Survival and Clinical Behavior of Hypertrophic Cardiomyopathy in a Latin American Cohort in Contrast to Cohorts from the Developed World

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Background: Hypertrophic cardiomyopathy (HCM) is the most common hereditary heart disease with diverse phenotypic, genetic expression and clinical presentations. The evolution of patients with HCM in Latin America has not been properly described being the frequency, the long-term prognosis as well as the predominant phenotypic expression still unknown. The aim of this study was to determine the survival rate of HCM patients having different phenotypes in a Mexican cohort of patients.

Methods: Clinical and echocardiographic data obtained from 77 Mexican patients with recently diagnosed HCM were analyzed. The follow-up was of 12.5 years.

Results: 96.1% of patients were in functional class I/II according to the New York Heart Association, 2.6% in class III and 1.3% in class IV. Only 3.9% of them went to surgery for myectomy. During the follow-up, 17 patients (22%) died: 4/9 (44%) had apical HCM, 5/20 (25%) had obstructive septal asymmetric HCM, 6/35 (17%) had nonobstructive septal asymmetric HCM and 2/3 (15%) had concentric HCM. The survival rate was worse for patients with apical HCM, followed by those with obstructive and nonobstructive septal asymmetric HCM and patients showing concentric HCM had the best survival rates. There is significant difference in survival rates which declined in 65% in a 9 years-period. Log rank test showed significant differences (p < 0.002).

Conclusion: The survival rate of patients with HCM was worse in those with apical variety. The majority of patients received medical treatment. The indication for myectomy was below that observed in other international centers.

Keywords: Apical hypertrophic cardiomyopathy · Latinamerican cohort · Myectomy.

Introduction

Hypertrophic cardiomyopathy (HCM) is the most common hereditary heart disease in the world (prevalence of 1 in 500 individuals). It has great clinical and phenotypic variabilities. Despite its identification as an autosomal dominant feature, many genetic mutations are involved in the expression of the disease and the primary etiology is still elusive.¹²

Although HCM diagnosis is complicated by the genetic variability, it is generally characterized by a localized left ventricular thickening which is out of proportion with the hemodynamic load and unexplained by systemic conditions. Current guidelines suggest that diagnosis of HCM should be considered when there is a maximum ventricular wall thickening ≥ 15 mm or ≥ 13–14 mm in the presence of family history or...
compatible electrocardiogram when detected by echocardiography or magnetic resonance imaging (MRI).3,40

The outcome of HCM patients has not been properly described in the Latin American population; the frequency of the disease is unknown, as well as the predominant phenotypic expression. The long-term prognosis of these patients is also ignored.

To determine the survival rate of HCM patients having different phenotypes in a Mexican cohort from a third level outpatient center.

METHODS

Clinical and echocardiographic data obtained from 77 Mexican patients (37.6 ± 17 years old) with recently diagnosed HCM were analyzed according to the current guidelines. The average duration of the follow-up was of 6.6 ± 4.9 years.

RESULTS

Table 1 shows the demographic data of the patients and the average duration of the follow-up. Forty one patients (41/77, 53.2%) were found to be in functional class I according to the New York Heart Association (NYHA), 33/77 (42.9%) in functional class II, 2/77 (2.6%) in functional class III and only 1/77 (1.3%) in functional class IV. The Table 2 shows the NYHA functional class of different types of HCM.

In our series, 39% (30/77) of the patients started with an audible heart murmur [being more common in men (19/77) than in women (11/77), although not statistically significant]. The most common symptom was the presence of dyspnea, which occurred in the 46.7% (36/77), chest pain which was present in 35% (27/77) and palpitations that appeared in 28.6% (22/77) of the patients. Syncope was observed in the 14.3% (11/77, being slightly more common in men) and lipotimia in the 7.8% (6/77) of the patients.

