

Case 01/2008 – A Young Female Patient with the Familial Form of Hypertrophic Cardiomyopathy, who Evolved with Syncope, Complex Ventricular Arrhythmia and Cardiogenic Shock

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A 19-year-old female patient with the diagnosis of hypertrophic cardiomyopathy was referred to the hospital (Heart Institute (InCor), University of São Paulo Medical School, Brazil) for treatment.

The diagnosis of hypertrophic cardiomyopathy had been achieved at 5 years of age at the time of the cardiologic assessment carried out in the patient's family. The assessment was indicated considering the family history of several cases of the disease. The patient's father had a diagnosis of hypertrophic cardiomyopathy, which evolved to cardiac dilation and he was finally submitted to orthotopic heart transplant. Paternal uncles and grandparents also presented the disease. Two of the patient's brothers presented the same condition and one had died of sudden death.

The patient presented repeated episodes of syncope during the clinical evolution. She had been submitted to the implantation of an implantable cardioverter-defibrillator (ICD) three years before. After the implant, she started to present syncope episodes again and no defibrillating activity could be detected in the implanted device. She was then referred to Instituto do Coração (InCor).

At the first medical assessment at the hospital (11/16/2006), she complained of frequent episodes of palpitation associated to short-term general malaise, precordial pain, shortness of breath and pre-syncope. The last syncope episode had occurred four months prior to this medical visit. She also complained about shortness of breath triggered by strenuous physical effort.

The patient did not use beta-blockers or calcium channel antagonists. These drugs had been previously prescribed and used by the patient, but they had caused arterial hypotension and consequently, their use was withdrawn.

The physical examination (11/16/2006) disclosed

weight=56 kg, height = 1.56 m, body mass index (BMI) = 23 kg/m², regular pulse, heart rate = 60 bpm and BP=100 / 60 mmHg. Lung assessment was normal. The heart assessment showed systolic murmur at aortic focus +++/6 irradiating to the left sternum border and mitral area.

The electrocardiogram (11/13/2006) disclosed pacemaker rhythm, normofunctioning double chamber and left atrial overload.

Laboratory assessment (11/13/2006) showed hemoglobin = 13.6 g/dl, hematocrit = 41%, creatinine = 1.02 mg/dl, potassium = 4.6 mEq/l and sodium = 139 mEq/l.

The echocardiogram (11/28/2006) showed an aortic diameter of 24 mm, left atrium diameter of 44 mm, diastolic and systolic left ventricle diameters of 34 and 22 mm, respectively, with a left ventricle ejection fraction of 66%; the interventricular septum thickness was 18 mm and the left ventricular posterior wall thickness was 9 mm. There was a marked asymmetric hypertrophy of the septal and lateral walls with a hyperdynamic systolic performance, no alterations in segmental mobility, mild diastolic dysfunction, mild mitral insufficiency and maximum intra-ventricular gradient of 27 mmHg at rest.

Holter monitoring of the cardiac rhythm (11/27/2006) disclosed a sinus rhythm, alternating with the rhythm stimulated by the artificial pacemaker. The atrioventricular conduction alternated periods of normal conduction with others that presented ventricular stimulation by the pacemaker electrode. The heart rate (HR) varied from 59 to 158 bpm; the ventricular extrasystoles were polymorphic, isolated and rare (a total of 4 during the entire recording). The atrial extrasystoles were also rare and isolated (a total of 16). The symptoms of visual darkening and fatigue after physical exertion were related with increased cardiac frequency, without arrhythmias, during physical stress.

The ergorespiratory study revealed a maximum VO₂ of 18 ml.kg⁻¹.min⁻¹, with no increase in the systolic blood pressure during physical stress.

The patient received a prescription of propranolol, 40 mg. She, however, presented arterial hypotension and complained of the persistence of the episodes of pre-syncope. The clinical follow-up visit (Jan. 2007) showed BP= 120 / 80 mmHg with the patient in dorsal decubitus, 120 / 70 mmHg with the patient in the sitting position and 90 / 60 mmHg with the patient standing.

During the clinical visit she presented malaise and pre-syncope symptoms, with a heart rate of 120 bpm, which

Key words

Cardiomyopathy, hypertrophic; syncope; arrhythmia; shock, cardiogenic.

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improved after a few minutes when there was a decrease of the heart rate to 80 bpm.

On 01/13/2007 asymptomatic supraventricular paroxysmic tachycardia was documented during sleep.

The patient received a diagnosis of the familial form of hypertrophic cardiomyopathy, non-obstructive, without complex arrhythmia, with episodes of supraventricular paroxysmic tachycardia that caused hypotension and pre-syncope. Due to the patient's intolerance to beta-blockers and calcium-blockers, oral amiodarone therapy (600 mg) was initiated.

During the evolution, the patient sought emergency medical care (02/02/2007) as she had presented two syncope episodes; the assessment of the implantable cardioverter-defibrillator did not identify arrhythmia or defibrillator shock.

She evolved with the same general malaise and frequent pre-syncope episodes. On 02/05/2007 she had a syncope episode at home, which was accompanied by a family member who was a physician, presenting hypotension followed by the implantable defibrillator shock and cessation of symptoms. She had no symptoms when she arrived at the emergency department of InCor. The assessment of the implantable defibrillator showed ventricular tachycardia. Amiodarone was administered by IV route (300 mg followed by 900 mg IV within a 24-hour period).

The patient was admitted at the hospital and continued to have malaise episodes, characterized by precordial pain, sudoresis, bad peripheral perfusion and arterial hypotension associated to increase in the HR.

