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Atrial fibrillation after orthotopic heart transplantatation: Pathophysiology and clinical impact ☆

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ABSTRACT

Background: Atrial fibrillation (AF) is a well-established post-cardiac surgery complication. Orthotopic heart transplantation (OHT) represents a peculiar condition where surgical thoracic veins isolation and autonomic denervation occur. This study aims at investigating AF incidence in OHT in order to define its risk factors and to evaluate its prognostic impact.
Methods: 278 patients affected by OHT were recruited in our Cardiac Surgery Unit and retrospectively analyzed, using clinical, surgical and instrumental data.
Results: The patients cohort showed 45 post-operative (16.5%) and 20 late AF cases (7.2%). Only paroxysmal AF episodes were observed. Elderly donors and acute rejection resulted as risk factors in patients with post-operative AF episodes, who presented higher all-cause mortality at 11 years post-OHT ($p < 0.001$, Kaplan Meier analysis). The majority of late AF episodes occurred during hospitalization, due to renal failure or infections and more frequently in male patients; no significant correlation was observed with acute or chronic rejection or other characteristics.
Conclusion: Pulmonary vein isolation and vagal denervation lead to low AF incidence in OHT recipients. Acute rejection and graft status are the main risk factors for post-operative AF episodes, while other systemic conditions act as late AF triggers. The occurrence of AF episodes is associated with poor outcome and AF should be considered as a marker of clinical frailty.

1. Introduction

Atrial fibrillation (AF) is a well-established post-cardiac surgery complication, and it is associated with increased morbidity and mortality [1–3]. AF rarely represents a primary electric disorder, while most frequently it results from a large number of predisposing cardiac and non-cardiac conditions [4]. Pathogenesis of AF is usually linked with the interaction of three factors: triggers (1), which act on a predisposed atrial myocardial substrate (2), influenced by modulators (3). Catheter ablation using pulmonary veins (PVs) isolation and vagal modulation has emerged as valid treatment of paroxysmal AF since most of ectopic trigger beats originate from PVs and the autonomic nervous system is the most well-known modulator agent [5,6]. Surgical thoracic veins isolation and autonomic denervation are peculiar features characterizing the transplanted heart. Orthotopic heart transplantation (OHT) was initially performed through biatrial anastomosis, which leads to atrial distortion and alteration of the electrical pathways. Recently, bicaval anastomosis has become more popular as it provides a better preservation of the morphology and function of the atrium compared to the biatrial anastomosis [7]. Both techniques isolate the muscle sleeve of the PVs from the recipient. Previous studies showed controversial results about the rate of AF cases after OHT, the relative predisposing factors and long-term outcome [8]. In this study, we investigated the rate of AF in OHT as a model of complete PVs isolation and autonomic denervation, identifying the risk factors related to the development of the arrhythmia and evaluating the impact of AF episodes on the prognosis.

☆ This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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2. Methods

A population of patients who underwent OHT in our Cardiac Surgery Unit was retrospectively analyzed. Heart recipients < 16 years old and cases where perioperative death for surgical complications occurred were excluded from the cohort. The following clinical factors were collected:

- Donors: age, gender, body mass index (BMI), blood group
- Recipients: age, gender, BMI, blood group, data of right catheterization performed before transplantation
- OHT: time of graft ischemia, time of extracorporeal circulation (EC), graft anastomosis, graft-recipient mismatch of blood groups and gender, graft anastomosis (biatrial or bicaval; the bicaval anastomosis was the preferred technique after 1995).
- Follow up: clinical status, cardiac biopsies, occurrence of acute or chronic graft rejection, death date.

The occurrence of AF episodes was checked by reviewing electrocardiogram series (ECGs), Holter monitor recordings and all the available rhythm strips during the entire follow up. All the AF episodes occurred in the first hours after OHT, directly related to amine or isoprenaline infusion, were excluded. Post-operative AF episodes were defined as AF occurrences within the first 60 days after OHT[9], while AF episodes occurred after 60 days from OHT were classified as late AF.

