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REVIEW ARTICLE

Hypertrophic cardiomyopathy. An historical and anatomopathological review

*Manlio F. Márquez[1], Teresita de Jesús Ruíz-Siller[1], Rosario Méndez-Ramos[1], Erick Karabut[1], Alberto Aranda-Fraustro[2] and Silvia Jiménez-Becerra[2]**

[1]Department of Electrophysiology; [2]Department of Pathologic Anatomy, Instituto Nacional de Cardiología Ignacio Chávez. Mexico City, Mexico

Abstract

Hypertrophic cardiomyopathy (HCM) is characterized by the presence of an abnormal hypertrophy of the left ventricle (LV), without dilation, and in the absence of any condition or another cardiac or systemic disease capable of inducing such hypertrophy. This primary or idiopathic hypertrophy can occur with or without dynamic obstruction (induced by exercise) of the LV outflow tract, so in its natural history two fundamental aspects are highlighted: the production of symptoms by blocking the LV outflow tract and the occurrence of sudden cardiac death secondary to ventricular arrhythmias. This revision includes the work of different Iberoamerican investigators, who contributed in an important way to lay the groundwork of what we know nowadays as HCM. It also includes the main anatomopathological characteristics, from its initial description to the new perspective we have concerning the myofiber disarray as the main histopathologic feature. (Gac Med Mex. 2016;152:624-8)

Corresponding author: *Silvia Jiménez-Becerra, siloddi@yahoo.com*

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Background

Hypertrophic cardiomyopathy (HCM) is a disease of the myocardium which main characteristic is an abnormal ventricular hypertrophy, not related to other causes (i.e. intense physical exercise or heart diseases) known to induce hypertrophy (Fig. 1)[1]. Most cases of HCM are hereditary but 1) not all family members inherit the disease and 2) phenotypical expression in those affected is variable[2]. The entity we now refer to as HCM was described in 1907 by Schmincke as "muscular stenosis of the left outflow tract", who published the first autopsy cases of idiopathic muscular hypertrophy in two females[3]. It is accepted that it corresponds to Sir Russell Brock, 50 years later, the merit for this entity to be currently better known, since he described the first series of patients with dynamic obstruction of the left ventricle (LV) outflow tract. He named it "acquired subvalvular aortic stenosis"[4]. Since then, this condition has received different names, including "hypertrophy of unknown cause"[5], "pseudoaortic stenosis"[6] to indicate that, clinically, it mimics aortic stenosis, "asymmetric hypertrophy" to indicate that the septum is more hypertrophied than the LV free wall[7], among other denominations. Although Braunwald, et at. introduced the term "idiopathic hypertrophic subaortic stenosis"[8], the term that finally gain acceptance and the one we use nowadays (HCM) was coined by Cohen, et al.[9].

Correspondence:
*Silvia Jiménez-Becerra
Instituto Nacional de Cardiología Ignacio Chávez
Juan Badiano 1
Col. Sección XVI, Del Tlalpan
C.P. 14080 Ciudad de México, México
E-mail: siloddi@yahoo.com

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In Mexico, the first publication on this disease was made by Fishleder, et al.[10], whom, in 1962, two years before the now considered classical works by Braunwald and Cohen, reported 6 cases of HCM under the denomination of "dynamic subaortic stenosis". With this name they want to emphasize the hemodynamical behavior ("stenosis"), its location ("subaortic"), as well as its functional nature ("dynamic"). Since current medical literature is based on English language journals, some relevant articles on HCM published in Spanish language journals before 1975 are described in table 1 as a recognition for such pioneer work on the field[10-17].

Incidence and prevalence

Our understanding of HCM has dramatically increased thanks to many medical advances, but mainly due to increased clinical use of genetic molecular studies and advances on imaging techniques, both in echocardiography and magnetic resonance imaging, which have considerably increased the number of diagnosed cases[18]. The prevalence of HCM in Europe is estimated to be 0.33% (166,000 patients were diagnosed in 2011). Although there are no national statistics available in Mexico, a diagnosis of HCM was confirmed in 136 patients at the Ignacio Chávez National Institute of Cardiology between 2000 and 2014, out of a total of 81,460 individuals attended for a prevalence of 0.16% (data not published). In the same period, 467 autopsies were practiced, out of which only one case corresponded to HCM. This is not surprising; for example, in Italy, out of 54 autopsies of individuals younger than 40 years of age with sudden cardiac death (SCD) performed between 1993 and 2012, no one corresponded to HCM[19]. There are several explanations for these reduced numbers of HCM findings in autopsies; one of them might be that affected subjects die outside the hospital; another, that they die of heart failure after developing dilatation and the condition being catalogued as dilated cardiomyopathy. Finally, another possibility is that SCD can be the first manifestation of the disease[20].

