Long-term atrial arrhythmias incidence after heart transplantation

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Matteo Anselmino[1], Mario Matta[2], Andrea Saglietto[1], Chiara Gallo[1], Fiorenzo Gaita[3], Giovanni Marchetto[4], Mauro Rinaldi[4], Gaetano Maria De Ferrari[1], Massimo Boffini[4]

[1]Division of Cardiology, Department of Medical Sciences, "Città della Salute e della Scienza di Torino" Hospital, University of Turin, Turin, Italy

[2]Division of Cardiology, Sant'Andrea Hospital, Vercelli, Italy

[3]Cardiovascular Department, Clinica Pinna Pintor, Policlinico di Monza, Turin, Italy

[4]Division of Cardiac Surgery, Department of Surgical Sciences, Città della Salute e della Scienza, University of Turin, Turin, Italy

Corresponding Author:

Mauro Rinaldi, MD Prof

Division of Cardiac Surgery, Department of Surgical Sciences,

"Città della Salute e della Scienza", University of Turin, Italy

Corso Bramante, 88

10124 Turin, Italy

Phone 00 39 0116709598

Fax 00 39 0112369598

Email: mauro.rinaldi@unito.it

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Abstract

Objectives. Atrial arrhythmias after heart transplantation have rarely been investigated. The aim of this study is to assess incidence, type and predictors of atrial arrhythmias during a long-term follow-up in a large population of heart-transplanted patients.

Methods. Consecutive patients undergone to heart transplantation at our Centre from 1990 to 2017 were enrolled. All documented atrial arrhythmias were systematically reviewed during a long-term follow-up after heart transplantation. Atrial fibrillation (AF), atrial flutter and tachycardias were defined according to current guidelines.

Results. Overall, 364 patients were included and followed for 120±70 months. During the follow-up period 108 (29.7%) patients died and 3 (0.8%) underwent re-transplantation. Sinus rhythm was present in 355 (97.5%) patients. Nine patients had persistent atrial arrhythmias: 8 (2.2%) presented atypical flutter and one (0.3%) patient AF. Paroxysmal sustained arrhythmias were detected in 42 (11.5%) patients, always atrial flutters. At univariate analysis several echocardiographic (left ventricular end-diastolic diameter, TEI index, mitral and tricuspid regurgitation grade) hemodynamic (systolic and diastolic pulmonary pressure, capillary wedge pressure) and clinical (dyslipidaemia, weight, pacemaker implantation) parameters related to higher incidence of atrial arrhythmias.

Conclusion. Persistent atrial arrhythmias, and most of all AF, are rare among heart transplantation carriers, despite substantial comorbidities resulting in significant mortality. It can be speculated that the lesion set provided by the surgical technique, a complete and transmural electrical isolation of the posterior left atrium wall, represents an effective lesion set to prevent persistent AF.

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Highlights

- Heart transplantation creates electrical barriers, similar to surgical AF ablation.
- Heart transplantation carriers may experience non-AF paroxysmal arrhythmias (e.g. incisional atrial tachycardias).
- Persistent AF in heart transplantation carriers is extremely rare.
- Complete electrical left atrial posterior wall isolation prevents persistent AF.

Introduction

Heart transplantation is considered the standard treatment for selected cases of advanced end-stage heart failure[1]. The surgical technique, originally described by Lower and Shumway is characterized by the surgical incision on the posterior wall of both left and right atria, resulting in a final suture combining the LA posterior wall and the sinus of venae cavae of the recipient with the atrial cuffs of the graft[2]. To date, little has been reported concerning incidence and predictors of atrial arrhythmias in the long-term of patients after heart transplantation.

On top of this, the treatment of persistent atrial fibrillation (AF) in the general population is affected by poor outcome; indeed, not as good as for paroxysmal AF[3]. The standard catheter ablation (CA) approach of pulmonary vein isolation alone achieves poor results in patients with persistent AF, and additional substrate modification is often required to obtain satisfactory results. In fact, an ideal ablation set for persistent AF has not been established. Linear lesions in the left atrium (LA), resembling surgical maze procedure[4,5], and the ablation of complex fractioned atrial electrograms[6] or rotors[7] have been proposed, with promising but sometimes contrasting results.

