Case 5/2008 – 44-Year-Old Male Patient that Died of Cardiogenic Shock on the 6th Postoperative Day After Orthotopic Heart Transplant

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The patient was asymptomatic and ran 8 km daily up to 42 years of age, when he started to present effort dyspnea. The symptom persisted for six months and the patient then sought medical attention in his town. The patient knew he had bronchial asthma.

The electrocardiogram (July 2003) disclosed 2:1 Mobitz type II second-degree atrioventricular block. O echocardiogram (July 2003) showed a left atrium diameter that was at the upper limit of normality and increased thickness of the interventricular septum (Table 1).

The dynamic electrocardiogram by Holter system (July 2003) showed a minimum heart rate (HR) of 33 bpm, maximum heart rate of 72 bpm. The patient showed a sinus rhythm, with 2:1 atrioventricular block. There were 46 isolated ventricular extrasystoles and 13 isolated atrial extrasystoles.

The electrophysiological study (July 2003) showed a 2:1 atrioventricular block, A-H intervals of 228 ms (normal: 55-130), H-V of 68 (N=30-55). After atrial stimulation at intervals of 600 and 550 ms, a worsening in the atrioventricular conduction was observed with a 3:1 block, with no alteration in QRS duration. An atrioventricular block with nodal and hissian involvement was diagnosed.

The coronary angiography (July 2003) did not disclose obstructions in the coronary arteries and the ventriculography was normal.

An atrioventricular cardiac pacemaker implant was carried out (August 2003). The effort dyspnea persisted.

Table 1 - Echocardiograms

	July 03	July 04	October 2004	April 2005
Rhythm	Sinus 2:1	MP A-V	MP A-biV	Heart Transp.
Aorta (mm)	33	27	33	31
Left atrium (mm)	40	45	46	48
Right ventricle (mm)	Normal	44	41	Dilated
Left ventricle (LV)				
Diastolic diameter (mm)	45	62	64	52
Systolic diameter (mm)	29	55	55	
Ejection fraction (%)	71	24	29	35
Interventricular septum	15	10	10	12
LV posterior wall	10	9	10	11
Mitral valve failure	No	Moderate	Moderate	No
Tricuspid valve failure	No	Slight	Accentuated	Slight
Intraventricular thrombus	No	Yes	No	No

Key words

Cardiomyopathy, hypertrophic; cardiomyopathy, dilated; amyloidosis; shock, cardiogenic; heart transplantation.

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Nine months after the pacemaker implant, during a soccer game, the patient presented tachycardic palpitations, dyspnea and intense sudoresis with paleness and fainting sensation. A sustained ventricular tachycardia was diagnosed, which was reverted by electrical cardioversion. There was recurrence of the tachycardia one month after this episode and again electrical cardioversion was needed.

A new echocardiographic assessment (July 2004) disclosed dilation of the cardiac chambers, marked decrease in the left ventricular ejection fraction, with an image that was suggestive of apical thrombosis and moderate mitral failure (Table 1).

The patient was then referred to InCor (*Instituto do Coracao* – The Heart Institute) for treatment.

The physical examination (July 2004) revealed a HR of 80 bpm, BP of 100/80 mm Hg. Lung, heart and abdomen assessments were normal.

The electrocardiogram (23 of July 2004) showed a sinus rhythm, with ventricular stimulation by pacemaker triggered 200 ms after the P wave start and duration of stimulated QRS of 234 ms (Figure 1).

The electrocardiogram with inhibited pacemaker (26 July 2004) disclosed a sinus rhythm, 83 bpm, PR of 177 ms, duration of QRS 83 ms, QT of 391 ms, SAQRS + 120º backward and signs that were suggestive of left atrial overload, R wave amplitude that did not increase from V_1 to V_4 (Figure 2).

The chest X-ray showed a marked increase in the cardiac area. The myocardial perfusion scintigraphy (27 of July 2004) showed markedly low radiotracer uptake in the apical and anterior walls (apical and middle) and moderately low uptake in the inferior wall. The single-photon emission computed tomography (SPECT) showed diffuse hypokinesia and apical akinesia, with an ejection fraction of 35%. There was a marked lung uptake (Figure 3).

The phlebography of the left upper limb was suggestive of subclavian vein thrombosis. A diagnosis of hypertrophic cardiomyopathy was attained, with evolution to dilation, and the hypothesis of ventricular dilation caused by left ventricular desynchronization induced by QRS enlargement in the presence of stimulus via right ventricle was considered. Biventricular artificial cardiac stimulation was indicated. An atrium-biventricular and defibrillator pacemaker was implanted and the previous stimulation system was removed (23 of July 2004).

The drug therapy included captopril 75 mg, carvedilol 12.5 mg, spironolactone 25 mg, furosemide 60 mg, amiodarone 400 mg and Warfarin 2.5 mg, daily.

In spite of the changes in the stimulation and medication alterations the patient presented worsening of the dyspnea (Oct 2004), which started to occur triggered by small physical efforts, in addition to orthopnea, lower-limb edema and hepatomegaly.

The electrocardiogram (Oct 04) showed sinus rhythm, with ventricular stimulation by the pacemaker at the start and middle of the QRS (Figure 4).

The maximum O_2 consumption (V O_2 Max) (Oct 2004) was 12.9 ml/kg/min (normal for the age range: 40 ml/kg/min) and the slope between ventilation and CO_2 production was 59.3.

The right catheterism (Dec 2004) showed the following pressures (mm Hg): right atrium: 23/19/20; right ventricle: 22/19/20; pulmonary artery: 21/16/19; pulmonary occlusion: 18. The cardiac output was 3.4 l/min and the cardiac index was 1.07 l/min/m².

A cardiac transplant was indicated.

The patient was hospitalized for the transplant (30 March 2005); he complained of dyspnea after small efforts, BP was 100/70 mmHg, HR was 75 bpm and crackling rales were identified to the right.

