Effect of a Physical Exercise Program in a Patient with Marfan Syndrome and Ventricular Dysfunction

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Marfan syndrome (MS) is an autosomal dominant disorder that affects multiple organs and systems. Several cardiac alterations are present, with the main ones being aortic root and ascending aorta dilatation, mitral valve prolapse and left ventricle (LV) dilatation. Aerobic exercise has not shown to be a non-drug therapy that promotes anti-remodeling effect in patients with heart failure. This case report describes the echocardiographic changes in a patient with Marfan syndrome during four years of cardiovascular physical therapy.

Marfan syndrome (MS) is an autosomal dominant disorder that affects multiple organs and systems. It is relatively frequent (1:10,000) and it is caused by a mutation in the gene encoding fibrillin-1 and 2, an important constituent of the extracellular matrix. It occurs in all races and ethnic groups and is equally distributed between the sexes. Several cardiac alterations are present, with the main ones being aortic root and ascending aorta dilatation, mitral valve prolapse and left ventricle (LV) dilation, usually secondary to mitral or aortic regurgitation[1]. MS with LV dilatation more often results in sudden death, repolarization alterations and fatal ventricular arrhythmias. Musculoskeletal alterations are also present in SM which, together with other disorders, reduce functional capacity, making the prescription of physical exercise (PE) a challenge in this population[1].

Aerobic exercise training, when carried out for long periods, promotes the anti-remodeling effect in patients with cardiac hypertrophy and ventricular dysfunction[2,3], as well as in those with heart failure[4], as demonstrated in the Leipzig Heart Failure Training Trial (LHFTT)[5]. These alterations are obtained with moderate-intensity exercises (60% VO_{2peak})[2-4]. However, there have been no studies in the literature that evaluated the impact of an exercise program on cardiac remodeling in patients with MS.

Keywords

Marfan syndrome; exercise; cardiomegaly; ventricular dysfunction, left.

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This case report describes the echocardiographic history of a patient with MS with LV dilatation and hypertrophy and the reversal of these alterations throughout a cardiovascular physical therapy program carried out for four years.

Case report

The patient was a 33-year-old male, with no alterations in lipid profile and blood count. After developing angina in 1999, he received a diagnosis of MS and underwent surgery for stent implantation in the thoracic and abdominal aorta, drug treatment with beta-blocker (atenolol 50 mg/day), ACE inhibitor (Enalapril 20mg/day) and calcium antagonist (nifedipine 10 mg 2x/day), with no changes in the last three years.

At the pre-physical therapy period, the patient developed dyspnea on mild exertion and changes in cardiac geometry and function (Table 1).

He was referred to physical therapy in January 2005. His weight was 65 kg, height 202cm, BMI of 15.9 kg/cm^2; body fat percentage of 17.9%, 11.63 kg of fat weight, lean weight of 53.3 kg and reduced capacity physical at the exercise test (symptom-limited Modified Bruce): estimated 21ml/kg/min of VO_2max (VO_2 = vel x 0.1 + vel x incl x 1.8). He started a cardiovascular physical therapy three times a week in February 2006, performing aerobic exercises at 50% to 75% of reserve heart rate and resistance exercises with 60% of the maximum load. During the physical exercises, blood pressure, heart rate and cardiac and pulmonary auscultation remained within the expected. The four-year PE program was supervised by the same physical therapist; the program, which was carried out with increasing intensity, was interrupted only in the months of July and December.

The cardiac geometry and LV function were assessed by Doppler echocardiography in a GE equipment, model SFM Ving Med 800, with a 3.5 MHz transducer. Cardiac function and measurements were obtained at rest (Figure 1). The assessments were performed by the same echocardiographist, reducing the variability effect, and were obtained on the following dates and time intervals in relation to the physical therapy treatment:

(A) – 01/15/2003 – 2 years before; (B) – 12/18/2003 – 1 year before; (C) – 12/11/2004 – 1 month before; (D) – 11/06/2006 – 1 year and 10 months after; (E) – 09/10/2008 – 3 years and 8 months after; (F) – 05/01/2009 – 4 years and 4 months after.

At the last assessment, the patient's weight was 78kg; height: 202cm; BMI: 19.1kg/cm^2; body fat percentage: 16,8%; fat weight: 13.1kg; lean weight: 64.9kg and normal physical capacity for the age range ($VO_{2\ max}$ of 30.7ml/kg/min).

