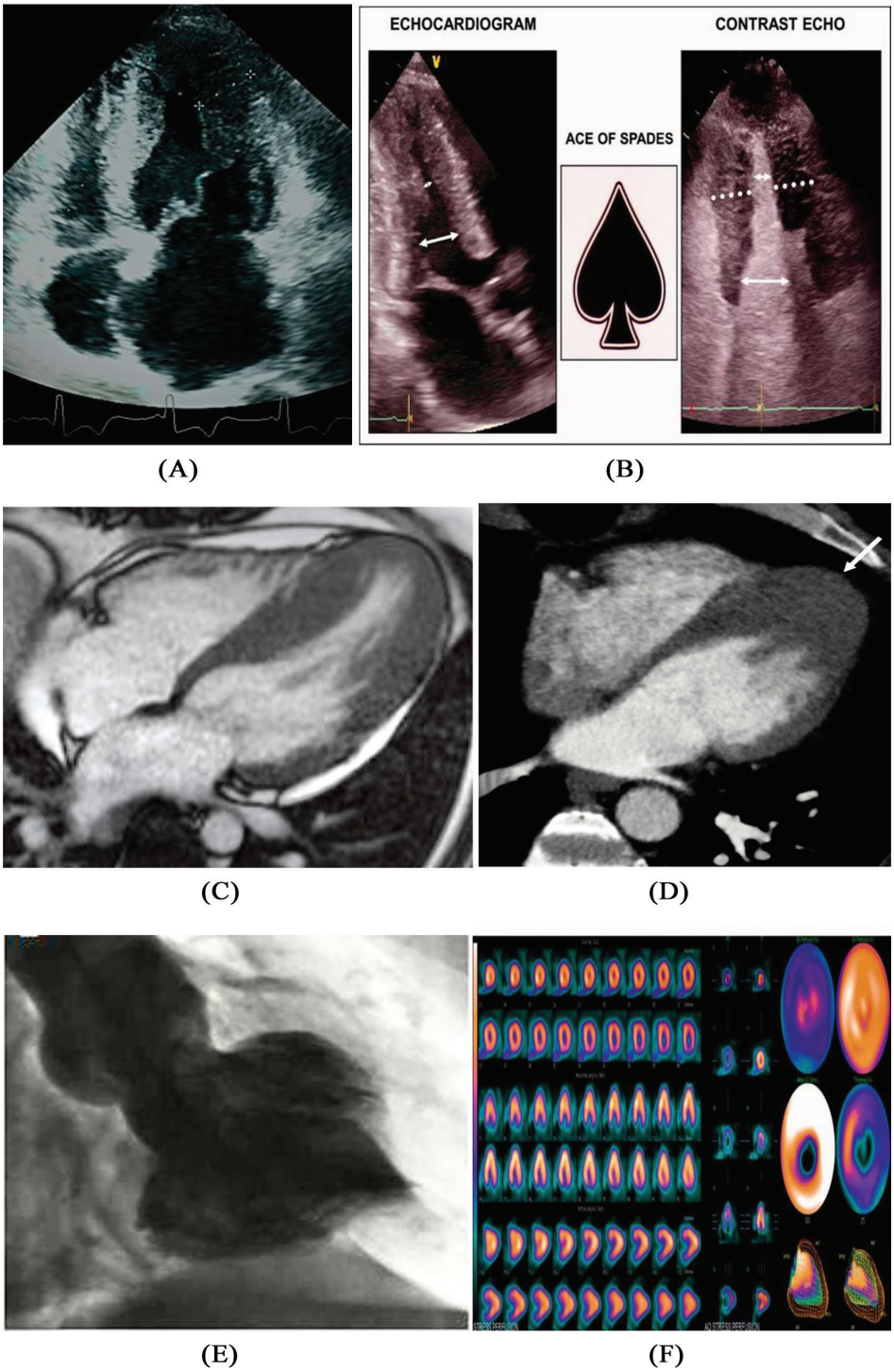

Figure 1. Imaging modalities for AHCM, A) Standard echocardiography in apical 4CH view, B) An echocardiogram and a contrast echocardiogram showing predominant apical hypertrophy and a narrowing of the left ventricular cavity at the apex, resulting in a so-called ace of spades morphology. In the echocardiogram, the left ventricular cavity is displayed in black; in the contrast echocardiogram, the left ventricular cavity is white. Arrows indicate the cavity diameter at the apex and the base, and dotted lines illustrate the significant left ventricular wall thickening at the apex, C) Cardiac MRI - 4CH View, D) Cardiac CT- 4CH View reveals stricking hypertrophy of apical segments (arrow), E) left ventricular angiography showing the characteristic diastolic "ace of spade" sign, F), SPECT (single photon emission computed tomography) in a patient of AHCM showing mild ischemia at the true apex.

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Contrast tuned imaging (CnTI) echocardiography

CnTI is an advanced technology for Contrast-Enhanced ultrasound (CEUS) Imaging. Based on low mechanical index and real-time scanning, CnTI represents the best way to use second-generation contrast media [19]. CnTI can be used for diagnosis and follow-up, as well as during interventional procedures. Its sophisticated architecture based on linear pulser technology, is capable of managing various typologies of pulsing techniques in order to optimize the beam forming management for a wide range of clinical applications.

CEUS has the advantages of the absence of ionizing radiation, widespread availability, even at the bedside, and the possibility to characterize a lesion as soon as it is detected on conventional 2-dimensional echocardiography, commonly used as the first technique for exploration of the left ventricular opacification and other areas [20]. In CnTI second generation contrast agents are utilized for left ventricular opacification. However, in the current case report we have employed CnTI echocardiography for left ventricular opacification sans intravenous contrast agent to recognize and substantiate the presence of AHCM. To our knowledge, this is the first report on CnTI echocardiography without deploying contrast agents.

