Section 1
Clinical cases

IRSTI 76.29.30 https://doi.org/10.26577/IAM.2022.v3.i1.01

Zh.N. Nurbay[1,2*], R.M. Tuleutayev[1], A.T. Jumabekov[2], K.B. Abzaliyev[1,3], M.A. Zhakaev[2]

[1]JSC "Research Institute of Cardiology and Internal Diseases", Almaty, Kazakhstan
[2]Kazakhstan Medical University "KSPU" Almaty, Kazakhstan
[3]Al-Farabi Kazakh National University, Almaty, Kazakhstan
*e-mail: zhanar256@gmail.com

CHARACTERISTICS AND RESULTS OF A SURGICAL TREATMENT OF PATIENTS WITH A HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy (HCM) is diagnosed in a presence of severe hypertrophy of the walls of the left ventricle (LV) with a predominant remodeling of n the interventricular septum and the posterior LV wall, when the LV outflow tract (LVOT) begins to obstruct outflow hemodynamics. Because of an extreme genetic etiology diversity of the pathology, the genes that cause it e remain unknown in about 40% of patients with HCM. With the development of NGS technologies, the work of identifying of new mutations has become slightly easier. In addition to rare pathogenic variants of the sarcomeric protein gene, relatively common genetic variants associated with HCM are increasingly being recognized. We performed an examination of 43 patients at the RIOC and ID JSC from January 2017 to August 2021 were examined, 21 of whom had severe HCM with LVOT obstruction that required surgical treatment. Pathology in female population occurred in 67% of cases, in men it was 2 times less – 33 22 patients (51%) had an obstructive form of HCM. The other 21 patients have initial signs of HCM (are under observation) and 35% were asymptomatic patients.

IT was established that 56% of the cohort had different types of mutations, in which it was found that 75% of patients had monomutations, and 25% had 2 mutations. In most cases, mutations were found in the myosin heavy chain (MYH7 – 42%) and myosin-binding protein C (MYBPC3 – 17%). In the group ofpatients that underwent a surgical treatment, 12 patients (57%) of patients had various mutations. Also, in 4 patients, we tracked the family history. Morrow myectomy was performed in 21 patients, 95% of them additionally underwent mitral valve repair with removal of secondary chords. In all operated patients, the pressure gradient on the LVOT decreased from 2 to 7+ 1.7 mm Hg. There were no lethal outcomes.

Key words: gene, mutations, patient characteristics, hypertrophic cardiomyopathy, Morrow myectomy

Introduction

Hypertrophic cardiomyopathy (HCM) is a heart condition, with left ventricular wall hypertrophy (LVH), characterized by disordered location of myocytes, as well as cardiac fibrosis [1]. According to world statistics, the prevalence of HCM is 1 in 500 among the adult population [2]. Generally, HCM is inherited as an autosomal dominant trait that causes variants of mutations in genes characteristic of the sarcomere. Although HCM is considered to be predominantly a monogenic disease, there are a growing number of theories that explain phenotypic diversity, such as alteration of gene variants, epigenetics and other regulatory mechanisms of gene expression, and environmental factors. Despite recent advances in genetic technology, it is impossible to definitively establish a causal relationship between some cases, especially in sporadic cases or in small families. Due to the extreme genetic diversity, the genes that cause the disease remain unknown in approximately 40% of patients with HCM [3]. With the development of NGS technologies, the work of searching for new mutations has become slightly easier. In addition to rare pathogenic variants of the sarcomeric protein gene, relatively common

variants associated with HCM are increasingly being recognized [4,5]. Exercise, diet, cardiac stress conditions, environmental exposure, and other diseases are non-genetic factors that alter expanding HCM variants. However, the underlying mechanisms have not yet been accurately described.

