

Analysis of Factors that Can Influence the Appearance of Acute Heart Transplant Failure

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Introduction and objective. Acute graft failure (AGF) is defined as significant failure of myocardial function in a newly implanted heart. The aim of the present study was to investigate a series of factors related to heart transplantation (HT) in relation to AGF.

Material and method. In a study of 287 consecutive HTs performed over a 14-year period, AGF was defined when: a) the surgeon observed ventricular dysfunction before closing the sternotomy; b) various inotropic drugs were required at high doses in the first days after surgery, or c) ventricular dysfunction was identified by routine echocardiography in the immediate postoperative period. Statistical analysis comprised a descriptive and univariate comparative study, followed by multivariate analysis based on application of a logistical regression model.

Results. The incidence of AGF was 22%. Predictors of AGF were female donor status (OR = 2.2; 95% CI, 1.2-4.4; $p = 0.02$), a disproportion of more than 20% in donor-recipient body weight (OR = 2.2; 95% CI, 1.1-4.3; $p = 0.02$), and background ischemic heart disease (OR = 2.5; 95% CI, 5.5-1.1; $p = 0.03$) or valve pathology (OR = 5.0; 95% CI, 7.0-1.5; $p = 0.01$).

Conclusions. AGF is a frequent pathology, which was present in 22% of our heart transplantation patients. Among the modifiable factors related to AGF was a clear disproportion in body weight and the size of grafts from female donors. Unmodifiable factors related to AGF were ischemic heart disease and valvular heart disease as a cause of heart transplantation.

Key words: Heart transplantation. Acute graft failure. Mortality. Multivariate analysis.

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Análisis de los factores que pueden influir en la aparición del fallo agudo del corazón trasplantado

Introducción y objetivo. El fallo agudo del injerto (FAI) se define como un fracaso significativo en la función miocárdica del corazón recién implantado. El objetivo de este trabajo fue estudiar una serie de factores relacionados con el trasplante cardíaco (TC) y analizar su relación con el FAI.

Material y método. Se han incluido 287 TC consecutivos realizados en un período de 14 años. Se consideró FAI cuando: a) el cirujano observó disfunción ventricular antes del cierre esternal; b) existió la necesidad de utilizar varios fármacos inotropos a altas dosis, o c) se produjo disfunción ventricular en las ecocardiografías durante el postoperatorio inmediato. Las variables se analizaron desde un punto de vista descriptivo, univariante y multivariante (modelo de regresión logística).

Resultados. La incidencia del FAI fue del 22%. Las variables predictoras de fallo agudo del injerto fueron: donante de sexo femenino (OR = 2,2; IC del 95%, 1,2-4,4; $p = 0,02$), discordancia mayor del 20% entre el peso del receptor y el del donante (OR = 2,2; IC del 95%, 1,1-4,3; $p = 0,02$) y cardiopatía de base isquémica (OR = 2,5; IC del 95%, 5,7-1,1; $p = 0,03$) o valvular (OR = 5,0; IC del 95%, 7,0-1,5; $p = 0,01$).

Conclusiones. El FAI es una afección bastante frecuente que se presenta, al margen de su gravedad, hasta en el 22% de los trasplantados cardíacos. Entre los factores modificables asociados a su presentación podemos encontrar la desproporción de pesos y el sexo femenino del donante. Los factores no modificables serían la cardiopatía isquémica y las valvulopatías como causa del trasplante.

Palabras clave: Trasplante cardíaco. Fallo agudo del injerto. Mortalidad. Análisis multivariante.

INTRODUCTION

Acute graft failure (AGF) is an early failure in the systolic function of a recently transplanted heart. It is not clear what factors favor its occurrence, although we do know that it has a negative impact on survival both directly, by producing severe ventricular dysfunction, and indirectly, by prolonging intubation and

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ABBREVIATIONS

AGF: acute graft failure.
CT: cardiac transplant.
PHT: pulmonary hypertension.

length of time needed to resuscitate, with increased risk of infection.

AGF is not an uncommon complication. In fact, in the Registro Español de Trasplante Cardíaco (Spanish Cardiac Transplant Register) it is listed as occurring in 35% of early deaths and 9% of total deaths.¹ Moreover, these numbers are probably underestimates, as other frequent causes of death in transplant patients may be triggered by an AGF, such as infections, multi-organ failure, and sudden death. In addition, it is the most significant predictive variable for early and later death. In the International Register it is also the reason for the majority of deaths in the early stages following transplantation (47%) and in the long term (20 to 25%).² We should not compare the percentages of the two registers, as the definition of graft failure in the International Register is not exactly the same as that in the Spanish Registry, which defines graft failure as failure of the transplanted heart at any time during the course of the transplant when the cause of death is unclear.

