Int Cardiovasc Res J.2022;**16**(2):80-84.icrj.122923

International Cardiovascular Research Journal
www.ircrj.com

Burned-out Phase in Apical Hypertrophic Cardiomyopathy (Echocardiographic Data of 230 Patients with Apical HCM)

Mohammad Ali Sadr-Ameli [1], MD; Azin Alizadehasl [2], MD; Zohre Rahbar [2,*], MD; Maryam Maharlou [2], MD; Sepehr Jamalkhani [3], MD; Davood Khoda Amorzideh [2], MD; Kamran Roudini [4], MD; Hooman Bakhshandeh [5], MD; Mahdi Khalili [3], MD; Zahra Shahidzadeh [3], MD, Marzie Bazzi [3], MD; Maedeh Barahman [6], MD; Nima Sarisarraf [3], MD; Masood Shekarchizadeh [3], MD, Behshid Ghadrdoost [1], MD

[1] Interventional Cardiology Research Center, Rajaie Cardiovascular Medical and Research Center, Tehran, IR Iran
[2] Cardio-Oncology Research Center, Rajaie Cardiovascular Medical and Research Center, Tehran, IR Iran
[3] Rajaei Cardiovascular Medical and Research Center, Tehran, IR Iran
[4] Imam Khomeini Hospital, Tehran University of Medical Sciences, Tehran, IR Iran
[5] Heart Research Center, Rajaie Cardiovascular, Medical and Research Center, Tehran, IR Iran
[6] Firoozgar Hospital, Iran University of Medical Sciences, Tehran, IR Iran

ARTICLE INFO

Article Type:
Research Article

Article History:
Received: 24 Jan 2022
Revised: 14 Mar 2022
Accepted: 24 Apr 2022

Keywords:
Hypertrophic Cardiomyopathy
Left Ventricular Dysfunction
Echocardiography

ABSTRACT

Background: Apical Hypertrophic Cardiomyopathy (ApHCM) is a rare form of hypertrophic cardiomyopathy with sarcomere protein gene mutations, which predominantly affects the apex of the left ventricle. Sudden Cardiac Death (SCD) and cardiovascular morbidity are less likely to occur in patients with isolated ApHCM. However, recent data suggested annual cardiac death rates of 0.5 - 4%, approaching those for classic HCM.

Objectives: The present study aimed to assess the prevalence of burned-out ApHCM and its predictors.

Methods: In this retrospective cross-sectional study, echocardiographic data and electrocardiography features of 230 patients with ApHCM including premature ventricular contraction and atrial fibrillation were gathered and analyzed at baseline and after a mean follow-up of five years. All data were obtained from the data registry of Rajaie Cardiovascular Medical and Research Center, Tehran, Iran. The data were included in a retrospective study, which was approved by the local Ethics Committee. The patients were divided into two groups as follows: 1- Left Ventricular Ejection Fraction (LVEF) ≥ 50% and 2- LVEF < 50% known as burned-out ApHCM. Data analysis was also based on LVEF. Generalized Estimating Equation (GEE) regression was performed to assess the association between the patients' characteristics and burned-out ApHCM. The clinical features demonstrating $P < 0.05$ in the univariate GEE analysis were included in a multivariate model to identify the independent predictors.

Results: The prevalence of burned-out ApHCM, defined as LVEF < 50%, was 13.9%. There was no significant difference between males and females in this regard ($P = 0.48$). After a mean follow-up of five years, atrial fibrillation was significantly more common in the patients with LVEF < 50% (48.7% vs. 24.4%, $P = 0.007$). Additionally, left atrial enlargement was identified as the most important predictor of BO-ApHCM (odds ratio = 2.4, $P = 0.003$). Moreover, right ventricular dysfunction was more severe in the patients with burned-out ApHCM ($P < 0.001$).

Conclusions: The prevalence of burned-out HCM was higher in the present study than in the previous studies (13.9%). Besides, right ventricular systolic dysfunction and left atrial enlargement were two main predictors of the ApHCM progression.

