

Results of heart transplantation in the urgent recipient - who should be transplanted?

Resultados do transplante cardíaco no paciente urgente - quem deve ser transplantado?

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Abstract

Objective: To evaluate immediate and long-term results of cardiac transplantation at two different levels of urgency.

Methods: From November 2003 to December 2012, 228 patients underwent cardiac transplantation. Children and patients in cardiogenic shock were excluded from the study. From the final group (n=212), 58 patients (27%) were hospitalized under inotropic support (Group A), while 154 (73%) were awaiting transplantation at home (Group B). Patients in Group A were younger (52.0±11.3 vs. 55.2±10.4 years, $P=0.050$) and had shorter waiting times (29.4±43.8 vs. 48.8±45.2 days; $P=0.006$). No difference was found for sex or other comorbidities. Haemoglobin was lower and creatinine higher in Group A. The characteristics of the donors were similar. Follow-up was 4.5±2.7 years.

Results: No differences were found in time of ischemia (89.1±37.0 vs. 91.5±34.5 min, $P=0.660$) or inotropic support (13.8% vs. 11.0%, $P=0.579$), neither in the incidence of cellular or humoral rejection and of cardiac allograft vasculopathy. De novo diabetes de novo in the first year was slightly higher in Group A (15.5% vs. 11.7%, $P=0.456$), and these patients were at increased risk of serious infection (22.4% vs. 12.3%, $P=0.068$). Hospital mortality was similar (3.4% vs. 4.5%, $P=0.724$), as well as long-term survival (7.8±0.5 vs. 7.4±0.3 years).

Conclusions: The results obtained in patients hospitalized under inotropic support were similar to those of patients awaiting transplantation at home. Allocation of donors to the first group does not seem to compromise the benefit of transplantation. These results may not be extensible to more critical patients.

Descriptors: Heart Transplantation. Thoracic Surgery. Post-operative Complications. Survival (Public Health).

Resumo

Objetivo: Avaliar os resultados imediatos e de longo prazo do transplante cardíaco em dois níveis diferentes de urgência.

Métodos: De novembro de 2003 a dezembro de 2012, 228 pacientes foram submetidos a transplante cardíaco. Crianças e os pacientes em choque cardiogênico foram excluídos do estudo. Do grupo final (n=212), 58 pacientes (27%) estavam hospitalizados e em suporte inotrópico (Grupo A), enquanto 154 (73%) aguardavam transplante em casa (Grupo B). Os pacientes do Grupo A eram mais jovens (52,0±11,3 vs. 55,2±10,4 anos, $P=0,050$) e tinham menor tempo de espera (29,4±43,8 vs. 48,8±45,2 dias, $P=0,006$). Não foram encontradas diferenças entre os sexos ou outras comorbidades. Níveis de hemoglobina foram menores e de

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Abbreviations, acronyms & symbols	
CPB	Cardiopulmonary bypass
GVD	Graft vascular disease
IABP	intra-aortic balloon pump
ICU	Intensive care unit
SPT	Portuguese Society of Transplantation

creatinina superiores no Grupo A. As características dos doadores foram semelhantes. O acompanhamento foi de 4,5±2,7 anos.

Resultados: Não foram observadas diferenças no tempo de isquemia (89,1 ± 37,0 vs. 91,5 ± 34,5 min, P=0,660) ou no suporte inotrópico (13,8% vs. 11,0%, P=0,579), nem na incidência de rejeição celular ou humoral e de vasculopatia do enxerto. Incidência de

diabetes de novo no início do primeiro ano foi um pouco maior no Grupo A (15,5% vs. 11,7%, P=0,456), e esses pacientes apresentaram maior risco de infecção grave (22,4% vs. 12,3%, P=0,068). A mortalidade hospitalar foi semelhante (3,4% vs. 4,5%, P=0,724), bem como a sobrevida a longo prazo (7,8±0,5 vs. 7,4±0,3 anos).

Conclusões: Os resultados obtidos em pacientes hospitalizados em suporte inotrópico foram semelhantes aos de pacientes que aguardam o transplante em casa. Alocação de doadores para o primeiro grupo não parece comprometer o benefício do transplante. Esses resultados podem não ser estendidos aos pacientes mais críticos.

