Phenotype, genotype and prognosis of Apical Hypertrophic Cardiomyopathies: A French multicentric cohort.

Hélène Martel[1], MD, Claire Lucas[1], MD, Hamza Benjelloun[2], MD, Grégoire Stolpe[1], MD, Julien Mancini[2], MD, PhD, Nicolas Michel, MD, Elsa Conte[1], , MD, Victor Morel[3], MD, Albert Hagege[4], MD, PhD, Patricia Réant[5], MD, PhD, Erwan Donal[6], MD, PhD, Jean-Christophe Eicher[7], MD, PhD, Karine N'Guyen[3], MD, PhD, Gilbert Habib[1], MD, PhD.

[1]AP-HM, La Timone Hospital, Cardiology Department, Marseille, France
[2]Aix-Marseille Univ, INSERM, IRD, AP-HM, SESSTIM, ISSPAM, Public Health Department, La Timone Hospital, BIOSTIC, Marseille, France
[3] AP-HM, La Timone Hospital, Department of Medical Genetics, Marseille, France
[4] AP-HP, Hôpital Européen Georges Pompidou, Cardiology Department, Paris, France
[5] CHU Bordeaux, Hôpital Haut-Lévêque, Cardiology Department, Bordeaux, France
[6] CHU Rennes, Hôpital Pontchaillou, Cardiology Department, Rennes, France
[7] CHU Dijon Bourgogne, Hopital Francois Mitterand, Cardiology Department, Dijon, France

Address for Correspondence:
Professor Gilbert Habib
Service de Cardiologie, Hôpital La Timone Boulevard Jean Moulin 13005 Marseille, France
Telephone: +33491387588 Fax: +330491474377 E-Mail: gilbert.habib3@gmail.com

Abstract :

Background: Apical hypertrophic cardiomyopathies (ApHCM) are characterized by hypertrophy located on the left ventricular (LV) apical segments. Their genetic origin and prognosis are still debated.

Aim: We compared the phenotype, genotype and prognosis of ApHCM to non-apical HCM.

Materials and methods: 208 consecutive patients from 5 French centres with a phenotype of ApHCM underwent echocardiography, cardiac magnetic resonance, genetic testing and follow-up. They were compared to 419 patients with non-apical HCM. Patients finally diagnosed with Fabry's disease (n=6) and amyloidosis (n=1) were excluded, resulting in 201 ApHCM for comparative analyses.

Results: Among the 208 ApHCM patients, genetic analysis was positive in 22.6% of patients, including 6 GLA and 1 TTR mutations. After excluding these latter 7 patients, ApHCM patients had higher LVEF, less LV obstruction (5 vs 23.2%, $p<0.001$), smaller left atrial volumes (37.9±14.2 vs 47.2±23.8 ml/m^2, $p<0.001$), more impaired GLS (-14.4±4 vs -15.3±4%, $p=0.019$), more frequent LV aneurysm (10.9 vs 1.4%, $p<0.001$), and less frequent mutations (20.4 vs 43.4%, $p<0.001$) than non-apical HCM. During a 5-year follow up, 12 (6%) rhythmic events occurred in the ApHCM group. All of them had a SCD-risk score<4%. Long-term survival was better in ApHCM ($p=0.026$).

Conclusion: ApHCM presents with less frequent mutations and better prognosis than non-ApHCM. However, rhythmic complications are frequent in ApHCM but are not predicted by the SCD-risk score. Apical aneurysms are more frequent in apical HCM. Fabry's disease may mimic an apical HCM phenotype and should be ruled out when facing an apical HCM pattern.

Key words : Apical Hypertrophic Cardiomyopathy – Genetic – Echocardiography – CMR – aneurysm

Introduction

Apical hypertrophic cardiomyopathy (ApHCM) was first described in 1976 by *Sakamoto* and al (1) as a subtype of HCM with a myocardial hypertrophy located on the left ventricular (LV) apical segments associated with deeply negative T waves on electrocardiogram. Few authors had focused on this rare disease which represents 3 to 10% of the "classical sarcomeric HCM" on caucasian population (2, 3).

Some authors differentiated "pure" ApHCM, in which hypertrophy is confined to the apex, from "distal" ApHCM, with hypertrophy extending to the midventricular level, clearly sparing the basal segments (4, 5), or "mixed" ApHCM defined as hypertrophy located both at the apex and other segments, but with hypertrophy predominating in the apical segments (6-8).

To date, only few studies analyzed the sarcomeric protein gene mutations associated with ApHCM (4, 8, 9, 10). They found a low efficiency of genetic analysis (with small panel of 9 to 12 genes analyzed) and mutations generally occurred in genes encoding for proteins of the thick sarcomere filament (MYH7 and MYBPC3 genes).

Although patients with ApHCM have been associated with good prognosis (1, 6, 11, 12), apical aneurysms, frequent in this population, are one of the main factors associated with ventricular arrhythmias (13, 14) and thrombo-embolic events (5, 6).

The purpose of our study was to describe phenotype, genotype and prognosis of ApHCM in a large French multicentric cohort and to compare them to non ApHCM.

Methods

Study population.

Patients were retrospectively included between 2011 and 2021 in 5 French tertiary referral centers in the university hospitals of Marseille, Bordeaux, Paris, Rennes and Dijon. All participating centres are tertiary/reference cardiomyopathy centres, part of the French cardiomyopathy network (Cardiogen), with broadly similar HCM management and follow-up approach.

All patients with apical HCM were consecutively included. They underwent comprehensive clinical examination, electrocardiogram, a trans-thoracic echocardiography (TTE), and genetic testing at inclusion. Most of them also underwent cardiac magnetic resonance imaging (CMR), and 48 hours Holter monitoring. CMR studies included measurements of left ventricular ejection fraction, presence of a LV aneurysm, and presence and visual quantification of late

gadolinium enhancement (LGE). Replacement fibrosis was assessed by CMR LGE, and was considered extensive when representing more than 15% of the left ventricular mass.

Diagnostic criteria.

The diagnosis of ApHCM was made by 2-dimensional echocardiography and CMR, based on the presence of left ventricular thickness > 15 mm (or ≥13 mm in patients with family history of HCM) (15) predominant on the apical segments that was not solely explained by abnormal loading conditions (uncontrolled arterial hypertension excluded). Obstruction was considered present when the resting or provoked peak gradient was ≥ 30 mmHg and the threshold for establishing a relationship with symptoms was ≥50 mmHg (15). Thus, three different ApHCM patterns were distinguished as previously defined: the "pure" ApHCM, with hypertrophy limited to the apical segments, the "distal" ApHCM, with hypertrophy extending to the midventricular level, sparing the basal segments and the "mixed" form with hypertrophy predominant in the apex but which could be present in basal segments (**Figure 1).** Left ventricular apical aneurysm was defined as a discrete thin-walled dyskinetic or akinetic segment of the most distal portion of the left ventricle. (15) No core-lab review was performed, neither for echocardiographic nor for CMR studies.