At present, it is believed that AGF must result from numerous causes, which makes studying it difficult. As a result, the few published studies that address this problem in depth attract attention. The clinical signs in primary graft failure are often evident minutes after reperfusion and can manifest as segmental or global hypokinesia, low cardiac output and hypotension, high stimulation threshold, elevated filling pressures, and dependence on multiple inotropic and pressure agents to maintain arterial pressure.³

The classic etiological factors involved in the development of early graft failure include: *a*) primary graft dysfunction, which may result from a traumatic, hemodynamic, or metabolic lesion of the heart before explantation, or from prolonged ischemia or poor preservation of the organ;⁴⁻⁶ *b*) technical problems, such as torsion of the anastomosis of the pulmonary artery, air embolism and bleeding, generally in patients with previous sternotomy and anticoagulant treatment;⁷ *c*) hyperacute rejection (which must be determined with a routine reactivity screen to an antibody panel in the recipient,^{8,9} although specific crossmatch with the donor is rarely available prior to heart implantation), and, finally, *d*) refractory pulmonary hypertension (which also should be tested for before transplantation using a preoperative hemodynamic screen of the recipient during pre-transplant testing).^{4,10,11}

The aim of this study was to identify the factors that may be associated with or are predictors of the occurrence of AGF in patients with cardiac transplants (CT). We analyzed several variables about the characteristics of the recipient and those of the donor, as well as those of the surgical intervention itself, which are usually available from transplant patient records.

PATIENTS AND METHODS

Patients

We included all patients who had transplants in our medical center from November, 1987, to December 31, 2000, from the time the procedure was initiated. There were a total of 287 orthotopic CTs. We did not include heart-lung transplants, retransplants, or pediatric transplants in patients younger than 10 years of age in the study.

Hemodynamic protocol

Hemodynamic studies were performed systematically in CT candidates. When the pulmonary systolic pressure was higher than 50 mm Hg or the pulmonary arteriolar resistance was higher than 2.5 Wood units, or both, vasodilators (nitroprussiate) or inotropic drugs (dobutamine), or both, were administered, and the effect on the right pressures was evaluated at infusion.

Immunodepressive and immediate postoperative protocol

1. Preoperative: cyclosporine and azathioprine or mycophenolic acid.

2. Intraoperative: corticosteroids.

3. Postoperative: first day, OKT3 and corticosteroids; second day, OKT3, corticosteroids or azathioprine or mycophenolic acid, or both; third day, OKT3, corticosteroids, azathioprine or mycophenolic acid, and, if renal function had resumed, cyclosporine.

Echocardiography was performed daily for the first few days after transplant. The only inotropic drug systematically administered, in accordance with our center's protocol, was isoproterenol to maintain cardiac frequency at between 100 and 110 beats per minute.

Definition of acute graft failure

AGF is considered to be at least a moderate ventricular dysfunction during the first 3 days following transplant. This dysfunction, whether on the left or right, is diagnosed by: *a*) the surgeon after transplantation and in the absence of recovery when closing the sternum; *b*) the need for catecholamines (dopamine+dobutamine+adrenaline+noradrenalin) at moderate or high doses, or *c*) an echocardiographic test performed during the first 3 days after implantation.

Parameters analyzed

The variables studied are from the recipient's and donor's pre-transplant studies and the surgical record, and are detailed in Table 1.

Type of study

A form listing all the variables was systematically completed during the first days after CT. At that time, it was decided whether AGF was present according to the aforementioned criteria. The analysis was performed on the data, which was collected prospectively.

Data analysis

Quantitative variables are expressed as mean \pm standard deviation, and the categorical variables as percentages. Descriptive statistics of all the variables and a univariate analysis were performed by using the Student *t* test for independent samples and the χ^2 test. For multivariate analysis, we chose forward logistical regression analysis, using AGF as a dependent variable and using as independent variables those with a significance of less than 0.05 on univariate analysis. The statistical program used for the calculations was the Spanish-language version of SPSS version 7.5.