Table 1 - Echocardiographic variables

Variables	Moments						* Reference values
	A	B	C	D	E	F	
L Atrium (mm)	38	47	47	44	40	40	31-33
STD (mm)	10	11	18	13	11	11	7,9-8,4
LVPW (mm)	10	11	13,5	12	11	11	7,8-8,2
RWT	0,38	0,32	0,39	0,40	0,37	0,38	0,33-0,35
LVMI (g/cm^2)	115,0	150,0	182,6	168,6	162,0	158,0	71,3-78,9
LVEDD (mm)	53	69	69	60	59	58	46,8-48,6
LVESD (mm)	29	53	48	40	38	39	26,7-29,2
LV Mass (g)	251	328	394	364	341	331	119-138
EDV (ml)	135	194	247	177	205	195	73-156
ESV (ml)	32	135	108	106	54	59	18-57
EF (%)	76	39	45	60	73	69	69,8-71,5

*SDT – septal diastolic thickness; LVPW – left ventricular posterior wall; RWT – relative wall thickness; LVMI – left ventricular mass index; LVEDD – left ventricular end-diastolic diameter; LVESD – left ventricular end-systolic diameter; LV mass – left ventricular mass; EDV - end-diastolic volume; ESV – end-systolic volume; EF (%) – ejection fraction. *Reference values14. Except for EDV and ESV.*

Discussion

Cardiac remodeling is defined as reversible alterations or not of the structures and biochemical phenomena of muscle and/or interstitial compartments of the myocardium, being of adaptive nature, but followed by functional deterioration[6].

The effect of beta-blockers on cardiac remodeling is well known, preventing LV hypertrophy and dilation. However, it is important to emphasize that the patient had been using this therapy for two years before starting the physical therapy, and the effects of beta-blocker therapy on the reversal of cardiac remodeling can be observed as early as two months after the treatment has been initiated[7].

ACE inhibitors promote the cardiac anti-remodeling effect, mainly when administered in the early stages of post-AMI. These effects may be secondary to the reduction in neurohumoral activity, anti-ischemic effect and reduction of matrix metalloproteinases 2 and 9, factors that either isolated or in combination, contribute to the occurrence of cardiac hypertrophy[8].

The effect of calcium antagonists on cardiac hypertrophy depends on the decrease in arterial hypertension[9]. In this report, the patient had no history of arterial hypertension, and thus, an effect of therapy with calcium antagonists on cardiac hypertrophy reduction is not justified. Moreover, the cardiac hypertrophy caused by arterial hypertension is the concentric type, and in the present report, the patient had eccentric hypertrophy.

The remodeling effect can be explained by trophic alterations in cardiomyocytes. However, a population of myocytes would be able to reenter the cell cycle and replicate when exposed to specific stimuli and among those is PE, in which the effects on cardiac anti-remodeling have been drawing attention in different diseases, with significant increases in EF and decrease in ventricular mass, thickness and diameter[2-5].

The anti-remodeling effect in HF through PE seems to depend on the time of the intervention, a minimum of six months[2-5,10]. The cardiac anti-remodeling effect induced by PE seems to be strongly influenced by the synthesis/activity of nitric oxide (NO)[11], but NO production is normal in patients with MS. Other possible mechanisms by which PE triggers the anti-remodeling effect is the anti-adrenergic effect, lower double product and improved baroreflex, triggered by the improvement in contractile efficiency. A more recent retrospective analysis of the Leipzig Heart Failure Training Trial (LHFTT) attributes, in part, the reduction in cardiac hypertrophy to the increase in stroke volume at rest (observed in this report) and during physical exercise, as well as the decrease in post-load through the reduction in vascular peripheral resistance[12]. The PE promotes improvement in relaxation velocity and shortening of the cardiac muscle by increasing the synthesis of the calcium transport protein (SERCA-2), increasing the calcium concentration and sensitivity to calcium by cardiomyocytes, significantly contributing to the improvement of ventricular function[13].

Thus, the cardiac anti-remodeling effect seems to depend on ventricular function improvement, which, in turn, depends on several factors.

Physical exercises have shown to be a therapeutic option of multiple aspects and their effectiveness and safety in MS have already been investigated. Several studies have shown the effect of cardiac anti-remodeling promoted by PE, especially in patients with left ventricular dysfunction, but the mechanisms involved are yet to be fully clarified, especially in patients with MS.

