

Cell Therapy in Dilated Cardiomyopathy

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A forty-one-year-old male with systolic heart failure, FC-III NYHA, clinical stage C due to dilated cardiomyopathy was submitted to an autologous transplant of the mononuclear fraction of bone marrow via coronary artery system through heart catheterism. Two months after the procedure, there was a decrease in plasma BNP and cardiac area reduction at the thorax X-ray and nuclear magnetic resonance. The echocardiogram showed decrease of the secondary regurgitation and mitral ring dilatation. There was a better performance at the ergospirometry, with increase of the maximum oxygen consumption and consequent reduction in drug therapy. The absence of adverse events characterized by clinical/hemodynamic instability, enzymatic alteration or electrocardiogram demonstrate the safety and feasibility of this procedure carried out and described with pioneering spirit in dilated cardiomyopathy.

INTRODUCTION

Despite the progresses made regarding the drug therapy of chronic systolic heart failure, which is the evolution stage of several cardiomyopathies such as dilated cardiomyopathy, the number of individuals who present the syndrome increases worldwide, constituting a serious public health problem. For a significant number of individuals, the syndrome progresses even with drug therapy. Thus, heart failure Functional Class (FC) III and IV of the New York Heart Association has been one of the main causes of hospital admissions, using a large part of healthcare resources with a high mortality rate (40%/year). The development of new, low-cost and low-risk therapeutic procedures, such as the myocardial implant of stem cells obtained from bone-marrow aspirate from the individual's own bone marrow, constitutes a promising therapeutic option for these advanced cases. From the 90s on, several experimental studies in animal models of cardiac lesion showed the capacity of bone marrow-derived cells to improve heart performance when injected directly into the myocardium or in the systemic circulation. In the beginning of the new millennium, the knowledge generated by experimental models started to

be utilized in clinics. In a pioneering work, Menasché and cols. performed a transplant of skeletal muscle satellite cells to the heart of an elderly patient with refractory heart failure, in France¹. After that, two groups in Germany and one in Hong Kong utilized bone marrow mononuclear cells in the treatment of patients with ischemic disease²⁻⁴. In Brazil, within the context of the project developed at the Instituto do Milênio de Bioengenharia Tecidual (Tissue Bioengineering Millennium Institute), the same cells were used to treat patients with post-ischemic heart failure⁵ and, more recently, in patients with chronic Chagas disease cardiopathy⁶

CASE REPORT

The patient was a forty-one-year-old male, with a history of 12 years of progressive symptoms of systolic heart failure due to dilated cardiomyopathy. In the last two years, he had presented significant functional limitation, fatigue when performing everyday activities such as showering, and episodes of orthopnea and nocturnal paroxystic dyspnea. Inflammatory and serological markers (including those for Chagas disease) were negative. Coronary flow was free of obstructive lesions at the coronary angiography. The patient was undergoing optimized therapeutics in the Heart Failure Clinic with daily use of Digoxin 0.25 mg, Furosemide 80 mg, Spironolactone 25 mg, Captopril 75 mg, and Carvedilol 50 mg. At physical examination, the patient's weight was 66.4 kg, blood pressure (BP) was 100/60 mmHg, cardiac frequency (CF) was 76 bpm, respiratory frequency (RF) was 20 rpm, regular cardiac rhythm with B3, holosystolic murmur 3+/6+ with dorsal irradiation, audible vesicular murmur with no adventitial sounds, and palpable liver at 1 cm from the right costal edge with no lower limb edema. After informed consent, the patient underwent the Minnesota Living With Heart Failure Questionnaire (MLWHFQ), thorax X-ray, measurement of plasma BNP, inflammatory markers and serum enzymes, nuclear magnetic resonance, echocardiogram, 12-derivation electrocardiogram, 24-hour Holter, ergospirometry and hemodynamic study.

For the cell implant to the heart, 50 mL of the patient's bone marrow was aspirated from the iliac crests. The mononuclear fraction was separated after pre-filtering (bone marrow filtering system - Washington University - USA) and centrifuged through a Ficoll gradient. After resuspension in 20 mL of autologous serum solution (5%), 10^8 cells were injected in the coronary artery system (10 mL in the DA, 4 mL in the CX, 6 mL in the CD) with no occurrence of pain, arrhythmia or hemodynamic instability during the procedure and in the immediate post-procedure period.