Descritores: Transplante de Coração. Cirurgia Torácica. Complicações Pós-Operatórias. Sobrevida.

INTRODUCTION

Despite advances in medical and surgical treatment of heart failure, heart transplantation is still the elective treatment for patients refractory to other medical therapies or conventional cardiac procedures. The criteria for selection of candidates for transplantation have been gradually extended and the selection of donors and recipients is essential to the success of a transplantation program^[1-3].

However, a significant reduction in supply has forced the spectrum of selection of donors to be broadened. Thus, the profile has changed from a young donor who died of cranio-cerebral trauma to that of an older donor whose death resulted from primary neurological disease. The latter is often accompanied by other types of diseases and cardiovascular risk factors, conditions which determine the choice of the recipient from a scarce and rarely ideal donor.

As a result, we have seen an increase in the number of patients in advanced stages of the disease at the time of transplantation, who are admitted for decompensated heart failure requiring intensive pharmacologic support and, at times, cardio-circulatory and mechanical respiratory support in those with worse clinical status, a situation that increases the urgency for transplantation, generally associated with greater risk of failure.

On a national level, the criteria/priority for heart transplantation of the Portuguese Society of Transplantation (unpublished data; Table 1) include seven degrees in descending order of priority. As a result of this and other types of stratification, the most critical patient passes ahead of others whose clinical condition allows them to wait longer. However, these criteria do not explain or quantify the risk profile. We know that the immediate results of cardiac transplantation are very sensitive not only to the quality of the donor organ but also to the clinical status of the candidate to transplantation^[4-6].

Strictly following the scale of priority or urgency for transplantation, we end up transplanting sicker hospitalized patients undergoing intensive treatment for decompensated heart failure, always accompanied by variable multiorgan function deterioration. This will result in a natural increase of morbidity and mortality after transplantation, triggering the question of *who should be transplanted* (?), which can raise probably insoluble questions of ethics in organ distribution.

In this study, we analyzed and compared the early and late results of transplantation following the criteria of priority in use by the Portuguese Society of Transplantation (SPT), in basic clinical aspects similar to the international scale INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support)^[7,8].

Table 1. Heart transplantation.

Priority (descending order) and their criteria (Portuguese Transplantation Society - SPT)		
I	Emergency	Primary graft failure in the first 24 hours after cardiac transplantation
II	Emergency	a) Patients in cardiogenic shock requiring ventricular assistance b) Patients in cardiogenic shock requiring artificial heart
III	Emergency	Patients in cardiogenic shock with intra-aortic balloon counterpulsation
IV	Emergency	Patients in cardiogenic shock requiring mechanical ventilator support
V	Urgent	Patients being admitted to both UCI and inotropic support to maintain adequate cardiac output
VI	Urgent	Patients with more than one hospitalization in the ICU in the last 6 months
VII	Elective	Includes the remaining patients

METHODS

Origin, definition and collection of data

In the period from November 2003 to December 2012, 228 patients were consecutively submitted to heart transplantation at this Centre. Exclusion criteria for this study included patients previously transplanted with other organs (n=2), patients under 18 years of age (n=8), and patients with emergency priority (\leq grade IV, n=8). Thus, the study population included 212 patients, 58 of whom were in the ICU, under inotropic support without respiratory and/or mechanical ventricular assistance (SPT grade V; Group A), and 154 were at home on a waiting list with two or more hospitalization episodes in the ICU in the last 6 months (SPT grade VI; Group B).

The data were obtained from a national database, especially designed for the prospective registration (online platform) of data from the recipient, donor, surgery, immunosuppression protocol and follow-up of patients undergoing cardiac transplantation.

All surviving patients were followed via regular consultations at the Surgical Centre by a medical/surgical team, from

one to 10 years, and no patient was lost to follow-up. The mean follow-up in this study was 4.5 ± 2.7 years (total, 961.8 patient-years).

Recipients and Donors

Table 2 shows data from pre-operative variables of the recipients in groups A and B, as well as the results of the comparative analysis. When compared with the population of Group B, patients in Group A were younger ($P=0.05$), had lower body mass index (BMI; $P=0.005$), had significantly lower serum haemoglobin ($P=0.001$), higher total bilirubin ($P=0.014$) and creatinine ($P=0.01$), and shorter time on the waiting list ($P=0.006$).

