

# Clinical and functional capacity of patients with dilated cardiomyopathy after four years of transplantation

*Evolução clínica e capacidade funcional de pacientes com cardiomiopatia dilatada após quatro anos do transplante*

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## Abstract

**Objective:** To evaluate patient with cardiomyopathy's progress after cardiac transplant, by analyzing his survival, complications and cardiovascular responses after nearly four years of surgery.

**Methods:** The survey was conducted from February to May 2011, with patients undergoing cardiac transplantation at Dr. Carlos Alberto Studart Gomes Hospital - Messejana Hospital (HDM). The sample consisted of all transplanted patients in 2007 in this hospital. Initially an evaluation form developed by the researchers, which was based on collected data from patients' medical records, was applied, about trans and postoperative period. After collecting these informations, patients underwent the six-minute walk test (6WT). The marks found in walking distance were compared with reference marks expected for this population by using Enright and Sherrill's equation.

**Results:** From all the 24 patients who underwent cardiac transplantation in HDM in 2007, 14 were evaluated and 10 were excluded. Regarding the complications, in the transoperative period, the most evident was the right ventricular dysfunction (64.3%) and tachycardia (64.3%) was more evident on the postoperative period. Analyzing the 6WT it was observed a decrease of 11.6% in walking distance when compared with the estimated distance (486 ± 55 m, 550 ± 59 m, respectively).

**Conclusion:** Survival of heart transplant patients was equivalent to about 70%. The results of this study before the 6WT showed that patients' cardiovascular responses are below the estimated, nevertheless within the normal range established.

**Descriptors:** Cardiomyopathies. Cardiomyopathy, dilated. Heart transplantation. Walking.

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Abbreviations, acronyms and symbols	
IAC	Intra-aortic balloon
CPB	Cardiopulmonary bypass
RVD	Right ventricular dysfunction
EF	Ejection Fraction
HDM	Hospital de Messejana – Dr. Carlos Alberto Studart Gomes
CHF	Congestive heart failure
BMI	Body mass index
CMP	Cardiomyopathy
LL	Lower limbs
NO	Nitric oxide
PO	Postoperative
SOLVD	Studies Of Left Ventricular Dysfunction
SIRS	Systemic inflammatory response syndrome
6MWT	Testing of the six-minute walk
Tx	Transplant

### Resumo

**Objetivo:** Avaliar a evolução do paciente miocardiopata após transplante (Tx) cardíaco, analisando sua sobrevida, complicações trans e pós-operatórias e respostas cardiovasculares após cerca de quatro anos do procedimento cirúrgico.

**Métodos:** A pesquisa foi realizada no período de fevereiro a maio de 2011, com pacientes submetidos a Tx cardíaco

no Hospital Dr. Carlos Alberto Studart Gomes - Hospital de Messejana (HDM). A amostra foi composta de todos os pacientes transplantados no ano de 2007 no referido hospital. Inicialmente, foi aplicada uma ficha de avaliação, coletando dados dos prontuários, sobre a evolução do paciente no período trans e pós-operatório até a alta hospitalar. Após a coleta dessas informações, os pacientes foram submetidos ao teste da caminhada dos seis minutos (TC6). Os valores encontrados na distância percorrida foram comparados aos valores de referência esperados para a população utilizando a equação de Enright e Sherrill.

**Resultados:** Do total de 24 pacientes que realizaram Tx cardíaco no HDM no ano de 2007, 14 foram avaliados e 10 excluídos do estudo. Com relação às complicações, no período transoperatório, a mais evidenciada foi a disfunção do ventrículo direito (64,3%) e, no pós-operatório, quadro de taquicardia (64,3%). Analisando o TC6 observou-se diminuição de 11,6% na distância percorrida quando comparada à distância estimada ( $486 \pm 55$  m,  $550 \pm 59$  m, respectivamente).

**Conclusão:** Os resultados obtidos neste estudo perante o TC6 evidenciam que as respostas cardiovasculares dos pacientes avaliados estão abaixo do estimado, contudo dentro da faixa de normalidade estabelecida.

**Descritores:** Cardiomiopatias. Cardiomiopatia dilatada. Transplante de coração. Caminhada.

## INTRODUCTION

The cardiomyopathies (CMP) are a group of diseases associated with mechanical and/or electrical myocardial dysfunction. This disorder is often accompanied by dilation or inappropriate ventricular hypertrophy and heart failure [1]. Patients with this impairment may progress to progressive heart failure that consequently can lead to death of cardiovascular origin or physical disability [2].