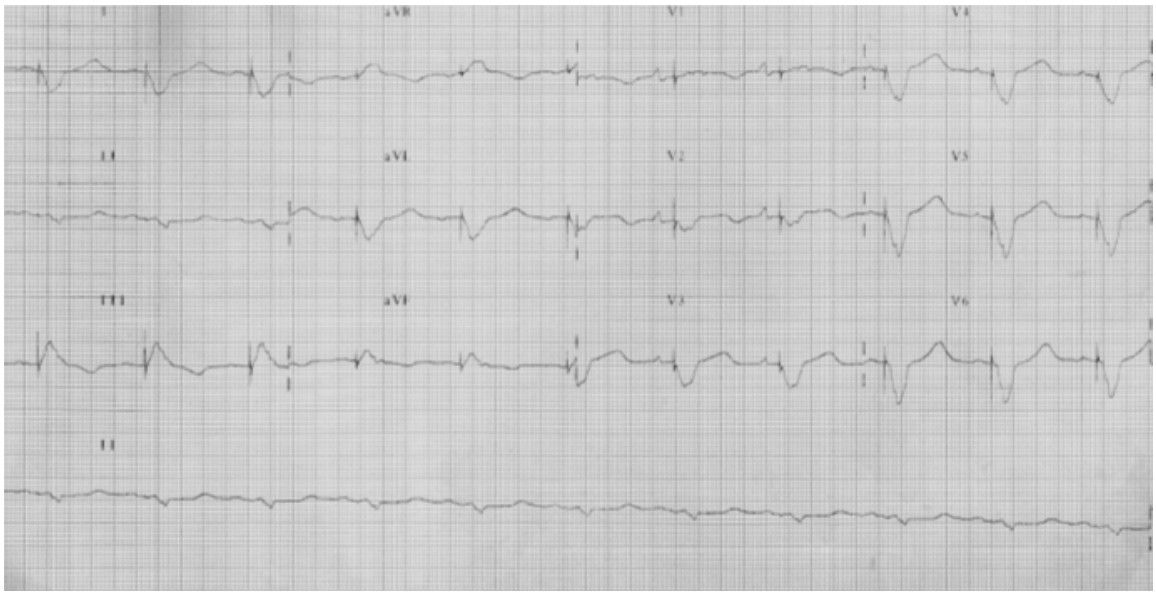

Figure. 1 - ECG- sinus rhythms, pacemaker triggered by atrial activity, ventricular stimulation by pacemaker 200 ms.

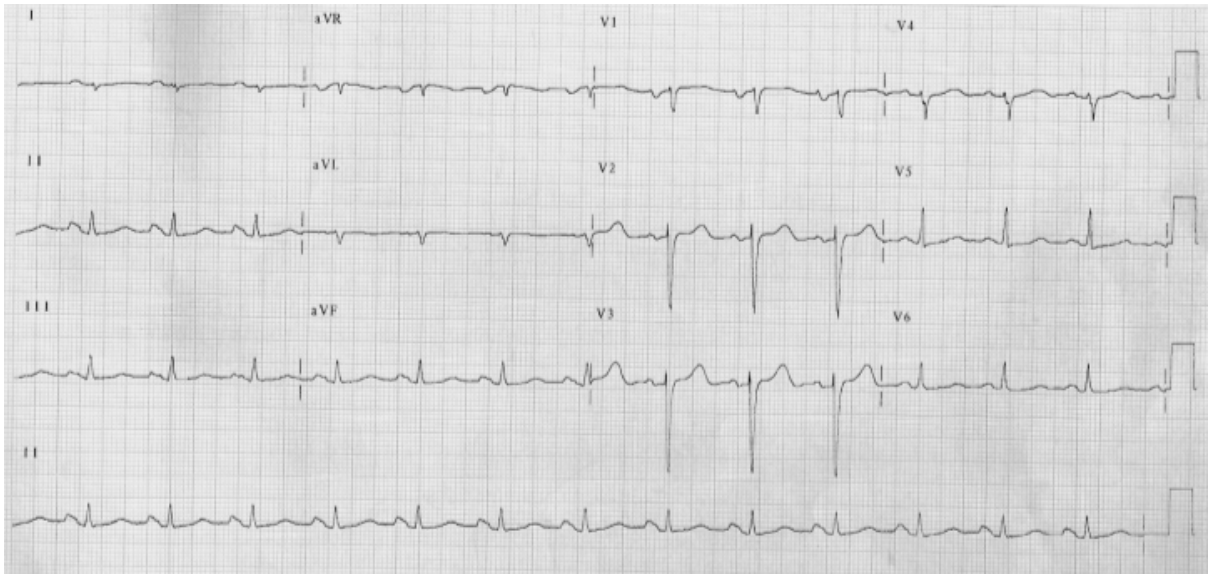

Figure. 2 - ECG - sinus rhythm, signs that were suggestive of left atrial overload, septal power decrease.

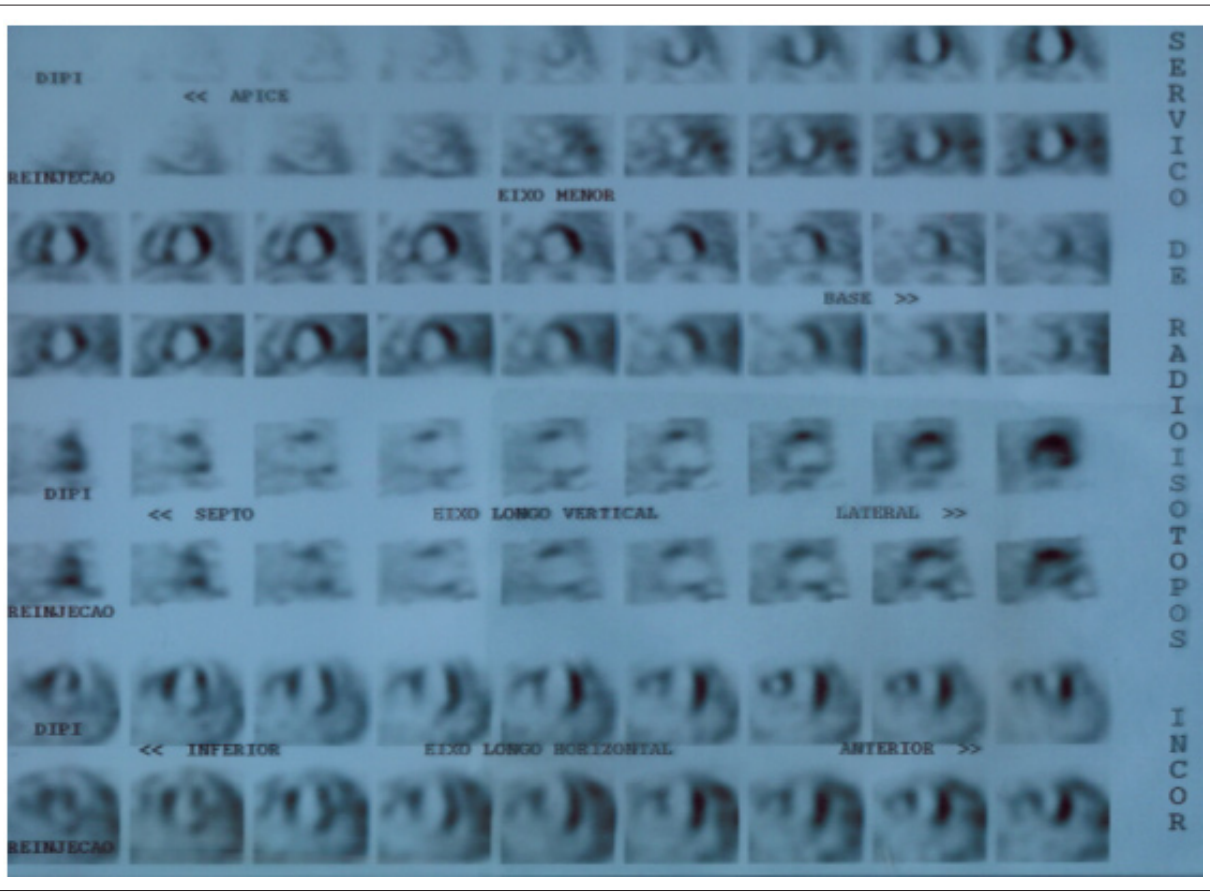

Figure 3 - Myocardial perfusion scintigraphy - markedly low radiotracer uptake in the apical and anterior walls (apical and middle) and moderately low uptake in the inferior wall.