The electrocardiography showed sinus rhythm in 64 (83.1%) patients, pacemaker rhythm in 9 (11.7%) and atrial fibrillation in 4 (5.2%).

The echocardiographic study made it possible to characterize, that in our cohort, 45% of the patients had non obstructive septal asymmetric HCM. The distribution of phenotypic

| Table 1. Demographic data of studied population |
|-----------------------------------------------|
| HCM                                          |
| n (%)                                        |
| Total                                        |
| Female                                       |
| Male                                         |
| p value                                      |
| n (%)                                        |
| Age (mean ± SD), years                       |
| 37.6 ± 17                                    |
| 37.9 ± 16.6                                  |
| 37.5 ± 17.5                                  |
| ns                                           |
| Weight (mean ± SD), kg                       |
| 67.6 ± 17                                    |
| 61 ± 17                                      |
| 72.6 ± 15                                    |
| 0.005                                        |
| Height (mean ± SD), cm                       |
| 161 ± 19                                     |
| 154 ± 11                                     |
| 166 ± 22                                     |
| 0.01                                         |
| Body mass index (mean ± SD), kg/cm           |
| 25.5 ± 5                                     |
| 25.3 ± 6                                     |
| 25.7 ± 3.8                                   |
| ns                                           |
| Smoking, n (%)                               |
| 26 (33.8)                                    |
| 5 (16)                                       |
| 21 (46)                                      |
| 0.007                                        |
| Systemic arterial hypertension, n (%)         |
| 15 (19.5)                                    |
| 10 (32)                                      |
| 5 (11)                                       |
| 0.02                                         |
| Diabetes mellitus, n (%)                     |
| 6 (7.8)                                      |
| 2 (6.5)                                      |
| 4 (8.7)                                      |
| ns                                           |
| Dyslipidemia, n (%)                           |
| 11 (14.3)                                    |
| 4 (13)                                       |
| 7 (15)                                       |
| ns                                           |
| Disease evolution (mean ± SD), years          |
| 6.6 ± 4.9                                    |
| 7.4 ± 5.5                                    |
| 6.1 ± 4.5                                    |
| ns                                           |
| Phoenotypes of HCM*, n (%)                   |
| Non obstructive septal asymmetric HCM        |
| 35 (45.5)                                    |
| 14 (40)                                      |
| 21 (60)                                      |
| ns                                           |
| Obstructive septal asymmetric HCM            |
| 20 (26)                                      |
| 12 (60)                                      |
| 8 (40)                                       |
| 0.001                                        |
| Apical HCM                                   |
| 9 (11.7)                                     |
| 0 (0)                                        |
| 9 (100)                                      |
| 0.009                                        |
| Concentric HCM                              |
| 13 (16.9)                                    |
| 5 (38.5)                                     |
| 8 (61.5)                                     |
| ns                                           |
| Total                                        |
| 77 (100)                                     |
| 31 (40)                                      |
| 46 (60)                                      |
| ns                                           |

*Defined according echocardiographic parameters. SD: standard deviation, HCM: hypertrophic cardiomyopathy, ns: not significant

| Table 2. NYHA functional class of different types of HCM |
|----------------------------------------------------------|
| NYHA functional class | Obstructive septal asymmetric HCM | Non obstructive septal asymmetric HCM | Concentric HCM | Apical HCM | Total, n (%) |
|-----------------------|-----------------------------------|---------------------------------------|---------------|------------|--------------|
| I                     | 9                                 | 18                                    | 9             | 5          | 41 (53.2)    |
| II                    | 10                                | 16                                    | 3             | 4          | 33 (42.9)    |
| III                   | 1                                 | 1                                     | 0             | 0          | 2 (2.6)      |
| IV                    | 0                                 | 0                                     | 1             | 0          | 1 (1.3)      |
| Total, n (%)          | 20 (26)                           | 35 (45.4)                             | 13 (16.9)     | 9 (11.7)   | 77 (100)     |

HCM: hypertrophic cardiomyopathy, NYHA: New York Heart Association
managed only with medical treatment. The rest (23.4%) underwent pacemaker implantation, alcohol septal ablation and septal myectomy, Table 4. In patients with stroke the cardiac rhythm was atrial fibrillation in one and in the other sinus rhythm with ventricular and supraventricular arrhythmias.