Genetic testing.

Patients underwent heterogenous genetic test for HCM since recommendation changed over the time of the study. They were tested from 5 sarcomeric protein genes to 167 genes (16) including in all patients Fabry's disease (GLA) and the Transthyretin gene (TTR). Mutations were considered pathogenic if they were class 4 (likely pathogen) or class 5 (pathogen). Indeed, we did not classify patients with VUS as having a positive genotype.

Prognostic analysis and design of the study

Major cardiac rhythmic events were defined as sustained ventricular arrhythmias, recovered sudden cardiac death, or cardiac death. Other rhythmic events included defibrillator implantation, non-sustained ventricular tachycardia, and supra ventricular arrhythmia. Other events included stroke, cardiac thrombus, and myocardial infarction.

We compared our cohort of ApHCM to a multicentric cohort of 419 consecutively included sarcomeric non ApHCM to assess differences of prognosis in this subtype of patients. The

patients finally diagnosed with Fabry's disease (n=6) and with amyloidosis (n=1) were excluded from the comparison between apical and non-apical HCM. Sixteen patients (14 with ApHCM and 2 with non-apical HCM) were excluded from survival analyses because date of diagnosis, last follow-up or event occurrence was not available. Other patients lost to follow-up were censored at the time of last information available. ESC SCD risk score at 5 years was calculated for each patient (17, 18) to assess the need for defibrillator implantation, but the final decision of ICD implantation was an individual decision by the treating center, who reported the main reason for ICD implantation in their patients.

Statistical analysis

Categorical variables were expressed as absolute counts (%) and compared using χ^2 or Fisher's exact test. Continuous variables were expressed as mean ± SD) and compared using t-tests or ANOVA. To study the risk of cardiac death after diagnosis, Kaplan-Meier survival curves were plotted and compared using log-rank test. The median follow-up was estimated using reverse Kaplan-Meier method. For all two-sided analyses, a $p < 0.05$ was considered statistically significant. All analyses were conducted using R 4.3.1 software (The R Foundation for Statistical Computing Platform, Vienna, Austria).

Results

Description of the apical HCM population *(n=208)*

Between 2011 and 2021, 208 patients were retrospectively included in the 5 centers (mean age: 53.1 ± 13.4 years, 69.2% male). There were no patients of Japanese origin in the study population. 96% of them had abnormal ECG with apical negative T waves and 30 % LV hypertrophy. Seventy-two patients (34.6%) were symptomatic at diagnosis: 14 had syncope, 16 had chest pain, 14 had dyspnea, 23 had palpitations, 5 had strokes, 1 recovered a sudden cardiac death. Eighteen patients (8.6%) were on supra ventricular arrhythmia at diagnosis.

All patients had an echocardiography (TTE) and 178 patients (85.6%) also underwent a CMR. Mean LV maximal wall thickness was 17.4 ± 3.1 mm on TTE and 18.0 ± 3.1 mm on CMR, respectively. We distinguished 3 populations as previously described of ApHCM: 53 (25.4%) pure ApHCM, 99 (47.6%) distal ApHCM and 56 (26.9%) mixed ApHCM. LV function was normal in TTE and CMR, except 2 patients with a LVEF <50%), but mean global longitudinal strain (GLS) was impaired at TTE (-14 ± 4%). Moreover, 9% of the patients had a restrictive filling pressure pattern. Eight patients (3.4%) had midventricular obstruction. On CMR, 63.9%

of patients had LGE and 23.1% had more than 15% of LGE. We found 23 (11.1%) LV aneurysms and 4 LV thrombi. Among the 23 patients with LV aneurysms identified by echocardiography, 22 also underwent CMR, with confirmation of the aneurysm in all. ***Table 1*** **presents the baseline characteristics of the 201 patients with apical HCM after exclusion of the 7 patients finally diagnosed with Fabry's disease (n=6) or with amyloidosis (n=1).**

Genetic findings

Genetic counselling revealed that 23.4% (n=43) were familial cases. A pathogenic mutation (class 4 or 5) was identified in 47 (22.6%) patients. Pathogenic mutations were identified on the following genes: MYBPC3 (n=16); MYH7 (n=11); GLA (n=6); TNNT2 (n=4); MYL2 (n=3). We noticed a double pathogenic mutation on MYBPC3 plus MYH7 and one TTR mutation (**Figure 2).**

Comparison between ApHCM and non-ApHCM (n=201) table 2)

We compared the ApHCM cohort, excluding the 6 cases of Fabry's disease and the patient with amyloidosis (n = 201) to a multicentric cohort of patients with non-apical HCM (n= 419). The major result was that there were significantly less pathogenic mutations in ApHCM cohort than in non-apical HCM cohort: 20.4% vs 43.4%, p <0.001 (Pearson's Chi-squared test). ApHCM patients were less dyspneic (43.8% vs 49.4%, p = 0.003) and had more hypertension (40.3% versus 28.6%, P=0.006). On TTE, LVEF was higher among ApHCM patients, the myocardium was thinner, patients were less obstructive, LAV were smaller, and GLS was more impaired. On CMR, there was no difference between the number of patients with LGE, but ApHCM patients had less extensive LGE (defined as LGE> 15%). As in TTE, LV wall was thinner. Finally, ApHCM patients had more LV aneurysms (10.9% versus 1.4%, P value <0.001) (**Table 2).**

Comparison between sub-types of ApHCM (n=201)

The 3 sub-groups of ApHCM were compared, excluding the 6 cases of Fabry's disease and the patient with amyloidosis (n = 201) (Table 3). The most frequent type was distal apical HCM (49%). The main differences between these 3 sub-types of ApHCM were: less frequent syncope, lower LVEF (p =0.008), and more frequent LGE (p= 0.022) in distal ApHCM. Concerning genetics, a pathogenic mutation was found in 12% (n=6) of pure ApHCM, 25.6% (n=25) of distal ApHCM, and 18.9% (n=10) of mixed ApHCM (p= 0.111).

Comparison of ApHCM with genetic positive versus genetic negative.

On an additional analysis, we also compared the genotype-positive patients with those who were found to have a negative genotype. The only difference observed was that patients with positive testing were younger at diagnosis (54.7 ± 16 versus 47.4 ± 15, P=0.009) and had more history of familial case of HCM (40% versus 12%, p<0.001).

