

# Hypertrophic cardiomyopathy in Saudi Arabian population: Clinical and echocardiographic characteristics and outcome analysis



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**Background:** Current published literature on hypertrophic cardiomyopathy (HCM) comes primarily from Western populations. There is no published data on clinical and echocardiographic characteristics and long-term outcome of HCM in an Arab population.

**Methods:** We conducted a retrospective analysis of all patients 16 years or older diagnosed with HCM at our institution. Detailed clinical and echocardiographic data were collected and outcome was analyzed.

**Results:** A total of 69 patients were identified as having HCM. The mean age was  $42 \pm 16$  years with 71% male patients. All patients were Saudi citizens with Arab ancestry. Details about family history and presenting symptoms were available for 44 and 48 patients consecutively. Nine (18%) patients were asymptomatic and were diagnosed based on abnormal cardiac auscultation. The commonest presenting symptoms were dyspnea with or without chest pain and palpitations occurring in 40 (81%) patients. Only 4 (9%) of 44 patients had a family history of HCM and /or sudden cardiac death (SCD). The most common ECG abnormality was left ventricular hypertrophy (LVH) present in 60 (86%) patients. The commonest septal hypertrophy morphology was mid-septal (catenoid) in 30 (43%) followed by neutral in 23 (33%), basal septal (sigmoid) in 3 (4%) and apical in 6 (8%) patients. Twenty (28%) patients had evidence of resting left ventricular cavity gradient of  $\geq 30$  mmHg. Eleven (16%) patients had evidence of biventricular hypertrophy. Left ventricular ejection fraction was normal in 65 (94%) patients. Over a median (25–75 percentile) follow-up of 7 years (4.5–10), only 3 patients died, all of non-cardiac causes. There were no cases of SCD during the follow-up period. Six patients required an implantable cardioverter-defibrillator (ICD); five for primary prevention and one for secondary prevention. Only 1 patient progressed to end stage dilated cardiomyopathy.

**Conclusion:** The natural history of hypertrophic cardiomyopathy in the Saudi population appears to be benign with catenoid morphology being the most common septal hypertrophy pattern. Risk of SCD appears to be quite low in this population.

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**Keywords:** Hypertrophic cardiomyopathy, Echocardiography, Septal morphology, Outcome

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## Introduction

**H**ypertrophic cardiomyopathy (HCM) is an autosomal dominant familial disease due to mutations of the myocardial sarcomeric contractile proteins and occurs all over the world across all races [1,2]. Hypertrophic cardiomyopathy is defined by the presence of significant left ventricular hypertrophy (LVH) in the absence of secondary factors like systemic hypertension and aortic stenosis [1]. The reported prevalence in the West is about 0.2% or 1:500 in the general population [3]. Hypertrophic cardiomyopathy is a diverse disease with variable phenotypic expression (i.e. LVH pattern) with a substantial percentage of patients living a normal life without any significant limitation and minimal risk of sudden cardiac death (SCD) [4–8]. However, some patients will have significant symptoms including dyspnea, chest pain, syncope leading to substantial morbidity as well as mortality reported to be as high as 3–6% [6]. The most feared complication of HCM is SCD due to ventricular arrhythmias though it has been reported to occur in only 0.1–1% of patients [5]. This apparent discrepancy between incidence of SCD in different studies has been attributed to selection bias in tertiary care centers [9]. The pattern of left ventricular hypertrophy is quite variable in HCM and is associated with difference in morbidity and mortality. For instance, it has been reported that apical HCM in the Japanese population as well as those in North America is associated with mostly benign outcome [10,11]. The most common pattern of LVH is asymmetric septal hypertrophy involving the basal anterior septum as well as anterior free wall [12]. Despite initial reports of a close relationship between septal morphology and hemodynamics in HCM, there has been no reported association between the patterns of hypertrophy and survival [13]. Recently several groups have reported an association of the septal morphology and sarcomeric mutation by genotypes that may help in better risk assessment and management of patients with HCM [14,15]. Resting left ventricular outflow tract obstruction (LVOTO) has been shown in some studies to be an independent predictor of subsequent heart failure and death [16]. Nearly all of the current published data on HCM comes from Western populations. A PUBMED search failed to show any published clinical or epidemiological study of HCM in the Arab/Middle Eastern population. We sought to look at the clinical and echocardiographic characteristics and outcome of HCM in the Saudi population.