During the follow-up time, 17 patients (22%) died: 4/9 (44%) with apical HCM, 5/20 (25%) with obstructive septal patterns is specified in detail in Table 1. The echocardiographic measurements of the whole group and of the HCM types are shown in Table 3, with statistically significant differences in relation to the thickness of the interventricular septum, to the left ventricular end-diastolic and end-systolic diameters and to the systolic pulmonary artery pressure (Fig. 1–4).

Regarding the treatment, the 76.6% of the patients were managed only with medical treatment. The rest (23.4%) underwent pacemaker implantation, alcohol septal ablation and septal myectomy, Table 4. In patients with stroke the cardiac rhythm was atrial fibrillation in one and in the other sinus rhythm with ventricular and supraventricular arrhythmias.

During the follow-up time, 17 patients (22%) died: 4/9 (44%) with apical HCM, 5/20 (25%) with obstructive septal

Table 3. Echocardiographic measurements of the HCM types

|                        | Total    | Non obstructive HCM | Obstructive HCM | Concentric HCM | Apical HCM | p value |
|------------------------|----------|----------------------|------------------|----------------|------------|---------|
| n, (%)                 | 77 (100) | 35 (45)              | 20 (26)          | 13 (17)        | 9 (12)     |         |
| LA (mean ± SD), mm     | 41 ± 9   | 43 ± 11              | 41 ± 6           | 40 ± 7         | 40 ± 8     | ns      |
| Interventricular septum (mean ± SD), mm | 19.7 ± 6 | 20.8 ± 6            | 22.4 ± 4.5       | 15.3 ± 3       | 14.5 ± 2.6 | 0.001   |
| Left posterior wall (mean ± SD), mm | 13.7 ± 1.9 | 13 ± 2              | 14 ± 3           | 13.5 ± 2.1     | 12.5 ± 1.8 | ns      |
| LVDD (mean ± SD), mm   | 40 ± 7   | 42 ± 6.8             | 36 ± 5           | 41 ± 10        | 41 ± 5     | 0.03    |
| LVSD (mean ± SD), mm   | 24 ± 5   | 25 ± 5               | 21 ± 4           | 25 ± 8         | 23 ± 5     | 0.06    |
| LVEF (mean ± SD), %    | 66 ± 7   | 67 ± 7               | 67 ± 8           | 64 ± 6         | 66 ± 5     | ns      |
| PASP (mean ± SD), mm Hg| 35 ± 12  | 36 ± 11              | 31 ± 9           | 44 ± 12        | 28 ± 6     | 0.02    |

LA: left atrium, LVDD: left ventricular diastolic diameter, LVSD: left ventricular systolic diameter, LVEF: left ventricular ejection fraction, PASP: pulmonary artery systolic pressure, SD: standard deviation, HCM: hypertrophic cardiomyopathy, ns: not significant

![Fig. 1. Parasternal long axis view with M mode (A), two-dimensional apical four-chamber view (B), short axis view at the level of both ventricles (C) and apical 4-chamber view with continuous wave Doppler (D), showing systolic anterior motion of the mitral valve with obstruction of the left ventricle outflow tract (white arrows). The characteristic appearance of the late peak is observed as a dagger. LA: left atrium, LV: left ventricle, RA: right atrium, RV: right ventricle, Ao: aorta.](image-url)
survival rates decline in 65% in a 9 years-period. Log rank test showed significant differences ($p < 0.002$). These results are shown in Fig. 5.