The clinical manifestations of HCM are very diverse. Individuals with HCM may present with a constellation of symptoms, including dyspnea on exertion, fatigue, palpitations, dizziness, syncope, atypical chest pain, and sudden cardiac death (SCD) resulting in diastolic ventricular dysfunction, cardiac arrhythmias, and LVOT obstruction as the underlying pathophysiological conditions [6,7]. The signs and symptoms of HCM do not necessarily correlate with the degree or severity of LVOT obstruction or the degree of LVH, and a significant proportion of young patients with HCM remain asymptomatic or minimally symptomatic throughout life [8]. HCM is the most common cause of sudden cardiac death in young people and often athletes, which is the most formidable complication that can occur as the first manifestation of the disease [9,10]. The catalysts that provoke acute life-threatening arrhythmia or sudden cardiac death (SCD) remain poorly understood, but it is important to consider anatomical obstruction and electrophysiological abnormalities. The risk of SCD is based on a history of cardiac arrest or sustained ventricular tachycardia (VT), unexplained syncope, a family history of sudden death suspected of being caused by HCM in one or more first-degree relatives, and documentation of maximum LV wall thickness (≥30 mm), nonsustained VT, and abnormal blood pressure response during exercise [8]. The progression of heart failure (HF), a clinical syndrome of dyspnea on exertion in patients with HCM, is disproportionate or occurs in the absence of volume overload and pulmonary congestion seen in typical patients with HF. This may occur in intravascular volume depletion, filling disturbance (e.g., diastolic dysfunction), arrhythmia (e.g., tachyarrhythmia), or myocardial dysfunction secondary to ischemia (due to mismatch in oxygen demand) and small vessel coronary artery disease [7,11]. LVOT obstruction is a fundamental feature resulting from dynamic ventricular septal enlargement exacerbated by systolic anterior mitral valve movement, which can cause acute or intermittent symptoms of HF [7]. Arrhythmias, including atrial fibrillation (AF is a major factor in thromboembolic stroke [6] and ventricular tachycardia, may precede the development of heart failure (HF) or complicate HF in HCM.

Materials and Methods

We examined 43 patients at the JSC RIOC and ID from January 2017 to August 2021, (Figure 1), 21 of whom had severe HCM with LVOT obstruction, which required surgical treatment – Morroy myectomy surgery. The age of patients ranged from 18 to 80 years, the average age was 57 years.

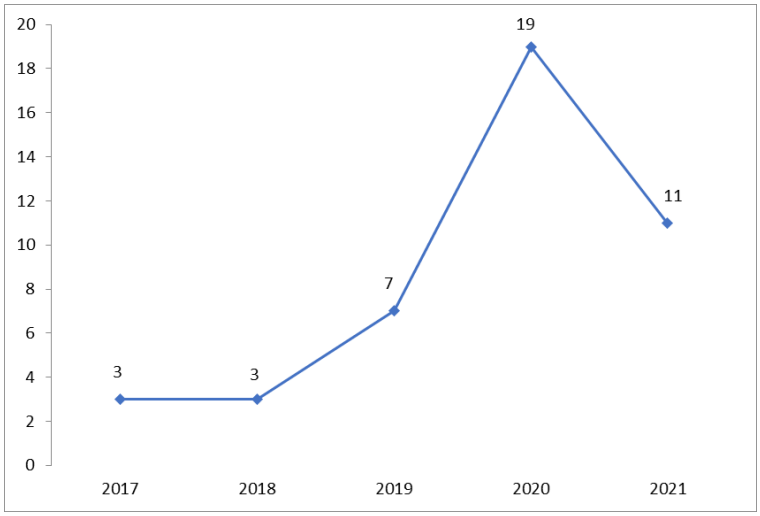

Figure 1 – Number of identified patients with HCM.

Interpreting the data, it was noted that since 2019 (2019 – 7 patients, 2020 – 19 patients) there has been an increase in diagnosed patients with HCM, which is due to the fact that the RIOC and ID database is the only source collecting the data with this pathology, patient negotiability (active training of cardiologists

in the city and regions), the presence of subspecialists in the functional diagnostic team who know this pathology.

The majority of the patients was referred from Almaty (42%) and Almaty region (47%), other regions (EKR, KZO, WKO) from 2 to 5%, which indicates that it is necessary to conduct seminars and training for general practitioners, cardiologists and patient community in remote regions of the Republic of Kazakhstan.

The research methods in our case in 100% of cases were the following: transthoracic echocardiography (ECHOCG) – as the gold standard, transesophageal EchoCG (TEECHOCG), electrocardiography (ECG), 24-hours Holter ECG. From laboratory research methods – NT-pro BNP (brain natriuretic hormone), for the diagnosis of heart failure. All operated patients underwent histological biopsy test (excised muscle folds). Next generation sequencing (NGS) is a method for determining the nucleotide sequence of DNA and RNA to obtain a description of its primary structure. The technology of the new generation sequencing method allows you to "read" several sections of the genome at once, which is the main difference from earlier sequencing methods. NGS is accomplished by repeated cycles of polymerase-induced chain extension or multiple ligation of oligonucleotides. During NGS, up to hundreds of megabases and gigabases of nucleotide sequences can be generated in one working cycle [6]. Genetic study (dry blood spot – spot) was sent to the DLE genetic laboratory, Brazil (MK Sanofi) and obtained results for possible mutations in 17 genes, as well as the exclusion of Fabry disease (the study went on for 1 year from 2020 to 2021).