Case Report

A 56-year-old male with a history of uncontrolled moderate hypertension presented to us with transient pricking type sensation in the left mammary region. The chest pain seemed to be atypical, and there was no sweating/shortness of breath/radiation to jaws or arms. The patient denied any family history of coronary artery disease, smoking or tobacco chewing. On clinical examination, the patient was healthy looking with a pulse rate of 67/min, BP of 150/106 mmHg, right upper extremity in the sitting position, respiratory rate was 15/min and SpO2 was 98% at room air. Systemic examination, particularly of cardiovascular system was unremarkable. The first and second heart sounds were normally heard without any clicks, murmurs or gallops sounds. Resting ECG was typical of AHCM with global "Giant" T wave inversions (Figure 2).

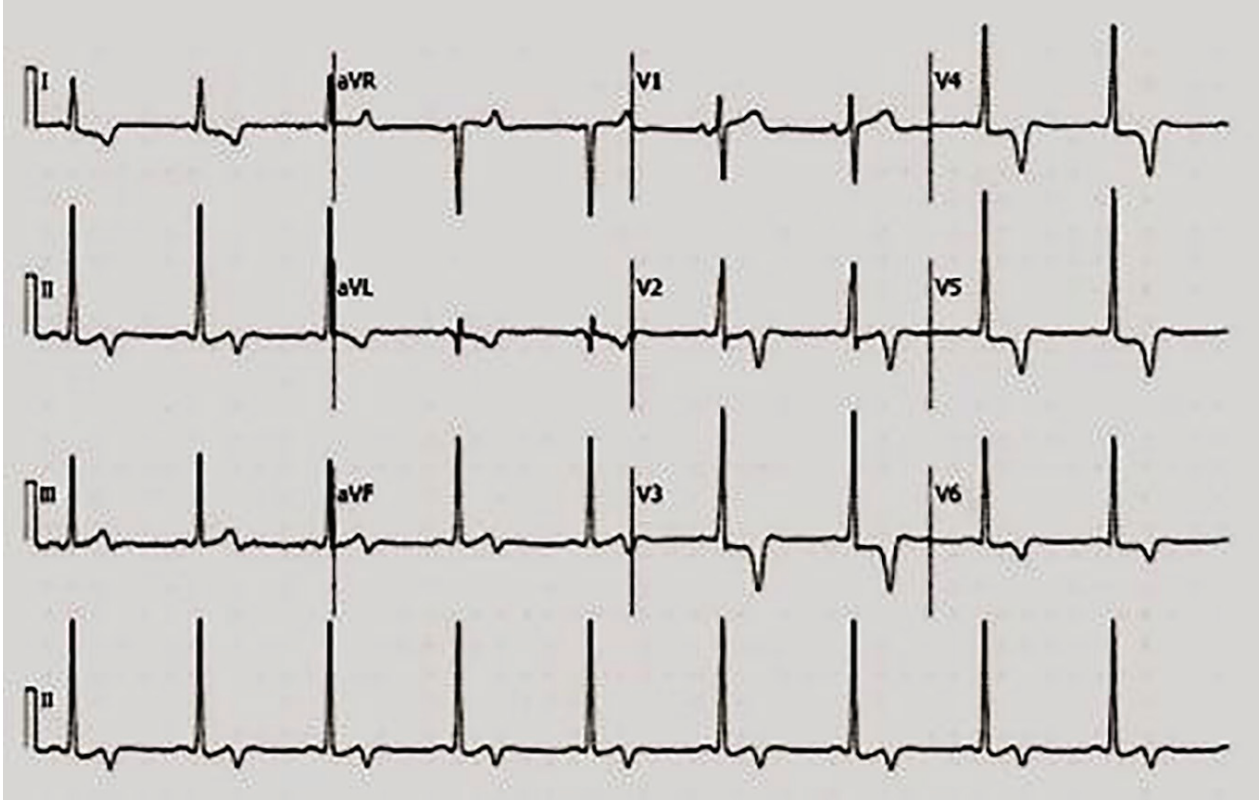

Figure 2. Resting ECG- identifies typical findings of AHCM with global "Giant" T wave inversion.

X-ray chest posteroanterior (PA) was normal without any cardiomegaly or apical bulge (Figure 3). The pathological investigations were all within normal limits. However, no genetic studies were performed.

Transthoracic Echocardiography (TTE)

Standard TTE was performed by the author in the left lateral decubitus position. 2-dimensional echocardiography was conducted in the parasternal long axis view (LX), parasternal short axis view (SX), apical 4-chamber view (4CH), apical 2-chamber view (2CH) and apical 5-Chamber view (5CH).

2-dimensional echocardiography

The standard 2-dimensional echocardiogram was apparently normal. There was no obvious hypertrophy of left ventricular and neither there was any left ventricular outflow obstruction. The left ventricular ejection fraction (LVEF) was 67% by biplane Simpson's method (Figure 4).

