Is shortage of heart donors a real problem? Insights from a Brazilian Mid-West heart transplant program

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Abstract

Background and aim of the study: In developed countries, the shortage of viable donors is the main limiting factor of heart transplantation. The aim of this study is to determine whether the same reality applies to Brazil. Methods: Between January 2012 and December 2014, 299 adult heart donor offers were studied in terms of donor profiles, and reasons of refusal. European donor scoring system was calculated, being high-risk donors defined as >17 points. Donor scoring system used to objectively determine the donor profile and correlate with donor acceptance and post-transplant primary graft dysfunction and recipient survival. Cox proportional hazard model was used in determining predictors of long-term mortality. Results: Rate of donor acceptance and heart transplants performed were 45.8% and 19.3%, respectively. Reasons for refusal were mostly non-medical (53.7%). The majority of donors were classified as high-risk (65.5%). Hearts from high-risk donors did not impact on primary graft dysfunction (14.3% vs 10%, P=0.6), neither on long-term survival (P=0.4 by log-rank test). Recipient's age greater than 50 years (HR 6.02, CI95% 2.41 – 16.08, P<0.0001) was the only predictor of long-term mortality. Conclusions: Shortage of donors is not the main limiting factor of heart transplantation in Mid-West of Brazil. Non-medical issues represent the main reason of organ discard. Most of the donors were classified as high-risk which indicates that an expanded donor pool is a routine practice in our region, and donor scoring does not seem to influence to proceed with the transplant.

INTRODUCTION

Heart transplantation is the gold standard treatment for patients with end-stage heart failure. However, the last decade experienced a plateau in the number of heart transplants[1], despite some promising results in North America lately[2]. As a consequence, the number of heart failure patients who would benefit from heart transplantation far exceeds the number of transplants performed.

Shortage of viable donors is certainly the most important limiting factor, leading to higher death rates[3] on the waiting list in developed countries and jeopardizing heart transplantation as an intention to treat principle. This shortage is magnified because many hearts are discarded as a consequence of strict selection criteria and concern for regulatory reprimand for less-than-optimal post-transplant outcomes[4]. On the contrary, in countries with well-established mechanical circulatory support programs, the bridge to transplant strategy is usually associated with long waiting lists. Last year, about half of transplants performed in developed countries[5] had a ventricular assist device placed at the time of transplant, and only 28% get transplanted by the end of the first year[6]. For that reason, donor allocation policies need to be constantly revisited[7] in order to provide a fair access to this therapy.

Economic, religious, and cultural differences amongst countries and regions in the same country prevail and they account for very different realities that explain the unequal access to heart transplantation. Lastly, and not least important, intensive care related to donor is probably less developed[8], which determines a very low rate of donor acceptance among the potential donor pool. Reasons for refusal vary considerably according to the individual transplant center, including medical and non-medical issues. There is no standardized approach to donor selection despite proposals to liberalize acceptance criteria. Available donor risk scoring system[9] may help in the decision-making process, eventually expanding donor pool to marginal donors.

The objectives of this study are 1) to determine whether the shortage of viable donors in Mid-West of Brazil limits heart transplantation; 2) to correlate donor risk scoring to donor acceptance in order to determine the influence of donor profile on the decision to transplant; 3) to delineate reasons for donor refusal and 4) to correlate donor risk scoring with post-transplant primary graft dysfunction and long-term survival.

METHODS

352 cardiac donor offers received between January 2012 and December 2014 were studied. Among those, 53 were excluded because of being pediatric donors offered to adults (37) or with incomplete data (16). The final cohort comprised 299 donor offers. Data were in part retrieved from the Ministry of Health National transplant registry and in part from each electronic donor's medical record. Study was approved by the Institutional Review Board, which granted its use for research purposes with patient consent waived.

Acceptance for transplant or refusal was determined. In case of the latter, reasons for refusal were classified into medical and non-medical, in order to determine whether shortage of viable donors do have a limiting effect on heart transplant development in Mid-West of Brazil.

Data extracted from the Ministry of Health National transplant registry included a complete medical history related to brain death, past medical history, habits and full laboratory workup. Other assessments included echocardiography and/or coronary angiography, when performed and available.