In this setting, the "cut and sew" performed during heart transplantation results in a complete electrical isolation of the recipient's posterior LA wall, pulmonary veins and venae cavae from the rest of the atria. This technique may therefore represent an in vivo, indirect model of a truly transmural lesion isolating the posterior wall and the venae cavae.

The present observational, retrospective study on a large population of heart transplantation recipients aims to assess incidence, type and predictors of atrial arrhythmias during a long-term follow-up, in order to provide additional knowledge concerning the ideal atrial surgical lesion set to treat persistent AF in the general population.

Methods

Study design

Consecutive patients undergone to heart transplantation at the Cardiac Surgery Division, "Città della Salute e della Scienza" Hospital, University of Turin, Italy, from 1990 to 2017, were retrospectively included. Inclusion criteria were: age over 18 years old, and orthotopic heart transplantation due to any underlying disease. Exclusion criteria were: death within the first month after transplant, and follow-up shorter than 6 months. The retrospective registry protocol was approved by the local Ethical Committee of the Hospital.

Surgical technique

Orthotopic heart transplantation was performed according to the bi-atrial technique in all patients, except one who received a heart transplant using the bi-caval technique. The bi-atrial technique was originally described by Lower and Shumway. Briefly, cardiectomy is performed leaving the two atrial cuffs with the orifices of the pulmonary veins and the venae cavae in the recipient. The graft is prepared creating two atrial cuffs. The LA is opened posteriorly connecting the orifices of the four pulmonary veins and trimming the tissue in excess. The right atrium is opened from the inferior vena cava towards the right atrial appendage. The two cuffs are then sutured to the recipient's cuffs. Our surgical team started performing heart transplantation back in 1986 when the bi-atrial technique was the approach used by all the transplant centres worldwide. Since then, our surgical policy has never changed, due to a lack of documented benefit of the bicaval vs the original technique in terms of long-term survival. The experience with this type of procedure reduces the "theoretical" complications related with the suture of the two right atria. The risk of sino-atrial node injury is prevented by opening the donor's right atrium from the inferior vena cava towards the atrial appendage leaving the node tissue far away from the suture line. The tricuspid annulus

distortion is avoided preserving enough tissue between the surgical suture and the atrio-ventricular groove.

From an electrophysiological point of view, the two techniques are equivalent because the left atria suture is the same and the ~~final~~ ultimate result is that graft atria are completely isolated from the recipient's atrial remnants.

Clinical follow-up

All patients included in the present analysis underwent routine clinical visit, ECG and blood tests at 1, 2, 3, 6, 9, 12 months, then every 2 months up to the second year after transplant and every 6 months, afterwards. In addition, right heart catheterization and endomyocardial biopsy were performed at 1, 2, 3, 6, 9 and 12 months; echocardiogram at 1, 3, 6, 12 months and then every year; cardiopulmonary exercise test and 24 hours Holter ECG every year and according to clinical demand. Coronary angiography was scheduled at one year after transplant and every 5 years thereafter. Additional investigations, such as longer duration monitoring or implantable loop recorder or additional right heart catheterizations were performed when needed according to symptoms and clinical presentation. All follow-up evaluations were performed at our Center. Baseline and follow-up clinical, echocardiographic, electrocardiographic, laboratory and hemodynamic characteristics of the enrolled patients were registered in a dedicated registry. All data were analysed by the Investigators according to current best practice. All available arrhythmic events, both ECGs and device interrogations, were re-analysed by two Investigators (M.A. and C.G.) aiming to differentiate between AF, atrial flutter and atrial tachycardia.

Study definitions

Sustained atrial arrhythmias were diagnosed by ECG, Holter monitoring or implanted devices, considering events lasting more than 2 minutes[8]. AF was defined by disorganized irregular (cycle variation beat-to-beat above 10%) atrial activity characterized by a rate over 300 beats per minute. Atrial flutter was defined by regular, organized atrial activity with a heart rate of 200 to 300 beats per minute. Atrial tachycardia was defined by regular organized atrial, non-sinusal activity with a heart rate of less than 200 beats per minute. As suggested by the recent guidelines[8], in case of sustained arrhythmia detected by implanted devices, the heart rate and the stability (regular vs. irregular) of cycles were used as criteria to discriminate AF from atrial flutter. Arrhythmias were classified as paroxysmal in case of episodes lasting less than 7 days, interrupting spontaneously or by cardioversion, while persistent episodes were those lasting more than 7 days.