1. Background

Apical Hypertrophic Cardiomyopathy (ApHCM) is a rare form of Hypertrophic Cardiomyopathy (HCM) that predominantly affects the apex of the left ventricle. It is an uncommon variant of HCM, in which detectable sarcomere protein gene mutations are less prevalent in comparison with other forms of HCM (1-6). Importantly, sudden cardiac death is less likely to occur in patients with

*Corresponding author: Zohre Rahbar, West 4th Unit, Number 8, Amir Soori Street, Fallahi Street, Zaafaranieh Town, Postal Code: 1987955318, Tehran, Iran. Cellphone: +98-9125878560,
Email: rahbar.zoh89@gmail.com.

isolated ApHCM. Additionally, cardiovascular morbidity may be less common compared to other HCM phenotypes. However, recent data have suggested the annual cardiac death rates of 0.5 - 4%, approaching those for classic HCM (1, 7-11).

The genetic basis of HCM has been discovered. Accordingly, it is predominantly caused by autosomal dominant mutations in sarcomeric protein genes (5, 9, 12-14). Up to now, several patterns of Left Ventricular Hypertrophy (LVH) have been described in HCM including asymmetric septal hypertrophy (classic HCM), reverse curvature HCM, neutral HCM, and ApHCM. Compared with classic HCM, ApHCM is more sporadic and has a lower frequency of sarcomere mutations. Besides, atrial fibrillation and sudden cardiac death risk factors differ from those in classic HCM (15-21). It is often first detected by transthoracic echocardiography when the degree of suspicion is high (7, 22-24). With imaging advances, the definition now relies on demonstrating LVH predominance in the Left Ventricular (LV) apex, with wall thicknesses in the apex of ≥ 15 mm and a maximal apical to posterior wall thickness ratio of ≥ 1.5 based on echocardiography or Cardiovascular Magnetic Resonance (CMR) (3, 7, 16, 25-27).

2. Objectives

The present study aims to assess the prevalence of burned-out ApHCM and its predictors.

3. Patients and Methods

In this retrospective study, echocardiographic data of 230 patients were gathered and analyzed. The patients were divided into two groups as follows: 1- Left Ventricular Ejection Fraction ≥ 50% and 2- LVEF < 50% (also known as Burned-Out ApHCM (BO-ApHCM)). Data analysis was also done based on LVEF. BO-ApHCM was diagnosed by an expert clinician based on physical examination and echocardiography. Echocardiographic measurements of the apical wall thickness were recorded. Other echocardiographic indices were available, as well. Among the 230 patients, 74 showed up for follow-up visits. Another analysis was done on these 74 patients to determine the predictors of ApHCM. All data were obtained from the data registry of Rajaie Cardiovascular Medical and Research Center, Tehran, Iran. These data were included in a retrospective study, which was approved by the local Ethics Committee.

3.1. Imaging Evaluation and Procedure

Echocardiographic studies were performed for all the patients using two ultrasound systems (Vivid S60 (GE Healthcare, USA) and Affinity 70C (Philips Healthcare, Andover, USA)) with a phased-array transducer of 2.5 MHz and a Pure Wave Convex transducer of 1 - 5 MHz. Echocardiographic images were taken in the left lateral and supine positions using the standard apical, parasternal, and subcostal views while recording the electrocardiograms. All the patients underwent 2D and color Doppler echocardiography at baseline. A central offline analysis of all the images was performed by an independent core lab, which collected and interpreted all the imaging data. It should be noted that all the individuals involved in these processes were blind to the clinical data and outcomes. Baseline echocardiographic measurements included inter-ventricular septum thickness, left ventricular and atrial systolic and diastolic diameters, LVEF, Systolic Pulmonary Arterial Pressure (SPAP), Mitral Regurgitation (MR), Aortic Regurgitation (AR), Right Ventricular (RV) function, and LV diastolic function. Pericardial effusion was also performed following the American Association of Echocardiography's guidelines. Finally, the percentage of patients with BO-ApHCM was determined and the related factors were evaluated.

3.2. Electrocardiographic Recording

Surface Electrocardiography (ECG) of all the patients at baseline and during the follow-up visits was evaluated by independent cardiologists who were blind to the clinical data and outcomes. The rhythm (sinus vs. atrial fibrillation) was assessed on the ECGs.