In order to identify the donor profile in Brazil, and stratify donors into levels of severity, the donor scoring system, as proposed by Smits and associates[9] , was used (Table 1). We used this particular scoring system because it is well validated in the literature. Donors were divided into high-risk when the scoring was [?]17 points or low-risk when scoring was <17 points. Donor scoring was correlated to donor acceptance for transplant. Of those transplanted, donor scoring was correlated to the presence of primary graft dysfunction and long-term survival. Confounding factors were taken into account on long-term survival, such as recipient age, primary diagnosis, urgency status at time of transplant, donor to recipient height ratio, weight and gender match, and ischemia time. The objective of using the donor scoring system is not to validate its use in Brazil, since there are exceptional differences in health care systems, particularly a validated donor management process with solid protocols in Europe. The primary aim of using the donor scoring system was to objectively characterize donor screening, and try to correlate it to our decision making during an organ offer, and the subsequent transplant outcomes.

Brazilian transplant system

Brazilian transplant system is supported and funded by the Ministry of Health. It is a consolidated and regulated system that is totally public and comprises the entire country, with a territory of 8.5 million square kilometers, divided into 26 states plus the Federal District, where Brasilia is located.

The actual number of cardiac transplantation performed in 2016 (357 procedures) was far below the predicted number of cardiac transplantation required by the Brazilian population. In addition, there are important disparities among country regions and states, being most of the transplant centers located in South-East. Rate of effective donors in 2016 was 14.6 per million of population which ranks Brazil in the 27th spot according to the International Registry in Organ Donation and Transplantation (*www.irodat.org/publications*).

Brazil's Mid-West region has a population of 15.4 million into three states plus the Federal District. In 2016, the rate of effective donors was 9.6 per million and the number of transplants was 3 per million of population (47 transplants). *Instituto de Cardiologia do Distrito Federal* is a tertiary care heart center with 150 beds that has a dedicated heart transplantation and mechanical circulatory support program over a decade. It is located in Brasilia, and it is the only high-volume program (> 30 heart transplants/year) in Mid-West. Recipients come from different parts of the country, but they are mostly from the same region. Donor allocation policies follow specific criteria in which prioritized patients (inotrope dependence, intra-aortic balloon pump or temporary mechanical assist devices, mechanical ventilation) have preference regionally before a national coverage. Logistics for long-distance procurement (>200 kilometers) in our center is organized and funded by Brazilian Airforce that provides military planes and personnel destined to this mission, coordinated with local police at the procurement site.

Data analyses

Normality of variables was determined by Shapiro-Wilkins test. Categorical variables are summarized as frequencies and percentages and continuous variables as means ± standard deviations (SD), or as median with interquarter range when data were skewed. Categorical outcomes were compared using either χ^2 and continuous outcomes by Student's T test or by the Wilcoxon rank-sum nonparametric test. Actuarial survival was studied by the Kaplan Meier method, and log-rank test used in the comparison of study groups. Cox proportional hazard model was constructed in order to account for variables related to post-transplant long-term survival. Hazard ratios with corresponding confidence intervals were determined. The level of significance was determined when the P value was less than 0.05. All analyses were performed using JMP for SAS® (Cary, NC, USA) statistical software version 14.

RESULTS

Among the 299 donor offers studied (Figure 1), 137 (45.8%) were accepted for transplant and the remainder refused. However, only 59 heart transplants were performed (only 43% of the accepted donors and 19.7% of the total number of donors offered). The gap between accepted donors and not performance of transplant was related to unavailability or inadequacy of logistics for long-distance procurement. Presumably, 78 heart donors (26.4%) that were potentially in good condition were not used because of logistics, a non-medical reason. That particular information certainly had an negative impact on our heart transplant waiting list on the same time frame. Between January 2012 and December 2014, 113 recipients were listed. Among them, 18 (15.9%) died on the waiting list without a heart transplant.

