

# Addition of long-distance heart procurement promotes changes in heart transplant waiting list status

*Incorporação da captação à distância promove mudanças na situação dos receptores em fila para transplante cardíaco*

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## Abstract

**Objective:** Evaluate the addition of long-distance heart procurement on a heart transplant program and the status of heart transplant recipients waiting list.

**Methods:** Between September 2006 and October 2012, 72 patients were listed as heart transplant recipients. Heart transplant was performed in 41 (57%), death on the waiting list occurred in 26 (36%) and heart recovery occurred in 5 (7%). Initially, all transplants were performed with local donors. Long-distance, interstate heart procurement initiated in February 2011. Thirty (73%) transplants were performed with local donors and 11 (27%) with long-distance donors (mean distance=792 km±397).

**Results:** Patients submitted to interstate heart procurement had greater ischemic times (212 min ± 32 versus 90 min±18;  $P<0.0001$ ). Primary graft dysfunction (distance 9.1% versus local 26.7%;  $P=0.23$ ) and 1 month and 12 months actuarial survival (distance 90.1% and 90.1% versus local 90% and 86.2%;  $P=0.65$  log rank) were similar among groups. There were marked incremental transplant center volume (64.4% versus 40.7%,  $P=0.05$ ) with a tendency on less waiting list times (median 1.5 month versus 2.4 months,  $P=0.18$ ). There was a tendency on reduced waiting list mortality (28.9% versus 48.2%,  $P=0.09$ ).

**Conclusion:** Incorporation of long-distance heart procurement, despite being associated with longer ischemic times, does

not increase morbidity and mortality rates after heart transplant. It enhances viable donor pool, and it may reduce waiting list recipient mortality as well as waiting time.

**Descriptors:** Heart Transplantation. Donor Selection. Cardiomyopathies.

## Resumo

**Objetivo:** Mostrar a incorporação da captação a distância em um programa de transplante cardíaco e a situação dos receptores em fila após a organização deste sistema.

**Métodos:** Entre setembro de 2006 e outubro de 2012, 72 pacientes foram incluídos na fila de transplante cardíaco. Transplante cardíaco foi realizado em 41 (57%), óbito em fila em 26 (36%) e melhora clínica em 5 (7%). Inicialmente, todos os transplantes foram realizados com captação local. Em fevereiro de 2011, teve início a captação a distância interestadual. Foram realizados 30 (73%) transplantes com captações locais e 11 (27%) em outros estados (distância média=792 km±397).

**Resultados:** Pacientes submetidos à captação à distância tiveram maior tempo de isquemia fria (212 min±32 versus 90 min±18;  $P<0,0001$ ). A taxa de disfunção primária de enxerto (distância 9,1% versus local 26,7%;  $P=0,23$ ) e de sobrevida

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Abbreviations, acronyms & symbols	
Cm	Centimeters

atuarial em 1 mês e 12 meses (distância 90,1% e 90,1% versus local 90% e 86,2%;  $P=0,65$  log rank) foram similares entre os grupos. Houve expressivo aumento na capacidade do centro em transplantar (64,4% versus 40,7%,  $P=0,05$ ) com tendência a redução de tempo em fila de espera (mediana 1,5 mês versus 2,4

## INTRODUCTION

Heart transplantation is the treatment of choice in end-stage heart failure patients with refractory optimized medical treatment, with no possibility of cardiomyopathy cause reversal. Transplant prolongs survival and substantially enhances quality of life. However, there are multiple limiting factors which make it inaccessible for most heart failure patients.

In 2012, heart transplantation was responsible for only 19.8% of the population requirements in Brazil<sup>[1]</sup>, and this negative scenario has been constant for the last decade despite the efforts of all Brazilian certified transplant teams. Certainly, the paucity of viable donors for heart transplant is the main limiting factor worldwide<sup>[2]</sup>, and it is not different in Brazil. As a consequence, there are direct impact on recipient waiting list status, characterized by prolonged waiting times and greater mortality prior to transplant, due to the fact that an important proportion of patients are in priority state, in cardiogenic shock with inotrope dependency and/or mechanical assist device use.

Besides that, there are regional differences, as well as local particularities. At Instituto de Cardiologia do Distrito Federal<sup>[3]</sup>, in a previous analysis of recipient waiting list from 2006 and 2011, the mortality prior to transplant was remarkably elevated (39%) due to lack of viable donors (74% of donor refusal) which was related to logistics issues on long-distance procurement in 46.7% and cardiac dysfunction in 22.1%. These numbers stimulated the development of a program of interstate long-distance heart procurement in order to increment our transplant capacity, reducing our waiting list times and mortality prior to transplant.