The electrocardiogram (02/09/2007) with inhibited pacemaker showed a sinus rhythm, left atrial overload and alterations in the ventricular repolarization (Fig. 1).

On 02/12/2007 the patient was submitted to an echocardiogram with increase of the pacemaker frequency from 60 to 90 bpm; an increase in the gradient of the left

ventricular outflow tract from 27 to 40 mmHg, as well as malaise symptoms, was observed.

An electrophysiological study was performed to conduct a possible ablation of the supraventricular paroxysmic tachycardia on 02/16/2007 under amiodarone use, with no induction of atrial or ventricular arrhythmias or retrograde conduction of the electro-cardiac stimulation.

The heart angiotomography (02/16/2007) showed a septal thickness of 30 mm and extensive and confluent late enhancement in the subendocardial region. The calcium score in the coronary arteries was 0 Agston.

On the 16th day of hospital admission (02/20/2007) she presented another episode of syncope at rest. After the episode, the heart rate was 96 bpm and BP was 70/40 mmHg. She improved after volemic expansion; the cardioverter-defibrillator device recording system did not show arrhythmia. In the afternoon of the same day she presented a new syncope episode with arterial hypotension, BP of 80/50 mmHg and HR of 76 bpm. During the electrocardiographic assessment, ventricular tachycardia with broad QRS complex and heart rate of 130 bpm were observed, which evolved to ventricular fibrillation, followed by the implantable cardioverter-defibrillator shock with reversion of the picture. She was transferred to the Intensive Care Unit (ICU) and amiodarone IV, 900 mg/day was maintained. Propranolol 10 mg, given orally, was initiated every 8 hours.

The propranolol dose was slowly increased, with no alterations in BP. However, the patient still presented the same previously related malaise episodes associated to slight increases in heart rate (70 to 90 bpm).

The pro-arrhythmic effect of amiodarone was considered and its dose was reduced, followed by an increase in the beta-blocker dose and decrease in the heart rate of the pacemaker entrance to 45 bpm. The tilt-test was indicated to investigate the possibility of a neurocardiogenic syncope.

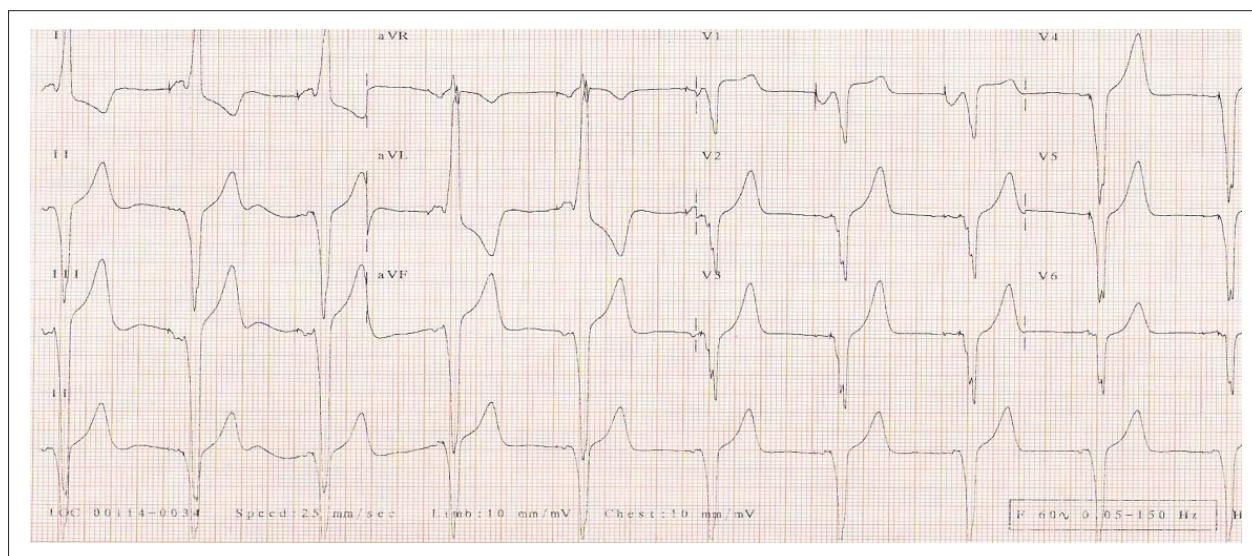


Fig. 1 - Sinus rhythm, left atrial overload; note the initial QRS complex narrowing and alterations in the ventricular repolarization.

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Laboratory assessment (02/22/2007) showed creatinine of 0.8 mg/dl, urea of 21 mg/dl, potassium 4.1 mEq/l and sodium 138 mEq/l.

On the following day (03/23/2007) amiodarone was prescribed at a dose of 200 mg administered orally every 12h, and the propranolol dose was increased to 30 mg administered orally every 8h. The patient presented several episodes of malaise with a Cheyne-Stokes respiratory pattern and heart rate between 60 and 100 bpm. Considering the increase of the intraventricular gradient associated to HR increases, the propranolol dose was increased to 40 mg administered orally every 8h and metoprolol was started, administered by IV route (3 ampoules during this period from 7 pm to 11 pm). Non-invasive ventilation was also started with positive pressure for the treatment of symptoms related to the Cheyne-Stokes respiratory pattern. She improved after the positive pressure respiration was started, with HR between 55 and 60 bpm and BP of 90/60 mmHg.