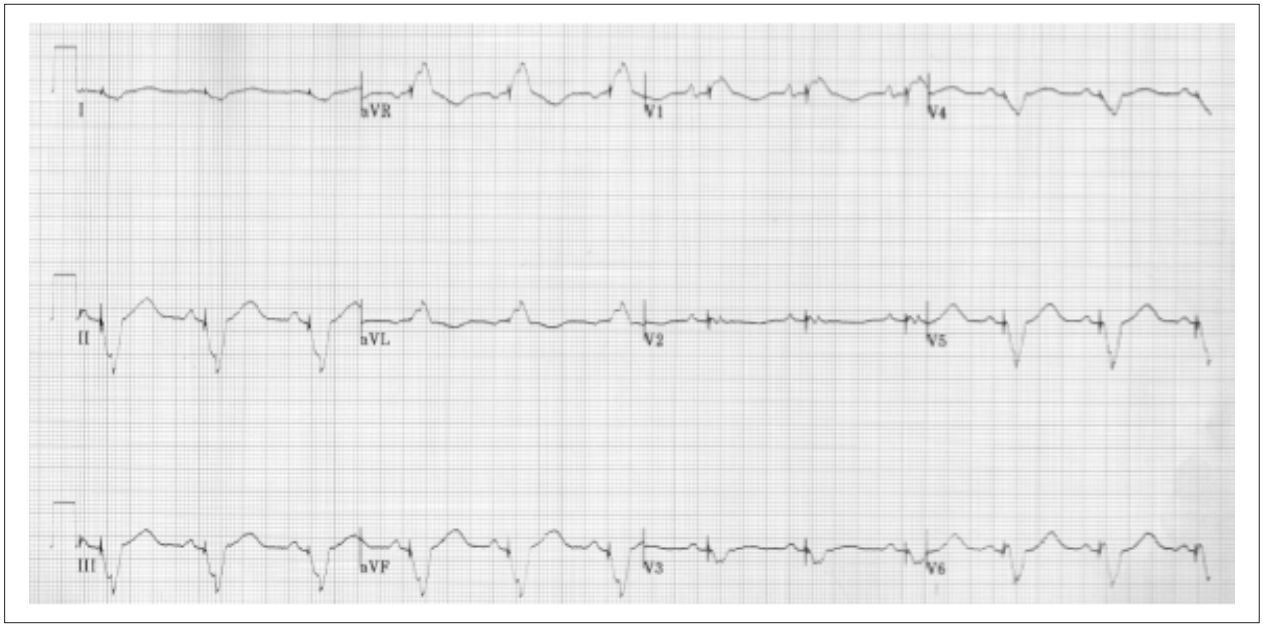

Figure 4 - ECG- sinus rhythm, with ventricular stimulation by the pacemaker at the start and middle of the QRS, compatible with ventricular stimulation in two sites.

The ventricular antiarrhythmic therapy capacity of the pacemaker was discontinued and 10 mg of vitamin K and 280 mg of aprotinin were administered by IV route.

The laboratory assessment (30 March 2005) disclosed hemoglobin 14.4 g/dl; hematocrit 44%, leucocytes 7200 /mm^3 (63% neutrophils, 2% eosinophils, 24% lymphocytes and 11% monocytes), platelets 133000/mm^3, potassium 4.2 mEq/l; sodium 138 mEq/l; urea 55 mg/dl; creatinine 1.3 mg/dl INR 1,5; serologies for hepatites, HIV, cytomegalovirus, Chagas disease and toxoplasmosis were negative.

A bicaval orthotopic transplant and De Vega plastic procedure were carried out in Tricuspid Valve (30 March 2005). The patient presented total atrioventricular block (TAVB) in the operating room and the epicardial pacemaker was turned on. After an uneventful first postoperative day, the patient started to presented hypotension, oliguria and vomiting.

During the postoperative evolution, the diagnoses of renal failure (creatinine 2.5 mg/dl, urea 127 mg/dl), anemia (hemoglobin 10.6 g/dl, hematocrit 32%), leukocytosis (10844/mm^3, 93% neutrophils, 3% lymphocytes and 4% monocytes) and thrombocytopenia (45000/mm^3), in addition to initial hyperamylasemia (887 U/l), which later decreased to 148 U/l.

The electrocardiogram showed the pacemaker stimulating atriums and ventricles (Figure 5).

The echocardiogram (4 April 2005) showed right ventricle dilation and hypokinesia, left ventricular diffuse hypokinesia with an ejection fraction of 35% (Table 1). On the sixth postoperative day, the patient presented ventricular fibrillation reverted with electrical cardioversion, with rhythm recovery, albeit without pulse and died on April 5, 2005.

Clinical aspects

A 44-year-old male patient, previously healthy, athlete, with no reports regarding his personal or family antecedents, presented for the diagnostic investigation of dyspnea.

The electrocardiogram showed a 2:1 second-degree atrioventricular block, later demonstrated to be Mobitz II at the electrophysiological study, with HV interval prolongation and worsening in the atrioventricular conduction with 3:1 block. The dynamic electrocardiogram by Holter system confirmed the maintenance of this conduction disorder throughout the day, with no evidence of associated tachyarrhythmias. The transthoracic echocardiogram disclosed an interventricular septum diameter of 15 mm and left ventricular posterior wall of 10 mm, with no indication of pressure gradients in the left ventricular outflow tract. The ventricular function was preserved until then. Considering these initial data, some considerations about the etiological diagnosis of the dyspnea must be made.

The low output, secondary to the bradycardia, could be the initial causal factor of the dyspnea and the heart pacemaker implant was well indicated, considering the findings of the electrophysiological study (worsening of the block during programmed atrial stimulation). The hypertrophic cardiomyopathy is another possible etiology of the symptoms presented by the patient. It is transmitted by dominant autosomal inheritance, characterized by asymmetric septal hypertrophy and can cause pressure gradient in the left ventricular outflow tract.