Considering the ECG presence of classical "Giant" T wave inversions, the apex of left ventricular was scanned to rule out

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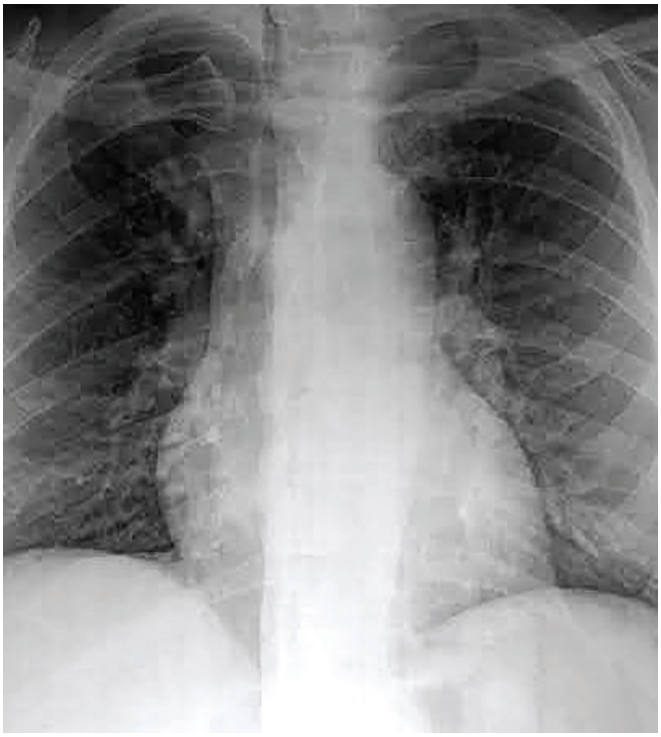

Figure 3. X-ray chest PA view was normal without any cardiomegaly or apical bulge.

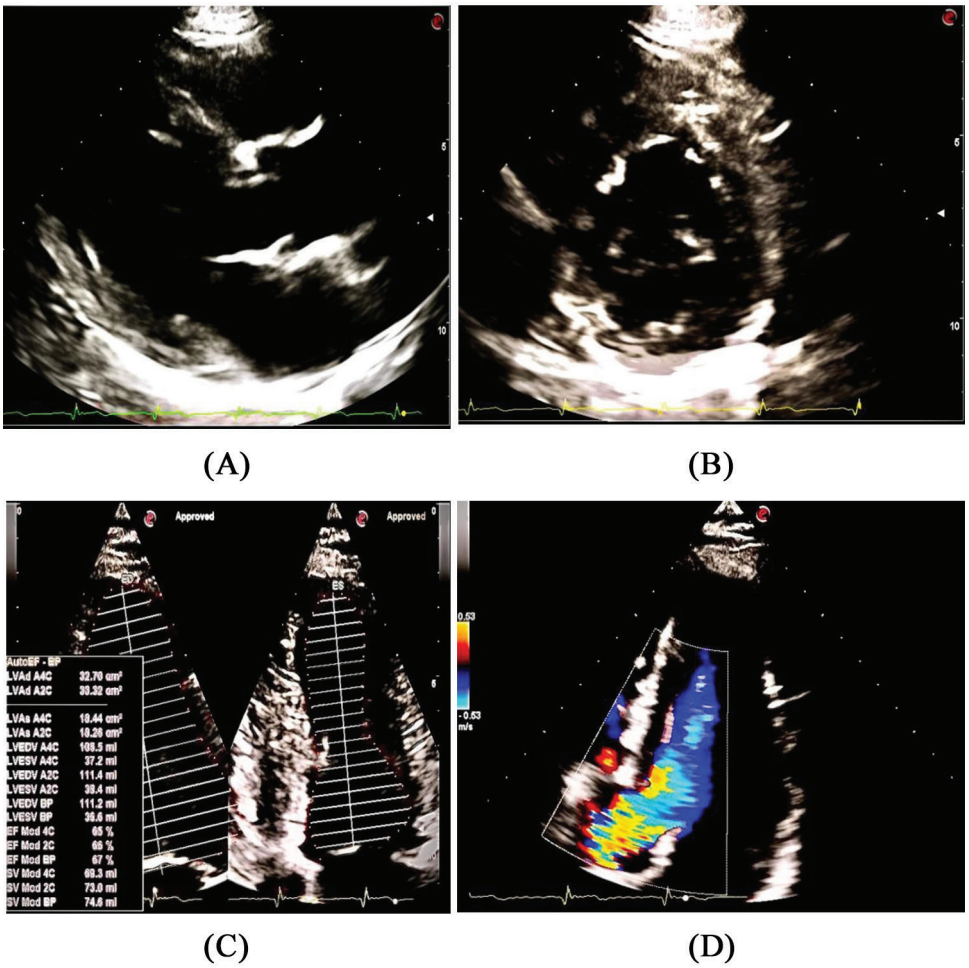

Figure 4. The standard echocardiogram was apparently normal. No hypertrophy of left ventricular muscular capacity was discerned and neither there was any left ventricular outflow obstruction. A) Parasternal long axis view (LX), B) Parasternal short axis view (SX), C) Biplane Simpson's method for determination of EF%, D) Apical 5-ch view - color flow imaging.

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AHCM. A nondescript thickening of the left ventricular apex and the upper anterolateral wall was detected, suggesting AHCM (Figure 5).

In the LX view there was presence of thickening of apical anterior septum (14 mm). Moreover, in the apical 4CH view in diastole, marked hypertrophy was detected at the left ventricular apex, apical anterior septum and apical lateral wall. Maximum left ventricular apical thickening was 20 mm and left ventricular apical and posterior wall ratio was 3.3:1. Furthermore, in systole the left ventricular cavity was significantly reduced in size along with hypokinetic motion of left ventricular apex.