Three hours later the patient complained of severe malaise and presented sudoresis, bad perfusion and dyspnea as well as arterial hypotension of 50/30 mmHg and HR of 55 bpm.

Despite the positive-pressure ventilation, volemic expansion with crystalloid and dopamine administration by IV route, she did not improve. She started to present ventricular tachycardia, treated by the implantable cardiofibrillator. She was submitted to an orotracheal intubation for respiratory support and noradrenaline was started. A few hours later (02/24/2007) she presented cardiac arrest with pulseless electrical activity, which did not respond to the resuscitation maneuvers.

Comments on the exams:

ECG (Figure 1)

The hypertrophic cardiomyopathy and other cardiac hypertrophies can present initial narrowing of the QRS complex due to intraventricular conduction disorders, which can simulate the presence of pre-excitation.

(Prof. Dr. Paulo Jorge Moffa)

Tomography

The patient was submitted to 64-Section CT (Toshiba Inc.) with non-ionic iodated contrast injection (Iopamiron® Schering) for the evaluation of the myocardial fibrosis.

Asymmetric septal hypertrophy was also observed with a 27 mm septum and the presence of late myocardial enhancement (fibrosis) with a confluent pattern predominantly at the junction between the septum and the right ventricular free wall.

(Dr. Afonso Akio Shiozaki).

Clinical Aspects

We shall comment here the case of a patient with a confirmed diagnosis of hypertrophic cardiomyopathy and a positive family history on the paternal side, with intermittent episodes of dyspnea, palpitation, precordial pain and pre-syncope, who, despite the presence of an implantable cardiofibrillator (ICD), presented repeated episodes of syncope, with some of them not being triggered by arrhythmias.

The hypertrophic cardiomyopathy is the most common genetically-inherited disease in cardiology, with a prevalence of 0.2%¹ among the general population and present in all age ranges, from newborns to octogenarians. It is characterized by myocardial hypertrophy with no underlying cause such as hypertension or aortic stenosis. It has an asymmetric presentation with a preference for the septum and anterolateral wall. Histologically, there is disarray of the muscle fibers due to alterations in the sarcomere protein, fibrosis and increase of the interstitial matrix; they are not all specific to hypertrophic cardiomyopathy, but should be present in at least 10% of the ventricular mass for a histological diagnosis². There is thickening of the intramural coronary arteries and ischemia, a mechanism co-responsible for angina, evolution to the dilated phase, arrhythmias and sudden death³. There is also increase of the left ventricular mass, decrease in ventricular volume and compliance, mitral regurgitation and obstruction of the left ventricular outflow tract, with 5% to 10% of the patients progressing to the dilated phase⁴, as in the case of the patient's father. There is an increased risk of death, especially sudden death, which is associated with ventricular arrhythmias.

The disease has an autosomal dominant pattern of inheritance in 50% of the cases, a figure which can be underestimated due to the variable gene penetrance, strict echocardiographic criteria and incomplete analysis of the families⁵.

Other forms are the consequence of sporadic mutations. There are at least 10 genes involved in the disease⁶, all related to sarcomere proteins and that involve more than 150 types of mutations, with the possibility of the presence of more than 1 mutation among the members of the same family with hypertrophic cardiomyopathy⁴. Additionally, the same gene can present variable expression^{6,7}. Thus, all these genetic characteristics justify the spectrum of presentation of the disease, with varied degrees of hypertrophy, onset of the disease manifestations and sudden death risk.

Obstruction of the left ventricular outflow tract at rest is present in 25% of the patients^{3,8}. However, it is important to stress that only one measurement at rest is insufficient for the analysis, considering its dynamic behavior⁸. During the systole, in addition to the septal hypertrophy itself, the anterior movement of the mitral valve (attributed to the Venturi effect) and septum deviation with constriction of the outflow tract are associated. These mechanisms are supported by the decreased venous return and post-load and increased contractility. Diastolic dysfunction and decreased cavity diameters are very common. It is noteworthy the fact that the patient was classified as having the non-obstructive form, but functionally she presented an intraventricular gradient of 40 mmHg with the pacemaker stimulation.

Most of the patients have mild symptoms. Dyspnea is the most common symptom³, followed by angina⁹ and less frequently, fatigue, palpitations, pre-syncope, syncope and congestive heart failure (CHF) symptoms in those who evolve to the dilated phase. Symptomatic individuals, like our patient, have a worse prognosis than the asymptomatic ones¹⁰⁻¹³. However, the diagnosis is frequently attained during the screening of family members.

Although it can present at any phase of life, the disease typically develops during puberty¹⁴. It is important to remember that, regarding the follow-up of family members, a single examination is not enough to rule out the disease, especially in adolescents and children.

The symptoms can be induced by several mechanisms³, which include: intraventricular gradient at rest or during stress, myocardial dysfunction, subendocardial ischemia, ischemia due to compression of the myocardial bridge, tachy- and bradyarrhythmias (the latter being uncommon), in addition to diastolic dysfunction.

The major complications associated to the disease are death, heart failure (HF), arrhythmias, cerebral vascular accidents (CVA) and infectious endocarditis¹⁵. The annual mortality in the reference centers, which usually include the symptomatic patients, is approximately 2% in adults, with values between 4 and 6% during childhood and adolescence¹⁶⁻²⁰. The most prevalent causes of mortality are sudden cardiac death, HF and CVA¹⁵.

Sudden death is more common in young people, whereas HF and CVA are more frequently observed at older age ranges. The mean age at death among patients with this disease ranges from 56 to 59 years¹⁰.