Reasons for donor refusal (Table 2) were non-medical in 129 (53.7%) and medical in 111 (46.3%). Another major non-medical reason was lack of basic complementary tests to determine donor heart's condition in 36 (15%). Among the medical reasons for donor refusal, the most prevalent ones were severe hemodynamic instability in 46 (19.2%) and ventricular dysfunction determined by echocardiography in 35 (14.6%).

Donor risk scoring

Overall mean donor score was 21.1 ± 7.6, being 196 (65.5%) classified as high-risk donors. Donor scoring was slightly higher in donors refused when compared to those accepted (21.9 ± 7.9 *vs* 20.1 ± 7; P=0.04).

The majority of offers were from long-distance donors (65.5%). Local and long-distance donor offers have differed in some characteristics, as shown in Table 3. Local donors have received higher dosages of norepinephrine at the time of procurement (P<0.0001) as well as have assessed more frequently with echocardiography and coronary angiogram, when indicated, than long-distance offers which did not have those available. Despite of that, donor scoring was similar among them (local 20.9 ± 8.1 *vs* long-distance 21.1 ± 7.3, P=0.82). High-risk donors were also present as frequently in local (67%) as well as in long-distance (74%) offers (P=0.2).

Recipient's priority state did not influence the acceptance of higher risk donors (recipient's priority/donor scoring 19.9 ± 6.9 vs recipient's elective/donor scoring 18.8 ± 6.7, P=0.54), as shown in Figure 2.

Primary graft dysfunction and long-term survival

Heart transplant data is depicted on Table 4. Recipient's mean age was 46.1 years. The main cause of cardiomyopathy was Chagas disease in 69% of patients. Thirty-eight percent were in a priority state prior to transplant. Mean cold ischemic time was 140.6 minutes.

Among the 59 heart transplants performed during the study period, hearts from high-risk donors did not impact on the frequency of primary graft dysfunction (14.3% *vs* 10%, P=0.6). In addition, mean donor score of those patients that had primary graft dysfunction was similar to those patients that did not (19.7 *vs* 19.2, P=0.8).

Actuarial survival (Figure 3) of transplanted patients using high-risk donors was 78.5%, 64.3% and 60%, and using low-risk donors was 90%, 80% and 71.2% at one month, one year and two years, respectively (log-rank=0.4). Recipient's age greater than 50 years (HR 6.02, CI95% 2.41 – 16.08, P<0.0001) was the only independent determinant of long-term mortality (Figure 4). Donor risk scoring (P=0.13) was not associated with long-term mortality on that model.

DISCUSSION

The present study demonstrates that, in some parts of the world, shortage of donors is not the most important limiting factor of heart transplantation. Our cohort comprises complete donor and recipient information of Brazilian's Mid-West region, with a population of over 15 million people. We have found that, over a two-year period, the donor's heart utilization rate was less than 20%. The main reasons for donor refusal were non-medical, which included lack of an organized system of heart procurement at distant sites and absence of complementary tests to assess heart's condition. Other less prevalent, but not least important factors, were severe hemodynamic instability and ventricular dysfunction on echocardiography. Gomes and colleagues[10] described disparities in access to transplantation services within Brazil's regions due to logistical challenges, uneven resource allocations and under-capacitated health care facilities. In Brazil, stark geographical and social inequalities in morbidity and mortality rates exist within and between these regions attributed to development status mainly related to differences in demographic density, GDP, and level of development.

The relatively high refusal rate in our center certainly had a negative impact on waiting list recipient's mortality of 15.9%. That mortality rates might be explained as well by unavailability of ventricular assist devices for those recipients in need. In the United States, approximately 60% of available hearts are discarded[11]. Institutions have algorithms for deciding which heart to transplant, but still the most prevalent criteria relies on personal experience and clinical intuition. Khush et al.[12] found in a large populational database that 48% of the potential donor hearts were rejected, in large part, because of female sex, older donor age, and medical comorbidities. Many of these hearts are being rejected needlessly. This is particularly relevant considering the decrease utilization of donor hearts over time. One study found that the use rates decreased by an average of 4.2% per year, from a high of 56% in 2002 to a low of 37% in 2007[11]. Feldman and colleagues[8]corroborated the low rate of donor utilization in Brazil in a cohort of very young donors (mean age of 23.5 years), mostly due to poor donor management protocols. Likewise our experience with long-distance donors, they[8] have confirmed the unavailability of echocardiography at donor assessment. This may reduce the use of many potential grafts because of concerns regarding organ quality and recovery. Suboptimal or even good grafts that are poorly managed could increase the risk of primary graft dysfunction[13]. Therefore, optimization of donation process is crucial to increase the number and the quality of heart transplantation[14].