When the CMP reaches an advanced stage of heart failure (NYHA functional classes III and IV), cardiac transplantation (Tx) becomes a form of treatment able to restore hemodynamic function, improve quality of life and survival of patients with return to functional class I [3]. Therefore, it is indicated for patients whose symptoms do not respond to drug therapies or other means of surgical repair [4].

The heart Tx, being a major surgery, can cause several complications. Among them we can highlight

bleeding and gas, coronary or systemic embolism through maneuvers to remove air from the cardiac chambers, initially inefficient (reperfusion). Additionally, there may be changes resulting from prolonged cardiopulmonary bypass (CPB) as hypotension, decreased cardiac output, coagulation disorders, dysfunction of pulmonary mechanics, immunological rejection, graft failure for countless reasons, among others [5,6].

The graft failure from different causes is considered the leading cause of death postoperatively (PO) and the Tx, in the immediate phase, predominates nosocomial infections associated with intraoperative contamination; later, opportunistic infections are common. Another major cause of early mortality is the right ventricular dysfunction in the immediate postoperative period, which constitutes 50% of all complications [6,7].

In Tx surgery, the donor's heart is completely disconnected from the sympathetic and parasympathetic innervation, and heart denervation is a complication

of the immediate postoperative period, on which bradyarrhythmias are observed. Arterial hypertension is also common after the Tx and affects 50% to 95% of the receptors due to the use of cyclosporine. Rejection episodes, a result from immune response of the recipient to the donor heart are more frequent and severe in the first few months after Tx, becoming more sporadic and benign later [8].

Regarding quality of life after heart Tx, most patients return to their normal activities and work, with few restrictions, leaving virtually no dyspnea on exertion (NYHA functional class I). Some studies have compared the quality of life of patients before and after cardiac Tx, showing that the procedure's success means not only ensuring the improvement of symptoms and survival of patients in end-stage heart disease, but allow them to achieve good levels of ability and physical quality of life [9-11].

After the clinical indication of cardiac Tx for cardiomyopathic patients, the therapeutic follow in the pre-transplant is delicate and expensive and assessments and monitoring of functional capacity on a regular basis should be performed. The cardiopulmonary assessment is the most accurate method, but its periodic execution is difficult, thus impeding a possible more detailed control of the patient who is in severe conditions [12].

However, the test of the six-minute walk test (6MWT) may be indicated as an alternative exercise tolerance assessment, which is a simplified, reproducible, inexpensive and easy to apply, and may provide clues as to the clinical stage, response to interventions, functional capacity, cardiorespiratory fitness, functional class, cardiovascular prognosis and quality of life [12].

Moreover, the kind of effort required by the test can be considered as a submaximal test, since it resembles more the daily activities than a maximal test [13].

Since 1980, there has been a growth in the use of the 6MWT in clinical practice, especially in heart failure. In the SOLVD study (Studies of Left Ventricular Dysfunction), the distance walked during six minutes was identified as independent variable and indicator of mortality and morbidity in patients with heart failure functional class II and III [13]. The emergence of this study allowed several correlations and better understanding of the 6MWT value [14].

Due to all the complications arising from a patient after cardiac Tx, the importance of this study is related to the improvement of care for these patients, once identified major complications in the postoperative period and the later patient's functional condition, most effective techniques can be used to minimize these complications in other cases. Thus, the aim of this research was to assess the patient's cardiac Tx myocardiopathy after assessing

their survival, trans- and postoperative complications and cardiovascular responses after about 4 years of surgery.

## METHODS

We performed quantitative, cohort and retrospective cross-sectional study from February to May 2011, with patients undergoing cardiac Tx in Messejana Hospital - Dr. Carlos Alberto Studart Gomes (HDM), in Fortaleza, CE.

This study was approved by the Ethics Committee of the institution (Report No. 104/2011) and followed the ethical principles according to Resolution 196/96 of the National Health Council, which established the principles for research involving human subjects [15], and all of participants signed a written informed consent.

The sample was composed of all patients transplanted in 2007 in that hospital. Inclusion criteria were considered: age above 18 years, regardless of gender, preoperative diagnosis of CMP progressing to heart failure functional class IV, having performed the cardiac Tx in 2007, presenting conditions and willingness to cooperate voluntarily with the study.

The study excluded transplanted patients who were in hemodynamically unstable condition in the period of data collection, defined by use of vasoactive drugs intravenously, and therefore in hospital, those with motor or neurological sequel that hindered the march and those who died up to the research.

Initially, we applied an assessment form developed by the researchers based on data collected from medical records of patients transplanted in HDM in 2007. This form contained items such as gender, age, weight, height, body mass index (BMI), duration of CPB, preoperative diagnosis, ejection fraction (EF) previous intraoperative impairments, postoperative impairments, age, donor's gender, donor/recipient weight ratio and ischemia time. We also collected information regarding the immunosuppression regimen and pulmonary vascular resistance.