Conclusions

Regarding Marfan syndrome, there is a clear recommendation in the guidelines to avoid physical exertion. This fact is often mistaken for not exercising at all. This case report is extremely interesting as it demonstrates the benefits of a PE program in a

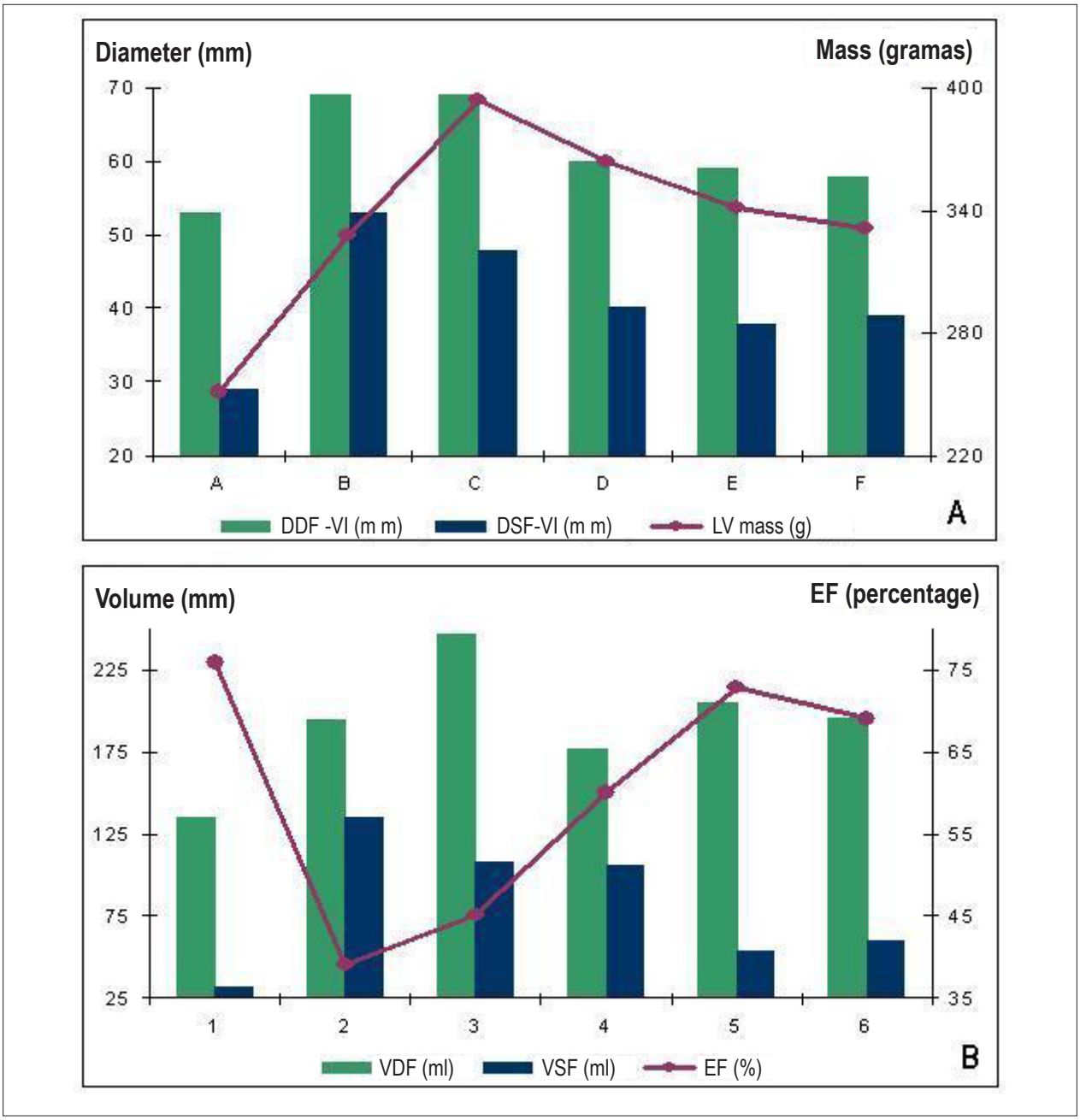

Figure 1 – *Absolute values of LVEDD (mm) – left ventricular end-diastolic diameter in millimeters; LVESD – left ventricular end-systolic diameter in millimeters; LV mass (g) – left ventricular mass in grams; EDV (mL) end-diastolic volume in milliliters; ESV (mL) -end-systolic volume in milliliters; EF (%) – ejection fraction in percentage.*

patient with MS in an even worse situation, in which in cardiac remodeling with hypertrophy is quite deleterious.

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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