The factors associated with death due to hypertrophic cardiomyopathy include: advanced symptoms at the time of the diagnosis, atrial fibrillation associated with embolic CVA, basal gradient > 30 mmHg, disease identification at childhood and left ventricular hypertrophy > 25 mm²⁰.

Syncope, a recurrent symptom in the patient, occurs at least once throughout the life of 15% to 25% of the patients. Another 20% of them will present pre-syncope. Many mechanisms are involved in the physiopathology of low output. The obstruction of the outflow tract is one of these mechanisms, aided by the venous return decrease, increased cardiac contractility and decreased left ventricular post-load²¹⁻²⁴. Therefore, orthostasis, hypovolemia, physical activity, vasodilators and tachycardia aid the low output and its symptoms. In the case of our patient, there was echocardiographic documentation of this mechanism with increased pacemaker stimulation, as well as blood pressure decrease with orthostasis. Another factor is the ischemia during physical stress due to previously described intramural coronary abnormalities, myocardial bridge and increased overload due to the intensification of the intraventricular gradient^{9,23-30}. An abnormal baropressure reflex is a present mechanism, for which there was no time to investigate in the patient above^{23,24,30}. Supraventricular arrhythmias are present in 25% to 50% of the patients and the most frequent is the atrial fibrillation, which is not well tolerated³¹. Whenever possible, anticoagulation therapy must be administered to these patients due to the elevated risk of thromboembolism³²⁻³⁴. Ventricular arrhythmias are considered responsible for a large number of sudden death outcomes, whereas bradyarrhythmias are quite rare.

The non-intervention treatments are based on observational data and not on randomized trials. The pharmacological therapy is not recommended for asymptomatic patients, as there is no evidence of prognostic improvement in this population³⁵.

The use of beta-blockers improves symptoms such as angina, dyspnea and syncope. However, the treatment response is variable, with two-thirds of the patients presenting improvement³⁶. Nevertheless, abrupt medication withdrawal must be avoided due to the rebound effect of hypersensitivity to receptors. Regarding the calcium-channel blockers, verapamil is the one with the largest experience and it is effective in those patients who do not tolerate beta-blockers³⁷. Disopyramide is an anti-arrhythmic drug with negative inotropic effect indicated in the literature³⁸, but it is not available in Brazil. All of them act by controlling the physiopathological mechanisms of the symptoms: decrease in cardiac contractility, decrease in HR and increase in diastolic filling time³⁷.

Conversely, the use of digoxin must be avoided, as well as vasodilators such as nitrates, angiotensin-converting inhibitors, angiotensin receptor antagonists and nifedipine. All of them potentiate the increase in the intraventricular gradient. Diuretics should be used with caution, as although they improve symptoms such as dyspnea and edema, they can aid the gradient and low-output increase.

The use of antiarrhythmic drugs is controversial, regarding the control of arrhythmias as well as prognosis and they do not substitute the ICD implant³⁹.

Non-pharmacological therapies such as myomectomy and alcohol septal ablation are indicated for patients with symptoms that are refractory to the optimized clinical treatment⁴⁰⁻⁴². The patient could benefit from such therapies, as there are data in the literature on symptomatic patients with an induced gradient > 30 mmHg who had their symptoms controlled by septal ablation⁴³. Nonetheless, it is important to stress that these data are from centers that have experience with these procedures. The bicameral pacemaker therapy was an alternative suggested in the beginning of the 80's; however, evidence from later trials showed a decrease of only 50% in the gradient with no improvement regarding tolerance to physical exercise⁴⁰⁻⁴³, suggesting an important interference of the placebo effect. The current recommendation of the American College of Cardiology/American Heart Association is to use it only in patients with sinus node dysfunction and atrioventricular blocking.

Sudden death is the most feared complication of the disease and the availability of effective prophylactic treatment (ICD), the identification of patients at increased risk acquired important clinical significance.

The two most important risk factors defined at the consensus of the American College of Cardiology/ European Society of Cardiology (ACC/ESC) in 2003 are previous arrhythmic events: reverted sudden death and spontaneous sustained ventricular tachycardia⁴⁴. These patients present a high risk of recurrence and there is no doubt about the indication of the ICD use.

Most patients do not survive the first ventricular arrhythmic event. Therefore, it is mandatory to identify the predictive factors to establish adequate primary prophylaxis.

The five major additional risk factors mentioned at the ACC/ESC consensus of 2003 are: family history of sudden death, syncope that is not clearly ascribable to another cause, presence of non-sustained ventricular tachycardia,

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left ventricular hypertrophy > 30 mm and abnormal pressure response to physical stress.

Other possibly implicated factors are: younger age at diagnosis¹⁶, gradient > 30 mmHg⁴⁵⁻⁴⁶, presence of diastolic dysfunction⁴⁷ and some specific genotypes⁴⁸.

The higher the number of risk factors, the higher is the risk of sudden death and the higher the chance of benefitting from the ICD implant. Patients with two or more major risk factors should receive an ICD as primary prophylaxis^{45,49}.

Our patient initially presented three major risk factors: family history of sudden death, repeated syncope episodes and a 30 mm septum. She received the correct therapy with the ICD implant, which was subsequently proved by the occurrence of appropriate shocks.

Due to dynamic nature of the disease, all patients must be evaluated annually, including the assessment of the arrhythmia risk with history, physical examination, echocardiography, Holter monitoring and ergometric stress test to evaluate the pressure response⁴⁷.

