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Original Article

Association of ST elevation with apical aneurysm in hypertrophic cardiomyopathy

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ABSTRACT

Objectives: Apical aneurysms in patients with hypertrophic cardiomyopathy (HCM) represent an underrecognized but clinically important subset of HCM patients. However it may be frequently missed by echocardiography because of poor image quality of left ventricular apex. We aimed to compare electrocardiographic STE in HCM patients with and without apical aneurysm.

Methods: We developed this clinical review using an extensive MEDLINE review of the literature and data from our laboratories; and some electrocardiographic parameters including STE were analysed in HCM patients with and without apical aneurysm.

Results: There were 29 HCM patients without apical aneurysm (Group 1; 52.6 ± 17.7years, 69% male) and 28 HCM patients with apical aneurysm (Group 2; 59.6 ± 13.2years, 57% male). The STE in V4-6 derivations were statistically more frequent in patients with apical aneurysm compared to those without aneurysm (93% vs 7%, $p < 0.001$). There was a positive correlation between the presence of the STE in V4-6 derivations and the presence of the apical aneurysm (Spearman's $\rho = 0.895$, $p < 0.001$).

Conclusions: Clinicians and specifically echocardiographers must pay special attention on the electrocardiography to correctly detect the frequently overlooked apical aneurysm in HCM patients, and should be careful for apical aneurysm particularly in the presence of STE in V4-6 derivations.

1. Introduction

Hypertrophic cardiomyopathy (HCM) is the most common genetic heart disease characterized by a diverse clinical and phenotypic spectrum.[1] The most common variant of HCM is characterized by patients with septal hypertrophy who may have left ventricular outflow obstruction, most commonly due to systolic anterior motion of the mitral valve which

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exacerbates symptoms and decreases survival.[1] But, variants of HCM occur that spare the proximal septum: patients with the apical hypertrophic cardiomyopathy (ACM) and mid-ventricular obstructive hypertrophic cardiomyopathy (MVO-HCM).

Apical aneurysms in patients with HCM represent an underrecognized but clinically important subset of HCM patients, often requiring a high index of suspicion, have been found to be associated with both ACM and MVO-HCM variants.[2–6] It has been reported that 10–25% incidence of all patients presenting with ACM or MVO-HCM subsequently develop apical aneurysms.[2–7]Whereas the reported prevalance is 2%,[2,5] a previous study reported the incidence of concealed apical aneurysm with MVO-HCM to be approximately 1.5% of all HCM cases.[4] Although the electrocardiogram and transthoracic echocardiography are the two most useful measures for the diagnosis of HCM,[3,8,9] diagnostic limitations of echocardiography primarily due to poor image quality of the left ventricular apex or due to apical foreshortening on planar imaging may cause misdiagnosis between the ACM and MVO-HCM variants, particularly in the presence of an undetected apical aneurysm.[2–6,8,10] Previous descriptions of an association of apical aneurysm with ST segment elevation (STE) have been confined to small patient series. Therefore, we aim to provide some electrocardiographic clues to help differentiating between HCM patients with and without apical aneurysm.

2. Method

Patients, admitted to our hospitals due to electrocardiographic abnormalities or clinical symptoms and diagnosed consecutively as having ACM without apical aneurysm (Group 1) included study. Since MVO-HCM patients with apical aneurysm (Group 2) were rare in our databases, a subsequent PubMed search was conducted using the terms ''hypertrophic cardiomyopathy,'' ''midventricular obstruction'' ''apical aneurysm,'' or ''apical diverticule'' ''apical pouch'', or ''apical outpouching''. The search was limited to English language articles published between January 1976 and January 2013. The clinical, electrocardiographic, echocardiographic, left ventriculographic (Video 1 and 2) or CMR data were collected.

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By means of two-dimensional echocardiography, patients were diagnosed as having ACM when they had left ventricular hypertrophy of wall thickness >15 mm predominantly localized to the left ventricular apex partially or wholly along the circumference, with the ratio of maximal apical wall thickness to basal posterior wall thickness being>1.5.[1,2] Left ventricular MVO-HCM was diagnosed when midventricular obliteration was caused by marked septal hypertrophy resulting in contact with a hypercontractile left ventricular free wall rather than by sytolic anterior motion of the anterior mitral valve leaflet.[2] A left ventricular apical aneurysm was defined as a discrete, thin-walled dyskinetic or akinetic segment of the most distal portion of the chamber with a relatively wide communication to the left ventricular cavity.[4]