Electrocardiographic and enzymatic monitoring was carried out during the first 24 hours post-procedure in an intensive care unit, with no alterations of these parameters (Table 1).

Enzymes	pre	6h	12h
CKmb	13	15	17
Troponin	0.5	0.5	0.5

The patient was released from the hospital seventy-two hours post-procedure, and returned every two weeks for follow-up; the exams described above were repeated after two months. At physical examination, the patient's weight was unaltered (66.5 kg), BP was 100/60 mmHg, CF was 60 bpm, RF was 18 rpm, with regular cardiac rhythm, but no B3, and reduction of the holosystolic murmur, now 1+/6+ and no irradiation.

The initial MLWHFQ score was 63, being reduced to 39 after the cell therapy. Thorax X-ray showed a pre-treatment thoracic cardiac index of 0.55, and post-treatment of 0.48 (Fig 1). The magnetic resonance also showed a decrease in the systolic and diastolic volumes of the left ventricle, going from 302 mL (FSV) and 371 (FDV) pre-treatment, to 217 and 263 mL, respectively, after cell therapy (Fig 2). However, there was no alteration in the ejection fraction, which remained around 17% (Simpson method).

Plasma BNP levels varied from 118 pg/ml (pre) to 39 pg/ml (post-therapy). An improvement in the mitral failure was observed at the echocardiogram as shown in figure 3.