Abnormal pressure response to exercise, a symptom present in our patient, occurs in 20 to 40% of patients with HCM^{50,51}. It is characterized by an increase in the systolic BP < 20 mmHg during exercise or abnormal decrease during the recovery phase^{52,53}. The development of gradient at the left ventricular (LV) outflow tract during exercise is not the only reason for that. Patients with non-obstructive disease can present this symptom and it seems to be related to an inappropriate vasodilation in the non-exercised muscles⁵⁰⁻⁵² and subendocardial ischemia⁵³. The patient presented extensive and confluent late enhancement in the subendocardial region at the cardiac CT, an alteration that can concur with fibrosis and myocardial ischemia.

Some patients with HCM occasionally present acute hemodynamic collapse secondary to the acute obstruction of the LV outflow tract, a situation that is compatible with the present case. The patient can complain of thoracic pain, palpitations, pre-syncope, postural hypotension and syncope and the diagnosis is confirmed by the echocardiogram. They present sinus tachycardia, hypotension, low jugular venous pressure, radiographic evidence of HF and systolic murmur of the LV outflow tract obstruction and mitral insufficiency. The syndrome can occur spontaneously or be precipitated by events that increase the obstruction, such as beta-blocker or calcium-channel blocker withdrawal, pre-load decrease due to dehydration or diuretics, post-load decrease due to the administration of vasodilators and tachycardia. In the case of this patient, this is a probable mechanism of the hemodynamic deterioration, considering that she presented compatible symptoms and, at the evolution, she presented ventricular tachycardia treated by the cardiorespirator. Milder cases can be treated with oral fluids and beta-blockers, whereas the pre-load increase with leg elevation and the intravenous (IV) administration of fluids are indicated for the more severe cases.

The vasopressor support, initially with dopamine and later with noradrenaline, was correct from a physiopathological point of view, although the literature recommends the use of phenylephrine⁵⁴. The IV administration of beta-blockers and disopyramide³⁸ are other treatment options.

Other contributing factors to the presented outcome would be the presence of myocardial ischemia, the negative inotropic effect of the drugs and dysautonomy with inadequate vasoconstriction. Pulmonary thromboembolism is another hypothesis that must be considered

(Dr. Paulo Harada, Dr. Fernando Morita)

Diagnostic hypothesis

Familial hypertrophic cardiomyopathy, of the obstructive type; hypotensive episodes due to dynamic obstruction and complex ventricular arrhythmias; final picture: myocardial ischemia or pulmonary thromboembolism.

(Dr. Paulo Harada, Dr. Fernando Morita)

Clinical Commentary

The patient was a young woman with a diagnosis of hypertrophic cardiomyopathy (HCM), of the non-obstructive type and presented complex ventricular arrhythmia, of genetic etiology with high penetrance in the family and high mortality. She presented a fast evolution, which is uncommon, that culminated in death, despite all attempts to treat her. The heredogram showed that, throughout three generations of the family with seven components, six (86%) had the disease. Of these, 5 (71%) died, four of them due to sudden death; these forms were called the "malignant forms" by Maron⁵⁵.

The predominant symptom was recurrent syncope and pre-syncope which, added to the family history of sudden death led to the indication of a cardiorespirator implant (performed at another Service), as arrhythmia is the most frequent cause. The latter persisted and therefore, the patient was referred to our Service. Syncope⁵⁶ occurs in approximately 15% of the patients with hypertrophic cardiomyopathy and it is little studied. The cause is ventricular and supraventricular arrhythmias, bradyarrhythmias, vasovagal syncope and LV outflow tract obstruction.

The complementary tests that were carried out showed moderate cardiac involvement (25-mm septum and 44-mm left atrium, with no significant gradient and no diastolic dysfunction); the magnetic resonance showed the presence of significant fibrosis. The electrophysiological study did not induce arrhythmias.

The clinical treatment with drugs was limited by the fact that the patient was hypotensive (did not tolerate the calcium-channel blocker). Nevertheless, considering the symptoms (palpitations), the use of beta-blocker at small doses was tried, followed by high-dose amiodarone, without success. Different programming of the pacemaker function was attempted, also without success. As the patient did not have obstruction, the invasive treatment with pacemaker, alcohol occlusion of the septal branch of the anterior descending coronary artery and aortic transvalvular cardiomyectomy were not indicated^{57,58}.

Regarding the sudden death predicting factors^{57,58-60}, the patient was young, presented sustained ventricular tachycardia, recurrent syncope, risk genotype, and there was no time to evaluate the hypotensive response to exercise. She died of sudden death, which initiated as arterial hypotension that did not respond to medication, followed by ventricular tachycardia and irreversible cardiorespiratory

arrest. In my opinion, the patient presented, in addition to all aforementioned risk factors, an alteration in the autonomic regulation that was determinant for the outcome, which is little known and little can be done about it. The acquired knowledge remains, that not every recurrent syncope is the result of complex ventricular arrhythmia. This fact had been previously observed by Medeiros et al.⁶⁰ in a group of 26 patients with two risk factors for sudden death submitted to ICD implant, of which 4 presented syncope recurrence without arrhythmic event. The subsequent study carried out by the tilt test was normal in those patients.

(Dr. Edmundo Arteaga)

Necropsy

At the autopsy, the heart weighed 400 g (the normal weight is around 250 to 300 g for females). There were two cables of the cardioresuscitator implanted in the right atrium and ventricle, with partial thrombosis in organization involving segments of these cables throughout their pathway in the jugular vein and superior vena cava, with no evidence of infectious processes at the histological assessment (Figure 2).

