Sildenafil for Noncompaction Cardiomyopathy Treatment in a Child: Case Report

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Introduction

Congestive heart failure (CHF) occurs when the heart can no longer maintain the baseline metabolic demand triggered by physiological venous pressure. In the pediatric population, it corresponds to a complex entity with multiple etiologies, depending on the age group assessed, being mainly associated with congenital structural malformations, cardiomyopathies, or secondary to arrhythmogenic, infectious, ischemic, toxic or infiltrative events[1].

The incidence of CHF in children also varies according to the underlying condition, ranging from 15% to 25% in patients with congenital heart defects. In structurally normal hearts, cardiomyopathy is the major factor associated with CHF, with a 40% incidence of CHF reported in those patients[1].

Isolated noncompaction cardiomyopathy is a rare disease, whose incidence in the general population ranges from 0.014% to 1.3%. It might result from a failure in compaction of the ventricular myocardium between weeks 5 and 8 of the embryonic life, leading to the persistence of myocardial trabeculations and deep recesses, which communicate with the ventricular cavity, generating myocardial thickening in two distinct layers (compacted and noncompacted). Initially reported in the pediatric population or with a congenital cardiopathy, it also affects adults with no other heart disease[2,3].

This failure in the regression of embryonic sinusoids is postulated to be due to the extremely high pressures that the ventricles undergo in that developmental period. However, the literature has reported a genetic aspect emphasizing the relationship of the disease with different genes, such as the mutation of gene G4.5 in families with severe infantile noncompaction cardiomyopathy, mutations P121L, CYPHER/ZASP, E101K, and a locus containing the disease gene in chromosome 11p15[3].

The major complications of patients with noncompaction cardiomyopathy are pulmonary thromboembolism, arrhythmias and CHF[3]. In addition to the usual treatment of CHF, new classes of drugs, such as the phosphodiesterase type 5 (PDE-5) inhibitors, have been studied[4]. They are currently used for the treatment of erectile dysfunction and pulmonary arterial hypertension, and began to be studied for the treatment of CHF after the demonstration of higher PDE-5 expression in myocytes and vascular muscle cells, as well as of markers of oxidative stress in patients with CHF[5].

We report, for the first time, the clinical and laboratory findings of a patient with noncompaction cardiomyopathy after the addition of sildenafil (PDE-5 inhibitor) to the usual treatment.

Case Report

The patient is a 6-year-old male, previously healthy, admitted with clinical findings compatible with CHF. The clinical investigation ruled out causes of CHF secondary to infectious, arrhythmogenic, infiltrative, toxic and ischemic processes and neuromuscular disorders. The serum level of type B natriuretic peptide (BNP) was 641 pg/mL. The echocardiographic findings were as follows: left ventricular (LV) ejection fraction of 19.1%; significant biventricular systolic dysfunction; LV diastolic dysfunction; significant LV dilation; and mild left atrial dilation. In addition, deep myocardial trabeculae were observed, communicating with the free LV cavity, with a noncompaction to compaction ratio of 3.2:1 and no structural malformation, establishing the diagnosis of bilateral cardiomyopathy of the noncompaction myocardial type (Figure 1). Drug treatment with angiotensin-converting-enzyme inhibitor (ACEI), diuretics and carvedilol was initiated.

After one year of clinical follow-up and optimized pharmacological treatment (diuretics, ACEI and beta-blocker), his symptoms and functional class worsened, a new hospital admission being necessary. Echocardiography showed persistent dilated cardiomyopathy of significant hemodynamic repercussion, with moderate tricuspid and mild mitral regurgitations. Because of the unfavorable diagnosis and clinical course, the patient was assessed aiming at heart transplantation. The hemodynamic evaluation showed cardiomyopathy with noncompaction of the ventricles and spongy myocardium, normal capillary angiography and mean capillary pressure of 25 mm Hg.

Rescue therapy with sildenafil at the dose of 2 mg/kg/day was indicated while awaiting a donor. The clinical and imaging follow-up every three months showed progressive improvement, with normalization of the ventricular function, of the BNP serum levels and of the symptoms (Table 1). The patient was then removed from the heart transplantation list, maintaining good quality of life.

Keywords

Heart Failure; Cardiomyopathy, Dilated / complications; Phosphodiesterase Inhibitors.