In countries with appropriate statistics available on SCD, HCM is one of the main causes of SCD in young subjects. Corrado, et al.[21] studied the cause of SCD in individuals younger than 35 years in Italy. They found that HCM was the cause of SCD in 6.3%, with a marked difference between athletes (2%) and young subjects who were not athletes (7.3%). As previously mentioned, one of the most concerning aspects both for doctors and for those who are diagnosed with the disease and their families, is the fact that SCD can be the first manifestation of the disease, even with mild exercise, not necessarily with extenuating sports activity.

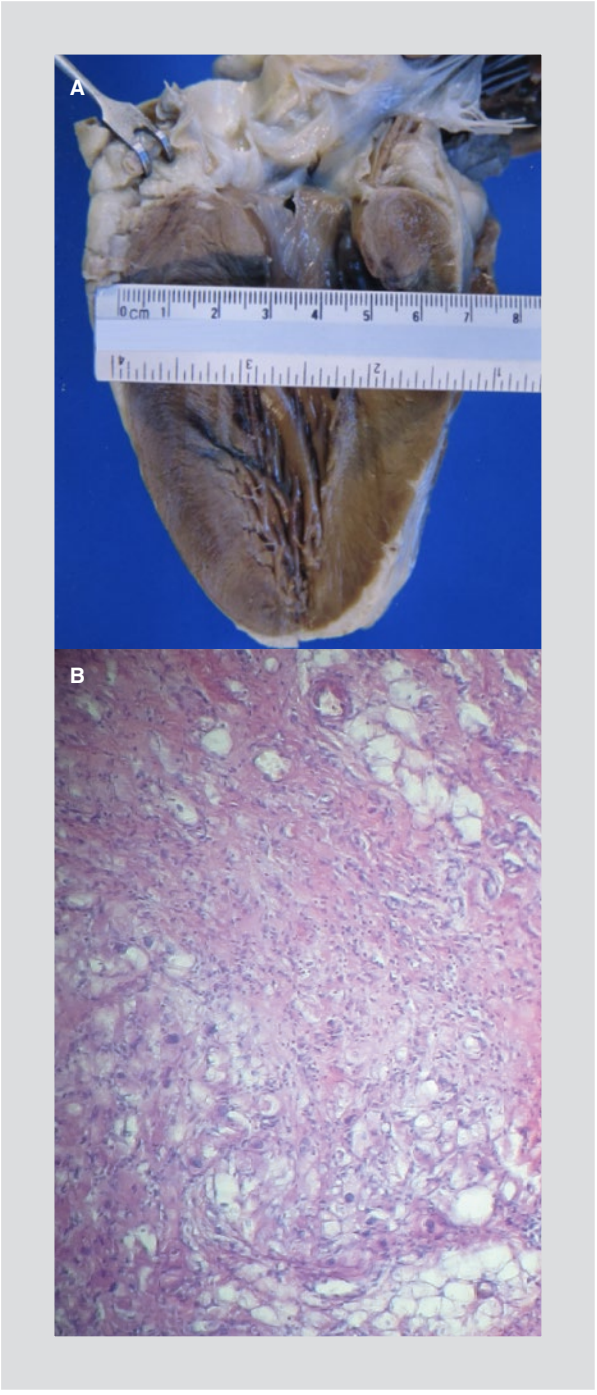

Figure 1. A: *anatomical pathology specimen of a heart with HCM showing interventricular septum significant thickening.* **B:** *interventricular septum histological slice of figure 1 A specimen, showing fiber disarray at the periphery and a fibrosis zone in the center.*