RESULTS

Descriptive and frequency analysis

The age of most of the patients who received a cardiac transplant in this series was between 50 and 59 years of age (mean, 52 years \pm 11 years; range, 12 to 67 years) and, although they received hearts from donors of all ages, the donors tended to be less than 29 years

of age (29 years \pm 11 years; range, 12 to 55 years).

Of note, most recipients were male (87.8%) who received hearts from male donors (69.7%). Other combinations of donor/recipient occurred less frequently, although 26.5% of the transplant patients were men who received hearts from women donors.

The overwhelming majority of transplant patients were transplanted with hearts from donors whose blood group was identical to theirs (87%). Weight and height of recipients and donors was proportionate in most cases; the percentage of transplant patients with disproportionate weights or heights (a difference greater than 20% for either variable) was 29%.

Univariate analysis

The accumulated incidence of AGF, according to the previously mentioned criteria, was 22%.

When analyzing patient characteristics in the individuals who exhibited signs of AGF, the most frequent characteristic was the occurrence of ventricular failure when the implanted heart came from a female donor. AGF also occurred more frequently when the blood type of the recipient or the donor was type O or when there was an apparent discrepancy between recipient and donor with regard to weight or height (recipient:donor correspondence was not between 0.8 and 1.2).

The right cavity pressure and the size of the cavity were greater in the group who developed AGF. There was also a greater incidence of biventricular failure. We observed significant differences between both groups with regard to baseline heart disease and the clinical stability of the patient at the time of transplant. Other differences between the groups studied are shown in Table 2.

TABLE 1. Variables analyzed

Recipient		Donor	Recipient/donor	Surgical parameters
Age	Presence of infection	Age		Amount of time with ischemia
Sex	IDDM	Sex	Ratio of weights	ECC time
Blood group	CAFO ^b	Blood group	Ratio of heights	Bicava technique
Weight	>20% overweight	Weight		Blood cardioplexy
Height	AHT	Height		
FS III-IV or IV	SPVD	Hospital donor		
IV inotropic drugs ^a	Respirators	>2 days UCI		
Hemodynamic study	Circulatory assistance	Dopamine		
Echocardiographic study	Previous cardiac surgery	Dobutamine		
Isotopic study	Treatment with amiodarone	Noradrenaline		
Baseline cardiopathy	CT situation	Cause of death		
Creatinine>2 mg/dL	Urgent CT	Echocardiography		
Bilirubin>2.5 mg/dL	ASAT/ALAT>100 mg/dL			

^aPatients requiring intervention (indicated) at the time of transplant. ^bPatients were those who had moderately or seriously impaired respiratory function test results. ^cDonors treated or not treated with these drugs, regardless of dose. FS indicates functional state; IV, intravenous; IDDM, insulin-dependent diabetes mellitus; CAFO, chronic air flow obstruction; AHT, arterial hypertension; SPVD, symptomatic peripheral vascular disease; CT, cardiac transplant; ASAT, aspartate-amino-transferase; ALAT, alanine-aminotransferase; ECC, extracorporeal circulation.

TABLE 2. Differences between the clinical characteristics of patients with and without acute graft failure (AGF)