Results and Discussion

In the Republic of Kazakhstan, as well as according to the world literature (Figure 2), in most cases, pathology occurs in women (67%), while in men it is 2 times less (33%). Ethnic origin, in 25 (58%) patients was recorded in Kazakhs, 14 (33%) cases in Russians and in 9% (4) in Uighurs.

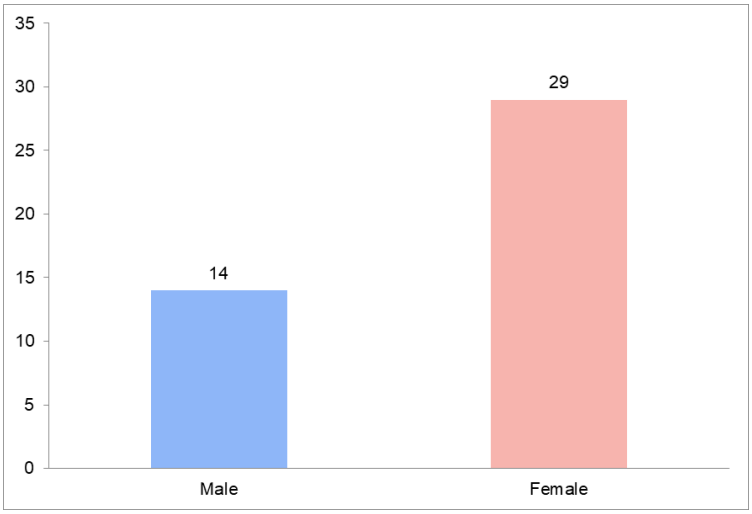

Figure 2 – Distribution by sex

In our study, 22 patients (51%) out of 43 had an obstructive form of HCM and were operated (21 patients) at the RIOC and ID, 1 patient was not operated because of frailty (80 years old and significant concomitant pathology (diabetes mellitus, acute renal failure)). The remaining 21 patients have had some initial signs of HCM (they are under observation, Transthoracic EchoCG is performed twice a year) Figure 3), other 35% were asymptomatic with echocardiographic lesions and positive genetics. 14% of patients have changes according to EchoCG, clinic (dyspnea, anginal pain), but did not have indications for surgical treatment at the time of the study. Periodic anginal pain was noted by 58% of patients, 6 patients described severe pain. Heart rhythm changes were not observed in 86% of patients according to the Holter ECG data, in 2 cases a pathology of the coronary bed was detected during coronary angiographythat required additional coronary bypass grafting. A concomitant pathology of the heart valves (mainly the mitral valve) was registered in after coronary angiography 49% of the patients.

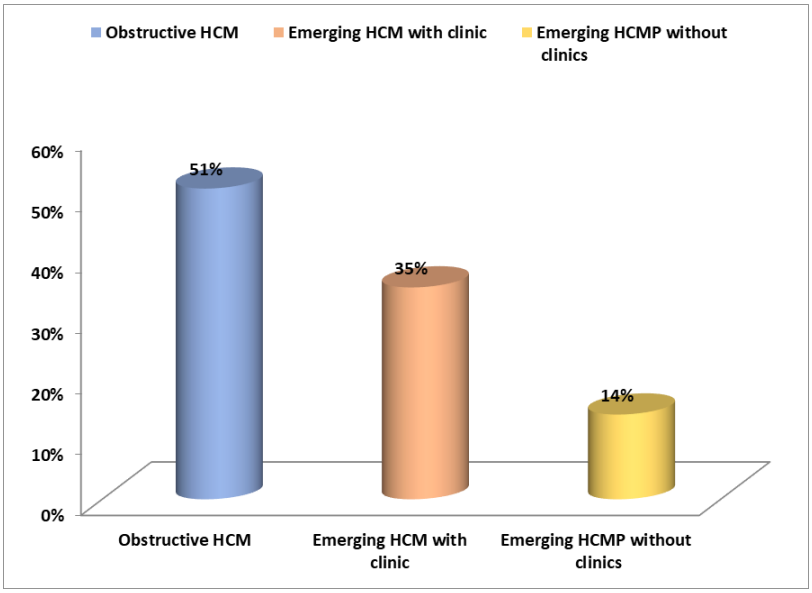

Figure 3 – Forms of HCM

The New York Heart Association Classification of the severity of chronic heart failure in 51% of patients had class III, 35% of patients had class II, and 14% of patients IV.