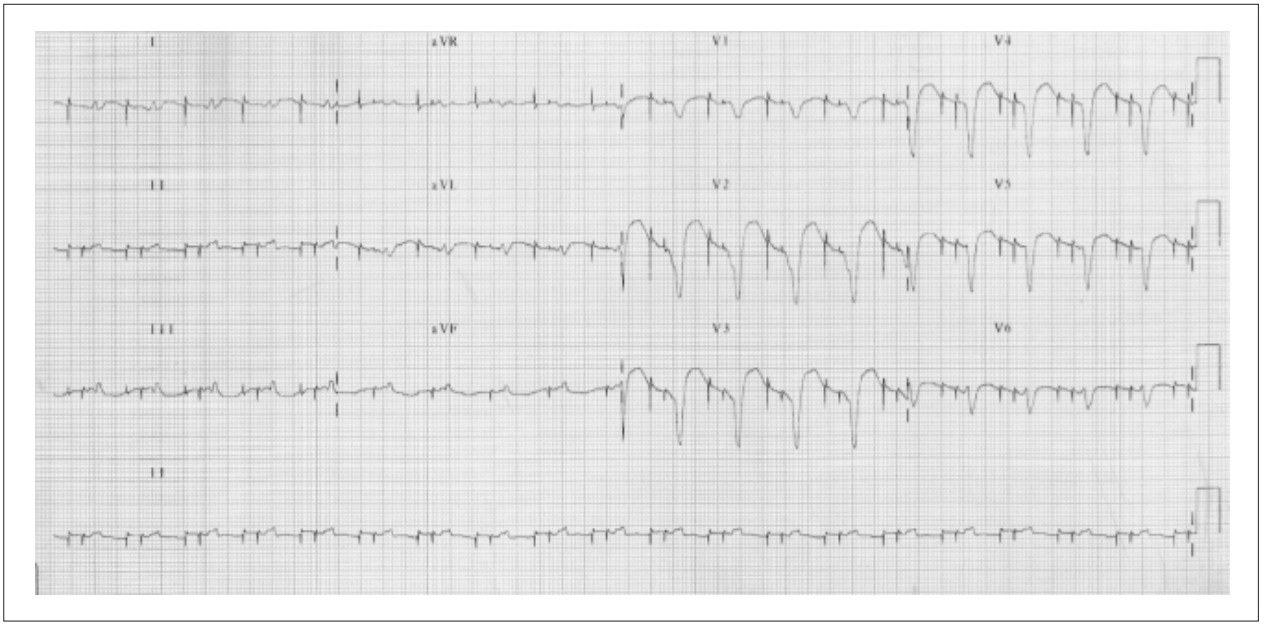

Figure 5 - ECG - functioning double-chamber pacemaker stimulating atriums and ventricles.

The increase in this gradient is generally associated to the worsening of symptoms and it is considered an independent predictor of the heart failure syndrome progression and mortality[1]. Effort dyspnea is the most common symptom, affecting more than 90% of the patients. It can result from a variety of mechanisms: diastolic dysfunction secondary to myocardial hypertrophy, ventricular emptying hindrance secondary to obstruction, mitral regurgitation and less commonly to the systolic function[2].

The initial distinction of the athlete's heart is subtle, when there are smaller degrees of septal hypertrophy, as in the present case. Athletes usually have a symmetric hypertrophy and of ventricular thickness of around 12 mm, which can, in extreme cases, reach 14 to 16 mm. Other common diseases, such as systemic arterial hypertension and aortic valvular stenosis can course with similar symptomatology; however, these entities were ruled out by the absence of clinical and laboratory findings. Rarer pathologies, such as sarcoidosis, amyloidosis and Fabry's disease are part of the differential diagnosis of the present case.

Systemic inflammatory disease such as sarcoidosis can affect the heart in 5% of the affected individuals, although autopsies have shown a subclinical involvement of up to 20 to 30% of the patients[3]. First-degree atrioventricular blocks due to disorders in the atrioventricular node of HIS bundle and several degrees of intraventricular blocks are common among patients with sarcoidosis[4]. These lesions can be initially silent, but can progress to a total atrioventricular block and cause syncope[4]. Ventricular arrhythmias are the second most important cause of cardiac involvement in sarcoidosis. Its granulomas can be foci of automatism or re-entry, resulting in the onset of sustained or nonsustained ventricular tachycardias[5].

The diagnosis of sarcoidosis as cause of cardiomegaly and heart failure can be difficult, especially with no evidence of other organs being affected. Many of these patients can receive the diagnosis of idiopathic dilated myocardiopathy; however, they present higher incidence of atrioventricular blocks, abnormalities of the ventricular wall thickness and segmental mobility, in addition to perfusion defects that affect preferentially the apical and anteroseptal regions[6]. The diagnosis of cardiac involvement is attained through the endomyocardial biopsy with the finding of non-caseous granulomas associated to the characteristic clinical picture.

Amyloidosis is a systemic disease characterized by the extracellular deposition of microfibrils that can affect the heart, basically causing right heart failure, with left ventricular dysfunction manifestations being rare. In spite of the high degree of cardiac conduction system involvement seen at autopsies, high-degree blocks are uncommon[7].

An unusual presentation is the disproportional accumulation of amyloid material in the interventricular septum, mimicking hypertrophic myocardiopathy[8,9]. The endomyocardial biopsy disclosed hyaline deposits of amorphous substance in the extracellular matrix, Congo-red positive, which turned into a green color at polarized light.

Fabry's disease is a lysosomal disease characterized by the deposit of globotriaosylceramide in the lysosomes. It results in a multi-systemic disease that manifests as peripheral neuropathy, angiokeratomas, corneal deposits and renal failure.

The cardiac involvement consists in concentric ventricular hypertrophy, heart failure, coronary disease and conduction disorders. Some patients present left ventricular hypertrophy as the only clinical manifestation of the disease.

After a few months of evolution, the patient courses with marked deterioration of the ventricular function and symptomatic ventricular tachycardias, relatively rare in patients with hypertrophic myocardiopathy and preserved

ventricular function, although rather more frequent after ventricular dilation[10].

The evolution to ventricular dysfunction and decrease in the hypertrophy (as documented in later echocardiograms) can be found in a small number of the patients with hypertrophic myocardiopathy (5 to 15%) and it is currently the commonest cause of indication for heart transplant in these patients[11-15]. It is more common in younger patients at presentation, those with more severe symptomatology, larger ventricular cavities and those with a family history of hypertrophic myocardiopathy with evolution to ventricular dilation.

The initial hypothesis that the pacemaker caused ventricular dyssynchrony and posterior dysfunction is based on several studies in which the delay in intraventricular conduction or left branch block were associated with a worsening of the symptoms and functional class, in relation to patients with normal intraventricular conduction[16-18].

Although the impact of dyssynchrony is higher in patients with established ventricular dysfunction, it has been demonstrated that the left branch block is associated with lower ejection fraction, when compared to healthy controls (54% *vs*. 62%)[19]. However, the present case's evolution was characterized by a fast and marked ventricular dysfunction in a heart with a previous normal function. Additionally, in the specific population of patients with hypertrophic myocardiopathy, these hemodynamic effects induced by the stimulation of the right ventricle can be of clinical use in symptom improvement. The simulation through an electrode cable positioned at the extremity of the right ventricle modifies the sequence of ventricular activation, which changes from down to up and from the right to the left side. This fact results in the paradoxical movement of the interventricular septum, causing it to separate from the left ventricular posterior wall during the systole and resulting in:

1) increase in the diameter of the ventricular chamber;

2) decrease in the anterior movement of the anterior leaflet of the mitral valve and

3) decrease in the left ventricular outflow tract gradient[20].

These effects, however, did not translate into improvement in the maximum O_2 consumption (VO_2 max) and of symptoms in randomized, double-blind studies, although they significantly decreased the left ventricular outflow tract gradient, thus currently making this therapy an exception[21-23].