	With AGF (n=64)	Without AGF (n=223)	P
Age of recipient, years	51±12 (13-64)	52±11 (12-67)	.5
Age of donor, years	28±11 (13-51)	29±11 (12-55)	.5
Male recipients	56 (88%)	196 (88%)	.9
Male donors	36 (56%)	164 (74%)	.01
Blood type of recipient			
Group A	31 (49%)	112 (50%)	.04
Group O	29 (45%)	86 (39%)	
Groups B and AB	4 (6%)	25 (11%)	
Blood type of donor			
Type A	28 (44%)	98 (44%)	.04
Type O	35 (55%)	113 (51%)	
Types B and AB	1 (1%)	12 (5%)	
Weight of recipient, kg	75±13 (40-105)	72±11 (39-114)	.09
Weight of donor, kg	69±11 (50-95)	70±11 (42-100)	.5
Ratio of recipient:donor weights			
<0.8	7 (11%)	16 (7%)	.01
0.8-1.2	36 (56%)	167 (75%)	
>1.2	21 (33%)	40 (18%)	
Height of recipient, cm	168±8 (143-180)	167±8 (145-190)	.4
Height of donor, cm	169±9 (155-192)	171±8 (150-190)	.09
Ratio of recipient:donor height			
<0.8	1 (2%)	0 (0%)	.0008
0.8-1.2	58 (91%)	223 (100%)	
>1.2	5 (7%)	0 (0%)	
FC III-IV and IV	39 (61)	111 (50)	.1
IV inotropic drugs	21 (33%)	44 (20%)	.04
Hemodynamics*			
RAP, mm Hg	15±8 (6-32)	12±5 (2-28)	.006
APSP, mm Hg	49±17 (24-89)	45±14 (17-102)	.08
mAPP, mm Hg	32±11 (17-52)	31±10 (13-57)	.4
dAPP, mm Hg	24±9 (11-40)	23±9 (5-43)	.4
CPP, mm Hg	22±10 (10-45)	24±8 (7-41)	.1
PVR, WU	2.5±1.6 (0.8-7.8)	2.7±3.2 (0.5-28)	.5
TPG, mm Hg	11±4 (5-19)	10±6 (2-30)	.1
Echocardiography			
APSP, mm Hg	40±13 (25-70)	42±13 (10-87)	.3
APSP>30 mm Hg	35 (55%)	124 (56%)	.9
RV, mm 24±12 (11-67)	21±7 (5-42)	.06	.1
RV>24 mm	23 (36%)	56 (25%)	
Isotopes			
LVEF, %	25±14 (7-75)	21±10 (9-68)	.1
RVEF, %	30±3+13 (10-58)	31±11 (9-59)	.6
RVEF>LFEF	32 (50%)	139 (62%)	.08
Baseline diagnosis			
IC	35 (55%)	107 (48%)	.004
DIMC	10 (16%)	79 (35%)	
Valvulopathy	10 (16%)	13 (6%)	
Other	9 (13%) 24 (11%)		
Creatinine>2 mg/dL	6 (9%)	29 (13%)	.4
Bilirubin>2.5 mg/dL	13 (20%)	30 (13%)	.2
ASAT/ALAT>100 mg/dL	22 (34%)	54 (24%)	.1
Infection	3 (5%)	5 (2%)	.4
IDDM	5 (8%)	35 (16%)	.06
CAFO	7 (11%)	13 (6%)	.2
>20% overweight	3 (5%)	5 (2%)	.4
AHT	16 (25%)	75 (34%)	.2
EVPS	4 (6%)	5 (2%)	.2
Respirator	12 (19%)	11 (5%)	.007
Circulatory assistance	5 (8%)	2 (1%)	.04
Previous heart surgery	14 (22%)	31 (14%)	.2
Amiodarone	1 (2%)	5 (2%)	.7

(Continues)

TABLA 2. (Continued)

	With AGF (n=64)	Without AGF (n=223)	P
CT situation			
Critical care	22 (34%)	35 (16%)	.004
Hospitalized	5 (8%)	27 (12%)	
Home	37 (58%)	161 (72%)	
Referring hospital			
Own hospital	17 (27%)	69 (31%)	.09
Community	21 (33%)	95 (43%)	
Rest of Spain	26 (40%)	59 (26%)	
>2 days in ICU	22 (34%)	85 (38%)	.6
With dopamine	29 (45%)	103 (46%)	.9
With dobutamine	4 (6%)	9 (4%)	.5
With noradrenaline	16 (25%)	54 (24%)	.9
Cause of death			
CET	36 (56%)	142 (64%)	.3
CH	26 (41%)	69 (31%)	
Other	2 (3%)	12 (5%)	
Echocardiography			
Normal	45 (70%)	153 (69%)	.9
Abnormal	2 (3%)	10 (4%)	
Not performed	17 (27%)	60 (27%)	
Ischemia duration, min	143±52 (50-250)	135±53 (50-280)	.2
ECC duration, min	143±93 (70-610)	106±40 (55-420)	.002
Urgent CT	22 (34%)	37 (17%)	.006
Bicava surgical technique	3 (5%)	19 (9%)	.2
Blood cardioplegia	47 (73%)	177 (79%)	.3

*Hemodynamic data are: baseline in 54% of patients, subject to intravenous vasodilator treatment for 35% of patients, and subject to treatment with vasodilators and intravenous inotropes in 11% of patients. RAP indicates right atrium pressure; APSP, arterial pulmonary systolic pressure; mAPP, mean arterial pulmonary pressure; dAPP, diastolic arterial pulmonary pressure; CPP, capillary pulmonary pressure; RVP, pulmonary vascular resistance; WU, Wood units; TPG, transpulmonary gradient; RV, right ventricle; LV, left ventricle; LVEF, left ventricular ejection fraction; RVEF, right ventricular ejection fraction; RVEF>LVEF, RV ejection fraction greater than 50% of the LV; IC, ischemic cardiopathy; IDMC, idiopathic dilated myocardiopathy; CET, craneoencephalic trauma; CH, cerebral hemorrhage; AGF, acute graft failure. The rest of the abbreviations are as defined in previous tables. Values are expressed as mean±standard deviation with range indicated in parenthesis.