Table 3 details the characteristics of the donors to patients of groups A and B, as well as the results of the comparative analysis, which showed no significant differences in any of the variables. However, male donors were the most common (82% vs. 73%). The cause of death was mostly traumatic (59.6% vs. 57.6%), but there was a growing trend in the number of donors dying from CVA, now approaching two thirds. In group A, there was a significant number of donors with prolonged inotropic or ventilator support (longer than one week, 12%).

Table 2. Recipient data.

	Group A (N= 58)	Group B (N=154)	P value
Mean age (years)	52.0 \pm 11.3	55.2 \pm 10.4	0.050
Male sex	45 (77.6%)	120 (77.9%)	0.958
Body mass index (Kg/m ²)	22.7 \pm 2.9	24.1 \pm 3	0.005
Diabetes mellitus	8 (13.8%)	35 (22.7%)	0.146
Hypertension	20 (34.5%)	58 (37.9%)	0.645
Reoperation	16 (27.6%)	49 (31.8%)	0.551
Etiology			
Ischaemic heart disease	21 (36.2%)	63 (40.9%)	0.533
Dilated cardiomyopathy	21 (36.2%)	55 (35.7%)	0.947
Other	16 (27.6%)	36 (23.4%)	0.786
Peripheral vascular disease	14 (24.1%)	54 (35.1%)	0.129
Carotid disease	1 (1.7%)	8 (5.2%)	0.264
Cardiac index (L/min/m ²)	1.9 \pm 0.5	1.9 \pm 0.5	0.997
Transpulmonary gradient (mmHg)	9.4 \pm 4.5	9.3 \pm 4.6	0.890
Pulmonary vascular resistance (WU)	3.3 \pm 2.0	3.4 \pm 2.4	0.820
Hemoglobin (g/dL)	12.2 \pm 2.2	13.2 \pm 1.9	0.001
Platelets	216 \pm 83	212 \pm 70	0.783
LDH (U/L)	272 \pm 184	250 \pm 120	0.361
AST (U/L)	42 \pm 55	43 \pm 47	0.903
ALT (U/L)	51 \pm 89	44 \pm 48	0.460
GGT (U/L)	137 \pm 112	118 \pm 112	0.273
Total bilirubin (mg/dL)	1.5 \pm 1.0	1.1 \pm 0.7	0.014
GFR (mL/min)	57.2 \pm 26.5	60.9 \pm 21.2	0.301
Serum creatinine (mg/dL)	1.6 \pm 1.2	1.4 \pm 0.4	0.010
Mean follow-up (years)	4.16 \pm 2.69	4.68 \pm 2.75	0.219
Time on waiting list (days)	29.4 \pm 43.8	48.8 \pm 45.2	0.006

LDH=Lactate dehydrogenase; AST=Aspartate aminotransferase; ALT=Alanine aminotransferase; GGT=Gamma-glutamyl transferase; GFR=Glomerular filtration rate or creatinine clearance

Table 3. Donor population data.

	Group A (N=58)	Group B (N=154)	P value
Mean age (years)	35.2±11.2	33.9±10.9	0.429
Age ≥ 50 years	8 (13.6%)	18 (11.6%)	0.677
Male sex	48 (82.8%)	114 (74.0%)	0.182
Donor female/receptor male	8 (13.8%)	28 (18.2%)	0.448
Weight ratio donor/recipient >1.2	22 (37.9%)	42 (27.3%)	0.132
Weight ratio donor/recipient <0.8	1 (1.7%)	5 (3.2%)	0.477
Inotropic support >7 days	4 (6.9%)	6 (3.9%)	0.358
Ventilation support >7 days	7 (12.1%)	18 (11.7%)	0.939
Cause of death			
Ischemic stroke	2 (3.4%)	2 (1.3%)	0.305
Haemorrhagic stroke	23 (39.6%)	50 (32.5%)	0.326
Traumatic brain injury	31 (53.4%)	92 (59.7%)	0.408
Other causes	2 (3.4%)	10 (6.5%)	0.392

Table 4. Operative data.