No standardized approach exist for management and weighing of donor and recipient risk factors, resulting in considerable variability between transplant centers in clinical practice[4]. Changing a local culture of rejecting a donor's heart for any reason is difficult, but feasible. Using a systematic, multidisciplinary approach to examine why they were turning down potential donor hearts, Smith and colleagues[15] improved their utilization rate from 46 to 75% and increased OHT numbers from 22 to 35 in 1 year without adversely affecting 1-year survival. Strategies to achieve this goal need optimization of the entire process of organ procurement, transportation, and functional recovery after transplant[14].

In order to attain a more objective clinical decision in assessing a heart for transplantation, the development of a validated donor risk score that takes into account all the relevant factors would be a useful tool for clinicians. Risk calculators in cardiac surgery[16,17] have gained great importance for predicting major adverse events after surgical procedures, which helped in indication for surgery, adequate patient consent and in inclusion criteria to controlled clinical trials. Two studies, Smits et al.[9] using European database and Weiss et al[18] using the UNOS database, designed and validated donor heart scores that accurately reflected the likelihood of donor heart acceptance and predicted long-term mortality.

In the present study, we used the European donor score to objectively stratify donor characteristics that possibly were taken into account in the decision to accept the organ, and subsequent transplant outcomes. The majority of donors were classified as high-risk. Donors accepted for transplantation had a slightly lower score when compared to those refused. Since the scoring system was calculated for the purpose of the study, it seems that other factors rather than the scoring system were used in the decision to proceed with the transplant. In our experience, recipient's clinical condition did not influence on the decision to accept a higher risk donor either. That information is against the general recommendation that expanded donor criteria hearts should be considered for sicker patients in urgent need of transplantation[19]. Long-distance procurement does not seem to have an impact on that too. Despite there were some differences between local and long-distance donors, they were mostly related to worse hemodynamics in the former and less access to echocardiography and coronary angiograms in the latter. As far as donor scoring system is concerned, high-risk donors were similarly prevalent in local and long-distance offers. Expanded donor criteria did not compromise survival or hemodynamics at 12 months in a previous study[20]. There is considerable evidence that use of marginal donors generally results in satisfying results and therefore is justifiable to alleviate the donor organ scarcity[21,22].

Donor scoring system did not have any influence on the occurrence of primary graft dysfunction and long-term mortality. As opposed to other donor-related factors, the only predictor of long-term survival in our population was recipient's age greater than 50 years. That information stresses the safety of expanding the donor pool to marginal donors. When determining the impact of donor scoring system on long-term mortality, we adjusted the analysis to previously well-known confounding factors[23] such as recipient age, primary diagnosis, urgency status at time of transplant, donor to recipient height ratio, weight and gender match, and ischemia time.

Recipient's age has been proposed as a risk factor for post-transplant complications[24]. One of the components of the RADIAL score[25], which predicts primary graft dysfunction, is recipient's age greater than 60 years of age. Joyce and colleagues[26] studied 24,540 heart transplants entered into the UNOS database. One of the predictors of 1-year post-transplant mortality was recipient's age > 55 years. Donor age and ischemic time were predictors in that model too, as opposed to our data. They created a new scoring system that would account for the interplay between donor, recipient and combined risk factors in predicting 1-year survival. Recipient health factors and comorbidities outweighed most donor factors. Most importantly, the most frequent component of a high-risk score was recipient age greater than 55 years along with the presence of an LVAD and end-organ dysfunction.