## Abbreviations

HCM	hypertrophic cardiomyopathy
SCD	sudden cardiac death
ICD	implantable cardioverter-defibrillator
LVH	left ventricular hypertrophy
LVOT	left ventricular outflow tract
A4	apical four-chamber
PLAX	parasternal long axis
DT	deceleration time
Sa	lateral and septal mitral annular systolic velocity
Ea	lateral and septal mitral annular early diastolic velocity
Aa	lateral and septal mitral annular late diastolic velocity
IVRT	isovolumetric relaxation time
Ar-A	difference (in milliseconds) between atrial systolic flow reversal in pulmonary veins and mitral A-wave duration
SAM	systolic anterior motion of mitral leaflet
MR	mitral regurgitation
ECG	electrocardiogram
VT	ventricular tachycardia
LVEF	left ventricular ejection fraction
LVOTO	left ventricular outflow tract obstruction
CMR	cardiac magnetic resonance

## Materials and methods

We retrospectively identified all patients between the ages of 16–80 years who were diagnosed with hypertrophic cardiomyopathy from an echocardiographic database between January 1997 and January 2007. HCM was diagnosed based on echocardiographic evidence of LVH  $\geq 15$  mm or between 12 and 15 mm in presence of family history of HCM. Patients with secondary causes of LVH like systemic hypertension and aortic stenosis or diagnosed infiltrative cardiomyopathy were excluded. Detailed baseline clinical characteristics including family history of HCM, presenting symptoms, ECG abnormalities and echocardiographic parameters were recorded. Patients were followed up for a median (25–75 percentile) of 7 (4.5–10) years in out-patient clinic or via telephonic contact in case of missed appointments. Primary end point was cardiac mortality as a result of SCD or progressive heart failure. Secondary outcome was all cause mortality. The study was approved by the institutional review board.

## Echocardiographic data

Standard views were obtained using Philips iE-33 (Phillips Healthcare, Andover, MA (USA)) and GE vivid E9 (GE Healthcare, USA). Two dimensional (2-D), M-Mode, color Doppler echocardiog-

raphy was performed in accordance with American Society of Echocardiography recommendations [17]. All echocardiograms were reviewed by two reviewers (NA, WA). Based on apical four-chamber (A4) and parasternal long axis (PLAX) views, we assessed the location and extent of the septal hypertrophy at the basal, mid and apical segments using 2-D image. If the 2-D image was suboptimal, M-Mode image was used. Right ventricular hypertrophy (RVH) was diagnosed as right ventricular free wall thickness of  $>0.5$  cm measured in subcostal or PLAX 2-D or M-Mode image. As suggested by Turer et al., the septal morphology was classified into the following four groups [15]:

- Sigmoid septum: maximal thickness in the basal anterior septum (Fig. 1).
- Catenoid: maximal thickness in the mid septum (Fig. 2).
- Neutral: uniform thickness of the septum with ratio of maximal septal wall thickness in each septal segment of  $\geq 0.8$  (Fig. 3).
- Apical: maximum thickness in the apical septum (Fig. 4).

Detailed Doppler indices were recorded. These included peak early (E) and late (A)

transmitral velocities, E/A ratio, deceleration time (DT), lateral and septal mitral annular systolic (Sa), early diastolic (Ea) and with atrial contraction (Aa) velocities, isovolumetric relaxation time (IVRT), difference (in milliseconds) between atrial systolic flow reversal in pulmonary veins and mitral A-wave duration (Ar-A). For calculating E/Ea ratio, we used the average (of lateral and septal annulus) Ea velocity. Left atrium (LA) volume was measured using the area length method and indexed to body surface area (BSA). The presence or absence of resting LVOT obstruction based on modified Bernoulli equation, systolic anterior motion of mitral leaflet (SAM) and presence of mitral regurgitation (MR) were quantified. Electrocardiogram (ECG) diagnosis of LVH was based on established criteria [18].

### Data analysis

Continuous variables with normal distribution were expressed as the mean  $\pm$  SD and median (25 and 75 percentile) when the distribution was not normal. When comparing groups the inde-

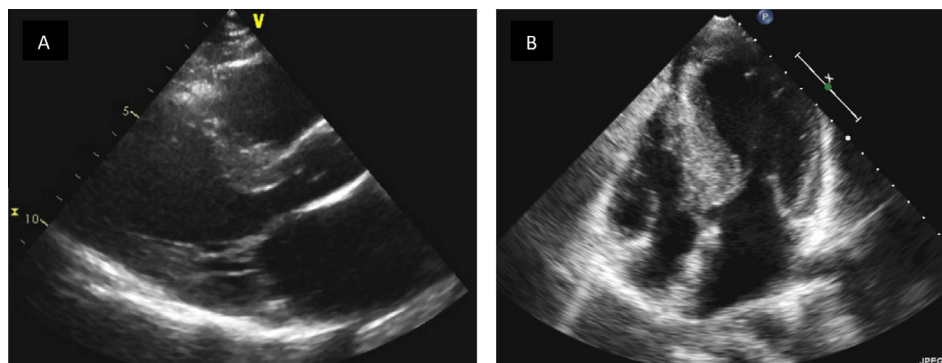


Figure 1. Parasternal long axis (A) and apical 4-chamber view (B) of sigmoid septal morphology.