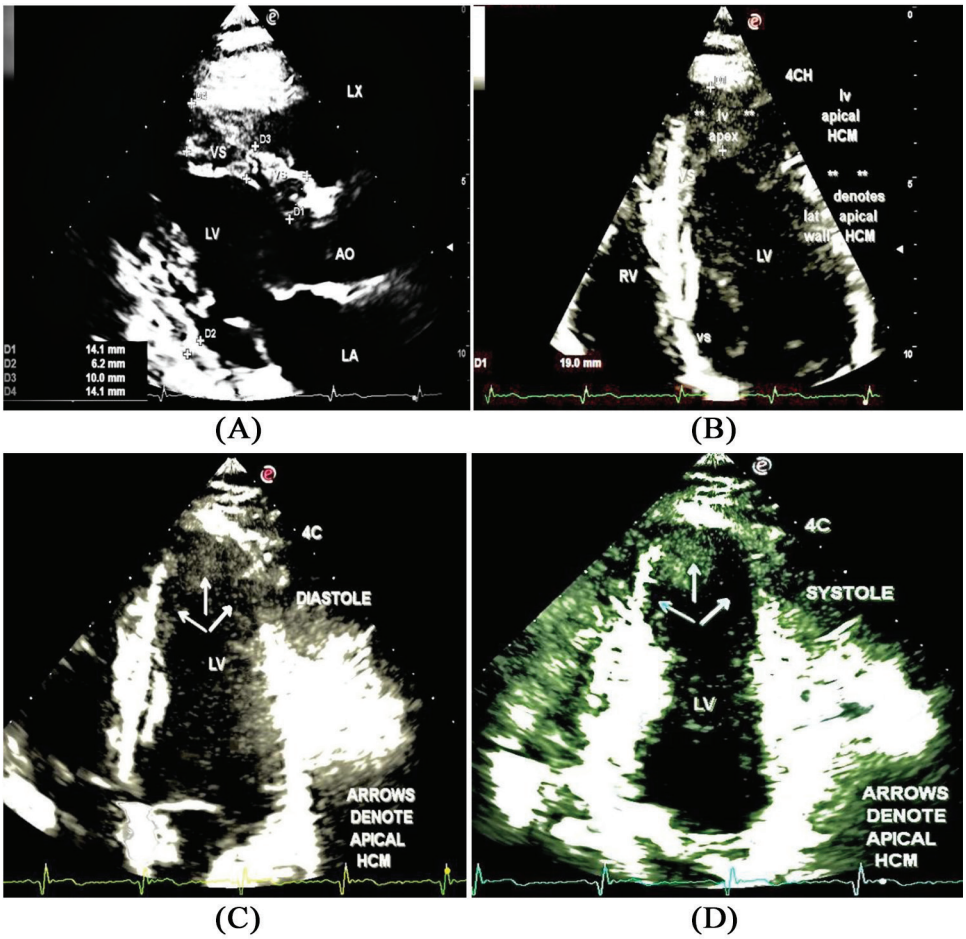

Figure 5. On focused echocardiography of the left ventricular, a nondescript thickening of apex and the upper anterolateral wall was detected which may be suggestive of apical hypertrophic cardiomyopathy. A) In the LX view, the apical anterior septum is thickened (14 mm), B) In the apical 4CH view, there is presence of marked thickening of left ventricular apex (19 mm), apical anterior septum and apical lateral wall, C) In another apical 4CH view in diastole similar thickening is visualized at the left ventricular apex, apical anterior septum and apical lateral wall, D) In the systolic frame the left ventricular cavity has significantly reduced in size along with the indistinguishable motion of left ventricular apex.

Left ventricular diastolic function

Pulse wave (PW) doppler study at the tip of mitral valve identified tall E and small A waves and on tissue doppler imaging (TDI) there was presence of small E` waves and E/E` ratio was 17:1, indicating a moderate grade left ventricular diastolic restrictive dysfunction (Figure 6).

Contrast tuned Imaging (CnTI) echocardiography

Left ventricular CnTI was accomplished by 4-dimensional XStrain Echocardiography (Figure 7). The standard apical 4CH view exhibited hazy and indistinct thickening of the left ventricular apex. Meanwhile, on contrast tuned imaging in diastole, there was distinctive AHCM discerned with notable hypertrophy of the left ventricular apex, apical ventricular septum, and apical lateral wall. The left ventricular cavity size was normal. We want to highlight that no intravenous contrast agent was utilized during CnTI imaging.

4-dimensional XStrain speckle tracking echocardiography

4-dimensional XStrain speckle tracking echocardiography was analyzed offline, and "Bull's" eye and polar mapping of left ventricular global and left ventricular apical strain analysis was conducted in apical 2CH, LAX, 4CH views (Figure 8). Moreover, global strain analysis was simultaneously performed. There were severely decreased values of left ventricular strain in apical segments (varying from -2% to -4%), and correspondingly the global strain values were conspicuously reduced (global strain 2CH being -10.11 %, global strain LAX being -11.02 %, global strain 4CH being -8.46 %, global strain

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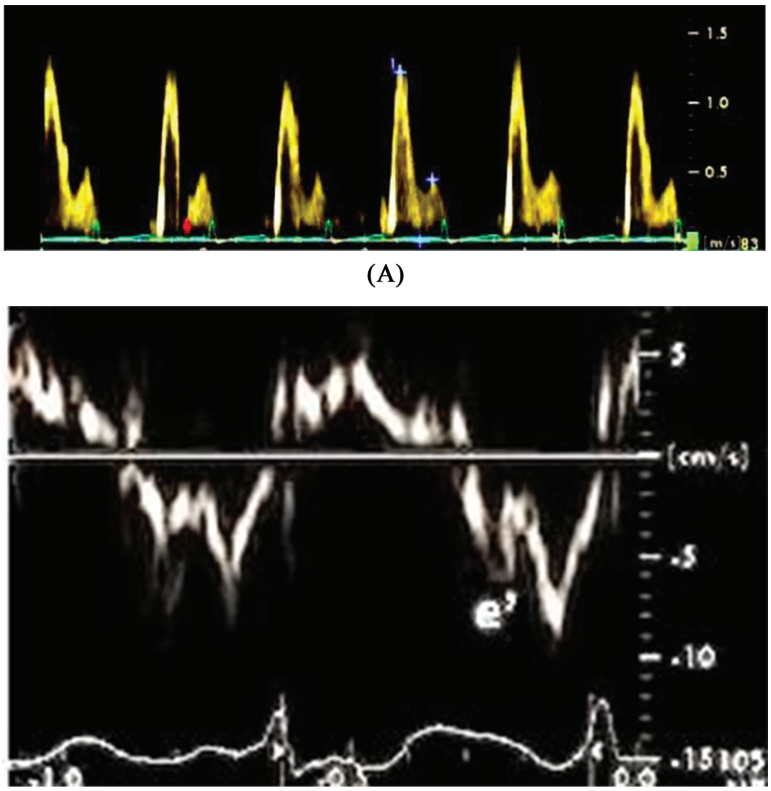