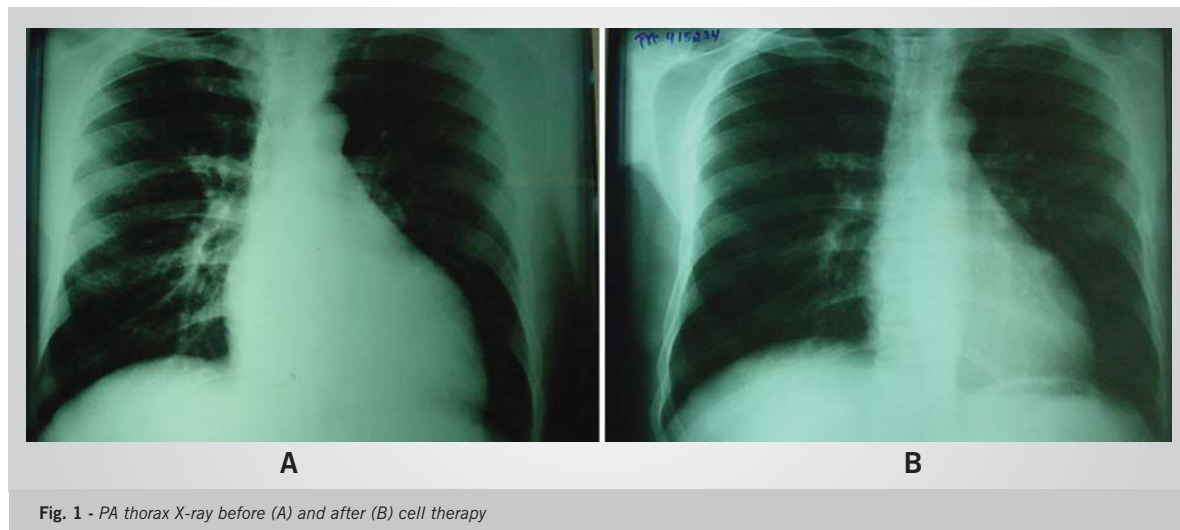


Fig. 1 - PA thorax X-ray before (A) and after (B) cell therapy

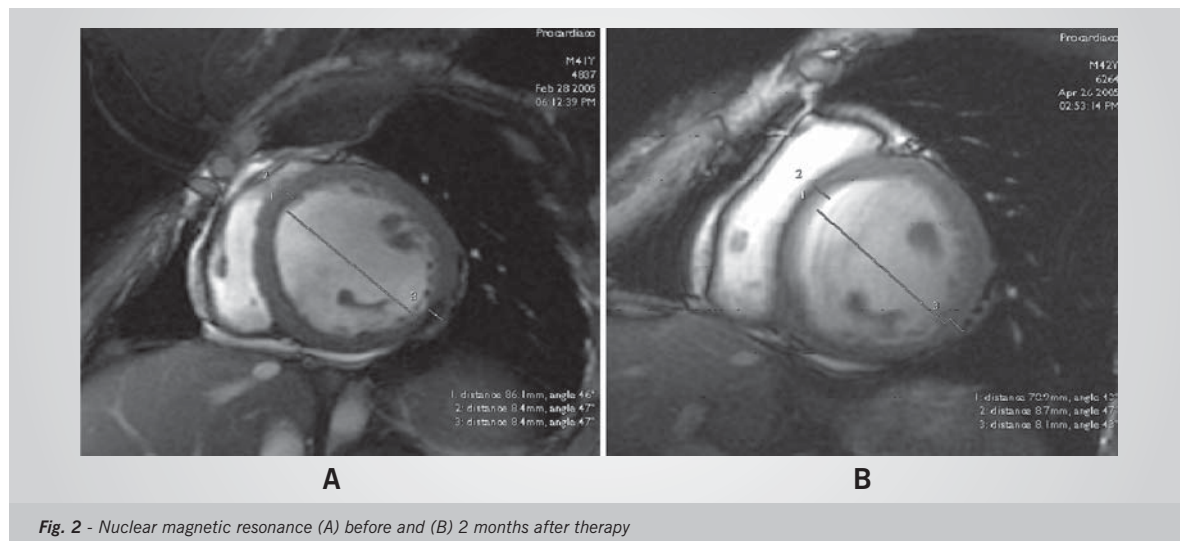


Fig. 2 - Nuclear magnetic resonance (A) before and (B) 2 months after therapy

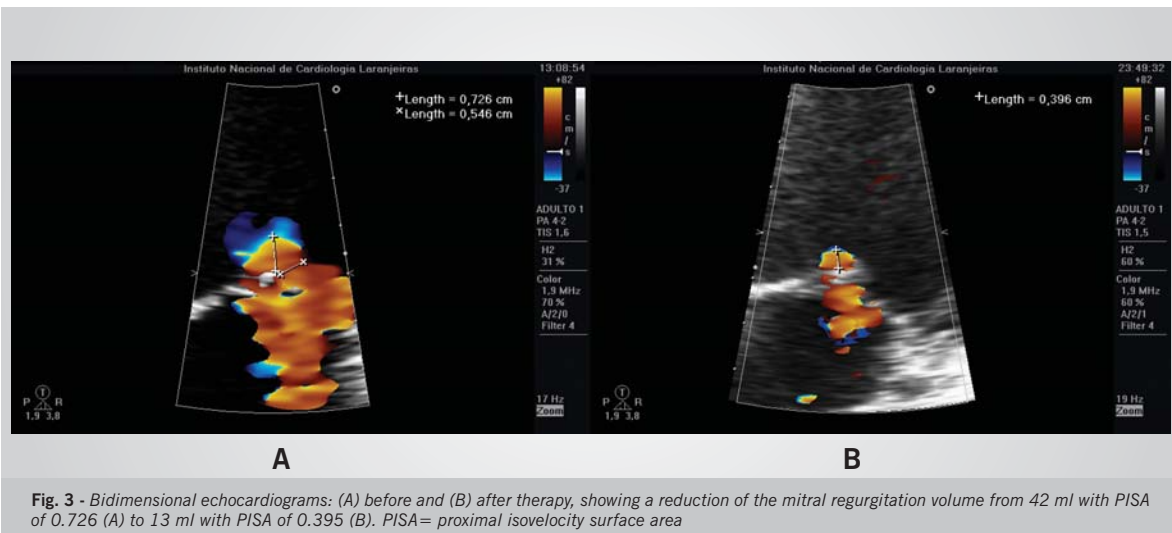


Fig. 3 - Bidimensional echocardiograms: (A) before and (B) after therapy, showing a reduction of the mitral regurgitation volume from 42 ml with PISA of 0.726 (A) to 13 ml with PISA of 0.395 (B). PISA= proximal isovelocity surface area

The improvement observed in the mentioned variables was followed by a better performance at the ergospirometry as shown in Table 2. It is noteworthy that the patient was classified as being in functional group III, by ergospirometry, before therapy, and improved to being group II after treatment. The favorable clinical evolution of the patient allowed us to decrease drug therapy with the reduction of the daily dose of furosemide (40 mg) and spironolactone (12.5 mg).