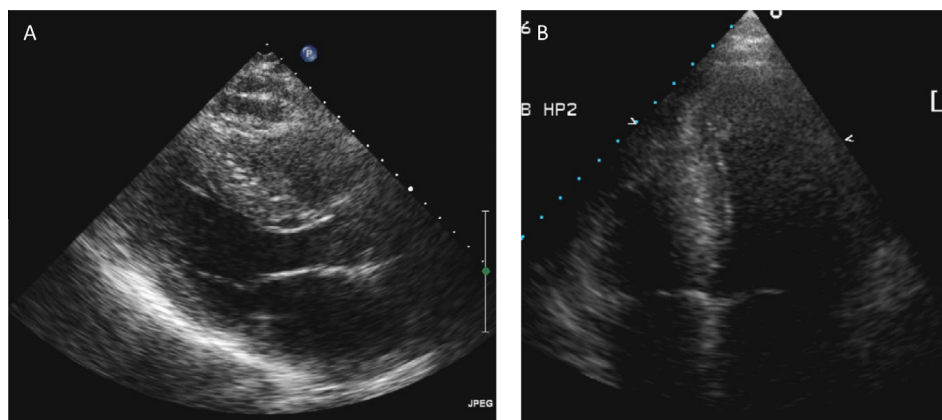


Figure 2. Parasternal long axis (A) and apical 4-chamber (B) view of catenoid (mid septal) morphology.

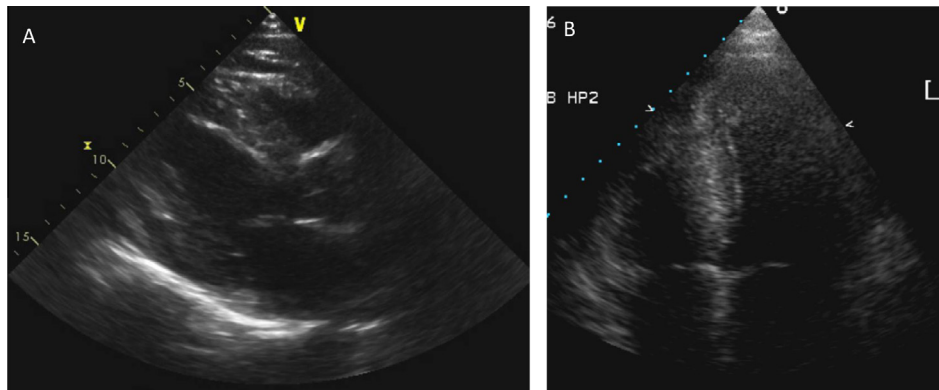


Figure 3. Parasternal long axis (A) and apical 4-chamber (B) view of neutral septal morphology.

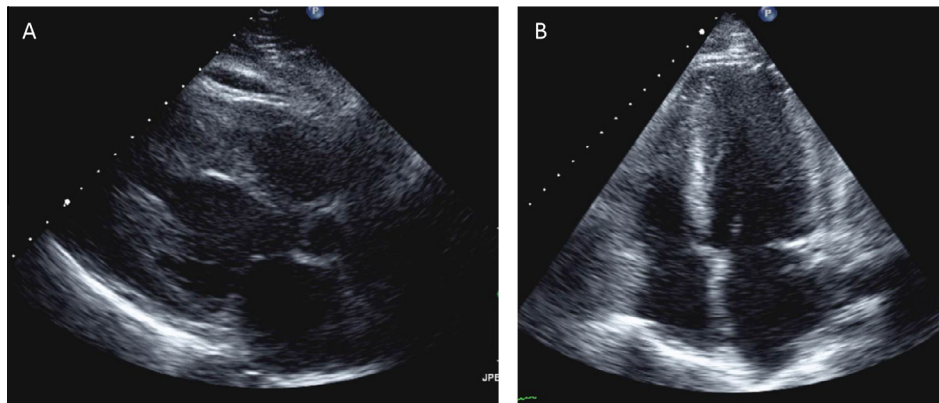


Figure 4. Parasternal long axis (A) and apical 4-chamber view (B) of apical septal morphology.

pendent samples *t*-test (2-tailed) was used to compare continuous data or Mann–Whitney test when appropriate and the Fisher’s exact test to compare proportions. A *P* value <0.05 was considered statistically significant.