Echocardiographic morphological and functional parameters were measured according to the definitions and recommendations from the available American Society of Echocardiography guidelines[9].

Statistical analysis

Continuous variables, presented as means ± standard deviation (SD) or median [interquartile range] (IQR), were compared by ANOVA test or Student's t-test after normal distribution was confirmed. Categorical variables, presented as counts and percentages, were compared in cross-tabulation tables by means of the Pearson chi-square test. Survivor curves were estimated using the Kaplan Meier method and equality of the survivor functions was tested by log-rank test. Multivariate analysis was performed through multinomial linear regression, including all items presenting a p-value of less than 0.05 at univariate analysis. All tests of significance were two-tailed, and a p value

<0.05 was considered to indicate statistical significance. All analyses were performed by SPSS 21.0 (IBM, USA) and STATA 12 (StataCorp, USA).

Patient and Public Involvement

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

Results

Overall, 364 patients undergoing heart transplantation at our Centre between 1990 and 2017 were enrolled. Among them 288 (79%) were males, and mean age at the time of transplant was 50.9±13 years. All patients underwent heart transplantation with biatrial technique, apart from one patient suffering from a congenital heart disease that contra-indicated this technique and underwent bicaval technique. Three (0.8%) underwent a second heart transplant for severe primary graft dysfunction of the first graft.

Baseline characteristics are reported in Table 1. The most common causes of heart transplantation were idiopathic dilated cardiomyopathy and ischaemic cardiomyopathy, affecting 165 (45.5%) and 141 (38.8%) patients, respectively. Several comorbidities were present: arterial hypertension (234 patients, 64.3%), diabetes (75, 20.7%), elevated BMI (202, 55.5%), history of previous stroke or TIA (37, 10%), peripheral artery disease (69, 19.0%), chronic obstructive pulmonary disease (22, 6.0%) and obstructive sleep-apnoea syndrome (21, 5.8%). Forty-eight (13.2%) patients had a history of AF or other sustained atrial arrhythmias before heart transplantation.

During a median follow-up of 120 (50-181) months, 108 (29.7%) patients died (time from transplant to death 113±7 months). Causes of death were: 24 (6.6%) advanced heart failure, 8 (2.2%) sudden death and 20 (5.5%) non-cardiac deaths (malignancies, terminal renal failure or neurological events). In the remaining 56 (15.4%) cases the cause of death was unknown. Complete follow-up details are reported in Table 2. NYHA class was 1.3±0.7, and 240 (71.4%) patients were asymptomatic in NYHA class I. Left ventricular ejection fraction at echocardiography was 57.0±10.2%. LA dilation was present in all patients, as per surgical technique, showing a mean LA indexed volume of 60.1±48.2 ml/m^2. According to the latest classification of acute cellular rejection of the International Society for Heart and Lung Transplantation, at ventricular endocardial biopsy, 89 patients presented acute cellular rejection ≥2R. Significant coronary disease was found in 22

(13.6%) patients. Concerning pharmacological therapy at follow-up, 210 (57.7%) were on diuretics, while only 2 (0.6%) assumed amiodarone as anti-arrhythmic medication (both due to ventricular arrhythmias). Of note, 54 (15%) patients had implanted devices for cardiac rhythm management. Three patients underwent catheter ablation, in all cases incisional atrial flutter was documented.

Overall, 355 (97.5%) patients were in sinus rhythm. Only 9 patients suffered from persistent atrial arrhythmias: 8 (2.2%) for persistent atypical flutter, and one (0.3%) for persistent AF. Median time to develop persistent atrial arrhythmias was 90 (30-180) months. Paroxysmal sustained arrhythmias were registered in 42 (11.5%) patients, and in 13 of them the episodes were detected only at implantable device interrogation. All patients with paroxysmal arrhythmias presented an atypical atrial flutter, and no cases of paroxysmal AF were detected. The full description of atrial arrhythmias during follow-up is presented in Table 3 and in Supplemental Figure 1 in the Online Supplement.

Predictors of atrial arrhythmias

Univariate analysis was performed to assess the relation between clinical and instrumental parameters and the occurrence of atrial arrhythmias.