By means of 12-lead electrocardiography, we measured the maximal voltage of negative T-wave in V3 to V6 leads, the voltage of S-wave in V1 and the maximal R-wave in V3 to V6. We also evaluated STE and T wave inversions in all leads. Repolarization abnormalities were defined by ST-segment elevation or depression 0.1 mV above or below the baseline at 0.08 s after the J point and T-wave inversion [Fig. 1, depressed ST segment (A), isoelectric ST segment (B), elevated ST segment (C)]

The patients were excluded, if: (i) they had poor quality ECG tracings (ii) they had an obstructive atherosclerotic coronary artery disease as a cause of apical aneurysm formation, or (iii) they had significant missing echo and CMR in their report.

The SPSS statistical software package (version 16.0; SPSS Inc, Chicago, Ill) was used to perform all statistical calculations. Continuous variables were expressed as mean ± SD, and compared using the Mann–Whitney *U* test. Categorical variables were expressed as numbers and percentages, and compared using the Chi^2test. Relationships between the categorical variables were evaluated Spearman's correlation analysis. For all tests, a value of $p < 0.05$ was considered significant.

3. Results

There were 29 HCM patients without apical aneurysm (Group 1; 52.6 ± 17.7 years, 69% male) and 28 HCM patients with apical aneurysm (Group 2; 59.6 ± 13.2years, 65% male). The clinical and electrocardiographic characteristics of the HCM patients with and without apical aneurysm were summarized in Table 1.

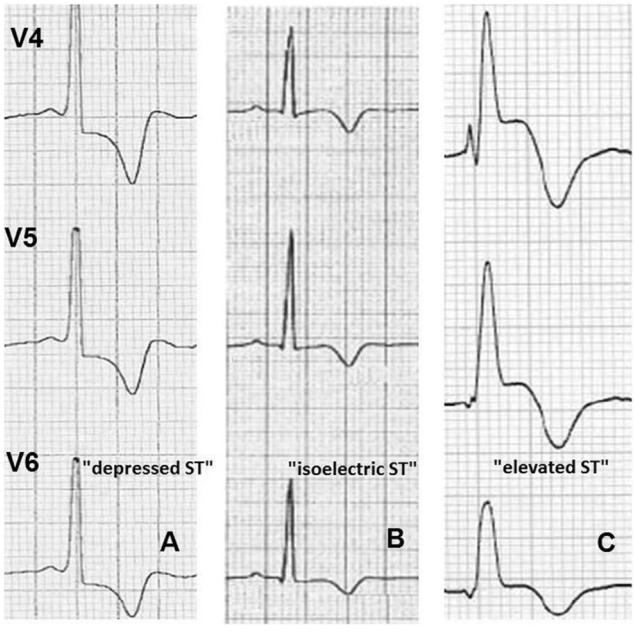

Fig. 1 – Electrocardiograms showing the three different ST segment changes in V4-6 leads as a depressed ST segment (A), an isoelectric ST segment (B), or an elevated ST segment (C).

Table 1 – Basal demographic and clinical characteristics features, and the comparison of electrocardiographic findings in HCM patients with and without apical aneurysm.

	Group 1 (apical aneurysm -) ($n = 29$)	Group 2 (apical aneurysm +) ($n = 28$)	p Value
Demographic Features			
Age at diagnosis (year; median-IQR)	55.0 (22)	56.5 (20)	0.13
Gender (male, %)	20/29 (69)	16/28 (57)	0.36
Asymptomatic (%)	10/29 (34)	6/28 (21)	0.27
Palpitation (%)	6/29 (21)	14/28 (50)	0.02
Chest pain (%)	15/29 (52)	10/28 (36)	0.22
Nonsustained VT (%)	2/29 (7)	7/28 (25)	0.06
VT/VF (%)	3/29 (10)	7/28 (25)	0.23
Syncope (%)	6/29 (21)	8/28 (27)	0.49
Thrombus in apical cavity (%)	0/29 (0)	7/28 (25)	0.02
TIA/CVA (%)	2/29 (7)	1/28 (4)	0.57
Electrocardiographic Findings			
SV1 (mV; median – IQR)	10.5 (10)	12.0 (5)	0.70
Max negative T-wave in V3-6 (mV; median)	9.5 (9)	5.0 (5)	0.001
Max R-wave in V3-6 (mV; median-IQR)	23.0 (15)	17.0 (9)	0.001
Negative T-wave (%) in 2-3-aVF	26/29 (90)	23/28 (82)	0.41
Negative T-wave (%) in V4-6	29/29 (100)	27/28 (96)	0.31
Negative T-wave (%) in 1-aVL	27/29 (93)	25/28 (89)	0.61
STE (%) in 2-3-aVF	2/29 (7)	17/28 (61)	<0.001
STE (%) in V4-6	2/29 (7)	26/28 (93)	<0.001
ST depression (%) in 2-3-aVF	6/29 (21)	0/28 (0)	0.01
ST depression (%) in V4-6	15/29 (52)	2/28 (7)	<0.001
ST depression (%) in 1-aVL	12/29 (41)	4/28 (14)	0.02