Limitations of the study

This is a single-institution clinical cohort study of a relatively small number of transplanted patients. The statistical power to determine post-transplant differences in outcomes is limited, and it may be subjected to chance. The calculation of long-distance donor scores is compromised by the unavailability of echocardiography and coronary angiograms. Posttransplant outcomes are worse than reported by the International Society for Heart and Lung Transplantation database, but they are compatible with the Brazilian Transplant Registry. Reasons for that were not the scope of this paper.

Conclusions

Our data suggests that shortage of donors is not the main limiting factor of heart transplantation in Mid-West of Brazil. A more organized organ procurement system and better donor intensive care protocols would enhance donor utilization rate. That would certainly reduce waiting list mortality. Most of the donors were classified as high-risk which indicates that an expanded donor pool is a routine practice in our region, and donor scoring does not seem to influence to proceed with the transplant. European donor scoring system in our population did not correlated with post-transplant primary graft dysfunction and long-term mortality, reflecting the need to develop a local scoring system.

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Table 1 –Donor scoring system calculator

Donor age (years)	<45 45-54 55-59 >60
Cause of death	Benign brain tumor Malignant brain tumor Circulatory CVA Drugs Intoxicated Intoxicated CO Meningitis
Donor history[a]	Compromised Uncompromised
Serum sodium (mmol/liter)	<130 130-139 140-149 150-159 160-164 165-169 >170 NA
Νοραδρεναλινε «μγ/κγ/μιν)	<0.1 0.1-0.4 0.41-0.8 >0.8 NA
Δοπαμινε/δοβυταμινε (μγ/κγ/μιν)	<5 5-7.5 7.51-10 >10 NA
Hypertension	Yes No NA
Cardiac arrest	Yes No NA
Echocardiography ventricular function	EF >55% EF 45-55% EF<45% NA
Valve function	Normal Abnormal NA
Ventricular hypertrophy	10 mm 11-12 mm 13-14 mm >14 mm NA
Coronary angiogram	Normal Irregularities, no stenosis 1-vessel stenosis (<50%) 1-vessel stenosis (>50%) >1-vessel stenosis

Adapted from Smits and colleagues[9].

[a] compromised history is defined by the presence of malignancy, sepsis, drug abuse or meningitis, or if a positive virology was registered.

Table 2 – Reasons for donor refusal in heart transplantation

Medical	Severe hemodynamic instability Ventricular dysfunction on echocardiography Active sepsis Recipient related refusa
Non-medical	Logistics for transportation unavailable Lack of complementary tests for heart donor assessment Important do