**DISCUSSION**

The diagnosis of HCM is hampered by the large phenotypic variability of the disease. It is generally characterized by a

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**Fig. 2.** Two-dimensional echocardiography, M mode and color Doppler of an obstructive septal asymmetric hypertrophic cardiomyopathy. Mitral valve calcification and systolic anterior motion of the mitral valve is observed (white arrow). In the apical 4-chambers view, a dilated left atrium and severe mitral insufficiency is shown (white arrow). LA: left atrium, RA: right atrium.

**Fig. 3.** Two-dimensional echocardiography in an apical 2 and 4 chambers view, tissue Doppler imaging and tridimensional 4 chamber view, showing apical left ventricular hypertrophy (arrow) and left atrial enlargement. LA: left atrium, LV: left ventricle, RA: right atrium, RV: right ventricle.
in the presence of familiar history of HCM (or compatible electrocardiogram), that is detected either by echocardiography or MRI. Paradoxically, in our study, the survival rate was worse for patients with apical HCM, followed by those with obstructive and nonobstructive septal asymmetric HCM and patients showing concentric HCM had the best survival rates. There is a significant difference in the survival rates which decline in 50% in a 20 month-period. Log rank test showed significant differences \((p < 0.001)\). This finding is controversial and brings light to the behavior of the HCM in Latin American patients, since in series from other world regions such as Asian populations, apical HCM is an atypical phenotype and it usually has an apparent benign course. However, sudden cardiac death did not differ between apical HCM and other HCM types in North America population.

Recent studies showed an increased rate of adverse outcomes in the long-term follow-up of patients with apical HCM and abnormal apical contractility, as occurred in our study. The aggressiveness of a particular variant of HCM could depend more on the genotype than on the morphological characteristics (i.e., phenotype). Kaluderic et al. alludes to the fact that specific mutations in certain genes have a clinical and prognostic relevance in HCM.

Table 4. Type of treatment, n (%)

| Type of treatment                        | n (%)            |
|-----------------------------------------|------------------|
| Medical                                 | 59/77 (76.6)     |
| Pacemaker                               | 9/77 (11.7)      |
| Alcohol septal ablation                 | 6/77 (7.8)       |
| Myectomy                                | 3/77 (3.9)       |

There is evidence that patients with mutations in the \(\beta\) heavy chain of myosin (MHC-\(\beta\)) have the disease at a younger age, with more severe hypertrophy and have an increased risk of sudden death when compared to patients with mutations at the alpha tropomyosin or MYBPC chain. This pathogenic mutation can only be identified in 50% of the patients. However, it is also important to note that the apical HCM has not been associated with a characteristic sarcomeric mutation, but seems to be the reflection of multiple genetic interactions. In fact, in the study of Arad et al. in 15 patients with documented apical HCM, only a limited number of genetic sarco-
mERIC DEFECTS WERE FOUND. ACTIN MUTATION GLU101LYS WAS FOUND TO BE CONSISTENTLY ASSOCIATED WITH APEICAL HCM. HOWEVER, AS HIGHLIGHTED EARLIER BY THE FINDINGS OF KALUDERIC ET AL., ACTIN MUTATIONS ARE GENERALLY ASSOCIATED TO BETTER PROGNOSIS THAN THOSE IN THE MHC-β.

NO GENE STUDY OF HCM WAS PERFORMED.

IN CONCLUSION, IN A MEXICAN COHORT OF PATIENTS WITH HCM, SURVIVAL RATE WAS WORSE IN PATIENTS WITH THE APEICAL VARIETY OF HYPERTR OPHIC CARDIOMYOPATHY WHEN COMPARED TO PATIENTS WITH CONCENTRIC HCM. THE MAJORITY OF PATIENTS AT OUR INSTITUTION ARE CONSIDERED FOR MEDICAL TREATMENT ONLY. THE INDICATION FOR MYOMECTOMY IN OUR COHORT IS LOWER THAN THAT OBSERVED IN OTHER CENTERS OF INTERNATIONAL ATTENTION.