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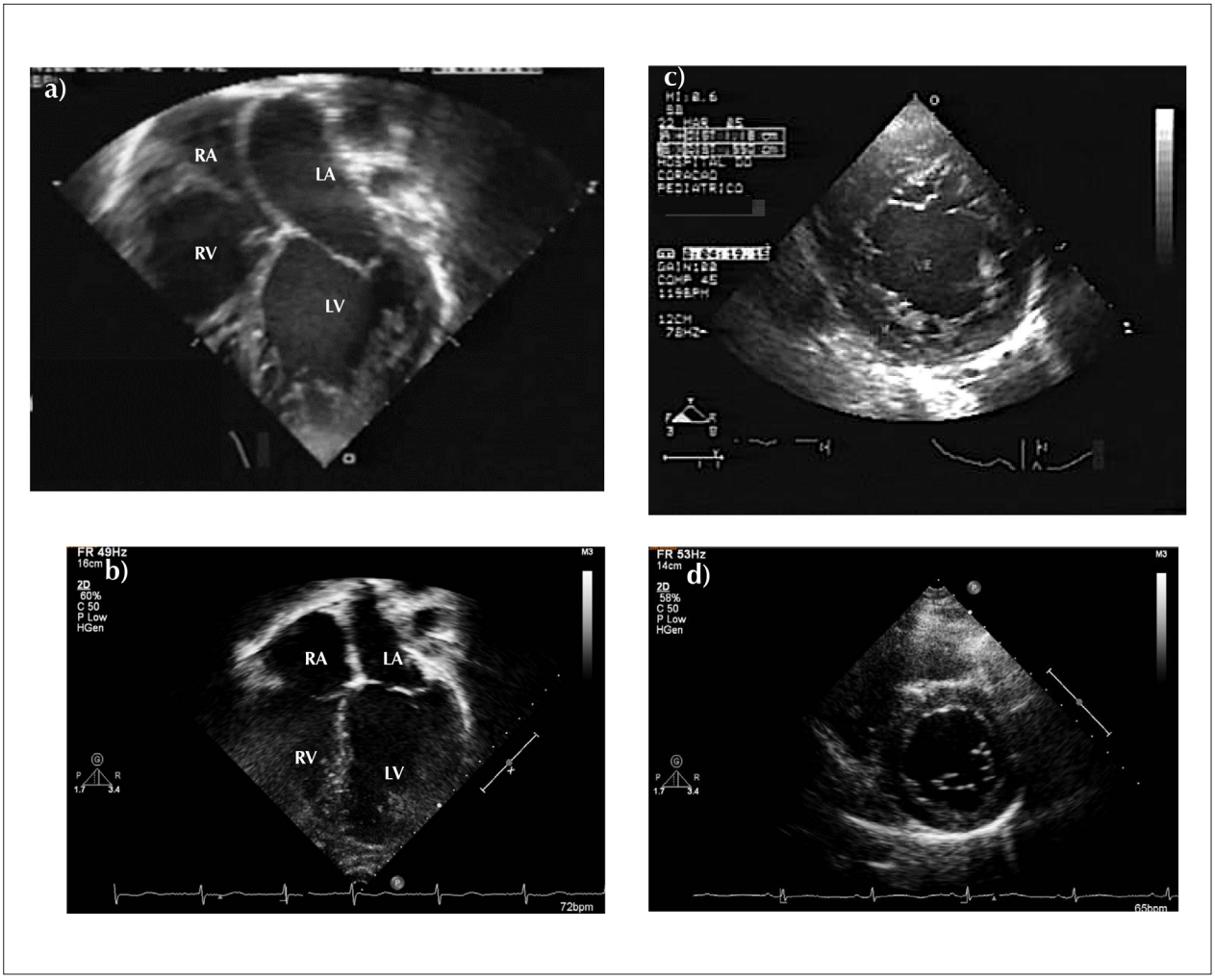

Figure 1 - *Echocardiographic study performed at the age of 6 years shows dilated left chambers, spongy left ventricle, and noncompacted to compacted myocardium ratio of 3.2:1, long axis plane (A) and short axis plane (C), and after 7 years of clinical drug treatment (B and D).*

Table 1 - Description of the clinical, laboratory and echocardiographic parameters before and after the introduction of sildenafil in the drug treatment

	Before sildenafil	During sildenafil administration	After sildenafil administration
HR (bpm)	100	80	79
SaO_2 (%)	90	99	99
Functional class	III	II	I
RV (mm)	23	19.1	14.7
LVEDV (mL/m^2)	208	122	95
LVESV (mL/m^2)	168	51.6	48.7
LVEF (%)	19	32-43	60
BNP (pg/mL)	641	15	42

HR (bpm): heart rate (beats per minute); SaO_2: oxygen saturation; RV: right ventricle; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; LVEF: left ventricular ejection fraction; BNP: brain natriuretic peptide.