Table 1. Articles on HCM published in Ibero-American journals prior to 1975

Author	Date	Number of cases	Males/ Females n (%)	Observations	Reference
Fishleder	1962	6	5/1	Clinical (systolic murmur of low localization, without thrill or radiation to the neck, its left behavior with the Valsalva maneuver, etc.) and phonocardiographic manifestations are described, as well as the carotid sphygmogram characteristics.	10
Bonetti	1965	3	Males	Hemodynamic and angiocardiographic findings are described. The article points out that the left ventricular infundibulum abnormal contraction site can be visualized with cineangiocardiography.	11
Glenny	1965	16	N/S	Clinical and phonocardiographic study.	12
Rotberg	1969	1	Female	A case is presented of double infundibular stenosis: aortic and pulmonary.	
Vidne	1970	9	N/S	Surgical results with myotomy (only two linear incisions) are described in two cases, as well as resection of a portion of the hypertrophic septal mass in seven.	13
Skromne	1972	1	Male	Report on a 2-year 4-month old boy with Ebstein disease in whom the postmortem study also demonstrated interventricular hypertrophy (14 mm), with no apparent cause. Histopathological data consistent with HCM.	14
Salazar	1973	26	20/6	A series of cases with ages ranging from 3 to 67 years, with an average of 31, is described. Two families with HCM and sudden death are described.	15
Cueto	1974	1	Female	The case presented was a newborn clinically diagnosed with myocarditis; the necropsy confirmed obstructive HCM.	16
Vallés Belsué	1974	23	14/9	Left ventricle cineangiographic findings in 23 obstructive HCM cases are presented.	17

The incidence of HCM in young individuals undergoing pre-sports participation testing in Italy was 0.07%[21], and although in Latin America there are no statistics on SCD in athletes, we do have examples of celebrities, curiously, all of them soccer players. In Mexico, the case of Antonio de Nigris, who died at 31 years of age while playing for a Greek soccer club. In Peru, Yair Clavijo, player of the Sporting Cristal team, died at 18 years of age during a soccer match. Figure 3 shows the heart of a 17-year old athlete, also a soccer player, who died suddenly[22]. The heart preserved its triangular shape, and the left ventricular cavity was normal. An important asymmetric thickening of the ventricular wall was observed, with the greatest thickening at the anterior basal region, which corresponds to the left ventricle outflow tract. This is characteristic of asymmetric septal hypertrophy and distinguishes apart from hypertrophy of other etiologies[23]. Figure 2 illustrates the disarray, or disarrangement of myocardial fibers.

Anatomical and histopathological changes

It is generally accepted that the first who describe the histopathological features was Teare[7], who reported 8 cases with a "disorganized and bizarre arrangement of muscle bundles associated with hypertrophy of individual muscle fibers and their nuclei". Since then, the literature generally emphasizes that HCM has three histopathological features (none is pathognomonic nor should be considered as gold standard): myocyte hypertrophy, myofibre disarrangement or disarray (in some areas of the heart) and interstitial and replacement fibrosis (plexiform)[24]. There are two relevant additional characteristics: The presence of abnormal intramural (intramyocardial) coronary arteries with thickened walls due to proliferation of smooth muscle and collagen in both, intima and media tunicas. This thickening reduces the lumen and could explain some exercise-related deaths[25]. The second characteristic corresponds to structural changes of the mitral valve apparatus: (1) Anomalous

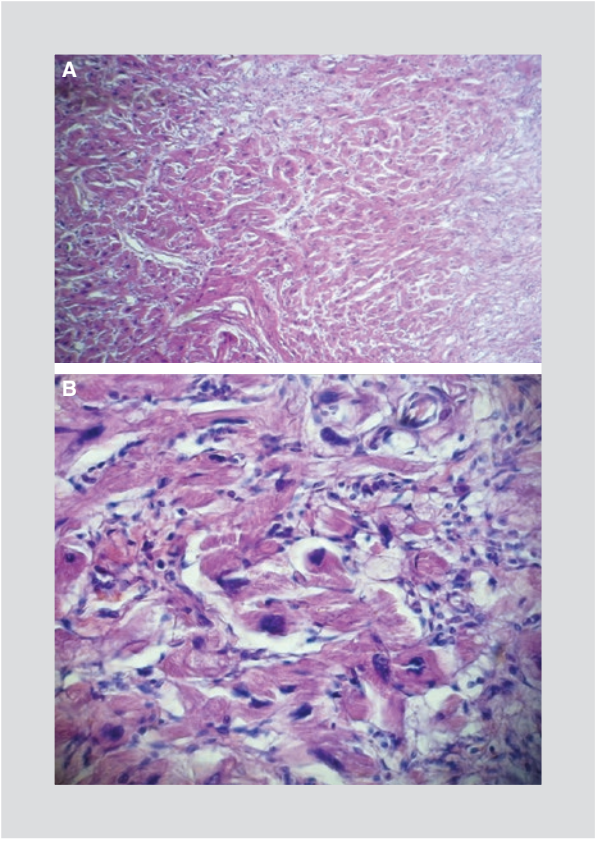

Figure 2. *Interventricular septum histological slices from figure 1 A specimen.* **A:** *with 10x enlargement, myocardial fibers disarray is shown (hematoxylin-eosin staining, 10x).* **B:** *with higher enlargement, cardiac myocytes with signs of hypertrophy are observed (hematoxylin-eosin staining, 20x).*