At the four-chamber cut, there was asymmetric hypertrophy of the LV wall, with higher thickness of the interventricular septum (around 2 cm) when compared to the free wall (around 1.2 cm), resulting in a ratio of approximately 1.67 (Figure 2). Such hypertrophy seems to restrict the LV outflow tract. The cross-section cut clearly showed a significant decrease in the LV cavity (Figure 3). In addition, there were areas of transmural fibrosis that were macroscopically identifiable in the septal, postero-septal, anterior and apical wall of the LV, as well as an area of subendocardial fibrosis related to the cardioresuscitator cable implant at the LV apex (figures 2 and 3). The atriums were dilated and there was endocardial thickening of the left atrium. The atrioventricular and ventriculoarterial valves did not show macroscopic abnormalities. The epicardial coronaries were normal, but the microscopic assessment disclosed scarce arterioles that showed irregular wall thickening with lumen narrowing. The histological assessment showed fiber hypertrophy and multiple foci of "cardiomyocytes in disarray", characterized by the loss of the usual parallel orientation between the fibers, which took on a random array (Figure 4).

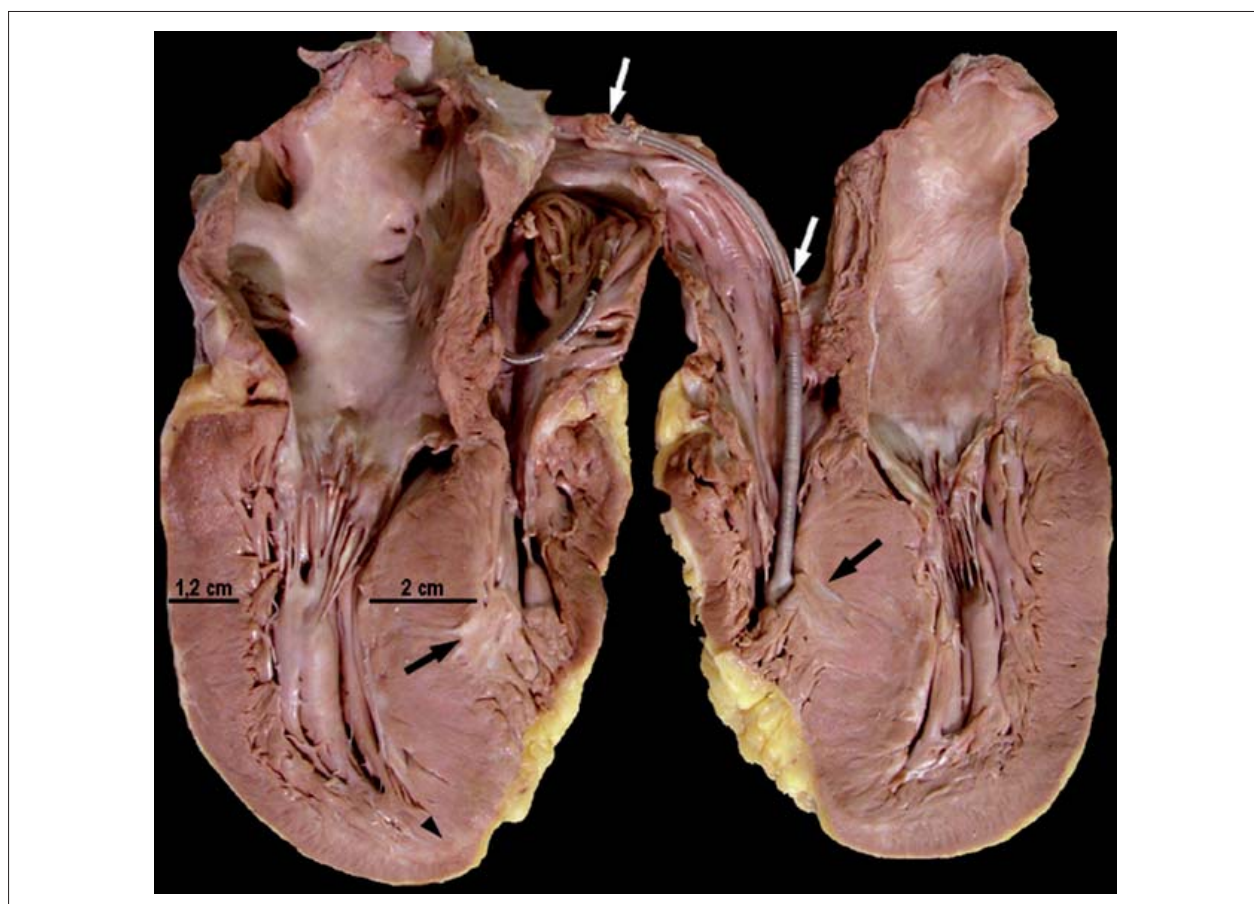


Fig. 2 - Macroscopy of the heart in two halves, with the four-chamber cut. The white arrows indicate partial thrombosis involving the cardioresuscitator cables inside the jugular vein and superior vena cava. Note the asymmetric hypertrophy of the left ventricle walls (LV) demonstrated by the difference of the measurements, shown by the arrows, in the free wall and septum. The black arrows indicate the area of fibrosis related to the cable implantation. The arrowhead points to the area of fibrosis present in the apical region of the LV.