IQR, interquartile range; Max, maximum; HCM; hypertrophic cardiomyopathy; VT, ventricular tachycardia; VF, ventricular fibrillation; TIA, transient ischemic attack; CVA, cerebrovascular accident; STE, ST segment elevation.

The STE in V4-6 derivations were statistically more frequent in patients with apical aneurysm compared to those without aneurysm (93% vs 7%, $p < 0.001$). There was a positive correlation between the presence of the STE in V4-6 and the presence of the apical aneurysm (Spearman's $\rho = 0.895$, $p < 0.001$).

4. Discussion

We found that the STE in V4-6 derivations were statistically more frequent in HCM patients with apical aneurysm compared to those without aneurysm. This finding may provide us a usefull electrocardiographic clue to correctly detect the frequently overlooked apical aneurysm in HCM patients.

The ACM was first described in the Japanese population in 1977 by Sakamoto et al as a unique entity characterized by myocardial hypertrophy with predominant involvement at the apex, the hallmarks of giant negative T waves (>10 mm) in the left precordial leads, and angiographic spade-shaped appearance of the left ventricular cavity (Fig. 2A).[8] Despite its relatively good prognosis,[7] long-term observations occasionally exhibited gradual progression of cardiac hypertrophy and apical aneurysm, but often presents a diagnostic challenge.[2,4,5] The other rare variant of MVO-HCM, which was first reported by Falicov et al in 1976, is characterized by the presence of pressure gradient between the apical and basal chambers of the left ventricle, and is also frequently associated with an apical aneurysm without significant atherosclerotic coronary artery disease.[11]

Classically left ventricular apical aneurysm has been considered a complication of acute myocardial infarction, but also has been reported as associated with HCM, Chagas' disease, sarcoidosis, congenital or idiopathic.[12] In most cases, the chronic apical aneurysm in the presence of the previous myocardial infarction manifested electrocardiographically by varying degrees of chronic STE.[12] Although ACM is often a relatively benign disease compared to obstructive HCM, the HCM patients with apical aneurysms have been noted to have a higher risk of systemic emboli due to apical intracavitary thrombus formation, ventricular tachyarrhythmias, sudden cardiac death (SCD) and perfusion defects on nuclear stress testing.[13] Therefore, definitive noninvasive diagnosis of ACM with or without apical aneurysm has some diagnostic and therapeutic implications.[13,14] Currently, the cardiovascular magnetic resonance imaging (CMR) is generally regarded as the gold-standard diagnostic test for HCM particularly in challenging HCM cases[15,16]; however, it is not commonly used in daily practice.

Since it has found to be associated with a higher risk of systemic emboli due to apical intracavitary thrombus formation and SCD related to ventricular tachyarrhythmias,[5,17] the recognition of an apical aneurysm in patients with HCM is important for diagnosis, therapeutic approaches and prognostic evaluation. It has been reported that HCM patients with large apical aneurysms (>4 cm diameter) are more likely to experience adverse disease complications than patients with small aneurysms (<4 cm diameter).[5] Again, the ventricular arrhythmia has been originated from the neck of the apical aneurysm and the associated extensive areas of myocardial fibrosis, which have been regarded as arrhythmogenic substrates for the generation of malignant ventricular tachyarrhythmias.[18] It is therefore not surprising that the majority of reported HCM related events in patients with MVO-HCM with