Clinical outcomes

Among the 201 patients with Ap-HCM, during a median 5-year follow up, there were 12 serious cardiovascular events (6%): 4 cardiac deaths, 3 aborted sudden cardiac death, and 5 ventricular tachycardia. Among these 12 patients, no patient had an ICD, and none of them had a theoretical indication for a preventive implantation (SCD risk score at 5 years <4%). One patient died of cancer. Moreover, we recorded 87 other cardiovascular events: supra ventricular arrhythmia in 34 (16.9%) patients, NSVT in 36 (17.9%), acute myocardial infarctions in 5, and stroke in 12 patients. Atrial fibrillation (AF) was present at diagnosis in 18 (9%) of patients and in a total of 52 (25.9%) patients including AF occurring during follow-up.

An ICD was implanted in 27 (13.4%) patients with apHCM (table 2). The indication was primary prevention in 20 of them. The reported reasons for ICD implantation in those patients were high ESC risk-score in 7 patients, diffuse LV fibrosis and/or LV aneurysm in 11 patients, and unknown in 2.

The comparison between ApHCM and non ApHCM revealed that ESC risk score was higher in non-apical vs apical HCM (2.71±1.96 vs 2.25±1.66, p=0.006). A significant better long-term survival was observed in apical HCM (Log Rank (Mantel-Cox): p=0.026) (**Figure 3).** No significant differences were observed concerning the clinical outcome of the 3 sub-types.

Sub population with an apical aneurysm

Among the 23 (11%) patients with an apical aneurysm, 8 had a pathogenic mutation (34.7%): MYBPC3 (n=2), MYH7 (n=1), TNNT2 (n=2), MYBPC3 and MYH7 (n=1), MYL2 (n=1), GLA (n=1). Two patients (8.7%) presented with a major clinical event during follow-up including 1 stroke and a VT in one patient and 1 sudden cardiac death in another patient, without significant difference with patients without aneurysm (p=0.329). In addition, 2 patients had a LV thrombus during their follow up.

Discussion

This study represents one of the largest multicentric cohort of ApHCM with genetic testing in Europe, with the following main results **(Graphical abstract):**

- We observed a low yield of pathogenic mutations (22.6%) among patients with ApHCM, especially in pure ApHCM (13%).
- The long-term prognosis of apical HCM is better than in non-apical HCM.
- However, rhythmic events are relatively frequent in these patients but are not predicted by the ESC risk score.
- No differences in terms of phenotype and prognosis were observed between the three subtypes of ApHCM (pure, distal and mixed).
- Apical aneurysms are more frequent in apical HCM.

Genetics of Apical HCM population

One of the main results of our study is that we found only 22.6% of pathogenic mutations among ApHCM population, which is significantly less than in our non-ApHCM cohort. This result agrees with previous studies focusing on genetics of ApHCM with 9 to 12 genes studied (4, 9, 11, 13). These results suggest that, unlike classical HCM, the apical HCM phenotype may not be primarily and only caused by sarcomeric gene abnormalities.

In addition, we found no specific mutation of ApHCM, and especially no association with pathogenic mutation of ACTC1 gene as previously suggested by *Arad* and al (9). The most frequent mutations observed in our study were on the classical sarcomeric genes MYBPC3 and MYH7 as for non ApHCM (15), which had already been described in literature [11].

Interestingly, we found an association between ApHCM and Fabry's disease (**Figure 4**): six patients had a pathogenic GLA mutation (2.9%) which was more than in previous studies focusing on screening of Fabry's disease (16, 19). This finding highlights the importance of thinking about Fabry's disease when an apical HCM is diagnosed, allowing an earlier specific therapy. Finally, we observed a family history of HCM in 20.7% of apical HCM, reinforcing the importance of genetic counselling in these patients

Comparison of ApHCM versus non ApHCM

Our study confirmed that apical HCM patients are a different population from classical HCM patients in terms of symptoms, imaging findings (significantly higher LVEF, thinner myocardium, less obstruction, smaller LAV index, more impaired GLS, more frequent restrictive pattern, less extensive LGE on CMR, and more frequent LV aneurysms).

We found 10.9% of apical aneurysm which is significantly higher than in our non ApHCM cohort (1.4%) and to the cohort of Maron (2%)[20]. This result corroborated the previous study of *Steinberg and al* [13] who found a higher prevalence of aneurysms among the population of patients with an ApHCM.

Comparison of sub-types of apical HCM

We separated our population into 3 distinct groups of ApHCM , as suggested by *Choi and al*[7] and *Kubo and al* [5]. First result was that the "distal form" was the predominant form while the "pure form" was more frequently observed un the Asiatic population [8]. In contrast to their studies, we didn't find in our cohort any significant difference in atrial fibrillation incidence, LAV index, and outcomes.

Finally, comparison of genetic findings between the 3 phenotypic groups of ApHCM, revealed that pure ApHCM had less pathogenic mutation than the two other groups.

Clinical outcome

ApHCM is often characterized on literature by is benign clinical course (6, 12, 21) but the reports are scarce and often focusing on Japanese population. Thanks to our wide multicentric cohort of more than two hundred patients we obtained interesting results on prognosis of these patients, and we could compare them to a cohort of non ApHCM.

We found a low cardiac mortality on the 5-year follow up, which is consistent with literature (6). Our result is also consistent with a former Korean study focusing on clinical outcome and CMR (12), which suggested that ApHCM had a better prognosis because of a relatively small burden of myocardial fibrosis and less diastolic dysfunction compared to non ApHCM. And this could be explained by a previous histological study (22) that showed a less extent of cardiac muscle cell disorganization on biopsy of myocardium of ApHCM than on biopsy of septal HCM.

Sub population with an apical aneurysm and indications for ICD implantation in apical HCM

The prognostic value of the presence of an apical aneurysm in HCM is debated. Although the 2020 American guidelines (23) consider the presence of an apical aneurysm as a major prognostic marker, the 2023 ESC guidelines recommend that the decision od implantation of an ICD should be individualized and based on conventional risk factors, rather than on the presence of an apical aneurysm only (15). In our series, among the subgroup of 23 patients with an apical aneurysm, we observed a relatively low incidence of serious cardiac events, without significant difference with patients without aneurysm. However, recent studies reported a relationship between the size of the aneurysm and the risk of subsequent events (24, 25).
Finally, among the 12 patients with serious rhythmic events, none of them had a theoretical indication for a preventive implantation (SCD risk score at 5 years <4%). These results suggest that a different risk score needs to be created to better evaluate these sub populations of HCM.

Limitations

Only Caucasian patients were reported in this study. The results of this study cannot be generalized to other patients. Although no significant association was observed in this cohort between the presence of an apical aneurysm and prognosis, we recognize that the study was underpowered to draw any definite conclusion.