Endomyocardial biopsies, executed in the apical septum of the right ventricle, were reviewed to evaluate cases of acute graft rejection. Specifically, the following standard protocol was applied: every week in the first month after OHT, every 2 weeks till the third month, every month till the first year or when clinically indicated. The histological rejection grading of 1990 was used, according to guidelines of the International Society for Heart and Lung Transplantation [10]; the histological grade of rejection was converted into a rejection score (RS), defined as the mean of the number of rejection events at one month and one year from OHT [11,12]. One-month RS was used as a marker of early acute rejection. To identify the presence of cardiac allograft vasculopathy (CAV), coronary angiographies were evaluated. CAV severity was classified according to the standardized nomenclature of ISHLT [13]. Bidimensional echocardiography was used to evaluate left ventricular ejection fraction (LVEF).

For all the patients, induction of immunosuppression was applied by a single dose of cyclosporin A (CsA, 5 mg/kg) and azathioprine (Aza, 3 mg/kg), administered 6 h before surgery, and a bolus of methylprednisolone (1 g i.v.) during cardiopulmonary bypass. Immunosuppression was induced at the day of surgery with increasing doses of CsA up to 2–12 mg/kg/day and of Aza up to 0.5–2 mg/kg/day.

After surgery, most of the patients had received anti-lymphocyte and/or anti-thymocite globulin for 3–5 days. The daily dose of CsA was adjusted according to the target levels and the renal function of the patients. Oral prednisone (0.1 mg/kg/day) was administered with CsA and Aza for the first 6 months, then tapered off. Acute rejection episodes, defined with grade > 2, were treated with one methylprednisolone daily bolus (1 g i.v) for 3 consecutive days. Anti-thymocite globulin was used to treat persistent 3A or 3B rejection despite standard acute rejection therapy.

11-years survival was considered for the analysis, as it corresponds to the median time of survival after OHT reported by the Registry of the International Society for Heart and Lung Transplantation [14]. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

3. Statistical analysis

Descriptive statistics such as proportions, means, and standard deviations were used to summarize the clinical data. For the variables with continuous values, normal distribution of the data was evaluated through histograms and q-q plots. Between-group comparisons were tested with two-sided Wilcoxon rank-sum test or Student's *t*-test for continuous variables and Chi-square test for categorical variables.

Multivariate logistic regression model was applied in order to test if there were clinical factors significantly associated to AF, considering: BMI of recipients, age and gender of recipients and donors, gender mismatch, group mismatch, ischemic time, anastomosis, EC time, one-month and one-year RS. Variables of the final model were selected with a step-down procedure: the decision to remove factors was based on a likelihood-ratio test. All the factors were first included in the full model considering main effects only, then they were sequentially removed if their removal did not result in a significant change of the likelihood.

To evaluate the probability of survival, Kaplan-Meier method and log-rank test were used, comparing the survival curves between sinus rhythm and AF groups of patients. Effects of baseline characteristics on 11-years mortality were evaluated through Cox proportional hazard model.

For all the statistical tests used, p-values < 0.05 were considered as statistically significant. All the statistical analyses were performed with the R package version 2.15.

4. Results

A total of 278 heart recipients were enrolled, 86.4% males, with mean age at OHT 51.2 (SD 12.8) years. All data are resumed in Table 1. The mean donor age was 33.6 (SD 14.3) years. 45.3% of the patients were treated with biatrial anastomosis, while 54.7% with bicaval anastomosis. The mean RS was 1.17 (SD 1.0) at one month and 1.03 (SD 0.6) at one year. 11-years survival rate was 61.5%.

65 (23.4%) patients experienced at least one episode of AF. Post-operative AF occurred in 69.2% (45/65) of the cases; late AF in 30.8% (20/65) of the cases. Only paroxysmal AF was observed. When an AF episode occurred, hemodynamic status and the presence of acute rejection were checked and corrected. 7 (10.8%) patients were treated with electrical cardioversion and 18 (27.7%) patients with pharmacological cardioversion with amiodarone; the other cases recovered to sinus rhythm either spontaneously or by adjusting the water and electrolyte balance. In 8 patients amiodarone prophylaxis was used during hospitalization, while only 2 patients were discharged with amiodarone therapy. Beta-blockers were not used in the first post-operative period.

The percentage of post-operative AF episodes was of 16.2%, showing a significant association with one-month RS (p-value = 0.019) and elderly donors (p-value = 0.029) from univariate analysis, as displayed in Table 1. This result was also confirmed by the multivariate logistic regression analysis (Table 2). Endomyocardial biopsy in 85% of the patients was performed close to the AF episode, showing signs of rejection in 68.9% of the cases (grade 1–2 in 8 patients, grade 3A-4 in 23 patients). Higher mortality was observed in patients who experienced post-operative AF episodes (57.8%, p = 0.004); also, one-year RS and old age in recipients and donors were found significantly associated with higher mortality (Table 3).