Multivariate analysis

Upon introducing variables with varying levels of significance in a logistical regression model, we found that the development of AGF was only associated with female sex of the donor, a difference of more than 20% between the weight of the recipient and that of the donor, and certain baseline heart diseases, such as ischemic cardiopathy or valvulopathy.

Figure 1 depicts a graph of the variables that were statistically significant.

DISCUSSION AND CONCLUSIONS

AGF is a relatively frequent complication that causes, on occasion, the death of patients who have received a heart transplant. Although it has an important impact on survival, there are few studies that have studied this entity. Moreover, the majority of studies, when they have analyzed predictive factors of morbidity and mortality, tend to cite AGF as an important factor in these variables, while failing to specifically discuss AGF in depth.

The reason that AGF has not been studied in depth

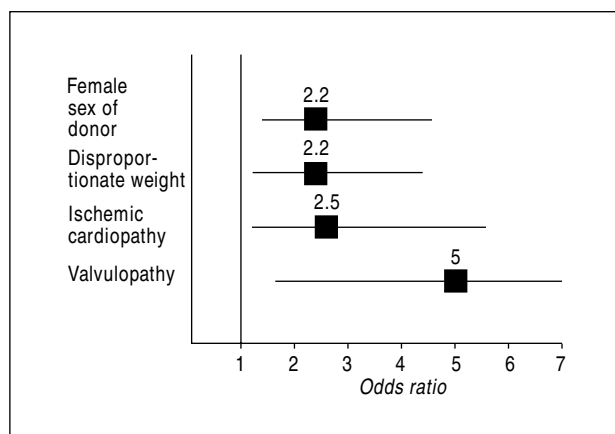


Fig. 1. Variables predictive of acute graft failure in the multivariate model.

is that it is thought to have a variety of causes, which renders it difficult to study and makes it difficult to draw conclusions about avoiding AGF and decreasing its incidence rate.

Given this, as well as the high incidence AGF and

AGF-attributable mortality, and the relative unpredictability of AGF, we performed a multivariate analysis, not of the unusual variables, but of those variables that are generally available to most CT teams in order to provide conclusions that are clinically useful.

On descriptive analysis, it is evident that the characteristics of these patients are quite similar, which is a result of our selection process before we enrolled them in the study. This fact is important since it was difficult to identify subgroups of patients at risk for particular complications when the majority of patients had similar characteristics. These general characteristics are not different from those of other transplant patients in Spain and appear annually in the Spanish Transplant Register published in the *Revista de la Sociedad Española de Cardiología*.¹

With regard to age, sex, and blood type of the recipient and the donor, only the sex of the donor was shown, on univariate and multivariate analysis, to have significant statistical significance; transplants performed with organs from female donors were associated with the occurrence of AGF. In other studies, an improved survival rate has been shown (although not specifically in reference to acute graft failure) in male recipients who received hearts from male donors as compared with other donor/recipient combinations;¹²⁻¹⁴ which led to the recommendation of more focused immunological followup and increased immunodepression treatment in cases where donor/recipient sex don't match. On the other hand, the combination of 2 variables, sex and body size (ie, a donor heart from a small female transplanted into a male who is larger), especially when the disparity in body size is greater than 30%, has been shown by the study by Young¹⁵ to be an independent predictor of the development of AGF.