Echocardiographic parameters, such as left ventricular end-diastolic diameter (p=0.025), Tei index (p=0.003), more than mild mitral and tricuspid regurgitation (p<0.001 and p=0.002), and haemodynamic parameters as systolic (p=0.007) and diastolic pulmonary pressure (p=0.001), capillary wedge pressure (p<0.001) and central venous pressure (p=0.004) related to higher incidence of any atrial arrhythmia (Table 1 and 2). Also, clinical features such as dyslipidaemia (p=0.040), weight (p=0.030) and previous pacemaker implantation (p=0.001) related to atrial arrhythmias occurrence. In contrast, LA volume was not related to atrial arrhythmias (p=0.969).

Notably, among the deceased patients, none developed persistent atrial arrhythmias during follow-up, while 15 (13.8%) reported paroxysmal atrial flutter. Kaplan-Meier estimate of survival in the study cohort stratified by atrial arrhythmias occurrence is shown in Figure 1. No association was found between arrhythmic events and survival ($p=0.176$). Clinical parameters such as renal function ($p<0.001$), diabetes ($p<0.001$), anaemia ($p<0.001$) and symptoms of heart failure (NYHA class II or higher; $p<0.001$) related to higher risk of death. Consistently, diuretic treatment ($p<0.001$), left ventricular end-diastolic diameter ($p<0.001$) and ejection fraction ($p<0.001$) were found to be related to death.

Multivariate analysis was performed to assess the independent effect of clinical and instrumental parameters on the incidence of atrial arrhythmias. None of the included parameters, however, showed significant independent correlation to the occurrence of any sustained atrial arrhythmia during follow-up (details reported in Supplemental Table 1 in the Online Supplement).

Discussion

The aim of the present study was to assess long-term incidence of atrial arrhythmias and in particular of AF in a large population of heart transplanted patients. The main findings are:

- a limited number of patients (2.2%) suffered from persistent incisional atypical flutter, as a consequence of surgical scars in the atria, while 11.5% patients suffered from paroxysmal episodes of atrial flutter;
- persistent AF is extremely rare (one case); the presence of relevant comorbidities (justifying high mortality) do not relate to a proportionate incidence of persistent AF (as expected in a cohort of not transplanted patients with such comorbidities).

AF is very common in patients suffering from structural heart disease, especially in those with enlarged LA[10,11,12,13]. In our study population of heart transplanted patients, despite a significant LA enlargement, there was a surprisingly low incidence of persistent AF. In fact, the significant incidence of organ rejection, along with the high prevalence of comorbidities such as renal dysfunction and diabetes, known to be related to AF occurrence, cardiovascular events and death[14,15], related only to the latter (overall mortality around 30%) but not to the incidence of persistent AF, that remained very rare (0.3%/10 years of follow-up). It can be argued that heart transplanted patients indeed carry a "healthy" heart, received from the donor, however, comorbidities such as hypertension, renal dysfunction, diabetes, for example, are still present. This population is therefore a subset at a potentially high risk of developing AF, nevertheless the incidence of AF itself remains considerably low. As a matter of fact, the incidence of AF in ~~similarly high-risk~~ non-heart transplanted populations with the same prevalence of such comorbidities is reported to be significantly higher (over 20% lifelong at the age of 55)[12,16] than the incidence we have found, and the duration of the present follow-up (above 10 years) strengthens this evidence.

A plausible explanation for this low occurrence of AF is the preventive role exerted by the surgical lesion set in the atria, representing a complete, transmural electrical barrier. Moreover, the quantity of LA tissue of the graft is quite limited, indirectly demonstrating the role of atrial mass in the pathogenesis of AF.

The incidence of AF in the long-term is indeed very low, despite a discrete number of patients experiencing a significant degree of chronic rejection, a condition that has specifically been related to AF occurrence and worse prognosis among heart transplanted patients[17,18]. This finding, in our opinion, strengthens the hypothesis of a protective role exerted by the surgical barriers of the transplant in preventing persistent AF in the long-term. Of note, our study was designed to assess the long-term incidence of AF, therefore patients presenting perioperative death, most of them caused by acute rejection, have not been included in the analysis; the results of this study therefore apply only to those patients presenting a favourable acute outcome of heart transplantation.