Table 3 – Frequency of donor scoring, according to type of heart procurement

Donor age (years) <45 45-54 55-59 >60	**Local (N=103)** 82 (79%) 21 (21%) 0 0	**Long-distance (N=196)** 158 (80%) 35 (18%) 3 (2%) 0	**Total (N=299)** 240 (80%) 56 (19%) 3 (1%) 0	**P** 0.4
Cause of death Benign brain tumor Malignant brain tumor Circulatory CVA Drugs Intoxicated Intoxicated CO Meningitis Respiratory SAB Sepsis TC	1 (1%) 1 (1%) 1 (1%) 23 (22%) 0 1 (1%) 0 1 (1%) 3 (3%) 1 (1%) 0 71 (69%)	0 1 (0.5%) 2 (1%) 54 (28%) 0 1 (0.5%) 0 0 5 (2.5%) 9 (4.5%) 1 (0.5%) 123 (63%)	1 (0.3%) 2 (0.7%) 3 (1%) 77 (26%) 0 2 (0.7%) 0 1 (0.3%) 8 (2.7%) 10 (3.3%) 1 (0.3%) 194 (65%)	0.4
Donor history[a] Compromised Uncompromised	13 (13%) 90 (87%)	38 (19%) 158 (81%)	51 (17%) 248 (83%)	0.13
Serum sodium (mmol/liter) <130 130-139 140-149 150-159 160-164 165-169 >170 NA	1 (1%) 10 (10%) 22 (21%) 27 (26%) 11 (11%) 9 (9%) 18 (17%) 3 (3%)	4 (2%) 23 (12%) 49 (25%) 47 (24%) 16 (8%) 19 (10%) 35 (18%) 2 (1%)	5 (2%) 33 (11%) 71 (24%) 74 (25%) 27 (9%) 28 (9%) 53 (18%) 5 (2%)	0.6
Νοραδρεναλινε «μγ/κγ/μιν) <0.1 0.1-0.4 0.41-0.8 >0.8 NA	23 (22%) 52 (50%) 11 (11%) 15 (15%) 2 (2%)	84 (43%) 82 (42%) 21 (11%) 7 (4%) 2 (1%)	107 (36%) 134 (45%) 32 (11%) 22 (7%) 4 (1%)	0.001
Δοβυταμινε (μγ/κγ/μιν) <5 5-7.5 7.51-10 >10 NA	102 (99%) 0 1 (1%) 0 0	194 (99%) 1 (0.5%) 0 1 (0.5%) 0	296 (99%) 1 (0.3%) 1 (0.3%) 1 (0.3%) 0	0.28
Hypertension Yes No NA	9 (9%) 94 (91%) 0	8 (4%) 188 (96%) 0	17 (6%) 282 (94%) 0	0.09
Cardiac arrest Yes No NA	19 (18%) 84 (82%) 0	22 (11%) 174 (89%) 0	41 (14%) 258 (86%) 0	0.08
Left ventricular function EF >55% EF 45-55% EF<45% NA	59 (57%) 9 (9%) 4 (4%) 31 (30%)	8 (4%) 0 0 188 (96%)	67 (22%) 9 (3%) 4 (1%) 219 (73%)	<0.0001
Valve function Normal Abnormal NA	69 (67%) 4 (4%) 30 (29%)	7 (3.6%) 0 189 (96.4%)	76 (25%) 4 (1%) 219 (73%)	<0.0001

Donor age (years) <45 45-54 55-59 >60	**Local (N=103)** 82 (79%) 21 (21%) 0 0	**Long-distance (N=196)** 158 (80%) 35 (18%) 3 (2%) 0	**Total (N=299)** 240 (80%) 56 (19%) 3 (1%) 0	**P** 0.4
Ventricular hypertrophy 10 mm 11-12 mm 13-14 mm >14 mm NA	64 (62%) 2 (2%) 3 (3%) 1 (1%) 33 (32%)	4 (2%) 1 (0.5%) 0 0 191 (97.5%)	68 (22.7%) 3 (1%) 3 (1%) 1 (0.3%) 224 (75%)	<0.0001
Coronary angiogram Normal Irregularities, no stenosis 1-vessel stenosis (<50%) 1-vessel stenosis (>50%) >1-vessel stenosis (<50%) >1-vessel stenosis (>50%) NA *Total score* (mean ± sd) *High-risk donor* (>17 points)	10 (10%) 3 (3%) 2 (2%) 0 2 (2%) 0 87 (84%) 20.9 ± 8.1 69 (67%)	0 0 0 0 0 0 196 (100%) 21.1 ± 7.3 145 (74%)	10 (3%) 3 (1%) 2 (0.7%) 0 2 (0.7%) 0 283 (94.6%) 21.1 ± 7.6 196 (65.5%)	<0.0001 0.82 0.20

Table 4 – Profile of transplanted heart recipients

Age (years) Gender match Type of cardiomyopathy Chagas Idiopathic Ischemic Valvular	46.1 ± 10.7 23 40 11 6 2	(39%)
Priority state[a] Yes No	23 36	(38%)
Donor/recipient height ratio	1.05 ± 0.06	
Donor/recipient weight ratio	1.22 ± 0.24	
Cold Ischemia time (minutes)	140.6 ± 69.1	