Figure 6. Left ventricular diastolic dysfunction in AHCM, A) pulse wave Doppler at the tip of mitral valve detects large E and small A waves, B) tissue doppler imaging shows small E' wave and E/ E' ratio was 17:1, indicating a moderate grade diastolic restrictive dysfunction.

being -9.86 % respectively). It would be noteworthy to state that according to the American Society of Echocardiography normal global longitudinal strain values are > -20% +2% in normal healthy adults.

Discussion and Review of Literature

AHCM is an anomalous phenotype of HCM with an increased prevalence in the Japanese population [21]. Typically, it is considered a benign condition and is incidentally detected by echocardiography. AHCM was first described in Japan by

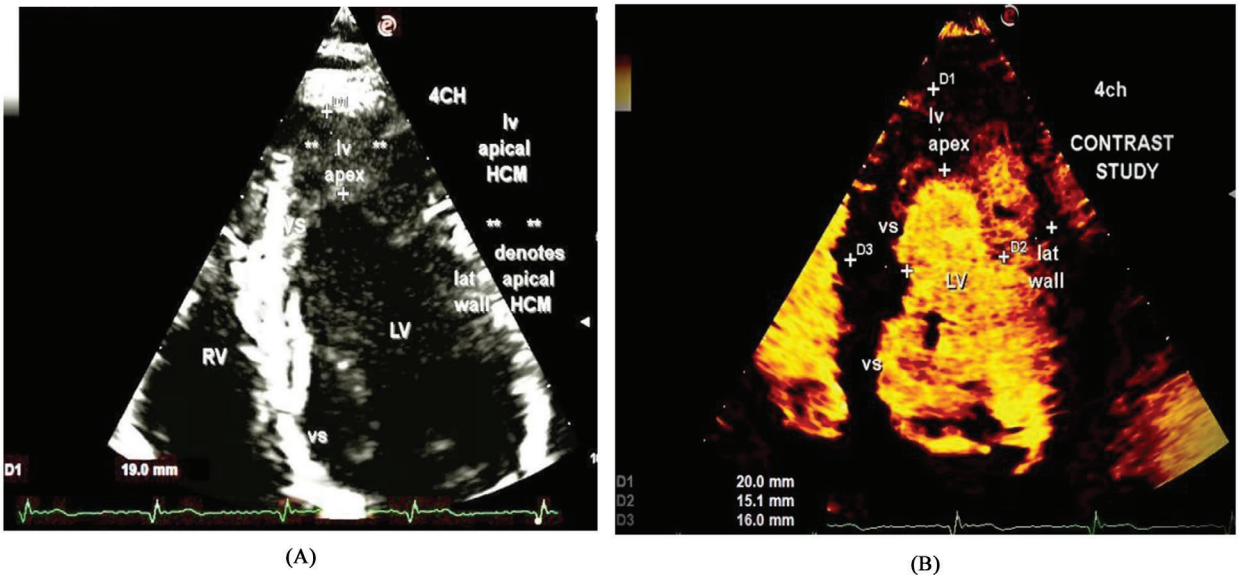

Figure 6. Left ventricular Contrast Tuned Imaging Echocardiography, A) Standard apical 4CH view showing hazy images of hypertrophic left ventricular apex, apical anterior septum and apical anterior wall, B) on contrast tuned imaging in diastole there is a distinctive AHCM discerned with notable hypertrophy of left ventricular apex, apical ventricular septum and apical lateral wall. The left ventricular cavity size is normal. The thickness of left ventricular apex, apical anterior septum and apical lateral wall was 20.0 mm, 15.1 mm and 16.0 mm respectively.

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Sakamoto et al. (1976) [2]. Yamaguchi et al., (1979) went on to describe the syndrome and its ventriculographic features [3]. Kitaoka et al., (2003) described the apical HCM in 15% of Japanese and 3% of American patients of HCM [21]. It is rare in the West (1 to 11%) but more common in oriental people and accounts for 13%-41% of all variants of HCM among Asian individuals [22,23]. In a study of 200 patients in Japan, Sakamoto observed that the prognosis of AHCM was generally benign [24].

Apical hypertrophic cardiomyopathy- morphological types

AHCM encompasses three morphological types: focal, diffuse, and mixed. Amongst them focal is the most common [7]. Our patient is presenting with pure focal type of AHCM.