Conclusion

Our study suggests that ApHCM is a distinct entity from classical HCM but without significant differences between the three sub-types of ApHCM. Patients with apical HCM have less pathogenic mutations than patients with classical HCM. Fabry's disease may mimic an apical HCM phenotype and should be ruled out when facing an apical HCM pattern. Prognosis of ApHCM is better than non- ApHCM, but rhythmic complications are frequent, and the SCD-risk score is not applicable to these specific population of HCM. Apical aneurysms are more frequent in apical HCM.

Funding source: none

Conflicts of interest: none reported by any author

Ethical and regulatory Aspects

Each center complied with their national ethical and regulatory standards. Patient and Public were not involved in this study.

Data Availability

Data, research materials, and analytical methods supporting this study are available through the corresponding author upon reasonable request

Pre-registered Clinical Trial Number : not applicable

REFERENCES

[1] Sakamoto T, Tei C, Murayama M, Ichiyasu H, Hada Y, Hayashi T *et al.*, 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. doi: 10.1536/ihj.17.611.

[2] Binder J, Ommen S, Gersh B, Tajik J, Nishimura R, Ackerman M *et al.* Echocardiography-Guided Genetic Testing in Hypertrophic Cardiomyopathy: Septal Morphological Features Predict the Presence of Myofilament Mutations. *Mayo Clin. Proc.* 2006; 81: 459-467. doi: 10.4065/81.4.459.

[3] Kitaoka H, Doi Y, Casey S, Hitomi N, Furuno T, et Maron B J. Comparison of prevalence of apical hypertrophic cardiomyopathy in Japan and the United States. *Am. J. Cardiol* 2003*;* 92: 1183-1186. doi: 10.1016/j.amjcard.2003.07.027.

[4] Gruner C, Care M, Siminovitch K, Moravsky G, Douglas Wigle E, Woo A *et al.* Sarcomere Protein Gene Mutations in Patients with Apical Hypertrophic Cardiomyopathy. *Circ. Cardiovasc. Genet.* 2011; 4: 288-295. doi: 10.1161/CIRCGENETICS.110.958835.

[5] Kubo T, Kitaoka H, Okawa M, Hirota T, Hoshikawa E, Hayato K *et al*. Clinical Profiles of Hypertrophic Cardiomyopathy with Apical Phenotype Comparison of Pure-Apical Form and Distal-Dominant Form: Comparison of Pure-Apical Form and Distal-Dominant Form. *Circ. J.* 2009; 73: 2330-2336. doi: 10.1253/circj.CJ-09-0438.

[6] Eriksson M J, Sonnenberg B, Woo A, Rakowski P, Parker T, Wigle E D et *al*., « Long-term outcome in patients with apical hypertrophic cardiomyopathy », J. Am. Coll. Cardiol. 2002; 39: 638-645. doi: 10.1016/S0735-1097(01)01778-8.

[7] Choi E.-Y, Se-Joong R, Jong-Won H, Yong-Jin K, Sang-Chol L, Duk-Hyun K et *al.*, « Phenotypic Spectrum and Clinical Characteristics of Apical Hypertrophic Cardiomyopathy: Multicenter Echo-Doppler Study », *Cardiology*. 2008; 110: 53-61.doi: 10.1159/000109407.

[8] Sugiura K, Kubo T, Inoue S, Nomura S, Yamada T, Tobita T, et al. Unveiling Clinical and Genetic Distinctions in Pure-Apical Versus Distal-Dominant Apical Hypertrophic Cardiomyopathy J Am Heart Assoc. 2025;14:e038208. DOI: 10.1161/JAHA.124.038208

[9] Arad M, Penas-Lado M, Monserrat L, Maron B J, Sherrid M, Ho C *et al.*, « Gene Mutations in Apical Hypertrophic Cardiomyopathy », *Circulation*. 2005; 112: 2805-2811. doi:10.1161/CIRCULATIONAHA.105.547448.

[10] Towe E C, Bos J M, Ommen S R, Gersh B J, et Ackerman M J, « Genotype-Phenotype Correlations in Apical Variant Hypertrophic Cardiomyopathy: Genotype-Phenotype Correlations in Apical HCM », *Congenit. Heart Dis.* 2015 ; 10: E139-E145. doi: 10.1111/chd.12242.

[11] Chen QF, Zou J, Katsouras CS, You S, Zhou J, Ge HB, et al. Clinical Characteristics and Outcomes in Patients With Apical and Nonapical Hypertrophic Cardiomyopathy *J Am Heart Assoc.* 2024;13:e036663. DOI: 10.1161/JAHA.124.036663

[12] Kim E K, Sang-Chol L, Ji Won H, Sung-A C, Sung-Ji P, Young K, *et al.*, « Differences in apical and non-apical types of hypertrophic cardiomyopathy: a prospective analysis of clinical, echocardiographic, and cardiac magnetic resonance findings and outcome from 350 patients », *Eur. Heart J. – Cardiovasc. Imaging.* 2016; 17: 678-686, doi: 10.1093/ehjci/jev192.

[13] Steinberg C, Nadeau-Routhier C, André P, Philippon F, Sarrazin J-F, Nault I *et al.*, « Ventricular Arrhythmia in Septal and Apical Hypertrophic Cardiomyopathy: The French-Canadian Experience », *Front. Cardiovasc. Med.* 2020*;* 7: 548-564. doi: 10.3389/fcvm.2020.548564.

[14] Furushima H, Chinushi M, Iijima K, Sanada A, Izumi D, Aizawa Y *et al.*, « Ventricular Tachyarrhythmia Associated with Hypertrophic Cardiomyopathy: Incidence, Prognosis, and Relation to Type of Hypertrophy », *J. Cardiovasc. Electrophysiol.* 2010; 21: 991-999. doi: 10.1111/j.1540-8167.2010.01769.x.

[15] Arbelo E, Protonotarios A, Gimeno J, Arbustini E, Barriales-Villa R, Basso C, Bezzina C *et al.*, « 2023 ESC Guidelines for the management of cardiomyopathies », *Eur. Heart J. 2023;* 44 : 3503-3626. doi: 10.1093/eurheartj/ehad194.

[16] Nguyen K, Roche S, Donal E, Odent S, Eicher J-C, Faivre L *et al.*, « Whole Exome Sequencing Reveals a Large Genetic Heterogeneity and Revisits the Causes of Hypertrophic Cardiomyopathy: Experience of a Multicentric Study of 200 French Patients », *Circ. Genomic Precis. Med.* 2019; 12. doi: 10.1161/CIRCGEN.119.002500.

[17] O'Mahony C, Jichi F, Pavlou M, Monserrat M, Anastasakis A, et Rapezzi C, « A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM Risk-SCD) », *Eur Heart J*. 2014; 35. doi: 10.1093/eurheartj/eht439.