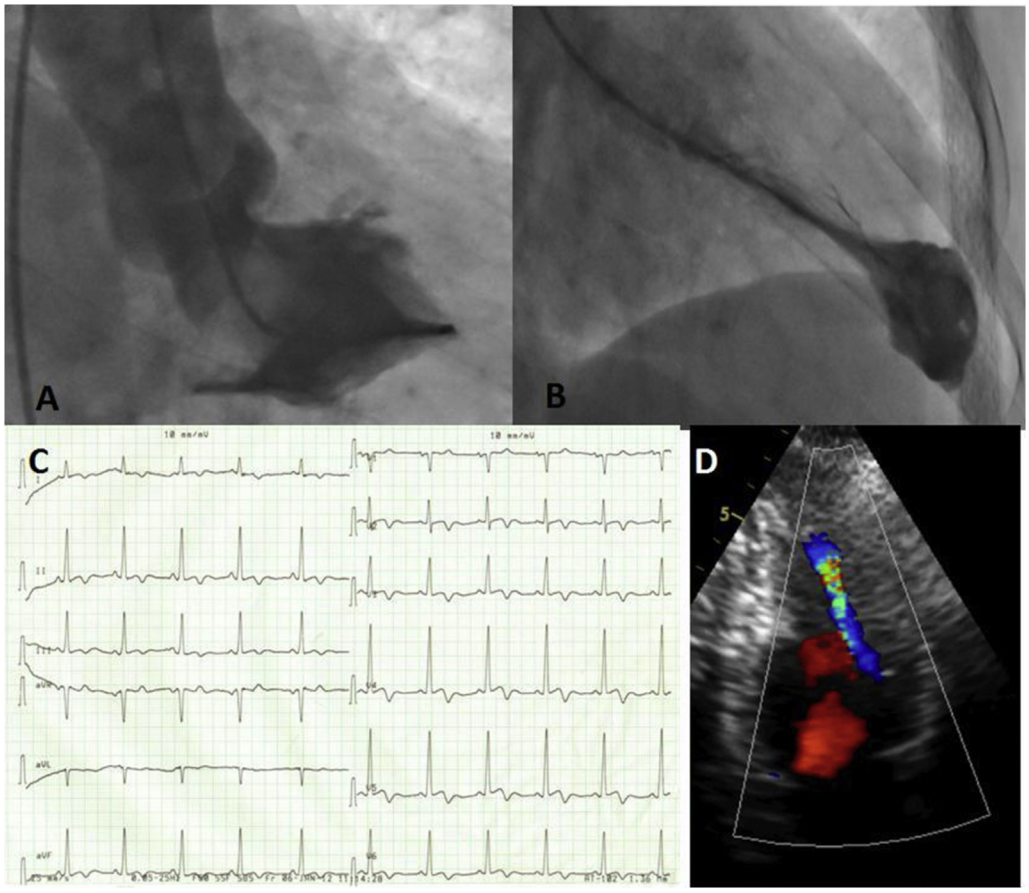

Fig. 2 – An example of hypertrophic cardiomyopathy patient with easily missed apical aneurysm diagnosis. Left ventriculogram showing the ace of spades configuration suggesting the apical hypertrophic cardiomyopathy without apical aneurysm (A); however, the left ventriculogram from the apical segment taken from the same patient showing the true apical aneurysm (B). This patient has an inferolateral T wave inversion with "ST elevation" on electrocardiogram (C). Echocardiogram showing a diastolic paradoxic jet flow (arrow) across the obliterated left ventricular apex toward the base (D).

an apical aneurysm may be due to ventricular arrhythmias.[3,4,19] However, the management of this subset of HCM is controversial, in part because patients may range from being asymptomatic to having life-threatening ventricular arrhythmias and SCD. Some authors report that the ventricular arrhythmias complicated with left ventricular apical aneurysm cannot be easily suppressed by medication, and suggest that a more-aggressive therapeutic approach, including medication, implantable cardioverter-defibrillator placement, cryoablation at the rim of the aneurysm and surgery by complete excision of the scar tissue and obliteration of the aneurysmal pouch to prevent SCD in selected patients with large or thin-walled aneurysms, must be considered.[20,21] On the other hand, others do not recommend prophylactic surgical resection despite the marked thinning of the aneurysm wall due to low risk of ventricular rupture.[5] In addition to arrhythmic features, cerebrovascular events also have been found to be frequent in this subset of HCM.[5] Therefore, presence of an apical aneurysm in a patient with HCM must be evaluated.