The main complaint was dyspnea of varying severity in 98% of patients, dizziness in 31 (72%) patients, of which syncope (semi-consciousness) was observed only in 5 (12%) patients. no complaints of dizziness in the remaining 12 (28%) patients. Of the concomitant pathology, type 2 diabetes mellitus was also detected in 4 patients (in 9% of cases). Concomitant arrhythmia at the time of the study was in 22 (49%) patients (Figure 4).

When analyzing the data (Figure 4) it was noted that among 22 (51%) cases, of sinus rhythm, in 3 (7%) an ICD device was implanted due to the risk of SCD, in total, arrhythmias occurred in 8 (19%) cases, 2% – incomplete block of the bundle of His branches, ventricular tachycardias were found in 2% of cases. In 19% of cases, ventricular extrasystoles.

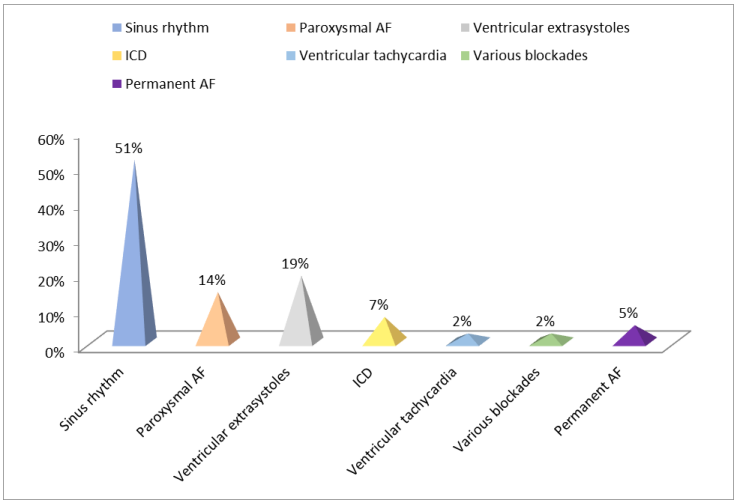

Figure 4 – Heart rhythms in patients with HCM according to the 24-hour Holter ECG and ECG data (Sinus rhythm, Paroxysmal atrial fibrillation, Ventricular extrasystoles, ICD – implantable cardioverter defibrillator, Ventricular tachycardias, Permanent form of atrial fibrillation).

The rhythm of the post-op patients (21) before discharge was: 18 (86%) sinus rhythm, 2 (10%) rhythm of the pacemaker, 1 (5%) had a permanent form of AF.

SAM syndrome was diagnosed among the 41 (95%) patients (mitral valve and 17 (40%) cases had damage to the valvular apparatus. According to the echocardiography, the maximum gradient on the LVOT at rest was 25 mmHg in post-op (21) patients, 85 mmHg after exercise, whilst in non-operated patients (23) the gradient was 15mmHgwith increase after a exercise to 47 mmHg.

Morrow myectomy was performed in 21 patients, 95% of them underwent additional mitral valve repair with removal of secondary chords, 10% (2 patients) had myocardial revascularization. In 100% of cases, all excised material was sent for histological test, according to which, hypertrophy and chaotic arrangement of cardiomyocytes, fibrosis were detected in 100% of cases.

Of the 43 patients who underwent a genetic study (Figure 5), 24 (56%) had various types of mutations, of which 18 (75%) patients (Figure 6) had monomutations, and 6 (25%) had 2 mutations.