Discussion

We report for the first time the case of a male patient at school age with noncompaction cardiomyopathy and myocardial dysfunction refractory to conventional clinical treatment, whose clinical, laboratory and imaging parameters significantly improved after the addition of a PDE-5 inhibitor (sildenafil) to the baseline drug treatment.

Noncompaction cardiomyopathy was first described in 1932, on autopsy. It is a heterogeneous disease with reserved prognosis. Its treatment is based on the progression to systolic heart failure in the presence of thromboembolic phenomena or arrhythmias secondary to LV impairment. Isolated noncompaction of the myocardium can be identified from childhood to adulthood, occurring in both sexes[6].

The prognosis is extremely variable, the complications being considerably less frequent in the pediatric age group[7]. In an adult case series, approximately 60% had sudden death or underwent heart transplantation six years within the diagnosis[1]. Similarly, in another case series, 47% of 34 adults with isolated noncompaction cardiomyopathy had the same outcome in a follow-up of 44 ± 39 months[2].

Phosphodiesterase type 5 is a specific enzyme that catalyzes the GMPc hydrolysis in several tissues, acting on the metabolism of intracellular nitric oxide. Its inhibition favors vasodilation, via permanence of intracellular GMPc[8]. However, in cardiac dysfunction, the beneficial effect of PDE-5 inhibitors seems related to the deviation of the cascade and to the increase in AMPc production, with an increase in intracellular calcium and contractility improvement[5]. That effect has also been related to the preservation of LV function and a reduction in fibrosis, apoptosis and LV hypertrophy, via inhibition of the RhoA/Rho-kinase pathway. That physiopathological pathway is associated with atherosclerosis, cardiac hypertrophy and post-infarction remodeling[8].

Sildenafil is a selective PDE-5 inhibitor initially used to treat erectile dysfunction and that has potential non-urological applications[4]. According to Freitas Jr. et al[9], the acute administration of sildenafil and sodium nitroprusside has been associated with reverse cardiac remodeling, a reduction in right cardiac chambers and an improvement in biventricular cardiac function[9]. The use of sildenafil improves oxygen uptake, cardiac index, depression, and quality of life, and reduces aortic stiffness and systemic vascular resistance in patients with CHF. Bocchi et al[5] have shown that, during exercise, the use of sildenafil improved physical capacity, the attenuation of heart rate increase and its reduction during recovery, on the treadmill exercise test[5]. Gómez-Sánchez et al[10] and Freitas Jr. et al[9] have shown that one single sublingual dose of sildenafil (100 mg) was effective and safe to reduce pulmonary pressure and its variables during the vascular reactivity test prior to heart transplantation, evidencing that, in addition to a significant reduction in the pulmonary artery systolic pressure and in pulmonary and systemic resistances, there was an increase in cardiac output and minimal effect on the systemic circulation[9,10].

Sildenafil has not been approved for routine use in the pediatric population, except for treating pulmonary arterial hypertension. However, the lack of other therapies that could contribute to improve the patient's functional class and revert his heart failure motivated the off-label use.

Although greater extrapolations cannot be performed based on one single case report, ours suggests that sildenafil might play an important role in the treatment of CHF in the pediatric population, even in the absence of pulmonary arterial hypertension. This emphasizes the need for studies designed for that purpose in that specific population.

Author contributions

Conception and design of the research: Fontes SRF, Elias PF, Souza R, Jatene IB. Acquisition of data: Redondo ACC, Fuenmayor G, Shiraishi KS, Fontes SRF, Elias PF. Analysis and interpretation of the data: Redondo ACC, Fuenmayor G, Shiraishi KS. Statistical analysis: Redondo ACC, Fuenmayor G, Shiraishi KS, Souza R. Writing of the manuscript: Redondo ACC, Fuenmayor G, Souza R. Critical revision of the manuscript for intellectual content: Redondo ACC, Fuenmayor G, Fontes SRF, Elias PF, Souza R, Jatene IB.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any post-graduation program.

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