The aim of this study was to show the addition of a long-distance heart procurement system on the heart transplant waiting list status.

## METHODS

Between September 2006 and October 2012, 72 patients (52 adults and 20 children) in stage D heart failure were listed as heart transplant recipients. Heart transplant was performed in 41 (57%), death on the waiting list occurred in 26 (36%) and

meses,  $P=0,18$ ). Houve ainda tendência a redução na mortalidade em fila de espera (28,9% versus 48,2%,  $P=0,09$ ).

**Conclusão:** A incorporação da captação a distância, apesar de associada a tempos prolongados de isquemia, não aumenta a morbimortalidade após o transplante cardíaco e aumenta o pool de doadores viáveis, podendo diminuir a mortalidade em fila e o tempo de espera por um órgão.

**Descritores:** Transplante de Coração. Seleção do Doador. Cardiomiopatias.

myocardial recovery occurred in 5 (7%). Initially, all transplants were performed with local donors. In February 2011, the program of interstate long-distance heart procurement was initiated. Thirty (73%) transplants were performed with local donors and 11 (27%) with long-distance ones.

All donors were evaluated with confirmed cerebral death (two neurologic exams with documented absence of cerebral blood flow or cerebral activity) and informed familial consent. Decision of acceptance of a donor involved a clinical assessment, electrocardiogram, chest x-ray, echocardiogram and determination of serum markers of myocardial necrosis. Those donor with age superior to 40 years old were submitted to coronary angiogram. The following criteria were not considered an absolute contraindication to donor refusal: previous history of cardiac arrest, active infection, dialysis dependent renal failure, severe electrolytic and acid base disturbances, as well as elevated vasopressor infusion. All local donors were assessed and procured in the same hospital where the transplant was performed. Transplants with long-distance donors required complex logistics, organized hospital work and coordinated air and land transportation. Long-distance donors were located in Goiânia/GO (3 times), São Paulo/SP (3 times), Rio de Janeiro/RJ (twice), Ribeirão Preto/SP (once), Sorocaba/SP (once) and Campo Grande/MS (once). The mean distance was 792 km±397. Interstate transportation was achieved with military airplanes nine times and commercial airplanes twice. Transportation within cities was by helicopters, ambulances or private cars. Coordinated action between procurement and implant teams was crucial in minimizing cold ischemic times.

The cardioplegic solution used in the donor heart was St Thomas, hearts were transported in sterile plastic bags filled with chilled saline solution packed in thermic coolers with packed ice in it. Bicaval technique was the transplant technique performed in all patients.

Pre, intra and postoperative profiles were prospectively collected and stored in electronic database. Patient clinical outcomes were followed up longitudinally. The study was approved by the Institutional Review Board according to Helsinki's law.

## Statistical analysis

Categorical variables were expressed by frequencies and

percentages and continuous variables by means and standard deviation or with 95% confidence intervals. Comparison between categorical variables were analyzed by chi square test, and between continuous variables by Student's t test and Wilcoxon, when applicable. Longitudinal temporal events were analyzed by the Kaplan Meier method and log rank test was used to determine possible differences among groups.

**RESULTS**

**Transplant recipient profiles**

Table 1 shows demographic, clinical, echocardiographic and hemodynamic characteristics of the two study groups.

There were no significant differences between them. The basic profile of this population is of relatively young patients, in the fourth decade, predominantly males and in functional class III. For the most part, they had type A and O blood groups, with Chagas and dilated cardiomyopathy, with no sensitization and favorable hemodynamic profiles to transplant.

**Intraoperative and postoperative periods**

Heart transplants with long-distance donors had greater ischemic times (212 min±32 versus 90 min±18; *P*<0.0001), as opposed to lesser aortic crossclamp times during implant (45 min±8.6 versus 69 min±17; *P*=0.0003).

Table 1. Preoperative characteristics of heart transplant recipients in both study groups.