	Group A (N=58)	Group B (N=154)	P value
Total ischemic time (min)	89.1±37.0	91.5±34.5	0.660
Mean CPB time (min)	98.5±39.5	99.7±32.0	0.813
Mechanical ventilation time (hours)	17.1±15.0	19.3±22.5	0.487
Inotropic support >48 hours	8 (13.8%)	17 (11.0%)	0.579
Mechanical assistance	0 (0%)	10 (6.5%)	0.047
Reoperation for bleeding	4 (6.9%)	6 (3.9%)	0.358
Associated procedure	1 (1.7%)	12 (7.8%)	0.101
Mitral valvuloplasty	1 (1.7%)	9 (5.8%)	0.207
Tricuspid annuloplasty	0 (0%)	1 (0.6%)	0.538
Coronary revascularization	0 (0%)	2 (1.3%)	0.383

CPB=Cardiopulmonary bypass

Statistical analysis

Continuous variables are presented as mean ± standard deviation and evaluated using independent (comparison between groups) and paired (over time) Student's t-test. Categorical variables are reported as frequency and percentage, and compared using the chi-square test. Survival and event-free survival were calculated using the Kaplan -Meier method. Statistical significance was defined as P-value <0.05. Data were analyzed using the IBM SPSS Statistics for Windows program (Version 20.0. Armonk, NY: IBM Corp; released 2011).

RESULTS

Surgery

Table 4 shows the data for variables related to surgery in groups A and B, as well as the results of the comparative analysis. Patients in Group B had a significantly higher incidence of mechanical circulatory support (P=0.044). Of the ten patients who needed this kind of assistance, 2 required only intra-aortic balloon pump (IABP), 3 required the use of a left ventricu-

lar assist device, and 5 required total circulatory support with ECMO. No statistically significant differences were observed in relation to other variables, namely times of ischemia and CPB, mechanical ventilation and inotropic support >48 hours.

Cellular and humoral rejection and graft vascular disease

Table 5 shows the data on acute cellular rejection, humoral rejection and graft vascular disease (GVD) in groups A and B. Ninety patients (42.5%) had no episodes of acute cellular rejection (grade 0R of the ISHLT). The remaining patients (n=122, 57.5%) had at least one episode of rejection; however, in 83 of them it was only mild (1R), requiring no treatment. The results of the comparative analysis of the two groups showed no statistically significant difference in any of the cellular rejection grades. Thirty nine patients (18.4%) had at least one episode of cellular rejection grade ≥ 2R, the majority (33, 84.6%) occurring during the first year. No statistically significant difference (P=0.309) was observed in the comparative analysis of survival free from cellular rejection grade ≥2R between groups A and B (Figure 1A).

Table 5. Evaluation of acute cellular rejection, humoral rejection and graft vascular disease.

	Group A (N=58)	Group B (N=154)	P value
Acute cellular rejection			
Grade 0R	23 (39.7%)	67 (43.5%)	0.613
Grade 1R	22 (37.9%)	61 (39.6%)	0.887
Grade 2R	11 (19.0%)	20 (13.0%)	0.276
Grade 3R	2 (3.4%)	6 (3.9%)	0.879
Grade \geq 2R	13 (22.4%)	26 (16.9%)	0.351
Grade \geq 2R (first 12 months)	10 (17.2%)	23 (14.9%)	0.680
Humoral rejection	1 (1.7%)	5 (3.2%)	0.551
Graft vascular disease	6 (10.3%)	14 (9.1%)	0.781