In our study, we found differences in the occurrence of AGF when we examined recipient-to-donor ratio with regard to weight and height; a recipient-to-donor weight or height ratio that did not fall between 0.8 and 1.2 increased the risk of AGF; this difference persisted on multivariate analysis with regard to weight only, which is probably due to the fact that there were few patients who fell outside of this ratio with regard to size. The relationship between disproportionate weights and an increase in post-transplant mortality is one of the most studied factors; it is almost universally accepted that recipient-to-donor weights should be comparable given the increased risk that excessive disproportion causes. On a related note, a recipient weight of less than 60 kg, independent of donor-to-recipient concurrence, has been shown to be an independent predictor of AGF¹⁶ and, similarly, it has been noted that cachexic patients who receive hearts from oversized donors have significantly higher postoperative mortality rates compared with other patient populations with regard to donor-to-recipient body

weight.¹⁷

The baseline cardiopathies that triggered CT were divided into 4 groups: ischemic cardiopathy; idiopathic dilated myocardiopathy; valvulopathy; and other. Ischemic cardiopathy and, in particular, valvulopathy are associated with a greater incidence of AGF. There are no studies in the literature that specifically link types of cardiopathy to the risk of developing AGF. Nevertheless, it has been shown that patients with ischemic cardiopathy have worse survival curves, and that these curves are evident from the beginning of the transplant process.¹⁸ It seems clear that these are patients more physically at risk due to the extant combination of risk factors for cardiovascular disease, as they generally have more generalized arteriosclerosis. On the other hand, patients with valvulopathy were those who, in our study, were at greater risk for developing AGF with a higher odds ratio. This could be related to the greater incidence of certain risk factors in these patients, such as pulmonary hypertension (PHT) or previous cardiac surgery.^{19,20}

Other parameters analyzed in this study have shown differences only on univariate analysis and do not demonstrate sufficient statistical power by themselves to be associated with an increased risk of resulting in AGF. All of these parameters are related to patients who are more unstable. The lack of statistical significance is a result of the low incidence of these variables in the patient sample analyzed. The variables that have been shown to be different on univariate analysis are: being on a respirator; being on circulatory assistance; hospitalization at the time of the CT; length of time on extracorporeal circulation; and transplant performed in the setting of extreme emergency. Of these variables, only respiratory assistance provided to the recipient was shown to have, in previous studies, an independent predictive value for the development of AGF,¹⁵ with the remainder of the variables being associated in a more typical and general manner with worse post-transplant survival.^{4,21,22}

Prior cardiac surgery, a variable associated with AGF in other studies,^{15,16} was observed more frequently in the group of patients who developed AGF (22% vs 14%), without the differences being statistically significant, perhaps due to insufficient sample size.

An accepted cause of early graft failure outside of the operating room is right ventricular failure due to a relatively fixed PHT in the recipient.^{3,11} The hemodynamic protocol used, in which the values recorded are baseline for patients without significant PHT and recorded after pharmacological testing in those patients with baseline PHT, could result in errors in correctly recording pulmonary pressures. Thus, lower pressures may be recorded in patients who have been treated with vasodilators or IV inotropic agents than in patients with slightly elevated pressures who have been

given these drugs. Taking this fact into account, only right atrial pressure was associated in a statistically significant manner with AGF on univariate analysis (15 mm Hg \pm 8 mm Hg in the group who developed AGF vs a 12 mm Hg \pm 5 mm Hg in the group who did not; $P=.006$), a result that, along with a transpulmonary gradient higher than 15 mm Hg, was also observed in the study by Segovia et al.¹⁶

Studies of these patient characteristics carry implicit limitations such as: *a)* some variables, although undoubtedly important, do not tend to be part of the database of transplant patients, such as transport temperature, necrosis enzyme values, the subjective opinion of the surgeons who perform the explant and implant with regard to the organ, and the state of the coronary arteries or the hemodynamics that maintain the organ at the moment of extraction; *b)* the increase in arterial pulmonary pressure that appears to have a clear association with the development of AGF of the right heart; the absence of correlation in our study may be due, as mentioned previously, to the fact that the analysis of pulmonary pressures has not been consistent in terms of the hemodynamic protocol used, and *c)* certain subgroups of patients at risk did not show significant differences, probably due to the small number of patients included in the study group. It would be interesting to perform the same study with larger databases such as, for example, those of the Registro Español de Trasplante Cardíaco (Spanish Cardiac Transplant Registry) which includes all the CTs performed in Spain (more than 3000 transplants).

After analysis of our study, we conclude:

- AGF occurs fairly frequently and appears at the height of its severity in up to 22% of patients who receive a cardiac transplant.

- Among the modifiable factors associated with the occurrence of AGF are disproportionate weights and female sex of the donor.

- Non-modifiable factors that favor the occurrence of AGF are ischemic cardiopathy and valvulopathy as the reason for transplant.

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