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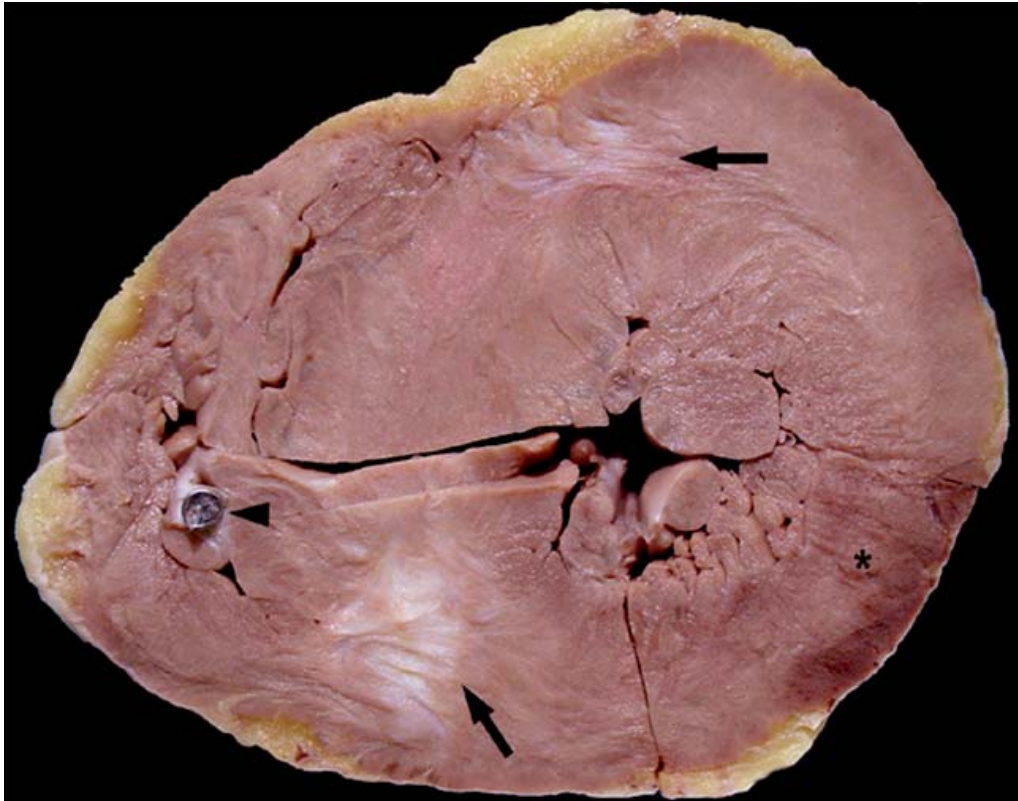


Fig. 3 - Cross-section of the heart, showing other areas of myocardial fibrosis (arrows) in the anterior and posterior-septal walls of the LV. The ventricular cavity is quite reduced. The shadowed area (asterisk) in the posterior-lateral wall of the LV consisted only of vascular congestion in the region. The arrowhead indicates the tip of the defibrillator cable, which was cut.

The disarray was present not only in the septal cuts, but also in the free wall of the LV. The staining by Masson's trichrome also highlighted the previously reported areas of fibrosis in the microscopic cuts (Figure 5).

The remaining organs showed signs of congestive heart failure, such as chronic passive hepatic and pulmonary congestion, with slight and focal plaques of atheroma in the pulmonary trunk and central pulmonary arteries and signs of shock, as follows: intra-alveolar pulmonary edema, cerebral edema with herniation of the cerebellar amygdala and hepatic centrilobular collapse with initial necrosis of hepatocytes. Cardiogenic shock was considered the immediate cause of death. There was no pulmonary thromboembolism, which was a clinical question.

(Dr. Jussara Bianchi Castelli)

Anatomopathological Diagnosis

Asymmetric hypertrophic cardiomyopathy; congestive heart failure, with chronic passive hepatic and pulmonary congestion and mild passive pulmonary hypertension; and cardiogenic shock.

(Jussara Bianchi Castelli)

Comments

The first significant information for the anatomoclinical

correlation in this case is the devastating family history, demonstrating the autosomal dominant genetic characteristic of the hypertrophic cardiomyopathy (HCM), which comprehends a number of mutations in the code for contractile protein production that construct the cardiac sarcomere⁶¹ and lead to the aberrant heart geometry and function. Additionally, there are the negative data for the other disorders that can potentially generate cardiac hypertrophy, such as systemic arterial hypertension and aortic stenosis, which our patient did not have.

At the macroscopic evaluation of the heart, the almost typical or classical phenotype of the disease was observed, represented by "asymmetric septal hypertrophy", which is a term used in the past as a synonym of the disease, considering the fact that it was present in most of the cases^{62,63}. For the classical description, it would be necessary to add only the septal endocardial lesion, called "mirror image" or "impact lesion"⁶⁴, which is generated by the constant impact of the anterior mitral cuspid on the wall of a quite hypertrophic and protruding septum, an aspect that would morphologically indicate an obstructive functional component, which was not present in this case. The symmetric hypertrophy format is also usual and the criterion that is still used for its definition is a septum / free wall ratio < 1.3; if the ratio is ≥ 1.3 , the hypertrophy is considered to be asymmetric⁶³, as in the present case. The increase in the atrial total weight and dilation are