Variables	Local (N=30)	Long-distance (N=11)	<i>P</i>
Mean age (years)	38±3.5	32±5.6	0.4
Male sex	17 (59%)	7 (64%)	0.77
Black race	14 (48%)	6 (55%)	0.74
Blood type			0.2
A	8 (28%)	6 (55%)	
B	3 (10%)	2 (18%)	
AB	2 (7%)	0	
O	16 (55%)	3 (27%)	
Functional class (NYHA)			0.27
III	19 (66%)	6 (55%)	
IV	11 (34%)	5 (45%)	
Priority state	6 (21%)	4 (36%)	0.92
Etiology			0.35
Chagas	14 (45%)	6 (55%)	
Idiopathic	6 (21%)	2 (18%)	
Ischemic	2 (7%)	0	
Congenital	1 (3%)	1 (9%)	
Valvar	2 (7%)	0	
Restrictive	1 (3%)	2 (18%)	
Amiloidosis	1 (3%)	0	
Previous cardiac surgery	3 (10%)	0	0.43
Previous cardioverter defibrillator	8 (28%)	5 (45%)	0.28
Previous cerebrovascular accident	0	1 (9%)	0.22
Systemic arterial hypertension	2 (7%)	0	0.54
Serum creatinine	1.3±0.15	1.1±0.22	0.45
Preformed antibodies > 10%	0	0	1
Echocardiographic parameters			
LVDD (mm)	66.9±13.8	61.9±15.5	0.34
LVSD (mm)	60.3±15.5	50.9±16.2	0.12
Left atrium volume	72.3±25.9	84.2±38.9	0.35
RV systolic pressure	48.3±3	60.4±13.7	0.06
Ejection fraction	24.6±12.4	33.2±17.1	0.1
Hemodynamic parameters			
Cardiac index	1.28±0.35	1.23±0.22	0.79
Transpulmonary gradient	4.4±4.3	3.8±3.7	0.76
Pulmonary vascular resistance	3.3±1.8	3±1.3	0.69

NYHA=New York Heart Association; LVDD= left ventricle diastolic diameter; LVSD=left ventricle systolic diameter; RV=right ventricle

Primary graft dysfunction, characterized by cardiac dysfunction on echocardiography in addition to clinical and hemodynamic signs of low cardiac output syndrome despite optimal medical treatment occurred in 9.1% of the long-distance donors and in 26.7% of the local donors ( $P=0.23$ ). Intensive care unit stay was similar ( $P=0.68$ ) in heart transplant recipients with long-distance donors (9.5 days average, 95%CI 5 - 15.5) and with local donors (8 days average, 95%CI 6.75 - 11.5). The same pattern occurred with total postoperative length of stay (long-distance donors: 36 days average, 95%CI 30 - 46; local donors: 39 days average, 95%CI 29 - 56;  $P=0.71$ ).

Cold ischemic timing did not determine greater hospital mortality. Ischemic times were similar between patients that died as well as in survivors (137 min±79 min versus 122 min±58 min,  $P=0.5$ ).

Actuarial survival, as shown in Figure 1, was similar among groups at 1 month and 12 months, respectively [long-distance donors 90.1% (95%CI 81.4% - 98.8%) and 90.1% (95%CI 81.4% - 90.1%) versus local donors 90% (95%CI 84.5% - 95.5%) and 86.2% (95%CI 79.8% - 92.6%);  $P=0.65$  (log-rank test)].

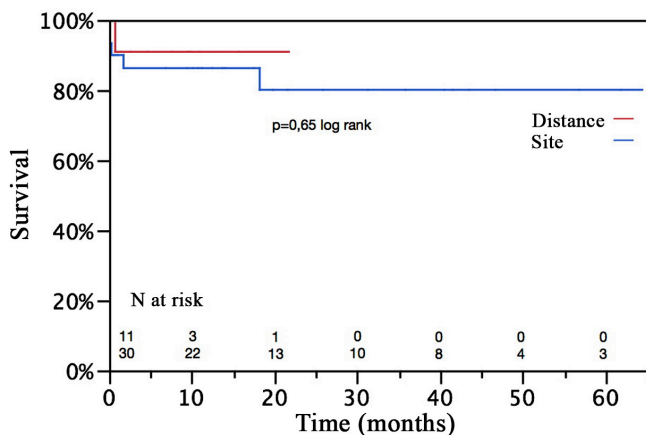


Fig. 1 - Actuarial survival after heart transplantation in both study groups, showing the number of patients at risk and the log rank test result.

### Situation on the waiting list

There was a marked increase in the number of heart transplants with the addition of a long-distance procurement program. The number of transplants went from 15 (in 52 months) to 26 (in 22 months). The higher number of transplants determined changes in heart transplant waiting list status. Effective heart transplant rate on the waiting list increased from 40.7% to 64.4% ( $P=0.05$ ). Moreover, there was a tendency of survival benefit on the waiting list, mortality decreased from 48.2% to 28.9% ( $P=0.09$ ). There was also a tendency of decrease in waiting list time for a transplant (with an average of 1.5 month versus 2.4 months,  $P=0.18$ ).