The myocardial perfusion scintigraphy findings are compatible with microcirculation alterations or disease of the large epicardial vessels; however, the absence of risk factors for coronary artery disease and the previous year's coronary angiography, make the first hypothesis the most probable one[24-26]. These findings, however, confer a higher risk of future cardiovascular events to patients with hypertrophic myocardiopathy and perhaps, an increase in mortality[27-29].

The implant of the cardiodefibrillator associated to the atriobiventricular pacemaker was carried out based on several publications[30], which demonstrated symptom and survival improvement with the cardiac resynchronization of patients with severe dysfunction and electrocardiographic evidence of ventricular dyssynchrony, in spite of the optimized clinical treatment, to provide additional benefit to that of the secondary prophylaxis of poorly tolerated ventricular tachycardias previously presented by the patient.

There is limited evidence regarding drug therapy of the final phase of hypertrophic myocardiopathy, when there is evolution to ventricular dilation and systolic dysfunction. This patient received the treatment already established for systolic dysfunction[31,32] in an attempt to decrease the morbimortality: ACEI, betablocker, spironolactone, loop diuretics and amiodarone plus oral anticoagulant agent, due to the history of ventricular arrhythmia and the presence of thrombus in the left ventricle[33].

The capacity to exercise is decreased even at the initial phases of heart failure. The cardiac output might be normal at rest; however, it is incapable of increasing adequately, even during slight efforts[34]. The maximum oxygen consumption (VO_2) provides the most objective information regarding the functional capacity of patients with heart failure, and it is very important for the decision-making of when indicating the heart transplant[35]. Studies have shown that patients with a maximum $VO_2 < 10$ml/Kg/min have a worse prognosis when compared to individuals with the same characteristics and higher functional capacity. Currently, the peak $VO_2 \leq 14$ ml/Kg/min is considered the cutoff for the indication of heart transplant in patients that present betablocker intolerance and 12 ml/Kg/min in the presence of this medication[36]. Another possibility is the measurement of the ventilatory efficiency that corresponds to the ratio between ventilation per minute and CO_2 production (VE/ VCO_2 slope), which is a much easier measurement to be obtained than maximum exercise capacity parameters and it is a better predictor of prognosis than the maximum VO_2, NYHA functional class or LVEF[37-39]. A VE/ VCO_2 slope >35 is associated with decreased cardiac output during exercise, increase in the pulmonary artery occlusion pressure, decreased survival, and is a poor prognosis predictor in patients with preserved exercise capacity[40,41].

The endomyocardial biopsy has been increasingly used to help the etiological diagnosis of short-term evolution ventricular dysfunction. Heart failure with an evolution longer than three months, associated to ventricular dilation and new ventricular arrhythmias, second- or third-degree atrioventricular blocks or clinical therapy failure during treatment for more than 15 days is indicated with a level of evidence IIa[42]. This procedure could help the diagnosis of the present case, as its evolution to dysfunction was very fast to be explained solely by dysfunction induced by pacemaker or by the natural evolution of hypertrophic myocardiopathy.

The patient was submitted to a bicaval orthotopic transplant and De Vega plastic procedure in the tricuspid valve. During the intraoperative period, he presented total atrioventricular block (TAVB), which required an epicardial pacemaker implant. Bradyarrhythmias occur in more than 50% of receptors in the immediate postoperative period and are probably related to sinus node or atrioventricular node dysfunction. Its etiology might be related to rejection (studies show that the tissue of the conduction system is a frequent target of cell and humoral rejection), prolonged ischemia time, problems related to the surgical technique, coronary anatomy abnormalities or donor's sinus dysfunction. Some studies correlate the occurrence of

bradyarrhythmias and the need for pacemaker after heart transplant to a worse prognosis[43]; however, these data have not been confirmed by other authors[44].

After the first postoperative day, the patient presented a picture of hemodynamic and multiple organic function instability. The fifth-postoperative day echocardiogram showed biventricular dysfunction with LVEF of 35% and the patient died on the sixth postoperative day. One must consider the main causes of early graft failure after heart transplant, which are: hyperacute rejection, acute rejection (cell and humoral), prolonged donor's ischemia time, reperfusion lesion and marginal donor.

The hyperacute rejection, which is rare nowadays due to the preoperative screening and cross-match carried out in sensitized individuals, is precipitated by the presence of preformed receptor's antibodies that react against endothelial epitopes of the graft[45]. It is present in cases of ABO system incompatibility, but it can also be present in individuals that are highly sensitized (women with multiple pregnancies, patients submitted to multiple blood transfusions). It usually occurs within the first 24 hours after the transplant and can be observed as early as during the surgical procedure, leading to catastrophic graft failure.

The acute rejection is a common problem after heart transplants. It occurs particularly in the first month, generally by cell rejection[46]. Only 5% of the cases present severe hemodynamic involvement[47]. The majority does not present symptoms, which, when present, vary from unspecific pictures to classic ventricular dysfunction syndromes. The echocardiogram demonstrates the presence of the systolic or diastolic dysfunction and both ventricles can be involved. The diagnosis is established by endomyocardial biopsy, according to the ISHLT (International Society for Heart and Lung Transplantation) score, revised in 2005[48]. A mononuclear, predominantly lymphocytic, inflammatory response can be observed, directed to the graft, with presence of damage to the myocytes. In severe cases, there is granulocyte participation. This is the main diagnostic hypothesis, considering the early clinical deterioration, although not in the first 24 hours, despite the lack of data about the immunosuppression regimen employed. The use of calcineurin inhibitors might have been avoided due to the onset of renal dysfunction with oliguria.

Some patients present a picture of hemodynamically significant rejection with little or no cell infiltrate or myocyte necrosis at the biopsy. These must present humoral rejection, associated to the deposition of antibodies that are detected at the immunofluorescence[49]. The humoral rejection can occur very early (2 to 7 days, usually in the first month post-transplant) and the graft dysfunction is severe in up to two-thirds of the early episodes, presenting hemodynamic involvement in up to 50% of them, which is rare in later episodes[50,51].

Other important causes of early graft dysfunction that must be considered are: prolonged ischemia time, significant if > 4 hours, reperfusion lesion (which can be the cause of transient dysfunction) right ventricular dysfunction due to pulmonary hypertension (unlikely, considering the right catheterism of the patient) and causes related to the donor's conditions, such as high doses of catecholamines, donor's depressed systolic function, coronary artery disease, old age and previous surgeries[52].

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• *Diagnostic hypothesis:* more probable: cardiac sarcoidosis, or less probable: hypertrophic cardiomyopathy;

• *Cause of death:* hyperacute rejection.

Necropsy

This patient presented systemic sarcoidosis. The disease was diagnosed only at the anatomopathological assessment of the heart removed for cardiac transplant (Figures 6 and 7). It affected the following organs: thoracic lymph nodes, lungs (parenchyma and pleura), liver, spleen, and most importantly, the heart. In this case, it caused dilation of the four chambers caused by the extensive substitution of the right ventricle myocardium by areas of granulomatous inflammation and fibrosis. As it determined congestive heart failure, it led to the indication of an orthotopic heart transplant.