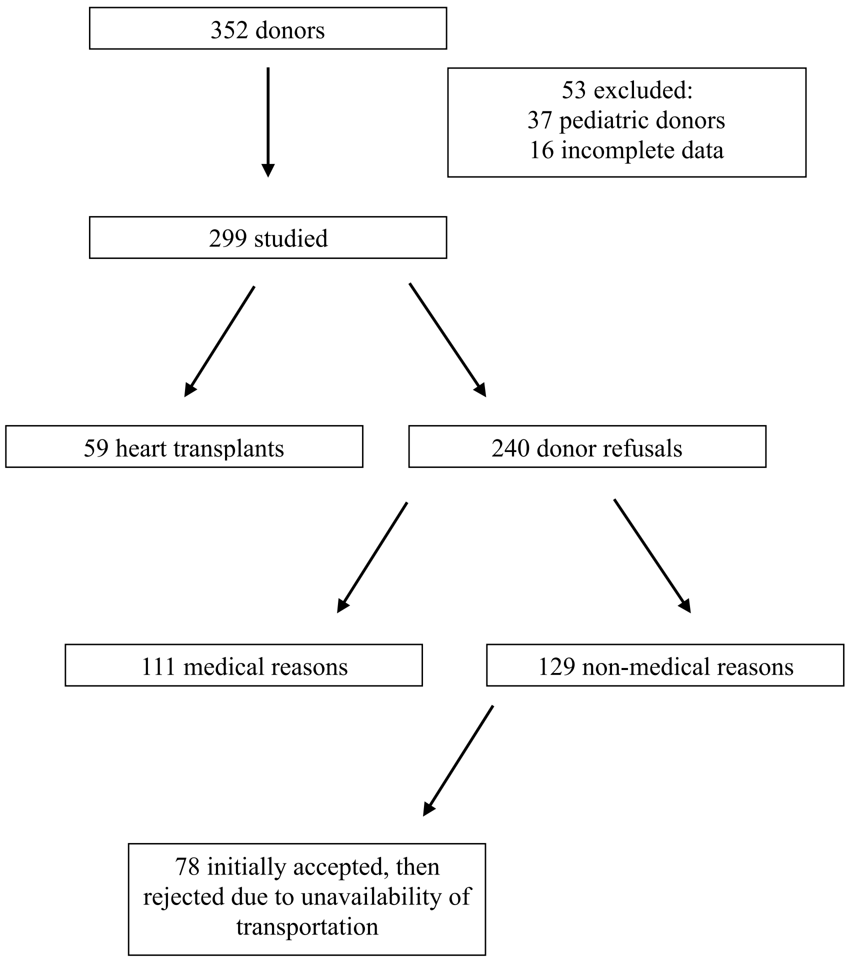
[a] Intravenous inotropes and/or intra-aortic balloon pump and/or temporary mechanical circulatory assistance Figure 1 – Donors flowchart. The actual number of accepted donors was 137 (59 transplants plus 78 that were rejected due to transportation unavailable)

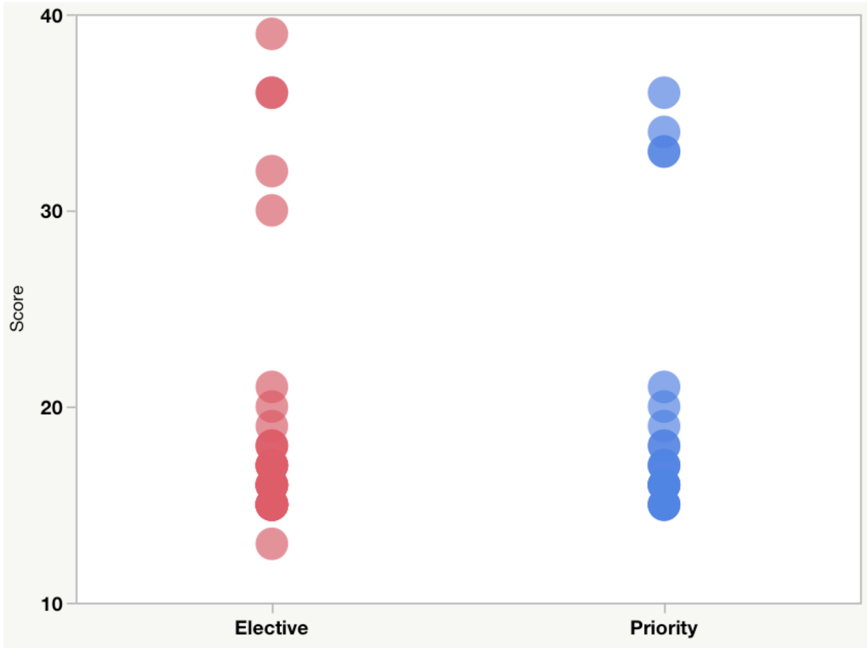
Figure 2 – Bubble plot of donor scoring distribution according to recipient's priority state prior to heart transplantation