[18] Elliott P, Anastasakis A, Borger M, Borggrefe M, Cecchi F, Charron P et *al*. « 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: The Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC) », *Eur. Heart J.* 2014; 35: 2733-2779. doi: 10.1093/eurheartj/ehu284.

[19] Hagege A, Caudron E, Damy T, Roudaut R, Millaire A, Etchecopar-Chevreuil C, *et al.* « Screening patients with hypertrophic cardiomyopathy for Fabry disease using a filter-paper test: the FOCUS study », *Heart*. 2011; 97: 131-136. doi: 10.1136/hrt.2010.200188.

[20] Maron M, Finley J, Martijn Bos J, Hauser T, Manning W, Haas T *et al.*, « Prevalence, Clinical Significance, and Natural History of Left Ventricular Apical Aneurysms in Hypertrophic Cardiomyopathy », *Circulation*. 2008; 118: 1541-1549. doi: 10.1161/CIRCULATIONAHA.108.781401.

[21] Webb J, Sasson Z, Rakowski H, Liu P, et Douglas Wigle E, « Apical hypertrophic cardiomyopathy: Clinical follow-up and diagnostic correlates », *J. Am. Coll. Cardiol*.1990;15: 83-90. doi: 10.1016/0735-1097(90)90180-W.

[22] Morimoto S, Sekiguchi M, Uemura A, Hiramitsu S, Kimura K, Ohtsuki M,*et al.* « Cardiac Muscle Cell Disorganization in Apical Hypertrophic Cardiomyopathy: A Cardiac Biopsy Study », *Jpn. Heart J.* 2003*;* 44: 505-513. doi: 10.1536/jhj.44.505.

23 - Ommen SR, Mital S, Burke MA, Day SM, Deswal A, Elliott P, Evanovich LL, Hung J, Joglar JA, Kantor P, Kimmelstiel C, Kittleson M, Link MS, Maron MS, Martinez MW, Miyake CY, Schaff HV, Semsarian C, Sorajja P. 2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2020 Dec 22;142(25):e533-e557. doi: 10.1161/CIR.0000000000000938. Epub 2020 Nov 20. PMID: 33215938

24 - Linden K, Green N, Muir A, Malcolmson JW, Mohiddin SA, O'Mahony C.Size Matters. Prevalence and Clinical Implications of Left Ventricular Apical Aneurysms in Hypertrophic Cardiomyopathy: A Systematic Review and Meta-Analysis. J Am Heart Assoc. 2025 Aug 5;14(15):e037234. doi: 10.1161/JAHA.124.037234. Epub 2025 Jul 29. PMID: 40728182

25 - Sherrid MV, Massera D, Bernard S, Tripathi N, Patel Y, Modi V, et al. Clinical Course and Treatment of Patients With Apical Aneurysms Due to Hypertrophic Cardiomyopathy.JACC Adv. 2024 Aug 27;3(10):101195. doi: 10.1016/j.jacadv.2024.101195. eCollection 2024 Oct.
PMID: 39280799

FIGURE LEGENDS

Figure 1: 3 Subtypes of ApHCM: Pure, distal and mixed.

Figure 2: Distribution of pathogenic mutations. Vertical axis: number of patients with the pathogenic mutation. Name of the gene (% of mutated patients)

Figure 3: .Long term Survival comparison between the ApHCM cohort and the multicentric cohort of 419 Septal HCM.

Figure 4: illustrative case of a patient with apical HCM and Fabry disease (c.931dupC mutation [p.Leu311Profs*4])
a: LV hypertrophy on EKG
b: apical HCM on echocardiography (yellow arrow)
c: reduced apical strain
d: apical hypertrophy on cardiac CMR
e: posterolateral LV enhancement (T1 mapping value was reduced (1025 ms)

Graphical abstract: Main results of the study: 201 apical HCM were compared with 419 non-apical HCM
Left panel: example of distal apical HCM (yellow arrows) with LV apical aneurysm (red arrow) on CMR and corresponding 2d strain, showing reduced deformation in the LV apex
Right panel: example of severe septal HCM (yellow arrow) on MRI and corresponding 2d strain, showing an anteroseptal reduced deformation
LV: left ventricle, RV: right ventricle, LA: left atrium

TABLE 1: Baseline characteristics of the 201 patients with Apical HCM

	ApHCM N = 201
MEDICAL HISTORY	
Age at diagnosis (yr)	*52.4 (16.7)*
Men	*143 (71.1%)*
Family history of HCM	*40 (19.9%)*
Family history of SCD	*34 (16.9%)*
History of hypertension	*81 (40.3%)*
NYHA class I/II/III and IV (n)	*116/74/11*
Chest pain	*15 (7.5%)*
Syncope	*24 (11.9%)*
TTE	
Mean LVEF (%)	*66.7 (7.0)*
LV max wall thickness Mean (mm)	*17.3 (3.9)*
LV significant mid obstruction	*10 (5%)*
LAVi (ml/m²)	*37.9 (14.2)*
LVEDVi (ml/m²)	*47.2 (18.2)*
GLS (%)	*-14.4 (4.3)*
Restrictive filling pattern	*18 (9.0%)*
CMR	
Pure ApHCM	*50 (24.9%)*
Distal ApHCM	*98 (48.8%)*
Mixed ApHCM	*53 (26.4%)*
LVEF (%)	*68.6 (8.0)*
LV Wall max thickness (mm)	*18.0 (4.0)*
Presence of LGE	*129 (64.2%)*
Proportion of LGE >15%	*48 (30.4%)*
LV aneurysm	*22 (10.9%)*
LV Thrombus	*4 (2%)*
GENETICS	

Pathogenic mutation (class 4 or 5)	*41 (20.4%)*

n (%) ; mean (SD)
HCM = hypertrophic cardiomyopathy; ICD = Implantable Cardioverter Defibrillator; IVS = interventricular septum; GLS = Global longitudinal strain; LAV = left atrial volume; LGE = Late gadolinium enhancement; LV = left ventricular; LVEF = Left ventricular ejection fraction; LVEDV = Left ventricular end diastolic volume; LVH = left ventricular hypertrophy; Max = maximum; NYHA = New York Heart Association; SCD = sudden cardiac death; SVT = Supra ventricular Tachycardia ; NSVT = Non sustained ventricular tachycardia; VT = Ventricular tachycardia; VF = Ventricular Fibrillation

TABLE 2: Comparison of clinical, TTE and CMR data between 201 apical and 419 non-apical HCM.