3.3. Statistical Analysis

Continuous variables were expressed as mean ± SD when normally distributed and as median (interquartile range) when non-normally distributed. Categorical variables were expressed as number and percentage. The two groups were compared regarding the continuous variables using t-test or a non-parametric test (Wilcoxon test) when the data were non-normally distributed. In addition, Fisher's exact test was used to compare the two groups concerning the categorical variables. Generalized Estimating Equation (GEE) regression was performed to assess the association between the patients' characteristics and BO-ApHCM. The clinical features with $P < 0.05$ in the univariate GEE analysis were included in the multivariate model to identify the independent predictors.

4. Results

Various parameters were evaluated to detect the risk factors of BO-ApHCM including SPAP, MR, AR, RV function, LV diastolic function, pericardial effusion, and atrial fibrillation. The patients' baseline demographic characteristics have been presented in Table 1. Gender and ECG features in ApHCM with normal and reduced EF have been illustrated in Table 2. Based on the results, the prevalence of BO-ApHCM was 13.9%. In addition, diastolic dysfunction was more severe in the cases with LVEF < 50% (21.9% vs. 10.6%, $P = 0.08$). RV dysfunction was also more severe in the ApHCM cases with LVEF < 50% (40.6% vs. 17.2%, $P < 0.001$). Moreover, the prevalence of atrial fibrillation was higher in the group with BO-ApHCM after a mean follow-up of five years (48.7% vs. 24.4%, $P = 0.007$). The echocardiographic indices in ApHCM have been presented in Table 3.

Table 1. Demographic Characteristics of the Patients with ApHCM

		ApHCM (n = 230)
Sex	Female	43%
	Male	56%
Age (years)		61 ± 15

Table 2. Gender and ECG Features in ApHCM with Normal and Reduced EF

		Baseline Analysis (n = 230)			Follow-up Visit Analysis (N = 74)		
		Normal EF (n = 198)	BO-ApHCM (n = 32)	P- value	Normal EF (n = 52)	BO-ApHCM (n = 22)	P- value
Sex	Male	56.6%	50%	0.48	53.1%	47.1%	0.66
	Female	43.4%	50%		46.9%	52.9%	
ECG features	Atrial fibrillation	1.2%	0%	0.99	24.4%	48.7%	**0.007**
	PVC in the first ECG	2.3%	0%	0.99	1.6%	5.9	0.37

Abbreviations: ECG, electrocardiography; EF, ejection fraction; BO-ApHCM, burned-out apical hypertrophic cardiomyopathy; PVC, premature ventricular complex

Table 3. Echocardiographic Indices in Apical Hypertrophic Cardiomyopathy (EF ≥ 50% vs. EF < 50%)

Echocardiography Indices	Severity	Baseline Analysis			Follow-up Analysis		
		Normal EF	BO-ApHCM	P-value	Normal EF	BO-ApHCM	P-value
SAM	No, mild	3	0	0.99	4.7	0	0.99
	Moderate, severe	97	100		95.3	100	
RVH	Yes	4%	9.4%	0.19	4.7%	23.5%	0.03
	No	96%	90.6%		95.3%	76.5%	
RV dysfunction	No dysfunction, mild	82.8%	40.6%	< 0.001	No dysfunction, mild 32.8%	11.8%	< 0.001
	Moderate, severe	17.2%	59.4%		Moderate, severe 67.2%	88.2%	
Left ventricular diastolic dysfunction	No, mild	89.4%	78.1%	0.08	79.7%	64.7%	0.2
	Moderate, severe	10.6%	21.9%		20.3%	35.3%	
MR	No, mild	12.1%	12.5%	0.99	96.9%	94.1%	0.51
	Moderate, severe	87.9%	87.5%		3.1%	5.9%	
AR	No, mild	70.2%	53.1%	0.05	68.8%	47.1%	0.1
	Moderate, severe	29.8%	46.9%		31.3%	52.9%	
Pericardial effusion	Yes	2%	0%	0.99	1.6%	94.1%	0.38
	No	98%	100%		98.4%	5.9%	

Abbreviations: SAM, systolic anterior motion; EF, ejection fraction; BO-ApHCM, burned-out apical hypertrophic cardiomyopathy; RVH, right ventricular hypertrophy; RV, right ventricle; MR, mitral regurgitation; AR, aortic regurgitation