### DISCUSSION

This paper described the importance of a long-distance heart procurement program and changes on heart transplant recipient status that happened later on.

We described that long-distance procurement can be done with good results if it is organized, with adequate logistics and optimal team coordination aiming a short cold ischemic time. Even working with prolonged ischemic times related to long-distance transportation, we verified that careful myocardial protection, effective heart decompression on procurement and organ preservation at low temperatures during transport are essential to transplant success. That was proved by lower primary graft dysfunction rates, similar intensive care unit and postoperative length of stays, independent of the ischemic time. An excellent actuarial survival post-transplant at 12 months stresses those concepts above.

Results from international registries bring some evidence that risk of mortality post heart transplant is maximized when it is performed above 4 hours of ischemic time, with long-term negative impact on survivors<sup>[2,4]</sup>. Those findings have relation to greater determination of low molecular weight serum myosin in the first week after transplant in prolonged ischemic time patients. Another important issue is the reperfusion injury on myocyte after ischemia. Mechanisms are well known, and it includes oxidative stress activation, of leukocytes, intracellular calcium influx, microcirculation disturbances and sympathetic activation<sup>[5]</sup>. However, we did not observe a direct relationship between cold ischemic time and mortality using conventional myocardial protection techniques as used in cardiac surgery.

On the other hand, some groups<sup>[6-9]</sup> have neglected this 4-hour “time limit”, in order to enhance transplant viability, especially in priority state patients and in children in which the lack of donors is even more pronounced. Lesser aortic crossclamp time in our study means that we cannot waste any time during surgery in order to minimize ischemic time. For instance, we routinely perform pulmonary artery and superior vena cava anastomoses on the beating heart, particularly when using the long-distance donors.

There are a great range of myocardial protection solutions on the market and modes of infusion in heart transplant<sup>[10-12]</sup>. However, there is controversy on the superiority of one solution over the others. In our study, we used the same cardioplegic solution in local and long-distance procurements with no differences in clinical outcomes besides small denominator. The technology of *ex vivo* perfusion is a promising field, and it is being developed. It may effectively preserve donor heart during prolonged transportation because avoids ischemia, anaerobic metabolism and reperfusion injury<sup>[13,14]</sup>.

The most important message of this paper is that you may increment the heart transplant center volume by incorporating a long-distance procurement program and as a consequence enhancing the heart donor pool. Implications on the waiting

list are direct and very positive, leading to lesser waiting list time for transplant and lesser mortality before the transplant.

Those concepts are fundamental nowadays. The number of recipients is constant and growing because of advanced heart failure is the final path of all cardiomyopathies. Transplant obviously does not fulfill all the demand of recipients. The international registry<sup>[2]</sup> and the Brazilian registry<sup>[1]</sup> clearly show a plateau in the number of transplants in the last decade, and the main reason for that is the lack of donors. Issues related to that are low notification of potential donors, lack of familial consent, lack of interest of intensive care teams in donor maintenance, and prioritizing kidney and liver procurement.

A skewed distribution of transplant centers in the Brazilian territory favors an underutilization of donors in remote areas of the country, which is unacceptable. Better distribution of centers across the country would expand heart transplantation in Brazil, as well as an optimal donor utilization<sup>[15]</sup>. Finally, organizing logistics related to long-distance procurement in Brazil must be a priority. This is a field that our country lags behind the successful experiences in North America and Europe that have had routine organized systems that allows optimal donor utilization and consequently multiply transplant centers capacity.

#### Limitations of the study

Firstly, this is a cohort study with prospectively collected data and its inherent limitations. The two study groups were not contemporary, and it may influence results due to the fact that gain of experience might occurred with time, especially when long-distance procurement has commenced. We did not obtain detailed donor characteristics, which it might determined a non-significant increase in primary graft dysfunction on the local donor group. As a matter of fact, the latter could have received most of the marginal donors.

#### CONCLUSION

Long-distance donor procurement, despite being associated with prolonged ischemic times, does not increment morbidity and mortality after the transplant. It enhances viable donor pool, and it may reduce recipient's mortality and waiting list times. It is particularly useful for priority patients.

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#### Authors' roles & responsibilities

FAA	Data collection, statistical analysis, manuscript writing
CFC	Data collection
FPT	Literature review and manuscript review
CSM	Data collection
RBC	Manuscript review
CRC	Literature review and text
NWV	Manuscript review
JGR	Manuscript review

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