OUR STUDY DESCRIBES THE PARTICULAR BEHAVIOR OF THE HCM IN THE LATIN AMERICAN POPULATION. IN THIS POPULATION THE DISEASE HAS A DIFFERENT CLINICAL COURSE THAN THAT CLASSICALLY DESCRIBED IN ASIAN COUNTRIES, WHICH IS ACCORDING WITH NORTH AMERICAN POPULATIONS. ALTHOUGH LARGER STUDIES ARE NEEDED TO CONFIRM THESE FINDINGS, IT SHOULD BE NOTED THE HCM IS GENERALLY UNDER-DIAGNOSED AND THEREFORE IT IS DIFFICULT TO GET LARGE NUMBER SERIES OF PATIENTS EVEN IN REFERRAL CENTERS SUCH AS OURS. JOINT AGENCY EFFORTS SHOULD BE MADE TO CREATE A REGISTER OF PATIENTS WITH HCM AND THEN DELINATE THE PARTICULAR BEHAVIOR OF THIS DISEASE IN LATINAMERICA AND MEXICO AND HELP TO REDUCE CARDIOVASCULAR DEATH IN THIS POPULATION.

REFERENCES
1. Maron BJ. Hypertrophic cardiomyopathy: an important global disease. Am J Med 2004;116:63-5.
2. Kaludercic N, Raggiani C, Pacoluci N. Genes, geography and geometry: the “critical mass” in hypertrophic cardiomyopathy. J Mol Diagn 2009; 11:12-6.
3. Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, Naido SS, Sushiura RA, Ommen SR, Rakowski H, Seidman CE, Towbin JA, Udelson JE, Yancy CW: American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the American Association for Thoracic Surgery, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 2011;58:e212-60.
4. McKenna W, Deanfield J, Faruqui A, England D, Oakley C, Goodwin J. Prognosis in hypertrophic cardiomyopathy: role of age and clinical, electrocardiographic and hemodynamic features. Am J Cardiol 1981;47:532-8.
5. Maron BJ, Gardin JM, Flack JM, Gidding SS, Kurosaki TT, Bild DE. Prevalence of hypertrophic cardiomyopathy in a general population of young adults. Echocardiographic analysis of 4111 subjects in the CARDIA Study. Coronary Artery Risk Development in (Young) Adults. Circulation 1995;92:785-9.
6. Kaple RK, Murphy RT, DiPaola LM, Houghtaling PL, Lever HM, Lytle BW, Blackstone EH, Smedira NG. Mitral valve abnormalities in hypertrophic cardiomyopathy: echocardiographic features and surgical outcomes. Ann Thorac Surg 2008;85:1527-33, 1535.e1-2.
7. Nagueh SF, McFalls J, Meyer D, Hill R, Zoghbi WA, Tam JW, Qafzehes NA, Roberts R, Marian AJ. Tissue Doppler imaging predicts the development of hypertrophic cardiomyopathy in subjects with subclinical disease. Circulation 2003;108:395-8.
8. He XW, Song ZZ. Evaluation of left ventricular function, rotation, twist and untwist in patients with hypertrophic cardiomyopathy. Exp Clin Cardiol 2003;18:e47-9.
9. Kimura A, Harada H, Park JE, Nishi H, Satoh M, Takahashi M, Hini S, Sasaoka T, Obuchi N, Nakamura T, Koyanagi T, Hwang TH, Choo JA, Chung KS, Hanagaw A, Nagai R, Okazaki O, Nakamura H, Matsuzaki M, Sakamoto T, Yoshima H, Koga Y, Imai Zumi T, Sasazuki T. Mutations in the cardiac tropomon I gene associated with hypertrophic cardiomyopathy. Nat Genet 1997;16:379-82.
10. Bonne G, Carrier L, Richard P, Hainque B, Schwartz K. Familial hypertrophic cardiomyopathy: from mutations to functional defects. Circ Res 1998;83:580-93.
11. Geisterfer-Lowrance AA, Kass S, Tanigawa G, Voepel HP, McKenna W, Seidman CE, Seidman JG. A molecular basis for familial hypertrophic cardiomyopathy: a beta cardiac myosin heavy chain gene missense mutation. Cell 1990;62:999-1006.
12. McKenna WJ, Monserrat Iglesias L. (Sudden death (V). Identification and treatment of patients with hypertrophic cardiomyopathy at risk of sudden death). Rev Esp Cardiol 2000;53:123-30.
13. Wigle ED, Rakowski H, Kimball BP, Williams WG. Hypertrophic cardiomyopathy. Clinical spectrum and treatment. Circulation 1995; 92:1680-92.
14. Maron BJ, Gott diener JS, Epstein SE. Patterns and significance of distribution of left ventricular hypertrophy in hypertrophic cardiomyopathy. A wide angle, two dimensional echocardiographic study of 125 patients. Am J Cardiol 1981;48:418-28.
15. Eriksson MJ, Sonnenberg B, Woo A, Rakowski P, Parker TG, Wigle ED, Rakowski H. Long-term outcome in patients with apical hypertrophic cardiomyopathy. J Am Coll Cardiol 2002;39:638-45.
16. Binder J, Attenahofer Jost CH, Klarch KW, Connolly HM, Tajik AJ, Scott CG, Julsrud PR, Ehrsam JE, Bailey KR, Ommen SR. Apical hypertrophic cardiomyopathy: prevalence and correlates of apical outpouching. J Am Soc Echocardiogr 2011;24:775-81.
17. Klarch KW, Attenahofer Jost CH, Binder J, Connolly HM, Scott CG, Freeman WK, Ackerman MJ, Nishimura RA, Tajik AJ, Om-
18. Woo A, Rakowski H, Liew JC, Zhao MS, Liew CC, Parker TG, Zeller M, Wigle ED, Sole MJ. Mutations of the beta myosin heavy chain gene in hypertrophic cardiomyopathy: critical functional sites determine prognosis. Heart 2003;89:1179-85.