Pathophysiology of apical hypertrophic cardiomyopathy

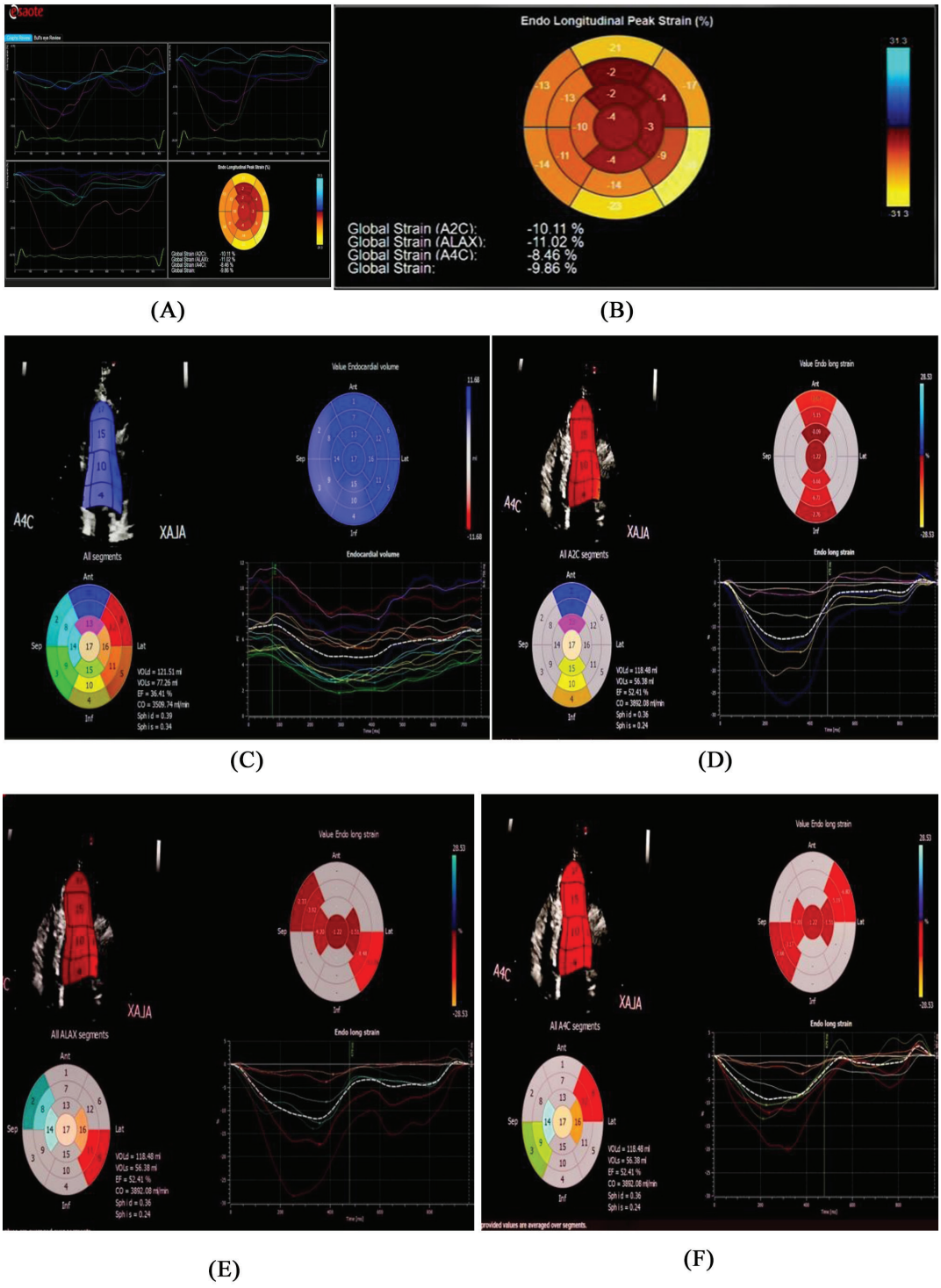

Figure 8. 4-dimensional XStrain Echocardiography, A) "Bull's" eye mapping of left ventricular global apical 2CH, LAX, 4CH and Global Strain, B) Polar mapping of left ventricular strain in our patient of AHCM, C) 4-dimensional XStrain derived end-diastolic volume, end-systolic volume, cardiac output and EF %, D) apical 2CH strain values, E) apical LAX strain values, F) apical 4CH strain range values.

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AHCM causes significant alterations in morphology and function of left ventricular (Figure 9). Left ventricular outflow tract obstruction and mitral regurgitation are conspicuously absent [1]. Nonetheless, two noticeable phenomena are found in patients with AHCM: MVOCO and aneurysm of left ventricular apex. MVOCO occurs due to considerable hypertrophy of midventricular muscular walls. Left ventricular diastolic dysfunction (Figure 10) produces escalation of left atrial filling pressure and its gross enlargement, which is implicated in the causation of dyspnea on effort, orthopnea and pulmonary edema [1]. In our case, the PW doppler of the mitral valve and TDI of left ventricular were indicative of moderate grade diastolic dysfunction.

SCD triggered by sustained ventricular tachycardia and/or ventricular fibrillation, is the most dreadful dilemma in patients of AHCM. Consequently, an implantable cardioverter-defibrillator may be a compelling strategy for SCD prevention in high risk AHCM patients [1].

Symptomatology

The symptomatology of AHCM is highly variable. AHCM is generally evident in early adulthood [4,25], and most series reported a mean age of 41 [4]. Nearly 54% of patients with AHCM are symptomatic, and the most common symptoms are chest pain, palpitations, dyspnea and syncope. Atypical chest pain is the most frequent symptom. Atrial fibrillation (12%), apical myocardial infarction (10%), ventricular arrhythmia and apical thrombosis with embolization may occur in up to 33% of cases [26]. Occasionally, SCD may be the first manifestation of AHCM [5]. Our patient only experienced infrequent episodes of atypical chest pain and was largely asymptomatic.