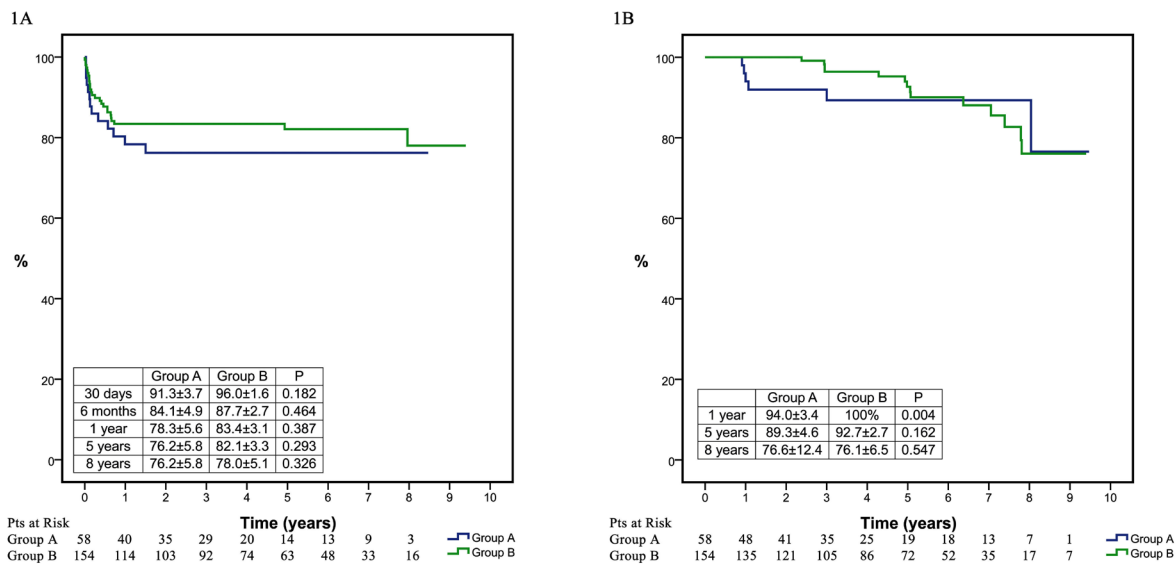


Fig. 1A - Survival free from cellular rejection grade \geq 2R in groups A and B. 1B - Survival free from graft vascular disease in groups A and B.

Humoral rejection was diagnosed in six patients (2.8%), with no significant difference between the study groups ($P=0.551$).

Graft vascular disease (diagnosed by coronary angiography, as some degree of “new” irregularity or stenosis in any of the major coronary vessels or its main branches, even if less than 50%) was diagnosed in 20 patients (9.4%). The comparative analysis of this event showed no significant difference in the incidence between the study groups ($P=0.781$). Survival free from GVD in groups A and B was not statistically different ($P=0.547$, Figure 1B).

De novo diabetes and severe infections

The incidence of de novo diabetes in the first year after transplantation was 12.7%, with no difference between the two groups (15.5% vs. 11.7%, $P=0.456$).

The incidence of serious infections requiring hospitalization and intravenous antibiotics during the first year post-transplantation was higher in Group A (22.4% vs. 12.3%), but the difference did not reach statistical signifi-

cance ($P=0.068$). Likewise, the incidence of pneumonia in the first 6 months was higher in Group A (17.2% vs. 9.7%), although the difference was not significant ($P=0.131$).

Behavior of renal function after transplantation

At the time of transplantation, patients in Group A showed a tendency to have lower rates of glomerular filtration (57.2 \pm 26.5 vs. 60.9 \pm 21.2 ml/min, $P=0.301$). However, early renal replacement therapy (\leq 1 month after transplantation) was necessary in only 4 patients, with no difference between groups.

In both groups, a tendency towards recovery of renal function was observed after one month of transplantation, although not statistically significant ($P=0.343$ and $P=0.480$ for groups A and B, respectively). However, this was followed by a progressive deterioration of the glomerular filtration rate, whose values dropped significantly in Groups A ($P=0.050$) and B ($P<0.001$) for the first sixth months post-transplantation, and continued to decline, though at a slower pace, up to twelve months after transplantation (Figure 2).

Mortality and survival

After a mean follow-up of 4.5±2.7 years (1 to 10 years; 961.8 patient-years), the overall mortality did not show significant differences between the two groups of patients (19% vs. 23.4%, P=0.491) and the same goes for comparison of in-hospital mortality and death at 6 months, 1 year, and late (Table 6). The most frequent causes of death in both groups were infectious (5.2% vs. 6.5%, P=0.721) and vascular (5.2% vs. 5.8%, P=0.850), with no statistical significance in the comparison between the two groups.

The comparative analysis of the survival curves (Figure 3) also showed no significant difference between the two groups (P=0.659) and mean survival is currently 7.8±0.5 years in Group A and 7.4±0.3 years in Group B.