After collecting this information, patients underwent the 6MWT according to the protocol recommended by Ferreira et al. [16]. The parameters measured were distance, Borg scale of dyspnea and lower limb (LL) at rest and after six minutes of the test. The values found on the distance traveled were compared to reference values for the expected population using the Enright & Sherrill equation [17].

### Demographic and surgical characteristics

Of the total 24 patients who underwent cardiac Tx in HDM in 2007, 14 were assessed and 10 were excluded from the study, and two were hemodynamically unstable, one was younger than 18 years and seven died. Of these,

three died in the immediate postoperative period, a 5 months after surgery due to rejection presentation and three after 1, 2 and 3 years of surgery, respectively, in the heart failure presentation. Among those assessed, 12 were male and 2 female, mean age  $55 \pm 11$  years, weight  $71 \pm 12$  kg, height of  $1.66 \pm 0.05$  m and BMI  $25 \pm 4$  kg/m<sup>2</sup>.

The patients presented a mean left ventricular EF before Tx of  $23 \pm 4\%$ . The preoperative diagnosis of the study participants ranged in three types of dilated CMP: idiopathic (nine patients), ischemic (three patients) and Chagas' disease (two patients). Regarding the donors' gender, 12 were male and only two female and presented a mean age of  $32 \pm 8$  years. All recipients had pulmonary vascular resistance less than 5 wood after test drug (sodium nitroprusside or inhaled nitric oxide), a criteria used for this transplant indication.

The weight ratio between the donor and recipient was  $1.1 \pm 0.5$ . The CPB time during Tx averaged from  $157 \pm 36$  minutes and the period of ischemia ranged from 20 to 69 minutes, with a mean of  $46 \pm 12$  minutes. The immunosuppression regimen used in the hospital was Cyclosporin A (dose guided by cyclosporin), mycophenolate mofetil (720 mg/day) and prednisone. During the assessment of patients (4 years after transplantation), medication remained the same excepted by prednisone.

Data were assessed using descriptive statistics with mean values, standard deviations and percentage through the SPSS statistical software, version 16.0. For inferential statistics we used the paired Student's t test when observed sample normality. In the variables that did not show normal distribution we applied the Mann-Whitney test for data normalization. We considered statistically significant when  $P < 0.05$ .

## RESULTS

### Surgical complications

The patients presented as more frequent intraoperative complication right ventricular dysfunction (RVD), nine (64.3%) patients with this complication, of which five (35.7%) used nitric oxide (NO), and only one (7.1%) had left ventricular dysfunction, under use of dobutamine. These changes were diagnosed by direct visualization of the organ and confirmed by measurement of pulmonary artery pressure using Swan-Ganz catheter. Two (14.3%) patients had difficulty to be disconnected from CPB and three (21.4%) had bleeding during disconnection. Two patients had hypertension and two hypotension, two required a temporary pacemaker, one had a systemic inflammatory response syndrome (SIRS), one had cardiac arrest, one had complete atrioventricular block and only one patient had no intraoperative complication, as described in Table 1.

Table 1. Surgical complications of 14 assessed transplanted patients

Complications	Total number (%)
Right ventricular dysfunction	9 (64.3%)
Use of nitric oxide	5 (35.7%)
Left ventricular dysfunction	1 (7.1%)
Difficult to disconnect CPB	2 (14.3%)
Bleeding during CPB disconnection	3(21.4%)
Hypertension	2 (14.3%)
Hypotension	2 (14.3%)
Temporary pacemaker	2 (14.3%)
SIRS	1 (7.1%)
Cardiorespiratory arrest	1 (7.1%)
Total atrioventricular block	1 (7.1%)

### Postoperative Complications

All patients had postoperative complications, such as tachycardia, abnormal sensory level, low-output presentation, pericardial effusion, sudden bradycardia, congestive heart failure (CHF), hypotension, hypertension, use of intra-aortic balloon (IAB), thrombocytopenia, rejection, sepsis, reoperation for bleeding (exploratory mediastinostomy), and renal dysfunction requiring hemodialysis (Table 2).