Heart rhythm following atrial compartmentalization

The discrepancy between clinical and cardiac conditions of the present population and the low incidence of persistent AF is noteworthy. Heart transplantation *per se* seems, in fact, to be protective against the occurrence of AF. More in details, the surgical technique connecting recipient's and donor's atria creates transmural electrical barriers that compartmentalize the native atria by isolating the pulmonary veins, which represents the cornerstone of AF ablation[19], but also by isolating the entire LA posterior wall, resulting in a critical reduction of myocardial mass. As demonstrated by experimental models, in fact, critical mass is a key component, along with the presence of a trigger and autonomic nervous system modulation, for AF occurrence and most of all for persistent AF perpetuation[20,21]: it is therefore not surprising that complete electrical isolation of the pulmonary veins and the LA posterior walls protects transplanted hearts from developing persistent AF. Additionally, another relevant factor in preventing AF is indeed the denervation of

the transplanted heart: by interrupting the modulation of the autonomic nervous system towards the heart, the risk of developing AF is further reduced[22].

The incidence, although low, of atypical atrial flutter is not surprising. The substrate for this arrhythmia is completely different from AF and relies on the presence of multiple conduction corridors, usually in proximity of surgical scars that support reentry circuits[23].

On top of persistent arrhythmias, paroxysmal events were recorded, mainly by implanted devices, in about 10% of the population. At each device memory electrocardiogram analysis, events showed regular atrial activity, consistent with atrial flutter, and not AF. The presence of paroxysmal arrhythmias lasting few minutes, in fact, further supports the protective role of the atrial surgical scar by effectively and permanently modifying the substrate[24,25], since even in the presence of an active paroxysmal trigger arrhythmias do not progress to persistent AF.

Few other studies analysed the incidence of persistent AF among heart transplanted patients[18,26-28], and these data have been recently merged in a meta-analysis, reporting a mean 10% incidence of AF over an heterogenic follow-up period spanning from 1 month to 11 years. In this analysis, AF occurrence was mostly related to patients' age, renal failure, diabetes, post-transplant rejection and mitral regurgitation. However, most of the included studies did not discriminate AF from atrial flutter, that were often analysed together, and this easily explains the somewhat higher incidence of reported compared to our study. In the present study, as detailed in the Methods section, we carefully discriminated, based on guideline's criteria, between AF, atrial flutter, and atrial tachycardia. Of note, in 3 (33%) of the 9 patients suffering persistent atrial arrhythmias the first clinical diagnosis of AF was modified to atrial flutter after focused revision of the ECGs. In addition, the majority of the paroxysmal events were misdiagnosed as AF and subsequently reclassified as flutter, after revision of the available tracings. In fact, considering both persistent and paroxysmal atrial arrhythmic events, and not only AF, also in the present population the incidence would be around 10%.

Current persistent AF ablation treatment

Despite different approaches, current results of persistent AF CA remain suboptimal[29]. In fact, a clinical trial investigating the outcome of persistent AF ablation by linear lesions, the STAR-AF II, reported a similar incidence of recurrences with the sole isolation of the pulmonary veins[30]. However, it should be noted that in this trial lines were made empirically and often not validated by pacing manoeuvres. It is known from previous observational experiences, that obtaining real transmural, continuous and durable atrial lesion sets with the current ablation tools is difficult[31], and this may represent the main determinant of the poor outcome of persistent AF transcatheter ablation. Conversely, the results of surgical AF ablation with linear lesions set are superior. In a long-term follow-up study, 10-year sinus rhythm maintenance was reported in 81% of long-standing persistent AF and valvular heart disease patients[25]. This result, however, was obtained only in case the atrial linear lesions were validated at a following electrophysiological study; in fact, also after surgery alone, despite direct contact and visualization, atrial lines were not complete in 42% of the cases.

Nowadays, the classical Cox-Maze "cut and sew" surgery is almost abandoned, due to its complexity, difficulty and procedure-related morbidity in unexperienced hands compared to recent open-heart and thoracoscopic techniques that employ radiofrequency or cryoenergy devices to perform pulmonary veins, posterior wall isolation and/or linear lesions[19,32]. However, the Cox-Maze biatrial "cut and sew" reported excellent results in terms of rhythm control[4], and still ideally remains the most effective way to maintain long-term sinus rhythm.

In this perspective, the atrial anastomoses during heart transplantation represent a true "cut and sew" of the tissue, and they represent an ideal atrial line lesions in vivo model, providing an indirect suggestion that performing truly continuous and transmural lesions isolating the posterior LA wall and the venae cavae, may represent an effective method to prevent AF.