Table 4. Echocardiographic predictors of BO-ApHCM

Echocardiographic Parameters	Odds Ratio (95% Confidence Interval)	P-value
RV dysfunction	10.978 (2.235 - 53.915)	0.003
IVS thickness	3.654 (0.978 - 13.130)	0.054
Left atrial enlargement	2.489 (1.362 - 4.549)	0.003
Diastolic dysfunction	2.225 (0.886 - 5.586)	0.088
Aortic regurgitation	1.887 (0.762 - 4.670)	0.169
Mitral regurgitation	2.248 (0.409 - 12.359)	0.351
Atrial fibrillation	1.321 (0.192 - 9.055)	0.776
Apical thickness	1.169 (0.405 - 3.366)	0.772

Abbreviations: RV, right ventricular IVS, interventricular septum.

Based on the results of the univariate GEE regression test, moderate or severe RV dysfunction had the highest odds ratio of 10 (P = 0.003), which could predict BO-ApHCM. In addition, left atrial enlargement could predict BO-ApHCM with an odds ratio of 2.4 (P = 0.003). The echocardiographic predictors of BO-ApHCM based on the univariate logistic regression test and odds ratios have been presented in Table 4.

5. Discussion

The current cross-sectional study aimed to determine the burned-out phase of ApHCM. The data were collected from the study participants during two visits. BO-ApHCM was defined as LVEF ≤ 50%. The prevalence of BO-ApHCM was 13.9%, which was higher than the rates reported in the previous studies (< 10%) (7, 15). This discrepancy might be due to the fact that the present study was performed in a tertiary referral center. Moreover, the findings demonstrated no significant gender difference in terms of the prevalence of BO-ApHCM.

Atrial fibrillation occurred in 48.7% of the patients according to the follow-up visits. In the previous studies, the prevalence of atrial fibrillation was 20 - 28%, which was lower compared to the current investigation (28). On the other hand, atrial fibrillation was more common in the cases with a maximum LVEF of 50% than in those with

LVEF > 50% (48.7% vs. 24.4%).

The present study results revealed a significant increase in the left atrial size at the five-year follow-up. Left atrial size (odds ratio = 2.489, P = 0.003) was an independent predictor of BO-ApHCM. In one study among patients with ApHCM, left atrial enlargement was the only predictor of atrial fibrillation and one of the predictors of cardiovascular morbidity (7).

Impaired LV relaxation in patients with HCM including ApHCM has been previously proposed as a mechanism for progressive left atrial enlargement and, subsequently, atrial fibrillation (7, 15). In the current research, diastolic dysfunction was more frequent and more severe among the patients with BO-ApHCM in comparison with the previous studies.

In the current investigation, more than half of the patients with HCM (57%) suffered from moderate to severe RV dysfunction. RV dysfunction was more severe in the cases with BO-ApHCM (59.4% vs. 17.9%) than in those without BO-ApHCM. RV dysfunction (odds ratio = 10.9, P = 0.003) was also an important predictor of BO-ApHCM.

Concerning valvular disorders in HCM, AR at the first visit was significantly higher in the patients with BO-ApHCM than in those without BO-ApHCM. During the follow-up, however, no significant difference was observed between the two groups in terms of MR and AR severity. Additionally, neither of these two variables predicted the progression of the disease to the burned-out phase.

The current study findings indicated that SPAP was significantly higher in the patients with BO-ApHCM compared to those without BO-ApHCM after five years (p=0.01). It is worth mentioning that the previous investigations have paid little attention to RV dysfunction and diastolic function in patients with ApHCM. This could be attributed to the overestimation of the prevalence due to the performance of the study in a tertiary center or an increase in the rate over time.

5.1. Conclusions

The prevalence of BO-ApHCM was higher in the present study compared to the previous studies. Besides, RV dysfunction and LA enlargement were two of the most important predictors of BO-ApHCM.

5.2. Limitation

This study had some limitations. Firstly, it was a retrospective study and was conducted using stored images for analysis. Secondly, only 74 out of the 230 patients showed up for follow-up visits. Therefore, further prospective studies are required to identify a beneficial model for the prediction of BO-ApHCM.

5.3. Ethical Approval

This study was approved by the Ethics Committee of Iran University of Medical Sciences, Tehran, Iran (code: IR.RHC.REC.1399.097).

5.4. Informed Consent

This was a retrospective study and informed consent was optional based on the journal's guideline.