Table 2. Postoperative complications of 14 assessed transplanted patients

Complications	Total number (%)
Tachycardia	9 (64.3%)
Sensorimotor level change	4 (28.6%)
Low cardiac output	1 (7.1%)
Pericardial effusion	7 (50%)
Sudden bradycardia	1 (7.1%)
Congestive heart failure (CHF)	2 (14.3%)
Hypotension	7 (50%)
Hypertension	3 (21.4%)
Intraórtico balloon (IAB)	1 (7.1%)
Thrombocytopenia	3 (21.4%)
Rejection	2 (14.3%)
Reoperation for bleeding	2 (14.3%)
Sepsis	1 (7.1%)
Renal failure	3 (21.4%)
Hemodialysis	1 (7.1%)

Table 3. Postoperative respiratory complications of 14 assessed transplanted patients

Complications	Total number (%)
Pleural effusion	6 (42.9%)
Atelectasis	8 (57.1%)
Respiratory infection	2 (14.3%)
Pulmonary infarction	1 (7.1%)
Respiratory failure	3 (21.4%)
Reintubation	2 (14.3%)

Some patients also had pulmonary complications, such as pleural effusion, atelectasis, respiratory infection, pulmonary infarction, respiratory failure and reintubation, as shown in Table 3.

#### Six-minute walk test

Assessing the 6MWT we observed a decrease of 11.6% in distance traveled when compared to estimated distance calculated using the Enright & Sherrill equation [17] ( $486 \pm 55$  m and  $550 \pm 59$  m, respectively), considered a statistically significant result ( $P = 0.011$ ).

In assessing the Borg scale of lower limbs, it was found that there was a change, with an increase of 69.2% compared with the rest of the test's 6 minutes ( $0.4 \pm 0.7$  and  $1.3 \pm 1$ , respectively), presenting, therefore, statistical significance ( $P = 0.016$ ).

In Borg scale of dyspnea we also observed changes, with an increase of 85.7% when compared with the rest of the test's 6 minutes ( $0.2 \pm 0.7$  and  $1.4 \pm 1.2$ , respectively), with statistical significance ( $P = 0.004$ ).

Regarding the SOLVD study, the average of the results obtained with the 6MWD was  $3.6 \pm 0.4$ , and all patients achieved level 3 or 4, classifying them as functional class I or II.

## DISCUSSION

The life expectancy of heart transplant patients has improved considerably, due to the very favorable results of cardiac Tx in recent years, with current survival rate of 80%, 70% and 60% at one, five and ten years, respectively [18]. This study corroborates this estimate, once found the value of 70.8% survival after approximately four years of cardiac Tx.

Among the complications in the immediate postoperative period of cardiac Tx, the pulmonary hypertensive crisis and RVD are secondary to this concern, since they have high percentage (50%), which can lead to high mortality and decreased life of the graft. In more severe cases, when there is no adequate response to therapy employed and persistence of severe pulmonary hypertensive crisis, NO inhalation is used because it is a selective pulmonary vasodilator. This gas aims at reducing pulmonary arterial pressure and hence improve the right ventricle performance [19].

In the study by Mejia et al. [19], they used the NO in a group of five cardiac transplant patients who had pulmonary hypertensive crisis and RVD and who have not responded well to the therapy. They identified in the group

increased CPB time, over 120 minutes, compared to other transplanted.

In this research, the RVD was also the complication that had the highest percentage (64.3%) of all complications in the immediate postoperative period. Of the nine (64.3%) patients with RVD, five (55.5%) made use of vasodilator therapy with NO and all of these also had a prolonged cardiopulmonary bypass time, over 120 minutes, which explains such complications.

Many factors during CPB, as the exposure of blood to nonphysiologic conditions and surfaces and the increase of pulsatile flow in a continuous stream, results in the development of SIRS [20]. This limited biocompatibility of materials causes multiorgan dysfunction after systemic perfusion, expressed by myocardial depression, vasomotor dysfunction, respiratory, renal and hepatic failure, cognitive imbalance and of thermal regulation for coagulopathy for bleeding, which characterizes the SIRS. It is the cause of mortality of CPB, manifesting in different degrees and in different organs, and its greatest manifestations affecting the heart and lungs [21]. All these factors may explain the occurrence of the various postoperative complications found in this study.

The distribution of the incidence of infectious processes follows the curve of rejection, being more frequent and more severe in the first few months after Tx, because in this phase the immunosuppression is more intense [3]. Despite advances in immunosuppressive therapy in the last decade, the acute cellular rejection of the transplanted heart remains an important factor associated with long-term morbidity and mortality [22].

Among the later complications such as rejection and infection, those related to graft vascular disease or side effects of immunosuppressive agents can affect the functioning of the kidneys and liver and increase blood pressure. In the study by Moraes Neto et al. [23] they observed that, of the 35 heart transplant patients followed up, seven (20%) died in the immediate postoperative period and thirteen (37.1%) had non-fatal complications, including rejection (five cases), infection (four cases), renal failure requiring hemodialysis (four cases) and bleeding requiring surgical exploration (three cases).