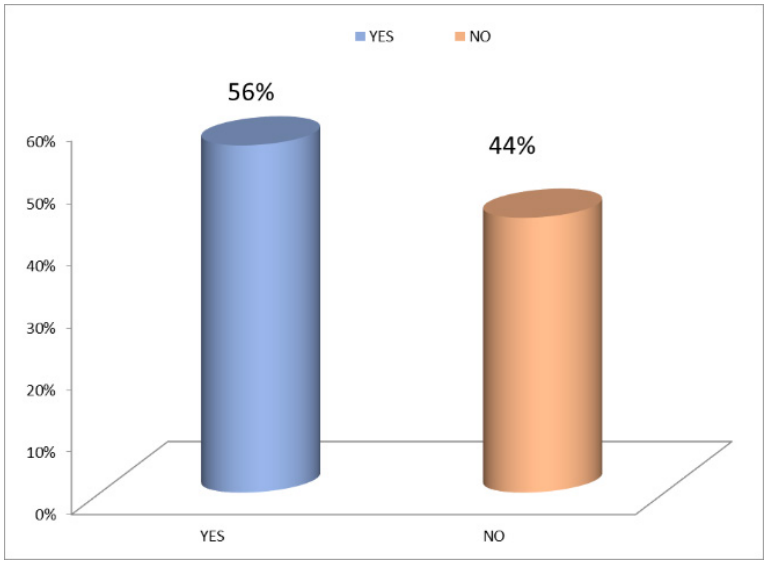

Figure 5 – The presence of identified genetic mutations of HCM in 43 patients

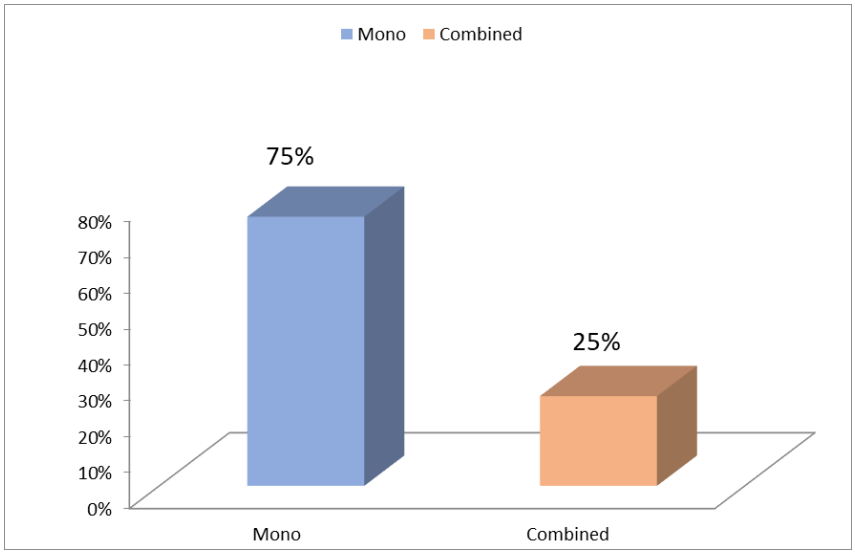

Figure 6 – Types of mutations

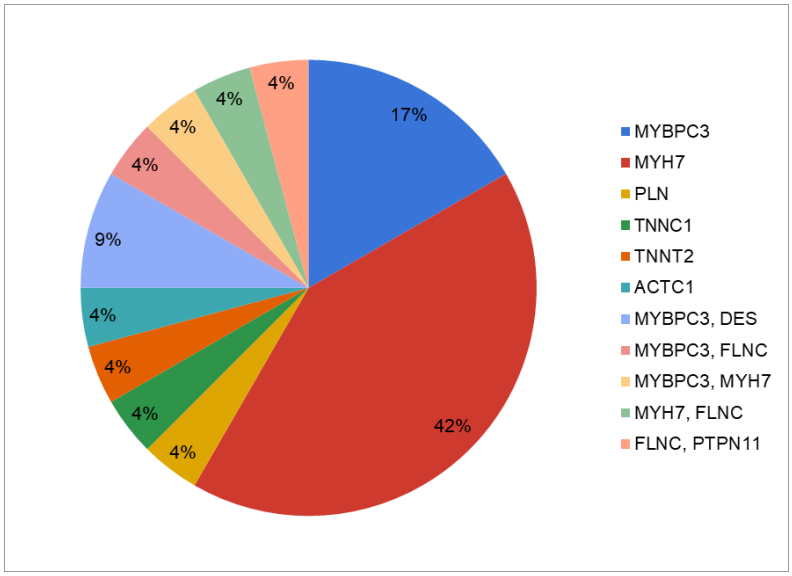

Figure 7 – Ratio of mutation varieties

According to our data (Figure 7), as well as, to the world literature, in most cases mutations were detected in the myosin heavy chain (MYH7 – 42%) and myosin-binding protein C (MYBPC3 – 17%), other variants were registered in 4-8%.