	ApHCM N = 201[1]	Non ApHCM n = 419[1]	P value

MEDICAL HISTORY			
Age at diagnosis (yr)	52.4 (16.7)	52.4 (15.5)	0.965[4]
Men	143 (71.1%)	279 (66.6%)	0.293[2]
Family history of HCM	40 (19.9%)	80 (19.1%)	0.773[2]
Family history of SCD	34 (16.9%)	49 (11.7%)	0.078[2]
History of hypertension	81 (40.3%)	120 (28.6%)	0.006[2]
Dyspnea	88 (43.8%)	207 (49.4%)	0.003[2]
Syncope	24 (11.9%)	55 (13.1%)	0.678[2]
TTE			
Mean LVEF (%)	66.7 (7.0)	62.7 (15.9)	<0.001[5]
LV max wall thickness Mean (mm)	17.3 (3.9)	20.9 (5.0)	<0.001[5]
LV significant mid obstruction	10 (5%)	97 (23.2%)	<0.001[2]
LAVi (ml/m²)	37.9 (14.2)	47.2 (23.8)	<0.001[5]
LVEDVi (ml/m²)	47.2 (18.2)	56.2 (19.5)	<0.001[4]
GLS (%)	-14.4 (4.3)	-15.3 (4.0)	0.035[4]
Restrictive filling pattern	18 (9.0%)	18 (4.3%)	0.019[2]
CMR			
LVEF (%)	68.6 (8.0)	66.6 (12.2)	0.059[5]
LV Wall max thickness (mm)	18.0 (4.0)	21.2 (5.5)	<0.001[5]
Presence of LGE	129 (64.2%)	221 (52.7%)	0.603[2]
LGE >15%	48 (30.4%)	148 (49.5%)	<0.001[2]
LV aneurysm	22 (10.9%)	6 (1.4%)	<0.001[2]
GENETICS			
Pathogenic mutation (class 4 or 5)	41 (20.4%)	182 (43.4%)	<0.001[2]
RYHTHMIC EVENTS AND OUTCOME			
ESC risk score (%)	2.25 (1.66)	2.71 (1.96)	0.006
ICD implantation	27(13.4%)	87 (20.8%)	0.026
VT or VF or recovered SCD	7 (3.5%)	27 (6.4%)	0.126[2]
Mortality	5 (2.5%)	17 (4.1%)	0.318

[1] n (%) ; mean (SD)
[2] Pearson's Chi-squared test
[3] Fisher's exact test
[4] Two Sample t-test
[5] Welch Two Sample t-test
ECG = electrocardiogram; HCM = hypertrophic cardiomyopathy; ICD = Internal Cardioverter Defibrillator; IVS = interventricular septum; GLS = Global longitudinal strain; LAV = left atrial volume; LGE = Late gadolinium enhancement; LV = left ventricular; LVEF = Left ventricular ejection fraction; LVEDV = Left ventricular end diastole volume; LVH = left ventricular hypertrophy; Max = maximum; NYHA = New York Heart Association; SCD = sudden cardiac death; SVT = Supra ventricular Tachycardia ; VNST = Ventricular Non sustain tachycardia; VT = Ventricular tachycardia; VF = Ventricular Fibrillation

TABLE 3: Comparison of clinical, genetic, TTE, CMR and prognostic data between pure, distal, and mixed HCM among the 201 patients with Ap-HCM

	Pure ApHCM N = 50[1]	Distal ApHCM N = 98[1]	Mixte ApHCM N = 53[1]	P value
MEDICAL HISTORY				
Age at diagnosis (yr)	53.7 (17.8)	51.7 (16.3)	52.6 (16.7)	0.800[4]
Men	29 (58%)	76 (77.6%)	38 (71.7%)	0.031[2]
Family history of HCM	13 (26%)	20 (20.4%)	7 (13.2%)	0.280[2]
Family history of SCD	9 (18%)	16 (16.3%)	9 (17.0%)	0.979[2]
History of hypertension	16 (32%)	41 (41.8%)	24 (45.3%)	0.311[2]
TTE				
Mean LVEF (%)	68.3 (6.4)	65.2 (6.6)	68.2 (7.7)	0.008[4]
LV max wall thickness Mean (mm)	16.9 (3.6)	17.2 (3.9)	18.2 (4.0)	0.195[4]
LV significant mid obstruction	3 (6%)	3 (3.1%)	4 (7.5%)	0.322[3]
LAV (ml/m²)	38.4 (15.0)	38.8 (15.1)	35.9 (11.4)	0.517[4]
VTDVGi (ml/m²)	48.8 (20.3)	44.9 (15.9)	49.9 (20.1)	0.270[4]
SGL (%)	-15.4 (4.5)	-14.1 (4.0)	-14.0 (4.5)	0.278[4]
Restrictive filling pattern	7 (14%)	5 (5.1%)	7 (13.2%)	0.126[3]
CMR				
LVEF (%)	69.0 (7.3)	67.7 (8.4)	70.0 (7.7)	0.302[4]
LV Wall max thickness (mm)	16.4 (4.1)	18.4 (4.0)	18.8 (3.6)	0.012[4]
Presence of LGE	25 (61.0%)	70 (83.3%)	34 (77.3%)	0.022[2]
Proportion of LGE >15%	8 (20.0%)	25 (32.1%)	15 (37.5%)	0.212[2]
LV aneurysm	6 (14.6%)	10 (12.5%)	6 (15.0%)	0.912[2]
LV Thrombus	2 (5.9%)	2 (2.8%)	0 (0.0%)	0.265[2]
GENETICS				
Pathogenic mutation (class 4 or 5)	6 (12%)	25 (25.6%)	10 (18.9%)	0.111[2]
RYHTHMIC EVENTS AND OUTCOME				
Syncope	8 (16%)	6 (6.1%)	10 (18.9%)	0.039[2]
ICD	7 (14%)	12 (12.2%)	8 (15.1%)	0.883[2]

SVT	13 (26.0%)	20 (20.8%)	10 (18.9%)	0.700[2]
NSVT	7 (14%)	19 (19.4%)	12 (22.6%)	0.498[2]
VT or VF or ressucited SCD	2 (4%)	4 (4.1%)	1 (1.9%)	0.787[3]
Stroke	0 (0%)	6 (6.1%)	3 (5.7%)	0.215[3]
All cause mortality	2 (4%)	2 (2.0%)	1 (1.9%)	0.721[3]
Cardiac mortality	1 (2%)	2 (2.0%)	1 (1.9%)	0.999[3]

[1] n (%) ; mean (SD)
[2] Pearson's Chi-squared test
[3] Fisher's exact test
[4] ANOVA test
ECG = electrocardiogram; HCM = hypertrophic cardiomyopathy; ICD = Internal Cardioverter Defibrillator; IVS = interventricular septum; GLS = Global longitudinal strain; LAV = left atrial volume; LGE = Late gadolinium enhancement; LV = left ventricular; LVEF = Left ventricular ejection fraction; LVEDV = Left ventricular end diastole volume; LVH = left ventricular hypertrophy; Max = maximum; NYHA = New York Heart Association; SCD = sudden cardiac death; SVT = Supra ventricular Tachycardia ; NSVT = Non sustained Ventricular tachycardia; VT = Ventricular tachycardia; VF = Ventricular Fibrillation