Limitations

First, the aim of this study was to assess long-term incidence of atrial arrhythmias in patients undergone heart transplantation. In our analysis the patients who died within the first month after transplant were excluded, aiming to exclude perioperative mortality. This may represent a selection bias excluding the most fragile ones. Although comorbidities were quite common also in the analysed cohort of patients, the sickest patients may have been excluded. Second, the retrospective design of the present study does not allow a comparison with a control population. Heart transplanted patients have peculiar features mainly due to their long history of low cardiac output. This does not permit a real comparison that would be in any case difficult and, perhaps, misleading. Third, in addition to the surgical atrial compartmentalization, another mechanism potentially impacting AF incidence could be the denervation of graft. The specific impact of autonomic system imbalance has not been assessed. Additionally, follow-up based on Holter ECG can underestimate the real incidence of paroxysmal, asymptomatic arrhythmias; however, persistent episodes are surely more accurately diagnosed, and the prevalence is remarkably low. Finally, age of the donors and ischaemic time of the transplanted hearts, that can affect transplantation outcome, were not considered in this study.

Conclusion

Persistent atrial arrhythmias are rare among heart transplanted patients, despite significant LA enlargement and comorbidities resulting in significant morbidity and mortality. In particular, persistent AF is extremely rare, likely relating to the surgical biatrial technique, resulting in electrical isolation of the entire posterior LA wall and caval veins sinus. Atrial anastomosis represents an in vivo model of complete and transmural atrial compartmentalization, and our

findings support the need of achieving effective and transmural LA lines to further assess their role in limiting persistent AF.

Table 1. Baseline clinical characteristics of the study population (364 patients).

	Total [n=364]	**No arrhythmias [n=313]**	**Any atrial arrhythmia [n=51]**	**p-value**
Age, years (SD)	50.9(13.0)	51.1(11.8)	49.9(12.8)	0.848
Sex, n(%)				0.325
Male	288(79.1)	245(78.3)	43(84.4)	
Female	76(20.9)	68(21.7)	8(15.7)	
BMI, kg/m2 (SD)	25.7(4.6)	25.6(4.7)	26.6(3.9)	0.178
Weight (kg)	74.3(15.9)	73.6(16.3)	78.7(11.8)	0.030
BMI >25. n(%)	202(55.5)	169(54.0)	33(64.7)	0.153
Dyslipidemia. n(%)	173(48.2)	150(48.7)	23(45.1)	0.040
Smoke history. n(%)				0.391
Previous smoker	41(11.3)	36(11.5)	5(9.8)	
Current smoker	10(2.8)	10(3.2)	0(0)	
Stroke risk factors. n(%)				
Hypertension	234(64.3)	206(66.0)	28(54.9)	0.124
Diabetes Mellitus	75(20.7)	67(21.8)	7(13.7)	0.593
Peripheral artery diseases	69(19.0)	59(18.9)	10(19.6)	0.593
Previous cerebrovascular event	37(10.2)	33(10.6)	4(7.8)	0.921
Hyperthyroidism, n(%)	17(4.7)	13(3.5)	4(7.8)	0.578
CKD grade (based on eGFR). n(%)				0.875
Grade 1	56(15.5)	46(14.7)	10(20.4)	
Grade 2	89(24.6)	77(24.6)	12(24.5)	
Grade 3	141(39.0)	122(39.0)	19(38.8)	
Grade 4	50(13.8)	44(14.1)	6(12.2)	
Grade 5 or dialytic therapy	25(6.9)	23(7.3)	2(4.1)	
OSAS. n(%)	21(5.8)	20(6.4)	1(2.0)	0.452
Genetic/autoimmune collagenopathies. n(%)	7(1.8)	7(2.2)	0(0)	0.884
Structural heart disease. n(%)				
Idiopathic dilated CM	165(45.5)	146(46.8)	19(37.3)	0.288
Ischemic CM	141(38.8)	122(39.0)	19(37.3)	0.802
Post-myocarditis CM	16(4.4)	13(4.2)	3(5.9)	0.580
Valvular heart disease	18(5.0)	13(4.2)	5(9.8)	0.086
Congenital heart disease	5(1.4)	5(1.6)	0(0)	0.363
Other CM	18(5.1)	13(4.2)	5(9.8)	
Mean CHA_2DS_2-VASc score. n(SD)	2.2(1.3)	2.2(1.4)	2.0(1.2)	0.176
Pre-transplantation rhythm. n(%)				0.616
Sinus rhythm	316(86.8)	274(87.5)	42(82.4)	
Persistent atrial flutter	3(0.8)	3(1.0)	0(0)	
Persistent atrial fibrillation	24(6.6)	19(6.1)	5(9.8)	
Paroxysmal atrial arrhythmias	21(5.8)	17(5.5)	4(7.9)	

BMI: body mass index; CM: cardiomyopathy; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; OSAS: obstructive sleep apnea syndrome;

Table 2. Clinical and instrumental parameters during follow-up.