In this study, the results were similar: it was found that, of 24 heart transplant patients in HDM in 2007, seven (29%) died and fourteen (58.3%) had non-fatal complications such as rejection (two cases), respiratory infection (three cases), acute renal failure (three cases, one of whom required hemodialysis) and reoperation for bleeding (two cases).

The postoperative pulmonary complications are factors that contribute to morbidity and mortality in any type of upper abdominal or thoracic surgery. Respiratory insufficiency in the PO can be triggered by anesthesia and central nervous system depression caused by it, by ineffectiveness of coughing, by limiting the ventilation due to pain and the use of prosthetic mechanical ventilation [24].

With a common history of cardiac Tx in 2007 and preoperative diagnosis of CMP progressing to heart failure functional class IV, subjects in the study showed significant improvement in cardiovascular function, assessed from the 6MWT outcomes, currently focusing on functional classes I and II (mean  $3.6 \pm 0.4$  as the level of the SOLVD study).

The SOLVD study was the first to demonstrate a strong correlation between the 6MWT and mortality. With the assessment of 898 patients with left ventricular dysfunction or radiological evidence of pulmonary congestion with a median follow-up of 242 days, a substudy of SOLVD group showed that mortality was 10.23% in patients who walked less than 350 m in the 6MWT (level 2), compared with 2.99% ( $P < 0.01$ ) of patients who walked more than 450 m in the test (level 4) [25].

Similarly, the study by Cipriano Júnior et al. [12] used the 6MWT in pre-heart transplant assessment, in which the analysis of the relationship between the 6MWT and clinical staging and cardiovascular prognosis primarily revealed that, despite belonging to an apparently homogenous group, both also now eligible for Tx heart they had a functional capacity, estimated by the distance traveled, very diverse, mainly for four patients who traveled a distance less than 300 meters [26].

Enright & Sherrill [17] proposed a reference equation for healthy individuals to predict 6MWD, considering variables such as age, gender, weight and height. However, there are few studies that verify the degree of deconditioning when compromising physical performance of transplanted heart individuals.

Regarding the distances traveled and predicted, this study observed difference between them for cardiac transplant patients. However, although this difference was statistically significant ( $P = 0.011$ ), the mean distance ( $486 \pm 55$  m) was found within the range of normality established by equation (mean of  $399 \pm 69$  m), or that is, patients walked 21.8% above the lower limit defined as normal according to the calculation provided by Enright & Sherrill [17].

As expected, the results of the lower limbs and dyspnea Borg scale suffered increased when compared the rest with

six minutes of the test, with both statistical significance ( $P = 0.016$  and  $P = 0.004$ , respectively). However, this increase is not enough to be of clinical significance, ranging from just extremely lightweight for something between very light and mild on the scale of the lower limbs, and something between none and extremely lightweight for something between very light and mild in dyspnea scale.

The post-heart transplant patients have better quality of life. But also often have physical deconditioning, muscle weakness and atrophy and lower aerobic capacity [27]. Regular physical activity plays an important post-transplant role and should be started early to restore physical capacity, enabling transplanted patients back to perform most of their daily activities and also recreation. When implementing a basic program of mobilization and respiratory therapy, cardiac transplant patients were able to retrieve the values of lung volumes and capacities and improve the useful functional capacity [28].

Recently, studies have demonstrated the usefulness of TC6 in the Tx area of solid organ, and the outcomes of the studies varied. The organ Tx is the ideal intervention for various terminal diseases that affect multiple organs such as the heart, lungs, kidneys, pancreas and liver. Although transplant patients may survive the surgery, all have reduced ability to exercise. Even as a submaximal exercise test, 6MWT assists in making the most appropriate therapeutic measures [24]. Moreover, it presents itself as a promising tool in the field of medical research, so Tx experts should also be aware of its both pre- and postoperatively advantages [29].

Although the present study has covered all heart transplant patients in HDM in 2007, taking into account the exclusion criteria, it was limited by the number of participating patients, so that the population assessed corresponded to a total of 58.3% of all patients transplanted in 2007 in that hospital. It is known that this might have favored or not the results.

Thus, it is believed that further studies should be performed with this profile of patients in the future, so they can have their increased survival with improved quality of life. For this, it is necessary to implement a cardiac rehabilitation program in our State as early as possible.

## CONCLUSION

A further evident complication in the perioperative period was right ventricular dysfunction, and the most frequently observed postoperatively, was tachycardia. The test results of submaximal functional capacity as assessed

by the 6MWT, after four years of transplantation are lower than estimated, but within the normal established range.

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