Acknowledgements

The authors would like to appreciate Mrs. Roghayyeh Sepordeh, the head nurse of the Echocardiography Department of Rajaie Cardiovascular Center. They would also like to thank all the participants who took part in the study.

Authors' Contribution

Study concept and design: A.S. and A.A.; analysis and interpretation of data: Z.R., M.B., and N. S.; drafting of the manuscript: Z.R., M.M., S.J., and M.S.; critical revision of the manuscript for important intellectual content: D.K., K.R., M.K., Z.S., and M.B; statistical analysis: H.B. and B.G.

Funding/Support

No financial support was received for this study. Azin Alizadehasl was supported by a research grant from the Interventional Cardiology Department of Rajaie Cardiovascular Research Center. No extramural funding was used to support this work. The authors were solely responsible for the design and conduct of the study, data analysis, and drafting and editing the manuscript.

Financial Disclosure

The authors have no financial interests related to the material in the manuscript.

References

1. Gruner C, Care M, Siminovitch K, Moravsky G, Wigle ED, Woo A*, et al.* Sarcomere protein gene mutations in patients with apical hypertrophic cardiomyopathy. *Circulation: Cardiovascular Genetics*. 2011;**4**(3):288-95.
2. Seidman C. Hypertrophic cardiomyopathy: from man to mouse. *The Journal of Clinical Investigation*. 2000;**106**(9).
3. Stephenson E, Monney P, Pugliese F, Malcolmson J, Petersen SE, Knight C*, et al.* Ineffective and prolonged apical contraction is associated with chest pain and ischaemia in apical hypertrophic cardiomyopathy. *International journal of cardiology*. 2018;**251**:65-70.
4. Wu B, Lu M, Zhang Y, Song B, Ling J, Huang J*, et al.* CMR assessment of the left ventricle apical morphology in subjects with unexplainable giant T-wave inversion and without apical wall thickness≥ 15 mm. *European Heart Journal-Cardiovascular Imaging*. 2017;**18**(2):186-94.
5. Begley D, Mohiddin S, Fananapazir L. Dual chamber pacemaker therapy for mid-cavity obstructive hypertrophic cardiomyopathy. *Pacing and Clinical Electrophysiology*. 2001;**24**(11):1639-44.
6. Yamada M, Teraoka K, Kawade M, Hirano M, Yamashina A. Frequency and distribution of late gadolinium enhancement in magnetic resonance imaging of patients with apical hypertrophic cardiomyopathy and patients with asymmetrical hypertrophic cardiomyopathy: a comparative study. *The international journal of cardiovascular imaging*. 2009;**25**(1):131-8.
7. Eriksson MJ, Sonnenberg B, Woo A, Rakowski P, Parker TG, Wigle ED*, et al.* Long-term outcome in patients with apical hypertrophic cardiomyopathy. *Journal of the American College of Cardiology*. 2002;**39**(4):638-45.
8. Kim H, Park J-H, Won K-B, Yoon H-J, Park H-S, Cho Y-K*, et al.* Significance of apical cavity obliteration in apical hypertrophic cardiomyopathy. *Heart*. 2016;**102**(15):1215-20.
9. Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P*, et al.* 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy. *Kardiologia Polska (Polish Heart Journal)*. 2014;**72**(11):1054-126.
10. Maron MS, Finley JJ, Bos JM, Hauser TH, Manning WJ, Haas TS*, et al.* Prevalence, clinical significance, and natural history of left ventricular apical aneurysms in hypertrophic cardiomyopathy. *Circulation*. 2008;**118**(15):1541-9.