19. Ommen SR, Nishimura RA. Hypertrophic cardiomyopathy. Curr Probl Cardiol 2004;29:239-91.

20. Braunwald E, Seidman CE, Sigwart U. Contemporary evaluation and management of hypertrophic cardiomyopathy. Circulation 2002;106:1312-6.

21. Elliott PM, Gimeno JR, Tomé MT, Shah J, Ward D, Thaman R, Mogensen J, McKenna WJ. Left ventricular outflow tract obstruction and sudden death risk in patients with hypertrophic cardiomyopathy. Eur Heart J 2006;27:1933-41.

22. Maron MS, Olivotto I, Betocchi S, Casey SA, Lesser JR, Losi MA, Cecchi F, Maron BJ. Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. N Engl J Med 2003;348:295-303.

23. O’Mahony C, Jichi F, Pavlou M, Monserrat L, Anastasakis A, Rapezzi C, Biagini E, Gimeno JR, Limongelli G, McKenna WJ, Omar RZ, Elliott PM; Hypertrophic Cardiomyopathy Outcomes Investigators. A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM risk-SCD). Eur Heart J 2014;35:2010-20.

24. Elliott PM, Poloniecki J, Dickie S, Sharma S, Monserrat L, Varnava A, Mahon NG, McKenna WJ. Sudden death in hypertrophic cardiomyopathy: identification of high risk patients. J Am Coll Cardiol 2000;36:2212-8.

25. Arad M, Penas-Lado M, Monserrat L, Maron BJ, Sherrod M, Ho CY, Barr S, Karim A, Olson TM, Kamisago M, Seidman JG, Seidman CE. Gene mutations in apical hypertrophic cardiomyopathy. Circulation 2005;112:2805-11.