Electrocardiography (ECG)

The most frequent ECG manifestations are negative T waves in the precordial leads, found in 93% of patients (conventionally a

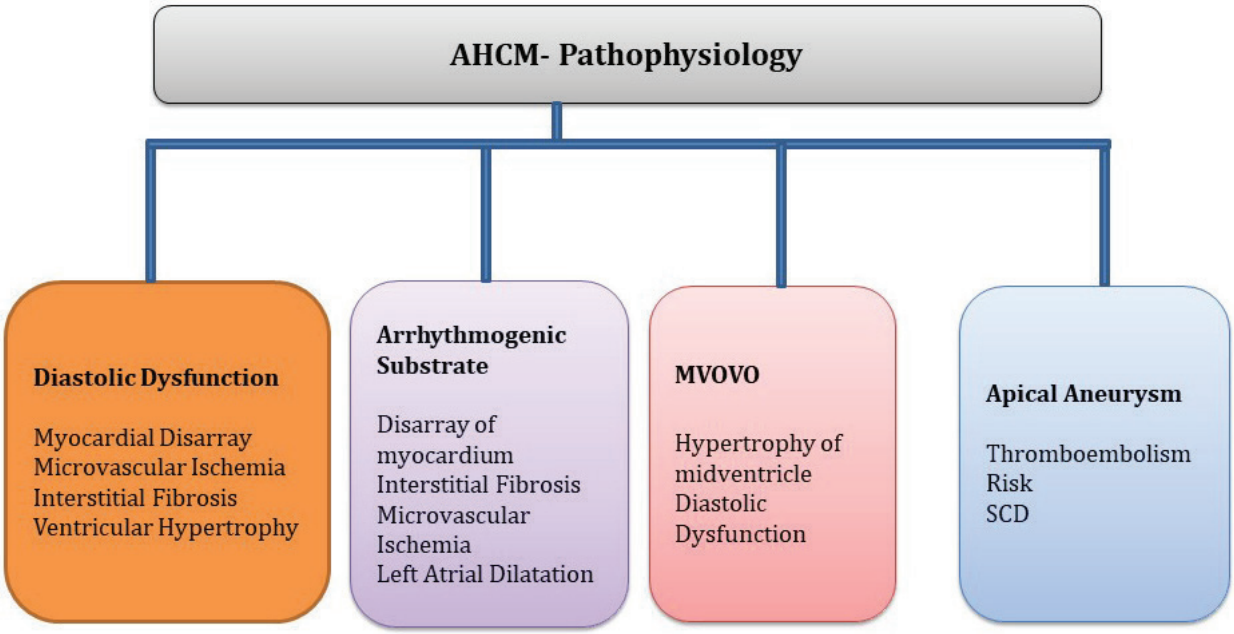

Figure 9. AHCM- Pathophysiology.

depth of >10 mm) and a documented left ventricular hypertrophy on imaging is seen in 65% of patients with HCM. Giant T wave negativity (defined as depth or voltage >1mV or 1.2mV in any of the leads) in the left precordial leads is the cardinal feature of AHCM and is found in 47% of patients [27]. Correspondingly, "Giant" T wave inversions were also encountered in our patient.

In AHCM, larger degree of T wave inversions does not correlate with severity of apical hypertrophy [28]. Presence of giant T wave inversions in Japanese HCM patients has been authenticated as a predictor of favorable outcome, and it is more common in sporadic cases of AHCM [29].

Transthoracic Echocardiography (TTE)

The preferred initial imaging test is TTE [30]. AHCM is exemplified by extensive circumferential hypertrophy of left ventricular apex which causes a distinctive spade-like morphology of left ventricular cavity in the apical 4CH view. Correspondingly, similar morphology was recognized in left ventricular long axis view of CMR and right anterior oblique view of left ventricular angiography [31].

Echocardiographic diagnostic criteria of hypertrophic cardiomyopathy and apical hypertrophic cardiomyopathy

Standard 2D echocardiography is the preferred imaging tool for the diagnosis of HCM. The current diagnostic criteria for HCM are an increase in left ventricular wall thickness ≥ 15 mm in at least one myocardial segment or ≥ 13 mm for patients with a first-degree relative with confirmed HCM, in the absence of abnormal loading conditions/other causes of LVH (e.g., hypertension, valvular heart disease) [32,33]. Meanwhile, asymmetric hypertrophy (a septal-to-posterior wall thickness ratio ≥ 1.3 in normotensive patients or ≥ 1.5 in hypertensive

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patients) may be suggestive of HCM, albeit it is not specific for HCM.

For AHCM echocardiographic diagnostic criteria [32,33] are the following: 1) asymmetrical left ventricular hypertrophy confined to the left ventricular apex below the papillary muscle level; 2) apical wall thickness ≥ 15 mm; 3) a ratio of maximal apical to posterior wall thickness >1.5. In our case, the maximum diastolic thickness of left ventricular apex was 20 mm, and the ratio of maximal apical to posterior wall thickness was 3.3:1.

Left ventricular Contrast study

Current generation contrast agents are microbubbles consisting of a shell and encapsulated gas. The echo reflecting properties of the contrast agents are decided by the size, shell and encapsulated gas of the microbubbles within the different contrast agents. Microbubble ultrasound dispersion is proportional to the sixth power of the radius, so the largest bubble capable of passing through the pulmonary microcirculation will have the best reflection properties [34-37].

The harmonic properties of microbubbles means that they reflect sound not only at the quintessential frequency of the ultrasound source but also at higher harmonics [38]. Characteristics of the three commercially available contrast agents are listed in Table 1. Contrast imaging employs the non-linear scattering properties of ultrasound contrast agents to expedite their recognition within the myocardial cavities [39-41].

Contrast tuned imaging (CnTI) echocardiography

CnTI is sophisticated technology for CEUS imaging [18]. Based on low mechanical index and real-time scanning, CNTI is an immaculate way to utilize second-generation contrast media. CnTI is delineated by:

- High Sensitivity- detection of the lowest intensity signals.
- High Homogeneity- same representation for signals whether emanating from same vessels or same tissues.
- High Spatial Resolution- recognition of very small structures (both hyperechoic and hypoechoic).
- High Temporal Resolution- real-time detailed analysis of arterial and venous phase.