## Results

A total of 69 patients were included in the study. Table 1 shows the clinical characteristics of the study population. Details about family history and presenting symptoms were available for 44 and 48 patients respectively. Only 5 (11%) patients had family history positive for HCM. Of a total of 48 patients, the most common presenting symptom was dyspnea alone or with additional symptoms like chest pain and palpitations, which occurred in 40 (83%) patients. Eight (16%) patients were asymptomatic. Only 2 patients presented with syncope and 1 of them was found to have evidence of non-sustained ventricular tachycardia (VT) on 24-hour Holter monitor. After a mean follow-up of 7 (4.5–10) years, there were no reports of sudden cardiac death. A total of 6 (8.6%) patients

Table 1. Clinical data.

Age (years)	42 ± 16
Male gender (%)	71
Atrial fibrillation (%)	15
Years follow-up after diagnosis	7 (4.5–10)
Family history ( <i>n</i> = 44)	
No history (%)	86
Hypertrophic cardiomyopathy (%)	5
Sudden death (%)	9
Symptoms ( <i>n</i> = 48)	
Dyspnea (%)	65
Syncope (%)	4
Palpitation (%)	10
Miscellaneous (%)	2
No symptoms (%)	18

Values are mean ± SD for variables with a normal distribution and median (25 and 75 percentile) for variables with a nonparametric distribution.

received an implantable cardioverter-defibrillator (ICD), 5 for primary prevention (presence of risk factors for sudden death) and 1 for secondary prevention. Four of these 6 (i.e. 66.6%) had catenoid morphology, 1 had sigmoid and 1 had neutral. Only 1 patient progressed to end stage dilated

Table 2. Echocardiography data.

Left ventricular ejection fraction (%)	68 ± 13
Septal thickness (mm)	21 ± 6.9
Posterior wall thickness (mm)	13 ± 3.7
Left atrial volume index (ml/m <sup>2</sup> )	34 (27-54)
E/A ratio	1.5 (0.9-2.1)
Deceleration time (ms)	219 ± 67
Isovolumic relaxation time (ms)	79 ± 29
Ar-A ≥ 30 ms (%)	23
Sa (cm/s)	7.5 ± 2.9
Left ventricular outflow obstruction (≥30 mmHg, %)	28
Septal morphology	
Neutral (%)	36
Catenoid (%)	42
Sigmoid (%)	12
Apical (%)	10
Biventricular hypertrophy (%)	16
Severe MR	7
Systolic anterior motion	39

Values are mean ± SD for variables with a normal distribution and median (25 and 75 percentile) for variables with a nonparametric distribution. Sa: highest lateral or septal mitral annular systolic velocity; Ar-A: difference (in milliseconds) between atrial systolic flow reversal in pulmonary veins and mitral A-wave duration.

cardiomyopathy requiring left ventricular assist device, however he died due to infectious complication prior to cardiac transplant. There were 2 additional non-cardiac deaths (due to renal failure and non-Hodgkin's lymphoma). Table 2 shows the echocardiographic findings in the study population. The most common septal morphology pattern was catenoid and neutral that accounted for 78% of the patients. ECG criteria for LVH were present in 60 (85.7%) patients. Paroxysmal atrial-fibrillation was noted in 10 (15%) patients. Six (8.5%) patients had normal ECG. Left ventricular ejection fraction (LVEF) was normal or super normal (i.e. ≥70%) in 65 (94%) patients and was between 40% and 50% in 4 (5%) patients. Forty-two patients (61%) had enlargement of the left atrium. Prolonged reversal in the pulmonary vein (Ar-A)

was a common finding indicating increased LV end-diastolic pressure. Systolic anterior motion (SAM) of the mitral valve was found to be present in 27 (39%) patients. Resting LVOT gradient (≥30 mmHg) was seen in 20 (28%) patients. Interventricular septum (IVS) was >30 mm in diameter in 4 patients. Of these 4, 2 had no left ventricular outflow tract obstruction (LVOTO) and 1 had LVOTO of 64 mmHg and 1 with 22 mmHg. Only 1 of these 4 patients with severe LVH had SAM. Thirty four (49%) patients had mild MR, 10 (14%) had moderate, 5 (7%) had severe and 19 (27%) had no MR. Table 3 shows a comparison between clinical and echocardiographic characteristics of patients with catenoid and neutral septal morphology. There were no significant differences between the two patterns of septal hypertrophy regarding age at presentation, gender, symptoms, LVEF, septal thickness and presence of LVOTO. The majority of our patients was either already on beta-blockers at the time of diagnosis or was placed on beta-blockers and/or calcium channel blockers after diagnosis was established. Only 1 patient was on amiodarone. There were no patients on disopyramide.