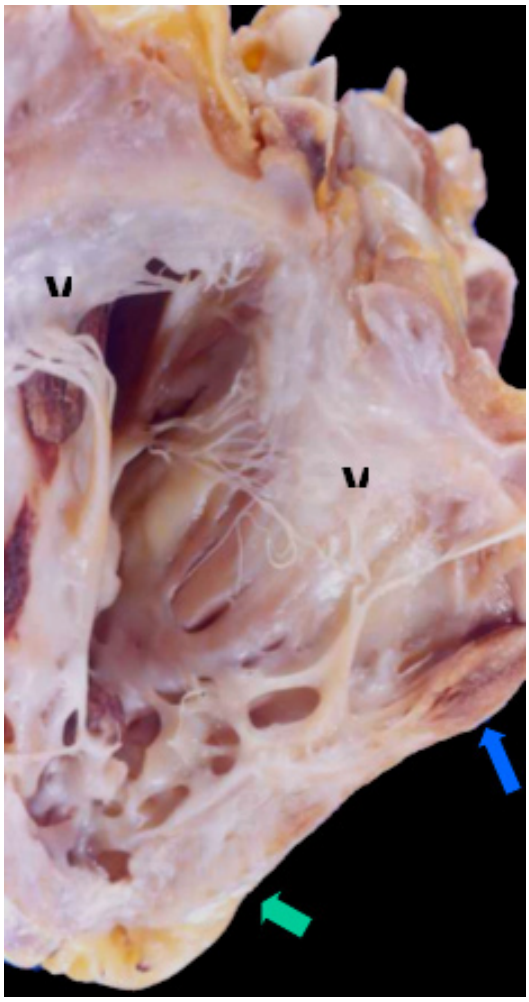

Figure 6 - Macroscopic aspect of the heart, showing the open right ventricle, which is dilated, with extensive areas of fibrosis (green arrow: compare with area of preserved myocardium indicated by the blue arrow). V – Tricuspid valve.

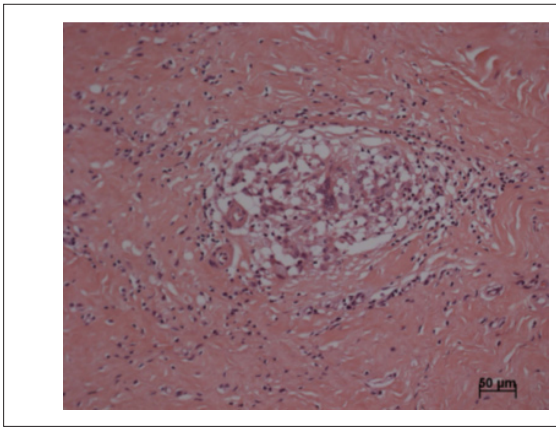

Figure 7 - Histological cut of the area of fibrosis of the transplant receptor's heart, with sarcoid granuloma. The search for alcohol-acid resistant bacilli and fungi were negative. Hematoxylin & eosin staining; 20x magnification.

After a good postoperative evolution for a few days, the patient presented a relatively fast worsening and died with biventricular dysfunction. The cause of the poor evolution was a mixed acute, humoral and cell rejection (Figures 8 and 9). The patient presented acute pulmonary edema – the final cause of death – in addition to a small pulmonary thromboembolism to the right, of which role, considering the degree of myocardial lesion, was secondary. There was also renal failure, which can be classified as pre-renal, due to the absence of significant pathological alterations in the kidneys.

Sarcoidosis is a rare disease, of which etiological factor is yet to be defined. The anatomopathological diagnosis is relatively easy, based on the finding of non-caseous granulomas and a negative

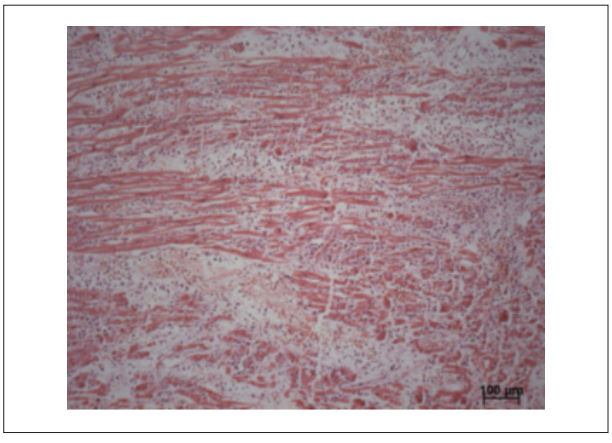

Figure 8 - Histological cut of the myocardium of the transplanted heart, showing extensive inflammatory mononuclear infiltrate and aggression and necrosis of myocardiocytes. Hematoxylin & eosin staining, 10x magnification.

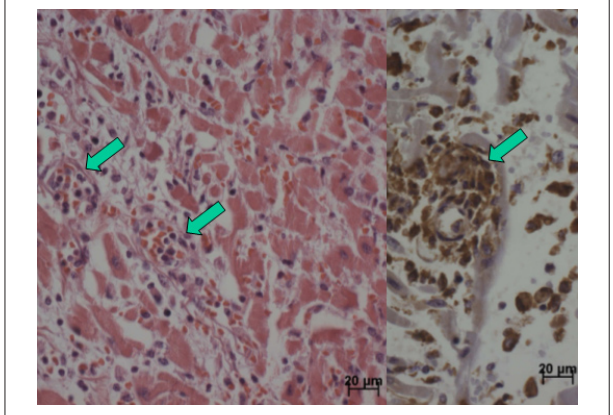

Figure 9 - Histological cut of the transplant heart. The arrows point to vessels containing inflammatory cells, including macrophages, of which positive immunohistochemistry reaction to CD68 (in brown color) is shown to the right. Hematoxylin & eosin staining; magnification and peroxidase reaction; 40x magnification.

result in the search for infectious agents[53]. The involvement of the heart has been detected in 20% to 30% of autopsies of patients with sarcoidosis.

The present case is the second one at InCor in which the diagnosis of sarcoidosis was made in the explanted heart. The same has occurred in other Centers[54]. Although the indication for transplant in known cases of the disease is controversial, due to possibility of recurrence, a comparative study has shown that the one-year survival is higher than in patients transplanted due to other causes[55].

In the last five years, there were 30 necropsies of adult patients at InCor that had been submitted to heart transplant. Eighteen of them died within 30 days of evolution. Among them, the most common cause of death (5 cases, 27.8%) was perioperative ischemia; there was rejection in 4 (22.2%), with two acute, this case, which was mixed, and a hyperacute one. Coagulopathy was responsible for the death in 2 patients (11.1%), right ventricular dysfunction due to pulmonary hypertension in 2 (11.1%) and other causes in the remaining patients. Mixed rejection, as in the present case, is the one that meets the anatomopathological criteria of both cell and vascular/humoral rejection[48,56].