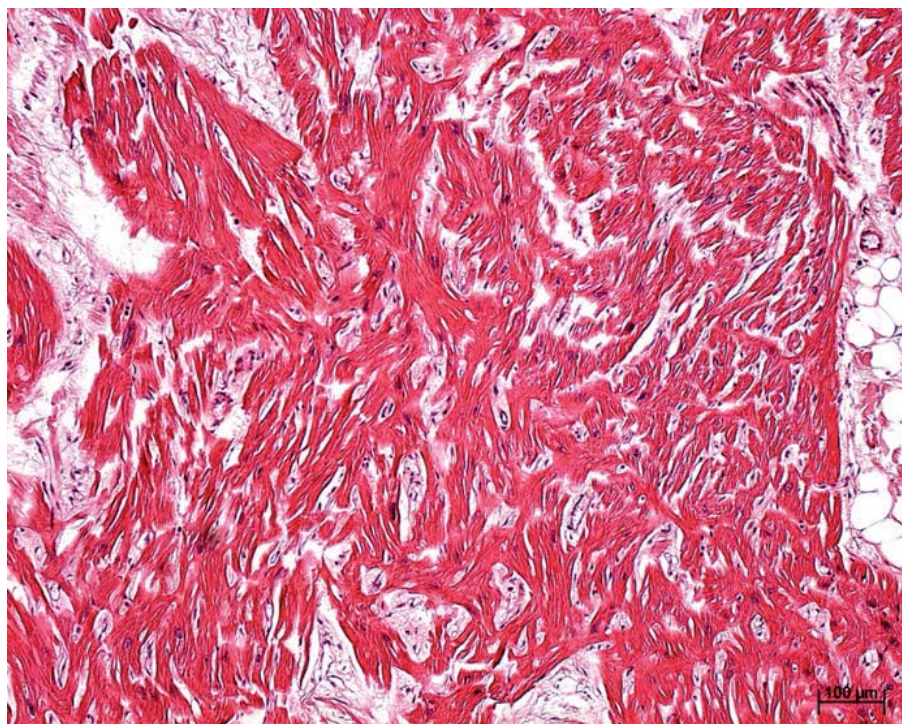


Fig. 4 - Histological section of the LV free wall, demonstrating one of the areas of myocardiocyte disarray. Note the loss of normal parallelism between the myocardial fibers, with oblique orientation of some of them (Hematoxylin & Eosin staining; 10X objective magnification).

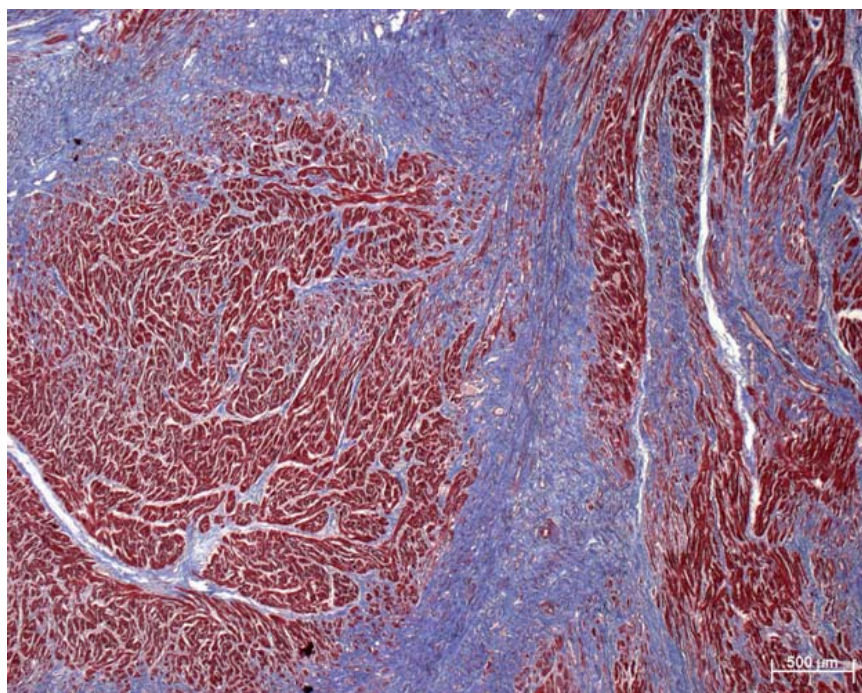


Fig. 5 - Histological section of the myocardium in the anterior wall of the LV. The staining clearly shows collagen fibers in blue (collagen type I), demonstrating the degree of fibrosis permeating the myocardial bundles in this region (Masson's Trichrome Staining; 2.5X objective magnification).

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also common findings in hypertrophic cardiomyopathy⁶².

At the light microscopy, the findings were also characteristic regarding the presence of myocardiocyte disarray, areas of fibrosis substituting the cardiac muscle and abnormal intramyocardial arterioles with narrow lumens, which are interrelated aspects, with the first possibly being the direct result of the structural and/or functional abnormality of the mutated sarcomeric protein and the others, a secondary response⁶⁴.

It is presumed that the disarray is present in at least 10% of the histologically assessed myocardium (in the present case, it was present in 15% to 20%), corroborating the diagnosis of hypertrophic cardiomyopathy together with

the other histological alterations, as the disarray alone is not pathognomonic⁶⁵. Additionally, at the light microscopy, the fiber disorientation has also been divided in subtypes, defining the expression of the disarray not only between fibers (fiber to fiber), but also between the bundles of myocardial fibers⁶⁵, which are aspects that must be considered, as well.

In summary, the diagnosis of hypertrophic cardiomyopathy is the result of the entire set of data of the clinical history, macroscopic aspects of the cardiac examination and the histological study with multiple cuts of the myocardium in its different regions. This set of data in the present case was very characteristic of HCM.

(Dr. Jussara Bianchi Castelli)

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