## Discussion

We have presented the first study on the clinical and echocardiographic characteristics and long-term outcome of Arab HCM patients. The early Western literature of higher morbidity and mortality in HCM patients was primarily from specialized HCM centers and hence subject to selection bias. Subsequent studies looking at the outcome of HCM in more general population have shown that the majority of patients with HCM have a benign course. Although our hospital is a tertiary care medical center, our study population showed similar benign outcome. The majority of our patients had cardiac symptom including predomi-

Table 3. Comparison between neutral and catenoid pattern of septal hypertrophy.

	Neutral (n = 25)	Catenoid (n = 29)	P value
Age (years)	43 ± 18	41 ± 16	0.71
Female gender (%)	28	38	0.57
Family history (%)	20	0	0.27
Dyspnea (%)	73	62	0.72
Left ventricular ejection fraction (%)	66 ± 16	69 ± 10	0.36
Septal thickness (mm)	20 ± 8	22 ± 6	0.41
Posterior wall thickness (mm)	13 ± 4	13 ± 4	0.48
Left atrial volume index (ml/m <sup>2</sup> )	32 (21-53)	34 (30-59)	0.20
Left ventricular outflow obstruction (%)	24	38	0.38
LVOT Gradient (mmHg)	61 (47-64)	30 (24-64)	0.35

LVOT: Left ventricular outflow tract.

nantly dyspnea as well as chest pain and palpitations; still there were no reports of SCD in this study population, which is quite reassuring.

Despite being from a completely different ethnic population, Arab patients also presented with catenoid morphology as the commonest hypertrophy pattern similar to western population [15]. This may also have been influenced by the fact that the average age in our study sample was 42 years, and young age has been reported to be associated more with catenoid morphology [14]. Turer et al. [15], in their study, reported that ICD implantation only occurred in patients with catenoid morphology mostly for primary prevention. Our study also showed that 66.6% of ICD's were implanted in catenoid morphology for primary prevention. Though Turer et al. reported more advanced diastolic dysfunction in patients with catenoid pattern, we did not find any statistically significant differences in clinical or echocardiographic findings between the two predominant septal morphological patterns i.e. catenoid and neutral morphology. The septal morphological classification as suggested by Turer et al. [15] and other groups [14] may have clinical utility because of the close association of catenoid morphology with sarcomeric mutations, LGE on cardiac magnetic resonance (CMR) imaging and that can help selecting patients who should be referred for further genetic testing since LGE on CMR has been linked to increased ventricular arrhythmias in HCM patients [14]. It is increasingly been recognized that there is value in performing CMR in all patients with HCM for better risk stratification of patients who are at risk for ventricular arrhythmias [19].

Resting ECG suggested the presence of LVH in 85.7% of patients. Since most patients in Saudi Arabia are primarily seen by an internist at their local Ministry of Health hospital, ECG can be a valuable simple tool to detect HCM in asymptomatic or mildly symptomatic non-hypertensive patients who can then be referred to tertiary care centers for further evaluation and management.

Although initially it was thought that all patients with HCM have some degree of LVOT obstruction, latest literature suggests that only one third of patients with HCM have resting LVOT obstruction (defined as gradient  $\geq 30$  mmHg) with an additional one third having the non-obstructive form of HCM [20]. Our data suggests similar findings. Standard Doppler echocardiographic parameters for grading the severity of diastolic dysfunction are considered to be not as valuable in HCM patients as in other patients with cardiac

disorders [21–23]. Nearly all patients with HCM have some degree of diastolic dysfunction. In the present population, dyspnea and enlargement of the left atrium was a common finding indicating increased LV filling pressure.

Most of our patients required only beta-blockers or calcium channel blockers with only 5 (7%) requiring myomectomy for symptomatic relief.

## Limitations

Our study has several limitations. It is a retrospective study. It represents a single referral center cohort and hence may not accurately reflect HCM characteristics in the general Arab population. However, the benign course in this referred and hence somewhat biased population suggests that HCM outcome in general population is perhaps even better. Patients with systemic hypertension were excluded from the study because this might explain the observed LV hypertrophy. Systemic hypertension is a common diagnosis in the population undergoing an echocardiographic investigation and it is conceivable that some of the patients excluded due to hypertension might have HCM.

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