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• *Anatomopathological Diagnosis:* cardiac and systemic sarcoidosis (explanted heart); mixed acute rejection, vascular/humoral and cell (transplanted heart)

• *Cause of death:* acute pulmonary edema

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References

1. Maron MS, Olivotto I, Betocchi S,Casey SA, Lesser JR, Losi MA, et al. Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. N Engl J Med. 2003; 348 (4): 295-303.
2. Wigle ED, Rakowski H, Kimball BP. Hypertrophic cardiomyopathy: clinical spectrum and treatment. Circulation. 1995; 92: 1680-92.
3. Chapelon-Abric C, de Zuttere D, Duhaut P, Veyssier P, Wechsler B, Huong DL, et al. Cardiac sarcoidosis: a retrospective study of 41 cases. Medicine (Baltimore). 2004; 83 (6): 315-34.
4. Yoshida Y, Morimoto S, Hiramitsu S, Tsuboi N, Hirayama H, Itoh T. Incidence of cardiac sarcoidosis in Japanese patients with high-degree atrioventricular block. Am Heart J. 1997; 134 (3): 382-6.
5. Sekiguchi M, Numao Y, Imai M. Clinical and histological profile of sarcoidosis for the heart and acute idiopathic myocarditis: concepts through a study employing myocardial biopsy. I Sarcoidosis. Jpn Circ J. 1980;44:249-63
6. Yazaki Y, Isobe M, Hiramitsu S, Morimoto S, Hiroe M, Omichi C, et al. Comparison of clinical features and prognosis of cardiac sarcoidosis and idiopathic dilated cardiomyopathy. Am J Cardiol. 1998; 82 (4): 537-40.
7. Mathew V, Olson LJ, Gertz MA, Hayes DL. Symptomatic conduction system disease in cardiac amyloidosis. Am J Cardiol. 1997; 80: 1491-2.
8. Dubrey SW, Cha K, Anderson J, Chamarthi B, Reisinger J, Skinner M, et al. The clinical features of immunoglobulin light-chain (AL) amyloidosis with heart involvement. QJM. 1998; 91 (2): 141-57.
9. Morner S, Hellman U, Suhr OB, Kazzam E, Waldenström A. Amyloid heart disease mimicking hypertrophic cardiomyopathy. J Intern Med. 2005; 258 (3): 225-30.
10. Shakespeare CF, Keeling PJ, Slade AK, McKenna WJ. Arrhythmia and hypertrophic cardiomyopathy. Arch Mal Coeur Vaiss. 1992; 85: 31-6.
11. Kubo T, Kitaoka H, Okawa M, Matsumura Y, Hitomi N, Yamasaki N, et al. Lifelong left ventricular remodeling of hypertrophic cardiomyopathy caused by a founder frameshift deletion mutation in the cardiac myosin-binding protein C gene among Japanese. J Am Coll Cardiol. 2005; 46 (9): 1744-6.
12. Spirito P, Maron BJ, Bonow RO, Epstein SE. Occurrence and significance of progressive left ventricular wall thinning and relative cavity dilatation in hypertrophic cardiomyopathy. Am J Cardiol. 1987; 60: 123-9.
13. Biagini E, Coccolo F, Ferlito M, Perugini E, Rocchi G, Bacchi-Reggiani L, et al. Dilated-hypokinetic evolution of hypertrophic cardiomyopathy: prevalence, incidence, risk factors, and prognostic implications in pediatric and adult patients. J Am Coll Cardiol. 2005; 46 (8): 1543-50.
14. Thaman R, Gimeno JR, Reith S, Esteban MT, Limongelli G, Murphy RT, et al. Progressive left ventricular remodeling in patients with hypertrophic cardiomyopathy and severe left ventricular hypertrophy. J Am Coll Cardiol. 2004; 44 (2): 398-405.
15. Harris KM, Spirito P, Maron MS, Zenovich AG, Formisano F, Lesser JR, et al. Prevalence, clinical profile, and significance of left ventricular remodeling in the end-stage phase of hypertrophic cardiomyopathy. Circulation. 2006; 114 (3): 216-25.
16. Duncan AM, Francis DP, Gibson DG, Henein MY. Limitation of exercise tolerance in chronic heart failure: distinct effects of left bundle-branch block and coronary artery disease. J Am Coll Cardiol. 2004; 43: 1524-31.
17. Shamim W, Francis DP, Yousufuddin M, Varney S, Pieopli MF, Ankor SD, et al. Intraventricular conduction delay: a prognostic marker in chronic heart failure. Int J Cardiol. 1999; 70: 171-8.
18. Baldasseroni S, Opasich C, Gorini M, Lucci D, Marchionni N, Marini M, et al. Left bundle-branch block is associated with increased 1-year sudden and total mortality rate in 5517 outpatients with congestive heart failure: a report from the Italian network on congestive heart failure. Am Heart J. 2002; 143: 398-405.
19. Grines CL, Bashore TM, Boudoulas H, Olson S, Shafer P, Wooley CF. Functional abnormalities in isolated left bundle branch block: the effect of interventricular asynchrony. Circulation. 1989; 79: 845-53.
20. Sociedade Brasileira de Cardiologia. Diretrizes brasileiras de dispositivos cardíacos eletrônicos implantáveis (DCEI). Arq Bras Cardiol. 2007; 89 (6): e210-e237.
21. Maron BJ, Nishimura RA, McKenna WJ, Rakowski H, Josephson MF, Kieval RS. Assessment of permanent dual-chamber pacing as a treatment for drug-refractory symptomatic patients with obstructive hypertrophic cardiomyopathy: a randomized, double-blind, crossover study (M-PATHY). Circulation. 1999; 99: 2927-33.
22. Kappenberger L, Linde C, Daubert C, McKenna W, Meisel E, Sadoul N, et al. Pacing in hypertrophic obstructive cardiomyopathy: a randomized crossover study. PIC Study Group. Eur Heart J. 1997; 18: 1249-56.
23. Ommen SR, Nishimura RA, Squires RW, Schaff HV, Danielson GK, Tajik AJ. Comparison of dual-chamber pacing versus septal myectomy for the treatment of patients with hypertrophic obstructive cardiomyopathy: a comparison of objective hemodynamic and exercise end points. J Am Coll Cardiol. 1999; 34 (1): 191-6.
24. Olivotto I, Cecchi F, Gistri R, Lorenzoni R, Chiriatti G, Girolami F, et al. Relevance of coronary microvascular flow impairment to long-term remodeling and systolic dysfunction in hypertrophic cardiomyopathy. J Am Coll Cardiol. 2006; 47: 1043-8.
25. Cecchi F, Olivotto I, Gistri R, Lorenzoni R, Chiriatti G, Camici PG. Coronary microvascular dysfunction and prognosis in hypertrophic cardiomyopathy. N Engl J Med. 2003; 349: 1027-35.
26. Maron BJ, Wolfson JK, Epstein SE, Roberts WC. Intramural ("small vessel") coronary artery disease in hypertrophic cardiomyopathy. J Am Coll Cardiol. 1986; 8: 545-57.
27. Sorajja P, Chareonthaitawee P, Ommen SR, Miller TD, Hodge DO, Gibbons RJ. Prognostic utility of single-photon emission computed tomography in adult patients with hypertrophic cardiomyopathy. Am Heart J. 2006; 151: 426-35.
28. Lazzeroni E, Picano E, Morozzi L, Maurizio AR, Palma G, Ceriati R, et al. for the Echo Persantine Italian Cooperative (EPIC) Study Group, subproject hypertrophic cardiomyopathy. Dipyridamole-induced ischemia as a prognostic marker of future adverse cardiac events in adult patients with hypertrophic cardiomyopathy. Circulation. 1997; 96: 4268-72.
29. Yamada M, Elliott PM, Kaski JC, Prasad K, Lowe CN, Gane JN, et al. Dipyridamole stress thallium-201 perfusion abnormalities in patients with hypertrophic cardiomyopathy: relationship to clinical presentation and outcome. Eur Heart J. 1998; 19: 500-7.
30. McAlister FA, Ezekowitz J, Hooton N, Vandermeer B, Friesen C, Spooner C, et al. Cardiac resynchronization therapy for patients with left ventricular systolic dysfunction: a systematic review. JAMA. 2007; 297: 2502-14.
31. Spirito P, Autore C. Management of hypertrophic cardiomyopathy. BMJ. 2006; 332: 1251-5.
32. Maron BJ, McKenna WJ, Danielson GK, Kappenberger LJ, Kuhn HJ, Seidman CE, et al. American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. J Am Coll Cardiol. 2003; 42: 1687-713.
33. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Gamiats TG, et al. ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. Circulation. 2005; 112: e154-235.
34. Reddy HK, Weber KT, Janicki JS, McElroy PA. Hemodynamic, ventilatory and metabolic effects of light isometric exercise in patients with chronic heart failure. J Am Coll Cardiol. 1988; 12: 353-8.
35. Pardaens K, Van Cleemput J, Vanhaecke J, Fagard RH. Peak oxygen uptake better predicts outcome than submaximal respiratory data in heart transplant candidates. Circulation. 2000; 101: 1152-7.
36. Mehra MR, Kabashigawa J, Starling R, Russell S, Uber PA, Parameshwar J, et