Word count : 4042

Figure 1

Click here to access/download;Figure;FIGURE 1.tiff

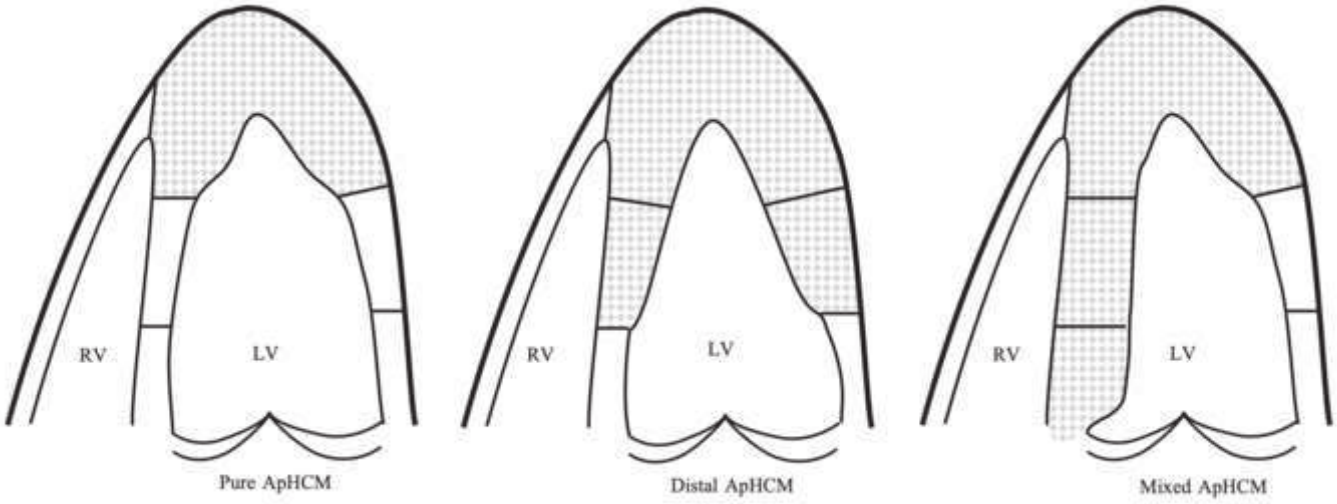


Figure 2

Click here to access/download;Figure;figure 2 new.tif

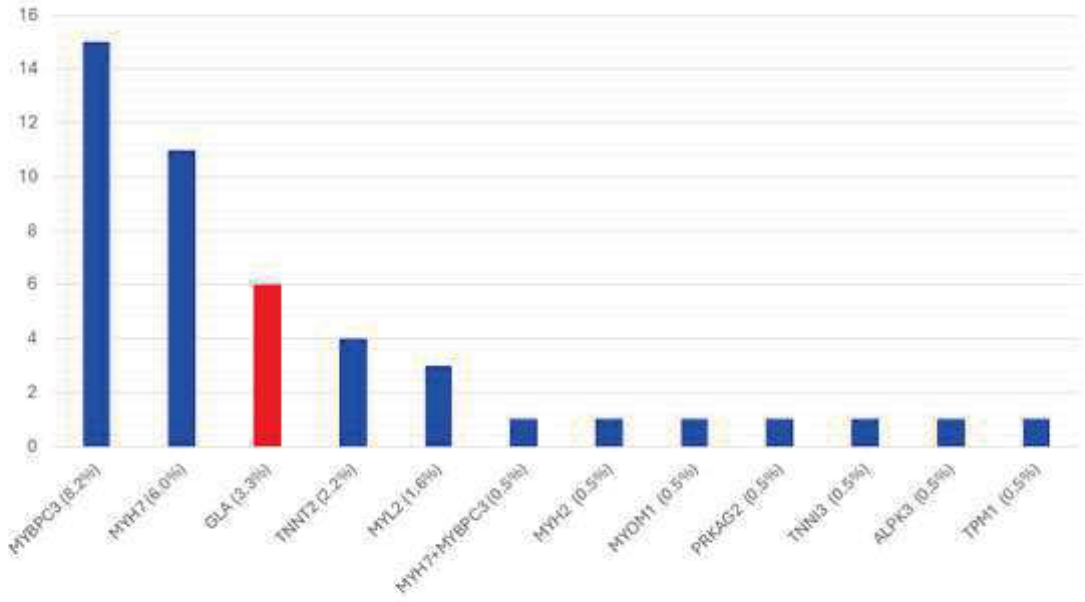


Figure 3

Click here to access/download;Figure;figure 3.tif

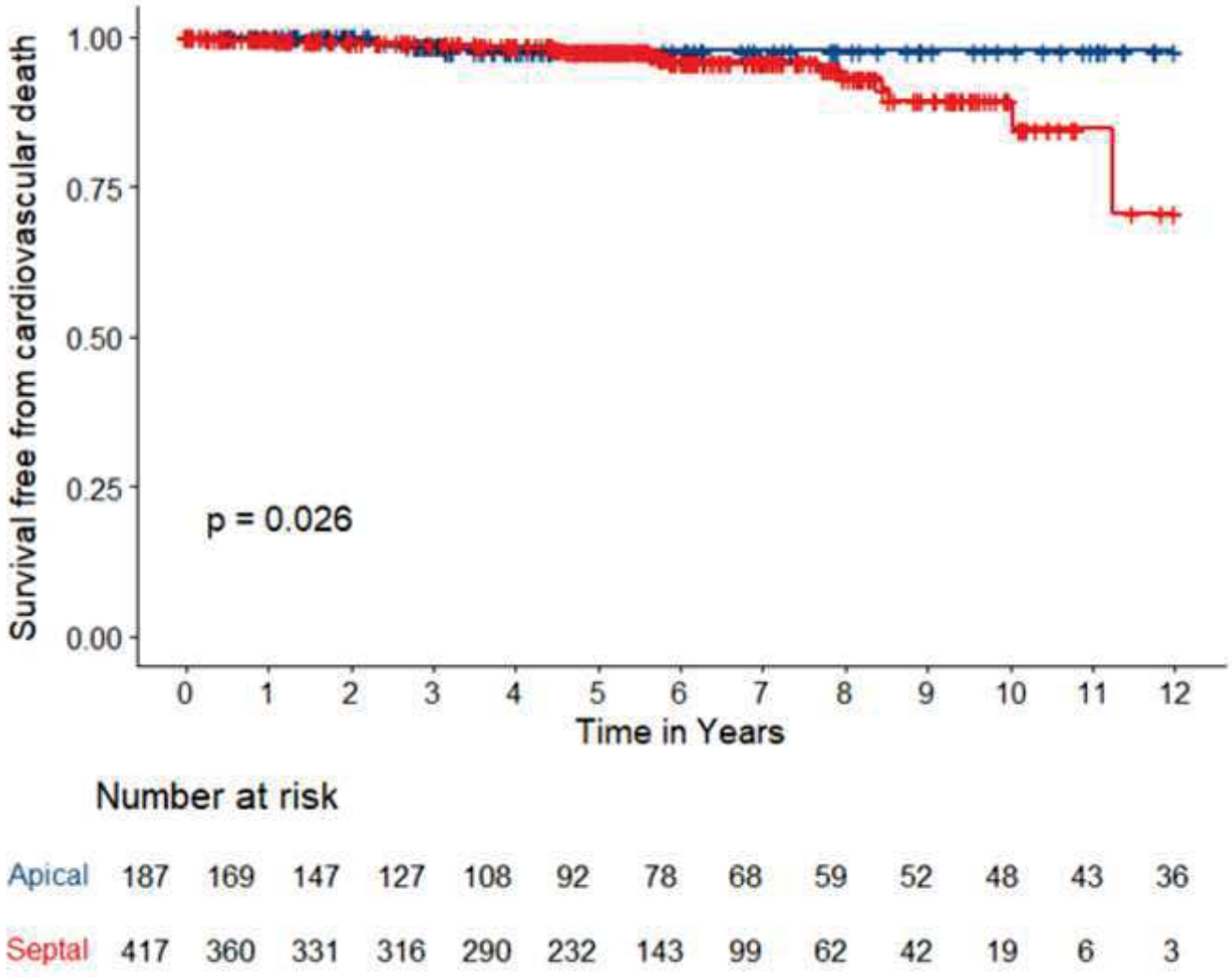
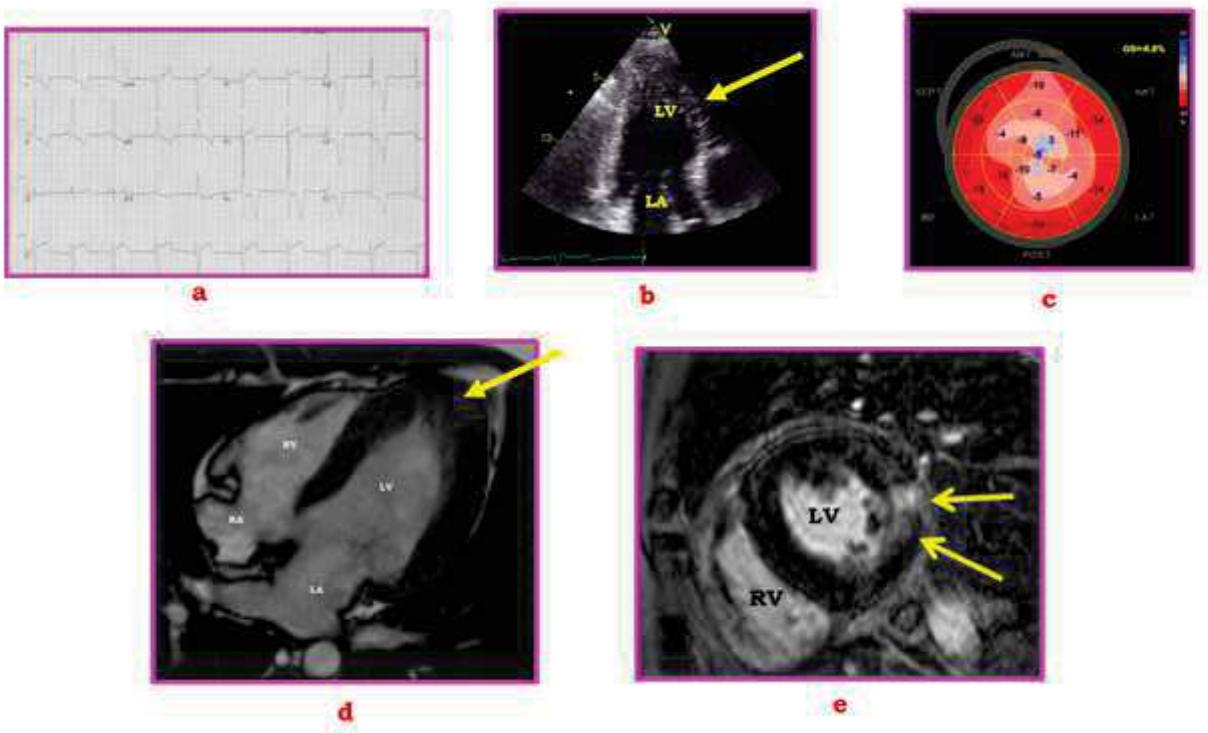


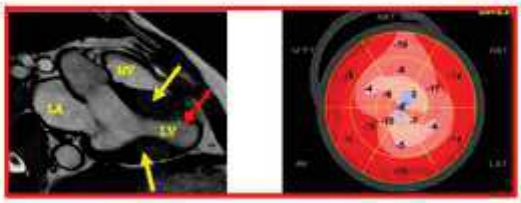
Figure 4

Click here to access/download;Figure;figure 4.tif

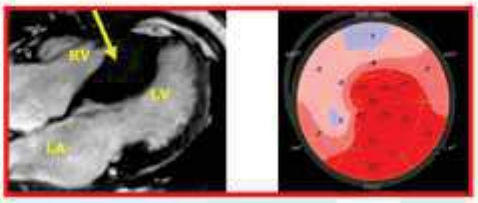


Graphical Abstract

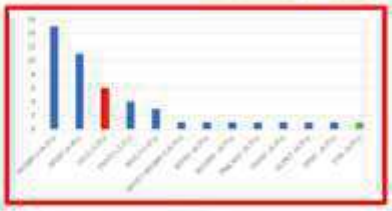
Click here to access/download;Graphical Abstract;GRAPHICAL ABSTRACT. mars 2026.tif

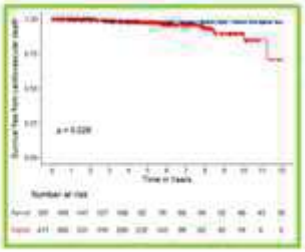


201 apical HCM



419 non-apical HCM





Key findings: apical vs non-apical HCM

- ✓ Low yield of pathogenic mutations (22.6%) among patients with ApHCM
- ✓ Fabry's disease may mimic an apical HCM phenotype
- ✓ Better long-term prognosis of apical HCM
- ✓ Frequent rhythmic events in ApHCM but not predicted by the ESC risk score
- ✓ Apical aneurysms are more frequent in apical HCM