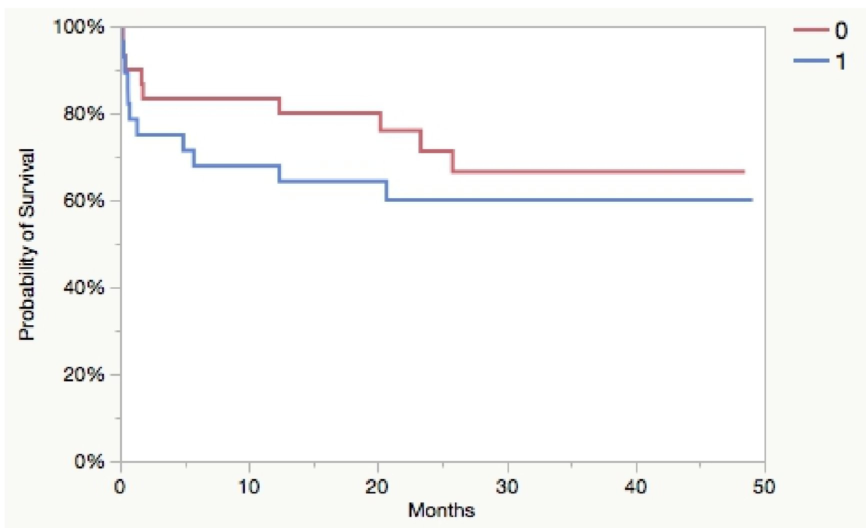
Figure 3 – Actuarial survival plots by heart donor risk profile. Red line (0): patients transplanted with hearts

from low-risk donor (<17 points); blue line (1): patients transplanted with hearts from high-risk donor (>17 points).

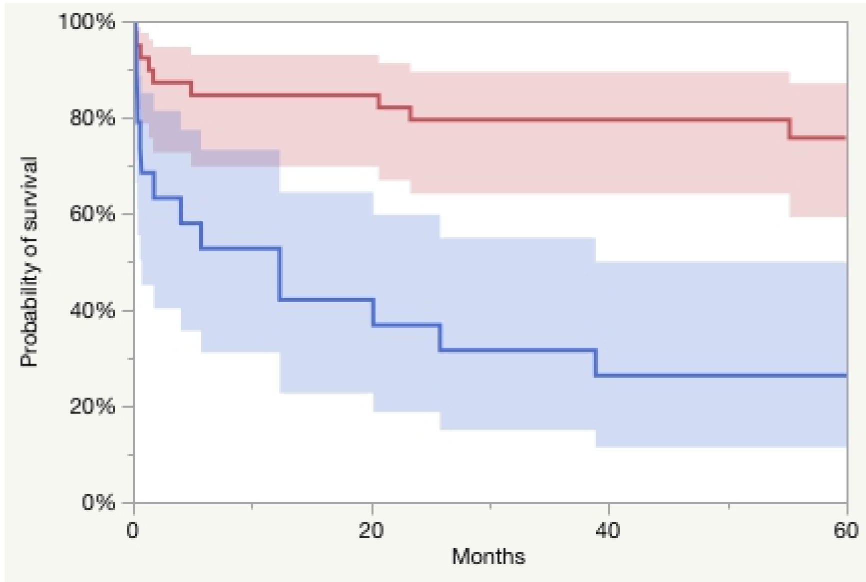
Figure 4 – Actuarial survival plots after heart transplantation by recipient's age. Solid red line: recipient's age less than 50 years with correspondent 95% confidence intervals; solid blue line: recipient's age greater than 50 years with correspondent 95% confidence intervals.







N at risk						
0	30	21	19	18	18	14
1	29	24	22	21	20	18



N at risk				
<50 years	39	34	32	15
>50 years	20	9	6	4