al. Listing criteria for heart transplantation: International Society for Heart and Lung Transplantation guidelines for the care of cardiac transplant candidates--2006. J Heart Lung Transplant. 2006; 25: 1024-42.

37. Kleber FX, Vietzke G, Wernecke KD, Bauer U, Opitz C, Wensel R, et al. Impairment of ventilatory efficiency in heart failure: prognostic impact. Circulation. 2000; 101: 2803-9.

38. Arena R, Myers J, Abella J, Peberdy MA, Bensimhon D, Chase P, et al. Development of a ventilatory classification system in patients with heart failure. Circulation. 2007; 115: 2410-7.

39. Gitt AK, Wasserman K, Kilkowski C, Kleemann T, Kilkowski A, Bangert M, et al. Exercise anaerobic threshold and ventilatory efficiency identify heart failure patients for high risk of early death. Circulation. 2002; 106: 3079-84.

40. Ponikowski P, Francis DP, Piepoli MF, Davies LC, Chau TP, Davos CH, et al. Enhanced ventilatory response to exercise in patients with chronic heart failure and preserved exercise tolerance: marker of abnormal cardiorespiratory reflex control and predictor of poor prognosis. Circulation. 2001; 103: 967-72.

41. Chua TP, Ponikowski P, Harrington D, Anker SD, Webb-Peploe K, Clark AL, et al. Clinical correlates and prognostic significance of the ventilatory response to exercise in chronic heart failure. J Am Coll Cardiol. 1997; 29: 1585-90.

42. Cooper LT, Baughman KI, Feldman AM, Frustaci A, Jessup M, Kuhl U, et al. The role of endomyocardial biopsy in the management of cardiovascular disease. Eur Heart J. 2007; 28: 3076-93.

43. Bacal F, Bocchi EA, Vieira ML, Lopes N, Moreira LF, Fiorelli A, et al. Uso de marcapasso provisório e definitivo em pacientes submetidos a transplante cardíaco ortotópico. Arq Bras Cardiol. 2000; 74: 5-8.

44. Kirklin JK, Young JB, McGiffin DC. Heart transplantation. New York: Churchill Livingstone, 2002. p. 375-89.

45. Azimzadeh A, Wolf P, Dalmasso AP, Odeh M, Beller JP, Fabre M, et al. Assessment of hyperacute rejection in a rat-to-primate cardiac xenograft model. Transplantation. 1996; 61: 1305-13.

46. Trulock EP, Christie JD, Edwards LB, Boucek MM, Aurora P, Taylor DO, et al. Registry of the International Society for Heart and Lung Transplantation: twenty-fourth official adult heart transplant report-2007. J Heart Lung Transplant. 2007; 26: 782-95.

47. Mills RM, Naftel DC, Kirklin JK, Van Bakel AB, Jaski BE, Massin EK, et al. Heart transplant rejection with hemodynamic compromise: a multiinstitutional study of the role of endomyocardial cellular infiltrate. Cardiac Transplant Research Database. J Heart Lung Transplant. 1997; 16: 813-21.

48. Stewart S, Winters GL, Fishbein MC, Tazelaar HD, Kobashigawa J, Abrams J, et al. Revision of the 1990 working formulation for the standardization of nomenclature in the diagnosis of heart rejection. J Heart Lung Transplant. 2005; 24: 1710-20.

49. Takemoto SK, Zeevi A, Feng S, Colvin RB, Jordan S, Kobashigawa J, et al. National conference to assess antibody-mediated rejection in solid organ transplantation. Am J Transplant. 2004; 4: 1033-41.

50. Reed EF, Demetris AJ, Hammond E, Itesai S, Kobashigawa JA, Reinsmoen NL, et al. Acute antibody-mediated rejection of cardiac transplants. J Heart Lung Transplant. 2006; 25: 153-9.

51. Taylor DO, Yowell RL, Kfoury AG, Hammond EH, Renlund DG. Allograft coronary artery disease: clinical correlations with circulating anti-HLA antibodies and the immunohistopathologic pattern of vascular rejection. J Heart Lung Transplant. 2000; 19: 518-21.

52. Naftel DC, Brown RN. Survival after heart transplantation. In: Kirklin JK, Young JB, McGiffin D. Heart transplantation. New York: Churchill Livingstone; 2002. p. 587-614.

53. Dubrey SW, Bell A, Mittal TK. Sarcoid heart disease. Postgrad Med J. 2007; 83: 618-23.

54. Donsky AS, Escobar J, Capehart J, Roberts WC. Heart transplantation for undiagnosed cardiac sarcoidosis. Am J Cardiol. 2002; 89: 1447-50.

55. Zaidi AR, Zaidi A, Vaitkus PT. Outcome of heart transplantation in patients with sarcoid cardiomyopathy. J Heart Lung Transplant. 2007; 26: 714-7.

56. Book WM, Kelley L, Gravanis MB. Fulminant mixed humoral and cellular rejection in a cardiac transplant recipient: a review of the histologic findings and literature. J Heart Lung Transplant. 2003; 22: 604-7.