	Total [n = 364]	**No arrhythmia [n=313]**	**Any atrial arrhythmia [n=51]**	**p-value**
Follow up duration, months (median-IQR)	120(50-181)	115.0(78.0)	149.0(86.0)	0.005
Deaths. n(%)	108(29.7)	93(29.7)	15(29.4)	0.965
Re-transplantation. n(%)	3(0.8)	3(1.0)	0(0)	0.483
Transplant rejection. n(%)	220(61.6)	194(86.6)	26(51.0)	0.678
Maximum grade of rejection, n(%)				0.664
0R	144(38.9)	120(38.3)	24(47.0)	
1R	131(35.3)	117(37.4)	14(27.44)	
≥2R	89(24.0)	76(24.3)	13(25.5)	
Mean NYHA class. n(SD)	1.3(0.7)	1.3(0.6)	1.2(0.7)	0.356
NYHA class. n(%)				
1	240(71.4)	208(73.0)	37(72.5)	0.355
2	64.0(19.0)	53(18.6)	11(21.6)	
3	23.0(6.8)	20(7.0)	3(5.9)	
4	1(0.3)	1(0.4)	0(0)	
Implanted pacemaker. n(%)	54(15)	34(11)	20(39)	0.001
Creatinine. mg/dl (SD)	1.9(1.3)	1.9(1.4)	1.9(1.3)	0.978
Haemoglobin. mg/dl (SD)	12.6(2.0)	12.6(2.0)	12.8(1.9)	0.496
Antiarrhythmic drugs, n(%)	2(0.5)	2(0.6)	0(0)	0.682
LVEDD. mm (SD)	46.5(7.0)	46.2(6.9)	48.6(7.1)	0.025
LVEDV. ml (SD)	91.9(30.4)	91.3(29.9)	96.6(33.5)	0.381
LA volume. ml/m^2 (SD)	60.1(48.2)	60.22(52.8)	59.8(13.7)	0.969
LVEF. % (SD)	57.0(10.2)	57.4(10.2)	54.7(10.0)	0.079
Tei index. n (SD)	0.41(0.75)	0.34(0.18)	0.74(1.8)	0.003
Valve regurgitation (more than mild)				
Mitral, n(%)	46(13)	32(10)	14(28)	<0.001
Tricuspid, n(%)	124(34)	98(31)	26(51)	0.002
Coronary artery disease, n(%)	22(13.6)	16(12)	6(20.7)	0.225
Cardiac catheterization				
PAPs. mmHg (SD)	29.9(8.4)	22.2(8.7)	33.4(9.1)	0.007
PAPd. mmHg (SD)	13.0(6.3)	12.5(6.1)	16.2(6.8)	0.001
PWCP. mmHg (SD)	12.3(6.0)	11.8(5.7)	15.4(7.1)	<0.001
Cardiac index. l/min/m^2 (SD)	2.9(0.95)	2.9(0.98)	3.0(0.79)	0.365