Echocardiography is the most common diagnostic tool used to evaluate the morphologic and functional features of HCM,[22] but has some limitations particularly in apical variants. Some echocardiographers miss the diagnosis of apical thickening if the apex is not clearly seen, or if a thickened apex is mistaken for apical foreshortening on planar imaging, necessitating the use of CMR modality[23] or contrast echocardiography[24] in patients in whom initial echocardiographic studies are nondiagnostic.[25]Even with left ventriculogram, the apical aneurysm could be missed (Fig 2A) unless it could not performed within the aneurysm (Fig 2B). In the presence of MVO, there is a significant intraventricular pressure gradient between the apex and the main left ventricular cavity. This systolic gradient, sometimes associated with a diastolic paradoxic jet flow on echocardiography (Fig. 2D, Video 3),[4,26] indicates the existence of a discrete apical chamber or a true apical aneurysm.[10,17] However, this diastolic paradoxical jet flow across the obliterated left ventricular apex toward the base can not always be detected by transthoracic echocardiography. In one study, it was present in 10% of patients with HCM.[26] Moreover, the intraventricular pressure gradients are present at rest in only one third of apical aneurysm patients.[5] For these reasons, there are reports of challenging clinical and surgical cases in literature due to overlooked or misdiagnosed

cases particularly between the MVO-HCM and ACM with a small non-obliterated area in ACM.[2,3,10,27]

Supplementary video related to this article can be found at http://dx.doi.org/10.1016/j.ihj.2015.05.019.

Although echocardiographic image enhancement with an intravenous contrast agent[24] and CMR[23] have been shown to improve the visualization of the endocardial–blood interface, clinical attention must be drawn to the unique electrocardiographic features that provide the initial clues to making the diagnosis. In present study, we found that STE in V4-6 derivations in addition to classically giant T wave inversion were well correlated with the presence of apical aneurysm in HCM patients. As many as half of patients with ACM are mildly symptomatic or asymptomatic, and many patients have been diagnosed only when giant negative T waves in the left precordial leads are noted incidentally on ECG.[8,23] However, it is also reported that this giant negative T waves may evolve in both positive and negative directions over time.[9,28] Transition from normal T waves to negative T waves can occur acutely or this process can take several years and usually remains unchanged thereafter. On the other hand, the disappearance of negative T waves may also occur slowly and progressively in patients, in whom apical aneurysm had developed.[8,9] Investigators have suggested that the progression of myocardial disease in the left ventricular apex could be a mechanism for the disappearance of negative T waves. However, the precise mechanism for these electrocardiographic changes remains to be determined. The mechanisms contributing to the formation of apical aneurysms in HCM are multiple and still to be clarified. Possible causes include the increased afterload and high apical pressure, ventricular remodeling, the increased oxygen demand due to increased myocardial thickness and decreased oxygen supply due to the decreased capillary network and apical myocardial infarction.[3,29] Maron et al showed that ST-T abnormalities were more prevalent in the patients with the involvement of substantial portions of both the ventricular septum and anterolateral LV free wall than in those with the isolated involvement of the anterior septum, posterior septum, or apical region.[30] They also reported that, 13 patient had the initial convex STE with negative T waves in lateral leads among the 28 apical aneurysm patients.[5] There were only two patients who had an STE in V4-6 without having apical aneurysm in literature[31,32]; however, one of them has no CMR data, so a conclusion about the absence of an aneurysm can not be made definitively. Similar to dynamic T wave changes associated with formation of apical aneurysm, some reported that STE during follow-up of HCM patients has also been associated with the development of an apical aneurysm.[14,33] In another case report, transformation of previous ST depression to ST segment normalization with concomitant disappearance of negative T wave was reported to be associated with the development of an apical aneurysm. Currently available studies report controversial results regarding resting ECG findings and prognosis in HCM. Haghjoo et al has reported ST-segment depression in the high lateral leads to be of prognostic significance in HCM patients in addition to generally accepted risk factors.[34] Furushima et al reported that the electrical storm was more common in patients with STE in precordial leads V4–V6,[18] and Maron et al reported that more than 40% of the HCM patients with an apical aneurysm presented with bursts of nonsustained monomorphic ventricular tachycardia on Holter electrocardiograpy.[5]

In conclusion, the 12-lead electrocardiography has traditionally been an integral part of the non-invasive evaluation of HCM patients. Clinicians and specifically echocardiographers must pay special attention on the electrocardiography to correctly detect the frequently overlooked apical aneurysm in HCM patients, and should be careful for apical aneurysm in the presence of STE in V4-6 derivations. This may be particularly useful when the left ventricular apical characteristics are not clearly defined due to technical challanges during basic transthoracic echocardiography.

Conflicts of interest

All authors have none to declare.

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