11. Chen CC, Lei MH, Hsu YC, Chung SL, Sung YJ. Apical hypertrophic cardiomyopathy: correlations between echocardiographic parameters, angiographic left ventricular morphology, and clinical outcomes. *Clinical cardiology*. 2011;**34**(4):233-8.
12. Arad M, Penas-Lado M, Monserrat L, Maron BJ, Sherrid M, Ho CY*, et al.* Gene mutations in apical hypertrophic cardiomyopathy. *Circulation*. 2005;**112**(18):2805-11.
13. Rowin EJ, Maron BJ, Haas TS, Garberich RF, Wang W, Link MS*, et al.* Hypertrophic cardiomyopathy with left ventricular apical aneurysm: implications for risk stratification and management. *Journal of the American College of Cardiology*. 2017;**69**(7):761-73.
14. Moon J, Fisher N, McKenna W, Pennell D. Detection of apical hypertrophic cardiomyopathy by cardiovascular magnetic resonance in patients with non-diagnostic echocardiography. *Heart*. 2004;**90**(6):645-9.
15. Hughes RK, Knott KD, Malcolmson J, Augusto JB, Mohiddin SA, Kellman P*, et al.* Apical hypertrophic cardiomyopathy: the variant less known. *Journal of the American Heart Association*. 2020;**9**(5):e015294.
16. Maron MS, Rowin EJ, Wessler BS, Mooney PJ, Fatima A, Patel P*, et al.* Enhanced American College of Cardiology/American Heart Association strategy for prevention of sudden cardiac death in high-risk patients with hypertrophic cardiomyopathy. *JAMA cardiology*. 2019;**4**(7):644-57.
17. Swoboda PP, McDiarmid AK, Erhayiem B, Broadbent DA, Dobson LE, Garg P*, et al.* Assessing myocardial extracellular volume by T1 mapping to distinguish hypertrophic cardiomyopathy from athlete's heart. *Journal of the American College of Cardiology*. 2016;**67**(18):2189-90.
18. Sheikh N, Papadakis M, Schnell F, Panoulas V, Malhotra A, Wilson M*, et al.* Clinical profile of athletes with hypertrophic cardiomyopathy. *Circulation: Cardiovascular Imaging*. 2015;**8**(7):e003454.
19. Choi E-Y, Rim S-J, Ha J-W, Kim Y-J, Lee S-C, Kang D-H*, et al.* Phenotypic spectrum and clinical characteristics of apical hypertrophic cardiomyopathy: multicenter echo-Doppler study. *Cardiology*. 2008;**110**(1):53-61.
20. Patten M, Pecha S, Aydin A. Atrial fibrillation in hypertrophic cardiomyopathy: diagnosis and considerations for management. *Journal of atrial fibrillation*. 2018;**10**(5).
21. Flett AS, Maestrini V, Milliken D, Fontana M, Treibel TA, Harb R*, et al.* Diagnosis of apical hypertrophic cardiomyopathy: T-wave inversion and relative but not absolute apical left ventricular hypertrophy. *International Journal of Cardiology*. 2015;**183**:143-8.
22. Stainback RF. Apical hypertrophic cardiomyopathy. *Texas Heart Institute Journal*. 2012;**39**(5):747.
23. ROH SY, KIM DH, Ahn J, Lee KN, Lee DI, Shim J*, et al.* Long-term outcome of catheter ablation for atrial fibrillation in patients with apical hypertrophic cardiomyopathy. *Journal of cardiovascular electrophysiology*. 2016;**27**(7):788-95.
24. Jenab Y, Pourjafari M, Darabi F, Boroumand MA, Zoroufian A, Jalali A. Prevalence and determinants of elevated high-sensitivity cardiac troponin T in hypertrophic cardiomyopathy. *Journal of cardiology*. 2014;**63**(2):140-4.
25. Klarich KW, Jost CHA, Binder J, Connolly HM, Scott CG, Freeman WK*, et al.* Risk of death in long-term follow-up of patients with apical hypertrophic cardiomyopathy. *The American journal of cardiology*. 2013;**111**(12):1784-91.
26. Kebed KY, Al Adham RI, Bishu K, Askew JW, Klarich KW, Araoz PA*, et al.* Evaluation of apical subtype of hypertrophic cardiomyopathy using cardiac magnetic resonance imaging with gadolinium enhancement. *The American journal of cardiology*. 2014;**114**(5):777-82.
27. Neubauer S, Kolm P, Ho CY, Kwong RY, Desai MY, Dolman SF*, et al.* Distinct subgroups in hypertrophic cardiomyopathy in the NHLBI HCM registry. *Journal of the American College of Cardiology*. 2019;**74**(19):2333-45.
28. Kubo T, Kitaoka H, Okawa M. Hirota. *Clinical profiles of hypertrophic cardiomyopathy with apical phenotype Circulation*. 2009;**73**:2330-6.