Contrast Enhanced Ultrasound (CEUS)

Ultrasound contrast agents are liquid suspensions of biocompatible gas-filled microspheres. When injected into a patient's vein, they circulate in the cardiovascular system, producing augmented ultrasound reflectivity. CEUS uses special biocompatible ultrasound contrast agents to improve the quality and reliability of ultrasound scans, thereby accurately diagnose medical conditions and monitor therapy. In our index patient CnTI echocardiography was performed, and the exquisite images of AHCM with spade-like morphology of left ventricular was illustrated in the apical 4CH view despite non-employment of intravenous contrast agents.

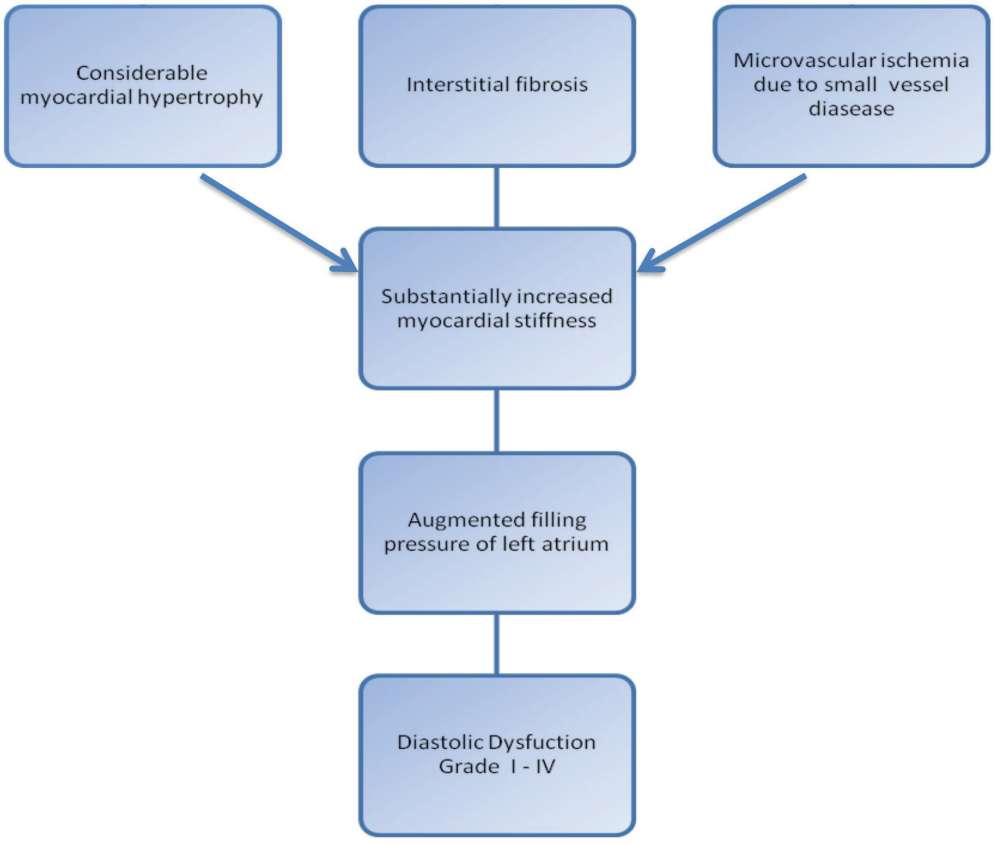

Figure 10. Mechanisms of development of diastolic dysfunction in AHCM.

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Table 1. Current commercially available ultrasound contrast agents.

Agent	Manufacture	Shell	Gas
Optison®	GE Healthcare	Albumin	Perfluoropropane
Definity® / Luminity®	Lantheus Medical Imaging	Lipid	Perfluoropropane Perfluoropropane
SonoVue® / Lumason®	Bracco Diagnostics	Amphiphilic phospholipids	Sulfur hexafluoride

Decorrelated Contrast Tuned Imaging technology (DCTI)

An exceptional CnTI offers DCTI function [18], which spontaneously captures the breaking frame and decorrelates the signal, thus eradicating all artifacts by increasing sensitivity in the late phase. DCTI is designed to boost the contrast information. By using specific decorrelation software and combining the technique with a low and high mechanical index, DCTI is able to detect even the feeble information from low concentrations of contrast agent circulating even after five minutes of the bolus injection. DCTI technology is depicted by:

- High-power transmission to destroy the microbubbles and saving the first frame after their demolition.
- Maximizing
- The diagnostic information by applying a decorrelation algorithm and integrating low and high mechanical index technologies.
- Heightened ability to distinguish between a signal coming from static tissue and contrast agent bubbles inside the vessels.

Conclusions

An AHCD presentation is of considerable significance because the majority of these patients are relatively young. Giant T inversions on ECG and the hallmark spade shaped hypertrophy of left ventricular apex are the cardinal manifestations of AHCM. AHCM will be increasingly recognized as a distinct, clinically noteworthy variant of typical HCM because of increased availability of multiple ultra-advanced imaging tools. With high level of suspicion of AHCM on clinical grounds and diagnostic ECG findings, left ventricular contrast echocardiography is the most reliable and productive study to unveil the existence of AHCM. With a long-term mortality of 0.1% per year AHCM is generally accompanied with favorable prognosis in both Asian and Caucasian populations. There is lesser incidence of sudden cardiac death in apical variant compared to patients with classical HCM. No medications are necessary in asymptomatic patients, even though reassuring the patient is definitely desired. Moreover, advising these individuals to give due importance to any episodes of syncope or pre-syncope. In symptomatic patients, beta-blockers are recommended for decreasing the symptomatology as well as overall mortality [4].

Disclosure statement

No potential conflict of interest was reported by the authors.

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