In the group of operated patients (21 patients), 12 (57%) patients had various mutations. Also, in 4 patients, we tracked a family history, with 1 patient who had all 3 children with mutations of the same type, in 1 operated patient, mother and aunt had identical mutations, and in 2 patients, mothers had mutations that did not match with children.

Conclusions

The study allowed us to analyze the main characteristics of the hypertrophic cardiomyopathy associated with the biology of sarcomeres. Establishing a diagnosis with a high risk of SCD dictates the need for more active tactics in relation to this category of patients (clarification of drug therapy, implantation of defibrillators-cardioverters and/or surgery). The strategy of therapeutic measures in HCM is complex even when analyzing the entire complex, including the results of gene diagnostics, clinical manifestations, anamnesis, hemodynamic parameters, and evaluation of the effectiveness of the treatment methods used. Of the clinical symptoms, dyspnea was manifested during physical exertion with syncopal phenomena in the form of dizziness and lipothymia. In recent years, scientific advances have given us the opportunity to find something new. This is the first time for us to study the genetic role leading to hypertrophic cardiomyopathy, understanding the major pathways involved in the underlying pathogenesis leading to the full spectrum of clinical phenotypes. The advent of NGS technologies has led to an expansion of the list of variants and genes involved in HCM.

References

1. Teekakirikul P., Padera R.F., Seidman J.G., Seidman C.E. Hypertrophic cardiomyopathy: Translating cellular cross talk into therapeutics. J. Cell Biol. 2012; 199:417–421.

2. Maron B.J., Gardin J.M., Flack J.M., Gidding S.S., Kurosaki T.T., Bild D.E. Prevalence of hypertrophic cardiomyopathy in a general population of young adults: Echocardiographic analysis of 4111 subjects in the CARDIA study. Circulation. 1995; 92:785–789.

3. Marian A.J. Hypertrophic cardiomyopathy: From genetics to treatment. Eur. J. Clin. Invest. 2010; 40:976–983.

4. Adalsteinsdottir B., Teekakirikul P., Maron B.J., Burke M.A., Gudbjartsson D.F., Holm H., Stefansson K., DePalma S.R., Mazaika E., McDonough B., et al. Nationwide study on hypertrophic cardiomyopathy in iceland evidence of a MYBPC3 founder mutation. Circulation. 2014; 130:1158–1167.

5. Dhandapany P.S., Sadayappan S., Xue Y., Powell G.T., Rani D.S., Nallari P., Rai T.S., Khullar M., Soares P., Bahl A., et al. A common MYBPC3 (cardiac myosin binding protein C) variant associated with cardiomyopathies in South Asia. Nat. Genet. 2009; 41:187–191.

6. Marian A.J., Braunwald E. Hypertrophic cardiomyopathy: Genetics, Pathogenesis, Clinical Manifestations, Diagnosis, and Therapy. Circ Res. 2017; 121:749–770.

7. Maron B.J., Rowin E.J., Udelson J.E., Maron M.S. Clinical Spectrum and Management of Heart Failure in Hypertrophic Cardiomyopathy. JACC Hear. Fail. 2018; 6:353–363.

8. Gersh B.J., Maron B.J., Bonow R.O., Dearani J.A., Fifer M.A., Link M.S., Naidu S.S., Nishimura R.A., Ommen S.R., Rakowski H., et al. 2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy. J. Am. Coll. Cardiol. 2011;58: e212–e260.

9. Maron B.J., Doerer J.J., Haas T.S., Tierney D.M., Mueller F.O. Sudden deaths in young competitive athlete's analysis of 1866 deaths in the united states, 1980-2006. Circulation. 2009; 119:1085–1092.

10. Maron B.J., Shirani J., Poliac L.C., Mathenge R., Roberts W.C., Mueller F.O. Sudden death in young competitive athletes: Clinical, demographic, and pathological profiles. J. Am. Med. Assoc. 1996; 276:199–204.

11.Maron B.J., Wolfson J.K., Epstein S.E., Roberts W.C. Intramural ("small vessel") coronary artery disease in hypertrophic cardiomyopathy. J. Am. Coll. Cardiol. 1986; 8:545–557