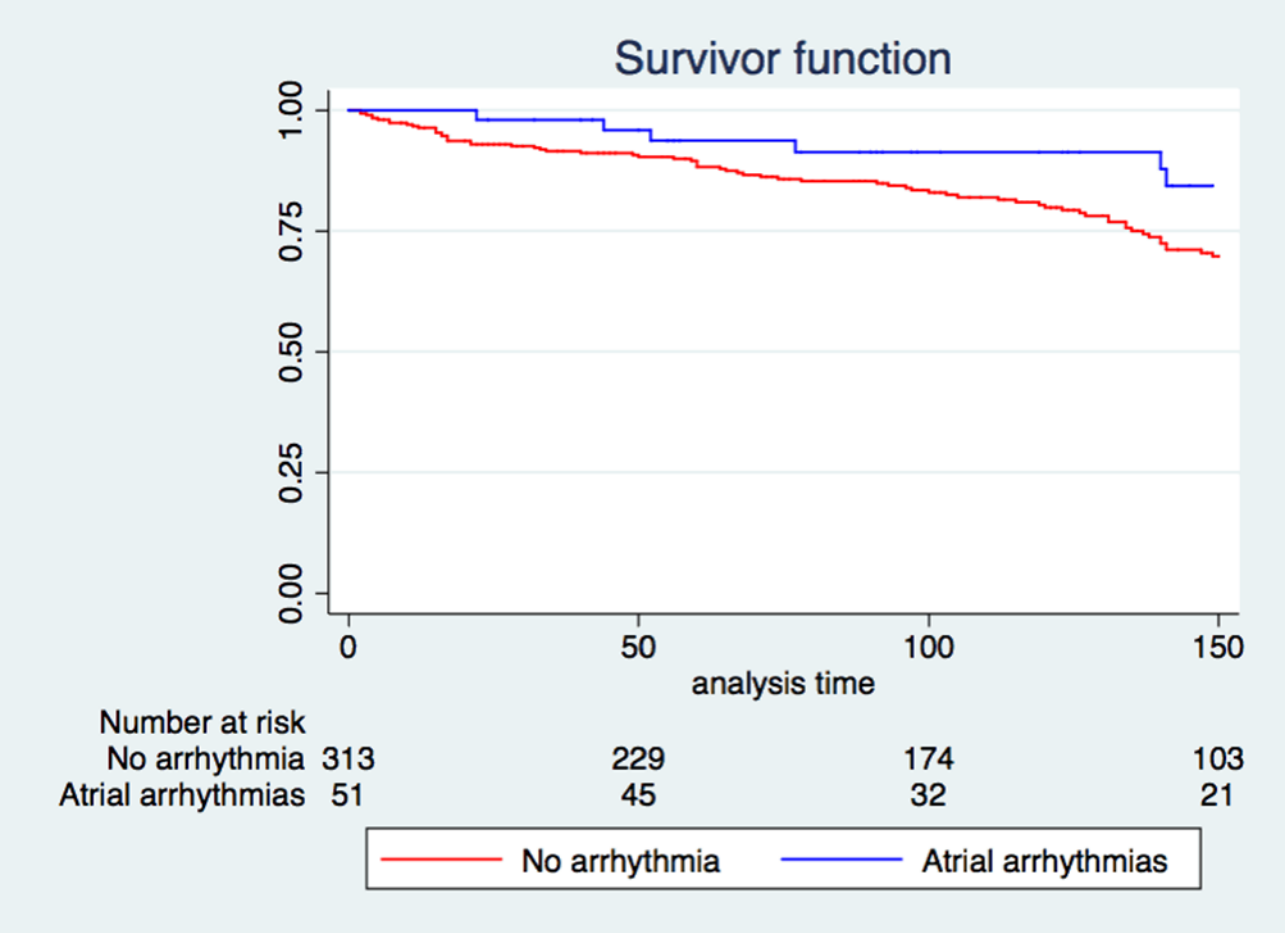
LA: left atrium; LVEDD: left ventricular end diastolic diameter; LVEDV: left ventricular end diastolic volume; LVEF: left ventricuslar ejection fraction; PAPd: diastolic pulmonary artery pressure; PAPs: systolic pulmonary artery pressure; PCWP: pulmonary capillary wedge pressure.

Table 3. Atrial arrhythmias detected during follow-up.

	Total [n = 364]
Rhythm at the end of follow-up; n(%)	
Sinus rhythm	355(97.5)
Persistent Atrial Flutter	8(2.2)
Persistent Atrial Fibrillation	1(0.3)
Paroxysmal atrial arrhytmias; n(%)	42(11.5)
Arrhythmic events without ECG documentation (device interrogation consistent with atrial flutter)	22(52.4)
Atrial flutter, ECG documented	20(48.6)
Mean episodes of paroxysmal atrial arrhythmia; n(SD)	1.3(0.75)
Mean time from transplantion to first atrial arrhythmic event; months (median-IQR)	90(30-180)
Procedures after transplantation; n(%)	24(6.6)
Cardioversion	21(5.8)
Catheter ablation (atrial flutter)	3(0.82)

Figure legends

Figure 1. Kaplan-Maier survival curves stratified by any atrial arrhythmias occurrence during follow-up (p=0.965). Analysis time is reported as months from transplantation.



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