insertions of the papillary muscle into the anterior leaflet favoring anterior displacement of the mitral valve and obstruction of the LV outflow tract[26]; (2) Mitral valve elongation and thickening have been also reported. The pathologic myocardium is thought to produce an excess of paracrine growth factors, which drives this valvular growth[27]. It is highly unlikely that these anomalies are secondary to mechanical or acquired factors, suggesting that HCM is not confined to cardiac muscle[28].

Hypertrophy and myofiber disarray are not uniform, they are not observed in the entire heart, and are found only in certain areas. In the interventricular septum, alterations predominate in the middle region, in comparison with right and left ventricular sides of the septum[29]. For this reason, endomyocardial biopsy is not 100% sensitive, since the representative zone may not be sampled. Nunoda, et al.[30] found HCM characteristic changes in 71% of their cases.

Specifically, myofiber disarray, which has been considered as a pathognomic finding, is now questioned regarding its diagnostic value in HCM, since it has been also observed in many congenital heart diseases and also in normal hearts[5] (specifically, in the septum and some small areas of the LV). It is also known that, in some areas, a disorganized histological appearance of fibers can be obtained by varying the orientation of the same tissue block with slices in parallel or cross-sectional to the heart's axis[31].

Attempts have been made to correlate genotype with histology; for example: patients with HCM and troponin T gene mutations have more myofiber disarray and, in spite of having less fibrosis and hypertrophy than those with an unknown genotype, they were more prone to SCD[32]. With the use of confocal microscopy, intercalated discs structural alterations have been found, specifically of desmosomes and gap junctions, as it was expected[33]. The remodeling of gap junctions, which are in charge of electrical impulse transmission, might be the substrate to generate and maintain ventricular arrhythmias in these patients.

HCM has been known since long to be able to evolve to dilated cardiomyopathy. Hina, et al.[34], in a 6.5-year follow-up of 51 patients with HCM classical criteria, observed that LV was dilated and LV ejection fraction decreased in 8 of them (15.7%). At HCM advanced stages, large amounts of fibrous tissue appear on the LV together with thinning of the wall and dilatation of cavities. Coppini, et al.[35] reported that mutations on genes that encode for thin filaments (tropomyosin, troponin, actin) are associated with greater systolic dysfunction than those affecting thick filaments (myosin).

The presence of myocardial bridges has been reported in up to 40% of cases with HCM. Although in a first report the presence of this anomaly in children was significantly associated with SCD[36], other groups have not confirmed this finding in children[37] or adults[38,39]. The myocardial bridge probably represents only another phenotypical expression of this disease.

In summary, HCM is a disease that has drawn the attention of many researchers since its original description. Although most texts generally focus on Anglo-Saxon investigators' initial contributions, here is shown that there were also important contributions of Ibero-American authors since the beginning. Clinically, this condition manifests itself in different ways, with SCD as the worst outcome. Histopathologically, in addition to the three classical features (myocyte hypertrophy, myofibre disarray and fibrosis), there are underrecognized findings that can be characteristic of the disease, such as coronary and mitral valve apparatus anomalies, which may have relevant clinical significance.

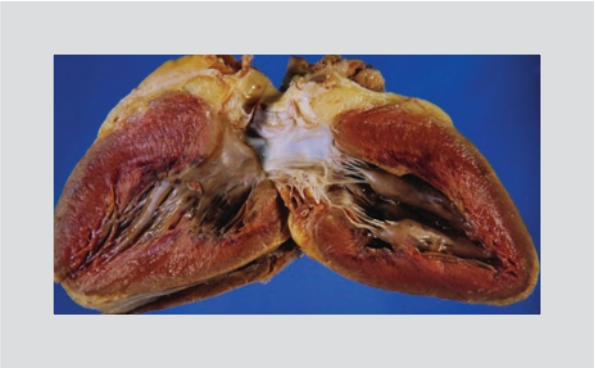

Figure 3. *Anatomical pathology specimen of a heart with HCM showing interventricular septum significant thickening* (originally published in Arch Cardiol Mex. 2004;74[S2:S334-7, with permission of the journal]).