Table 2 - Ergospirometry - Ramp Protocol

Variable	Pre	Post
Duration	5:49	11:40
Distance (miles)	0.15	0.38
Max. CF*	100	102
Max. Pot. (W)	55.9	130
Max. VO ₂ mL(Kg.min)	15.61	18.64
Functional group	III	II
T ½** (s)	>120	<90
O ₂ pulse (ml/beat)	10.3	12.1
LV/VCO ₂	29.7	23.8

*CF: cardiac frequency; **T1/2: time required for peak VO₂ to reach 1/2 the value at maximum stress

DISCUSSION

Cell therapy has been applied to patients with acute and chronic ischemic cardiopathy through the intracoronary release of bone marrow cells or intramyocardial injection¹⁻⁵. The action mechanism of bone marrow mononuclear cells (BMMC) remains to be clarified, and there is a great deal of controversy in literature on their capacity of regenerating cardiomyocytes⁷⁻⁹. Still, in all animal models of cardiopathy and clinical assays carried out to date, these cells promoted an improvement in cardiac function, although these studies were performed with the main objective of testing the safety and feasibility of this new procedure.

In patients with chronic Chagas cardiopathy with severe systolic dysfunction, the intracoronary release of BMMC also showed to be safe and resulted in functional improvement⁶. Based on these results, we utilized the intracoronary BMMC release model in a patient with dilated cardiomyopathy. In this case report, we observed that the procedure was carried out with no adverse events, suggesting the method is safe and viable. This observation, together with the improvement in the patient's clinical parameters and complementary exams leads us to propose cell therapy as an alternative to be investigated for the treatment of severe dilated cardiomyopathy.

REFERENCES

1. Menasché P, Hagege AA, Scorsin M, et al. Myoblast Transplantation for heart failure. *Lancet*. 2001;357:279-80.
2. Strauer BE, Brehm M, Zeus T, et al. Repair of infarcted myocardium by autologous intracoronary mononuclear bone marrow cell transplantation in humans. *Circulation*. 2002;106:1913-18.
3. Assmus B, Schächinger V, Teupe C, et al. Transplantation of progenitor cells and regeneration enhancement in acute myocardial infarction (TOPCARE-AMI). *Circulation*. 2002;106:3009-17.
4. Tse HF, Kwong YL, Chan JKF, et al. Angiogenesis in ischaemic myocardium by intramyocardial autologous bone marrow mononuclear cell implantation. *Lancet*. 2003;361:47-9.
5. Perin EC, Dohmann HF, Borojevic R, et al. Transendocardial, Autologous Bone Marrow Cell Transplantation for Severe, Chronic Ischemic Heart Failure. *Circulation*. 2003;107:r75-r83.
6. Vilas-Boas F, Feitosa GS, Soares MPB, et al. Transplante de Células de Medula Óssea para o Miocárdio em Paciente com Insuficiência Cardíaca Secundária a Doença de Chagas. *Arq Bras Cardiol*. 2004; 82 (2):181-4.
7. Orlic D, Kajstura J, Chimenti S, et al. Bone Marrow cells regenerate infarcted myocardium. *Nature*. 2001; 410: 701-5.
8. Balsam LB, Wagers AJ, Christensen JL, et al. Haematopoietic stem cells adopt mature haematopoietic fates in ischaemic myocardium. *Nature*. 2004; 428: 668-73.
9. Murry CE, Soonpaa MH, Reinecke H, et al. Haematopoietic stem cells do not transdifferentiate into cardiac myocytes in myocardial infarcts. *Nature*. 2004; 428: 664-8.