DISCUSSION

It is known that the pre-transplantation clinical situation of patients with the highest degree of urgency is different. Decompensated patients are refractory to ambulatory medical treatment

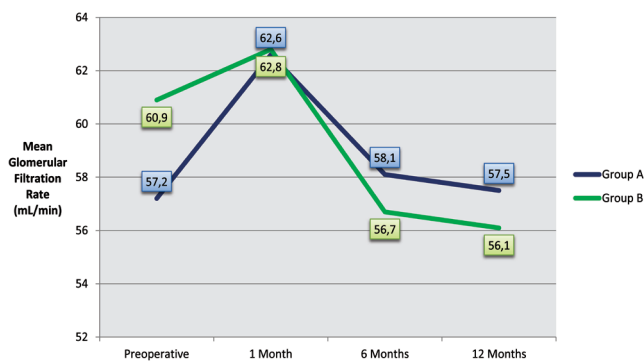


Fig. 2 - Evolution of the mean glomerular filtration rate during the first year after transplant in groups A and B.

for heart failure, which requires hospitalization in cardiac intensive care units where they are to undergo treatment with intravenous diuretics, inotropes (dobutamine and noradrenaline), and a large majority is treated with cardiotonics (levosimendan). On the other hand, patients having a lesser degree of urgency benefit from home and family environment as well as greater mobility, factors that contribute to improvement and even optimization of their psychological, nutritional, and muscular status, in addition to a drastic reduction of nosocomial infections. Undoubtedly, these are aspects that help decrease the potential for post-transplantation mortality and morbidity^[9].

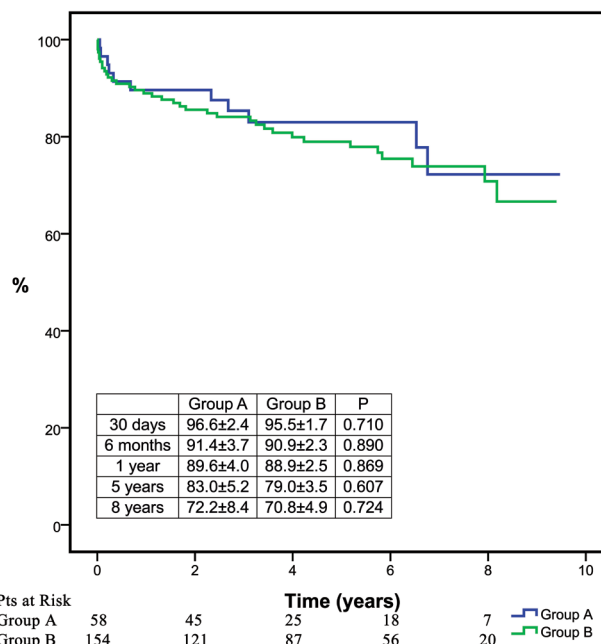


Fig. 3 - Actuarial overall survival in groups A and B.

Table 6. Mortality data and causes of death.

	Group A (N=58)	Group B (N=154)	P value
Mortality			
Overall	11 (19.0%)	36 (23.4%)	0.491
Hospital	2 (3.4%)	7 (4.5%)	0.724
Early (≤ 6 months)	5 (8.6%)	14 (9.1%)	0.915
Death ≤1 year	6 (10.3%)	17 (11.0%)	0.885
Late Death >1 year	5 (8.6%)	19 (12.3%)	0.446
Causes of death			
Cardiac	1 (1.7%)	6 (3.9%)	0.430
Vascular	3 (5.2%)	9 (5.8%)	0.850
Neoplastic	1(1.7%)	7 (4.5%)	0.337
Neuropsychiatric	2 (3.4%)	1 (0.6%)	0.124
Infectious	3 (5.2%)	10 (6.5%)	0.721

Nevertheless, in this series we found a higher incidence of perioperative graft dysfunction in Group B. The most severe cases, in which it was necessary to use mechanical support (0% vs. 6.5%, $P=0.047$), were also detected in this group. But there was no significant difference in mortality between the two groups (3.4% and 4.5%, respectively, $P=0.724$).

These results point to a little adjusted (skewed) priority rank. The clinical situation of this less urgent group of patients is not homogeneous. The control of symptoms does not imply an improvement in the long-term prognosis. In fact, Lietz & Miller^[9] and Mokadam et al.^[10] demonstrated deterioration in the clinical status in 32-48% of UNOS 2 patients (equivalent to our lower priority VI-VII) during the waiting time for transplantation. These patients come to transplantation in uncertain clinical condition (intermittent instability, recurrent and frequent decompensation, or chronic persistent symptoms), whose control is not always associated with a better prognosis. In addition, advances in the medical treatment of heart failure by cardiotoxic drugs and artificial devices have distorted the actual phenotypic presentation of heart failure in late stage^[11,12].