Conclusion

Hypertrophic cardiomyopathy is a disease that has drawn the attention of clinicians, surgeons and pathologists in the past. It has several anatomopathological characteristics of its own. Beyond left ventricular hypertrophy, myofiber disarray should be considered a quantitative rather than a qualitative marker for HCM. The genotype-phenotype correlation regarding different structural alterations and its clinical significance is currently being studied.

References

1. Elliott P, Andersson B, Arbustini E, et al. Classification of the cardiomyopathies: a position statement from the european society of cardiology working group on myocardial and pericardial diseases. Eur Heart J. 2007;29(2):270-6.
2. Méndez A. Cardiomiopatía hipertrófica. En: Cardiología SM de, ed. Tratado de Cardiología. México: Intersistemas S.A. de C.V.; 2004. pp. 424-32.
3. Schmincke A. Ueber linkseitige muskulöse Conusstenosen 1). DMW - Dtsch Medizinische Wochenschrift. 1907;33(50):2082-3.
4. Brock R. Functional obstruction of the left ventricle; acquired aortic subvalvar stenosis. Guys Hosp Rep. 1957;106(4):221-38.
5. Norris RF, Pote HH. Hypertrophy of the heart of unknown etiology in young adults; report of 4 cases with autopsies. Am Heart J. 1946;32(5):599-611.
6. Bercu BA, Diettert GA, Danforth WH, Pund EE, Ahlvin RC, Belliveau RR. Pseudoaortic stenosis produced by ventricular hypertrophy. Am J Med. 1958;25(5):814-8.
7. Teare D. Asymmetrical hypertrophy of the heart in young adults. Br Heart J. 1958;20(1):1-8.
8. Braunwald E, Lambrew CT, Rockoff SD, Ross J, Morrow AG. Idiopathic Hypertrophic Subaortic Stenosis. I. A Description of the Disease Based upon an Analysis of 64 Patients. Circulation. 1964;30 Suppl 4:3-119.
9. Cohen J, Effat H, Goodwin JF, Oakley CM, Steiner RE. Hypertrophic Obstructive Cardiomyopathy. Br Heart J. 1964;26:16-32.
10. Fishleder BL, Bermudez F, Friedland C. Estenosis subaórtica dinámica. Su diagnóstico clínico y por métodos gráficos externos. Arch Inst Cardiol Mex. 1962;32:430-51.
11. Bonetti F, Garcia S, Soni J. Estenosis Subaórtica Dinámica. Arch Inst Cardiol Mex. 1965;35:125-36.
12. Glenny JE, Greco HL, Cossio PR, Kreutzer E, Cossio P. Auscultación cardíaca (IX): Estenosis subaórtica muscular dinámica. Prensa Med Argent. 1965;52(44):2782-6.
13. Vidne BA, Aygen M, Garti I, Eshkol D, Levy MJ. Tratamiento quirúrgico de las estenosis aórticas subvalvulares. Prensa Med Argent. 1970;57(7): 327-33.
14. Skromne Kadlubik D, Franco Vázquez JS, Portilla Aguilar J, López Cuéllar MR. Dilatación Auricular Derecha y Cardiomiopatía Hipertrófica Primaria. Arch Inst Cardiol Mex. 1972;42(5):788-95.
15. Salazar E, Soriano G, Esquivel J. Estenosis Subaórtica Dinámica. Estudio de 26 casos. Arch Inst Cardiol Mex. 1973;43(5):661-82.
16. Cueto García L, Ortega Gaytán M, Benítez Bribiesca L, Rodríguez Jurado P, Madrid J. Cardiomiopatía hipertrófica primaria simulando miocarditis del recién nacido. Bol Med Hosp Infant Mex. 1974;31(5): 985-95.
17. Vallés Belsué F, Martín Judez V, Fernández de Miguel JM, Artaza Andrade M, Márquez Montes J, Maître Azcárate MJ. Cineangiografía en la Miocardiopatía Hipertrófica Obstructiva. Arch Inst Cardiol Mex. 1974;44(4):598-610.
18. Semsarian C, Ingles J, Wilde AAM. Sudden cardiac death in the young: the molecular autopsy and a practical approach to surviving relatives. Eur Heart J. 2015;36(21):1290-6.
19. Vassalini M, Verzeletti A, Restori M, De Ferrari F. An autopsy study of sudden cardiac death in persons aged 1-40 years in Brescia (Italy). J Cardiovasc Med (Hagerstown). 2016;17(6):446-53.
20. Kocovski L, Fernandes J. Sudden Cardiac Death: A Modern Pathology Approach to Hypertrophic Cardiomyopathy. Arch Pathol Lab Med. 2015;139(3):413-6.
21. Corrado D, Basso C, Schiavon M, Thiene G. Screening for hypertrophic cardiomyopathy in young athletes. N Engl J Med. 1998;339(6):364-9.
22. Aranda A, Soto V. Alteraciones estructurales de las miocardiopatías. Arch Cardiol Mex. 2004;74(s2):334-7.
23. De Micheli A, Medrano GA, Aranda A. Aspectos eléctricos de la hipertrofia del corazón izquierdo. Arch Cardiol Mex. 2003;73(2):135-42.
24. Hughes SE. The pathology of hypertrophic cardiomyopathy. Histopathology. 2004;44(5):412-27.
25. Maron BJ, Wolfson JK, Epstein SE, Roberts WC. Intramural ("small vessel") coronary artery disease in hypertrophic cardiomyopathy. J Am Coll Cardiol. 1986;8(3):545-57.
26. Klues HG, Roberts WC, Maron BJ. Anomalous insertion of papillary muscle directly into anterior mitral leaflet in hypertrophic cardiomyopathy. Significance in producing left ventricular outflow obstruction. Circulation. 1991;84(3):1188-97.
27. Hagège AA, Bruneval P, Levine RA, Desnos M, Neamatalla H, Judge DP. The mitral valve in hypertrophic cardiomyopathy: old versus new concepts. J Cardiovasc Transl Res. 2011;4(6):757-66.
28. Klues HG, Maron BJ, Dollar AL, Roberts WC. Diversity of structural mitral valve alterations in hypertrophic cardiomyopathy. Circulation. 1992;85(5): 1651-60.
29. Hoshino T, Fujiwara H, Kawai C, Hamashima Y. Myocardial fiber diameter and regional distribution in the ventricular wall of normal adult hearts, hypertensive hearts and hearts with hypertrophic cardiomyopathy. Circulation. 1983;67(5):1109-16.
30. Nunoda S, Genda A, Sekiguchi M, Takeda R. Left ventricular endomyocardial biopsy findings in patients with essential hypertension and hypertrophic cardiomyopathy with special reference to the incidence of bizarre myocardial hypertrophy with disorganization and biopsy score. Heart Vessels. 1985;1(3):170-5.
31. Becker AE, Caruso G. Myocardial disarray. A critical review. Br Heart J. 1982;47(6):527-38.
32. Varnava AM, Elliott PM, Baboonian C, Davison F, Davies MJ, McKenna WJ. Hypertrophic cardiomyopathy: histopathological features of sudden death in cardiac troponin T disease. Circulation. 2001;104(12):1380-4.
33. Sepp R, Severs NJ, Gourdie RG. Altered patterns of cardiac intercellular junction distribution in hypertrophic cardiomyopathy. Heart. 1996;76(5): 412-7.
34. Hina K, Kusachi S, Iwasaki K, et al. Progression of left ventricular enlargement in patients with hypertrophic cardiomyopathy: incidence and prognostic value. Clin Cardiol. 1993;16(5):403-7.
35. Coppini R, Ho CY, Ashley E, et al. Clinical Phenotype and Outcome of Hypertrophic Cardiomyopathy Associated with Thin-Filament Gene Mutations. J Am Coll Cardiol. 2014;64(24):2589-600.
36. Yetman AT, McCrindle BW, MacDonald C, Freedom RM, Gow R. Myocardial bridging in children with hypertrophic cardiomyopathy--a risk factor for sudden death. N Engl J Med. 1998;339(17):1201-9.
37. Mohiddin SA, Begley D, Shih J, Fananapazir L. Myocardial bridging does not predict sudden death in children with hypertrophic cardiomyopathy but is associated with more severe cardiac disease. J Am Coll Cardiol. 2000;36(7):2270-8.
38. Sorajja P, Ommen SR, Nishimura RA, Gersh BJ, Tajik AJ, Holmes DR. Myocardial bridging in adult patients with hypertrophic cardiomyopathy. J Am Coll Cardiol. 2003;42(5):889-94.
39. Basso C, Thiene G, Mackey-Bojack S, Frigo AC, Corrado D, Maron BJ. Myocardial bridging, a frequent component of the hypertrophic cardiomyopathy phenotype, lacks systematic association with sudden cardiac death. Eur Heart J. 2009;30(13):1627-34.