The more favorable response in Group A suggests that patients recently undergoing intensive anticongestive therapy reach transplantation better compensated from the cardiorespiratory point of view, regardless of the fact that the pre-transplantation analytical study showed a higher multi-organ involvement. In fact, bilirubin and creatinine were higher in this group, both variables which are thought to have a strong influence on early mortality after transplantation^[13-16].

In addition, patients coming from intensive care are usually more delicate because they are in unfavorable physical, psychological and nutritional situation, exposed to a hospital environment, and they have been subject to different clinical monitoring devices, some quite invasive. Consequently, there was a greater number of serious infections in the first months post-transplantation in Group A, with values close to statistical significance (22.4% vs. 12.3%, $P=0.068$). The greatest risk of developing serious infections in this group of patients should alert us to the need for taking more forceful prevention measures, including adaptation of the immunosuppression protocol.

Also analyzed in this study was the evolution of renal function, measured by serum creatinine level and creatinine clearance during the first year, when one would expect greater divergence. There was an improvement in the values of serum creatinine immediately after transplantation in both groups, but a gradual deterioration over years and no significant difference between the groups. The incidence of *de novo* diabetes, often related to renal dysfunction, was comparable between the two groups, which is justified by similar immunosuppression protocols.

Global survival at 8 years and survival free from severe rejection (2R or 3R) were similar in the two groups. These

results also reinforce the idea that the high risk of transplantation in these patients can be significantly reduced in units with high volume of transplantations^[17-20]. The advantage of having teams with greater experience to perform this procedure in high-risk candidates is well known, as the results have been proven superior in these centers^[21-23].

The main message derived from this study is that, despite their higher risk profile and a further deteriorated clinical situation, urgent but not emergency patients showed similar outcomes to those of patients with lower priority. This may, therefore, raise the question of waste of a non-insignificant number of donors used in emergency cases with poor results in detriment of patients in better clinical conditions who die or deteriorate while on the waiting list, again conditioning the outcome of the transplantation^[24]. Listing for transplantation of some of these patients should probably be revised or delayed to optimize their clinical state^[25]. Today, more efficient devices for temporary or permanent mechanical assistance (ECMO, ventricular assistance, artificial heart), can greatly improve the clinical situation and reverse multiorgan deterioration^[26].

In addition it seems important to call for other types of priority scales that include the characteristics of the recipient, other than the urgency of transplantation. Hong et al.^[24] distinguished five groups of risk for transplantation, according to the presence of pre-transplant risk factors, where groups of higher risk have a first year survival of only 47-66% and a median survival of less than six years, results that, again, seriously question the use of donors that could have greater benefits in lower risk groups. These authors go as far as to say that donors should be allocated in priority for lower risk recipient groups and, only after that, for high-risk groups. They even warned about the need to consider whether we should not exclude high-risk patients from transplantation because the advantage of transplantation in the short and medium term is reduced in these patients, even when compared to medical treatment^[27,28].

CONCLUSION

The number of patients awaiting transplantation has been increasing, unlike the supply of donors. This situation becomes more complex when one observes an increase in the number of non-priority patients whose clinical condition worsens in the waiting list, turning them into higher priorities. This panorama requires strengthening of the borders of donation as well as considering responsible and pragmatic allocation of available organs.

In our experience, the results obtained from patients in urgent priority were similar to those of patients awaiting transplantation at home. The allocation of donors in this group does not seem to reduce the success of transplantation, a consideration that can probably not be extended to patients in more critical situations.

Authors' roles & responsibilities	
DP	Analysis and/or interpretation of data, statistical analysis, final approval of the manuscript conception and design of study, drafting the manuscript; critical review of the content
PC	analysis and/or interpretation of data; statistical analysis; final approval of the manuscript
PA	Final approval of the manuscript; drafting of the manuscript; critical review of the content
MB	analysis and / or interpretation of data; completion of the transactions and/or experiments
MJA	analysis and/or interpretation of data; final approval of the manuscript; conception and design of the study; completion of the transactions and/or experiments; drafting of the manuscript; critical review of the content

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