20 patients (7.2%) experienced late AF episodes (Table 1), occurring in most of them during hospitalization because of renal failure

Table 1
Study population characteristics and comparison between patients with and without post-operative and late atrial fibrillation episodes.

	Total population (n = 278)	POAF episodes (n = 45)	p-value POAF episodes	Late AF episodes (n = 20)	p-value late AF episodes
Recipient					
BMI (Kg/mq)	23.58 ± 3.7	23.62 ± 4.8	0.757	24.80 ± 5.0	0.604
Age (years)	51.16 ± 12.8	51.65 ± 12.9	0.773	48.85 ± 15.3	0.754
Male gender (n, %)	238 (85.6%)	7 (15.6%)	0.807	4 (20.0%)	0.458
Donor					
Age (years)	33.58 ± 14.3	38.02 ± 14.4	0.029	33.40 ± 15.3	0.944
Male gender (n, %)	180 (64.7%)	26 (57.8%)	0.285	17 (85.0%)	0.049
Gender mismatch *(n, %)*	98 (35.3%)	18 (40.0%)	0.466	5 (25.0%)	0.319
Group mismatch *(n, %)*	34 (12.2%)	4 (8.9%)	0.450	5 (25.0%)	0.072
Anastomosis *(n, %)*			0.600		0.171
- Biatrial	126 (45.3%)	22 (48.9%)		12 (60.0%)	
- Bicaval	152 (54.7%)	23 (51.1%)		8 (40.0%)	
Ischemia time (min)	151.48 ± 53.3	155.86 ± 50.6	0.306	133.30 ± 67.2	0.062
EC time (min)	115.32 ± 37.7	110.17 ± 34.9	0.308	112.00 ± 11.0	0.171
Rejection score					
– 1 month	1.17 ± 1.0	1.53 ± 1.2	0.019	1.37 ± 1.1	0.248
– 1 year	1.03 ± 0.6	1.12 ± 0.6	0.157	1.14 ± 0.6	0.570
11-years mortality *(n, %)*	107 (38.5%)	26 (57.8%)	0.004	11 (55.0%)	0.115

AF: atrial fibrillation, POAF: post-operative atrial fibrillation, BMI: body max index, EC: extracorporeal circulation, RS: rejection score.

Table 2
Multivariate analysis: predictors of post-operative AF.

	Odds ratio	95% CI	p-value
Age of donors	1.04	1.01–1.07	0.007
1-month RS	1.40	1.03–1.92	0.033

RS: rejection score.

Table 3
Comparison between patients died and alive at 11 years from OHT.

	Alive at 11 years from OHT (n = 171)	Death at 11 years from OHT (n = 107)	p-value
Recipient			
BMI (Kg/mq)	23.43 ± 3.5	23.82 ± 4.1	0.802
Age (years)	49.6 ± 12.9	53.6 ± 12.3	0.006
Male Gender (n, %)	144 (84.2%)	94 (87.9%)	0.400
Donor			
Age (years)	32.12 ± 13.9	35.92 ± 14.8	0.039
Male Gender (n, %)	114 (66.7%)	66 (61.7%)	0.397
Gender mismatch *(n, %)*	54 (31.6%)	44 (41.1%)	0.105
Group mismatch *(n, %)*	20 (11.8%)	14 (13.1%)	0.745
Anastomosis *(n, %)*			0.536
- Biatrial	80 (46.8%)	46 (43.0%)	
- Bicaval	91 (53.2%)	61 (57.0%)	
Ischemia time (min)	154.67 ± 54.3	146.44 ± 51.6	0.211
EC time (min)	113.14 ± 36.4	118.78 ± 39.7	0.191
Rejection score			
– 1 month	1.07 ± 0.99	1.34 ± 1.15	0.079
– 1 year	0.98 ± 0.52	1.12 ± 0.66	0.046
AF episodes *(n, %)*	28 (16.4%)	37 (34.6%)	<0.001
POAF episodes *(n, %)*	19 (11.1%)	26 (24.3%)	0.004
Late AF episodes *(n, %)*	9 (5.3%)	11 (10.3%)	0.115

AF: atrial fibrillation, POAF: post-operative atrial fibrillation, BMI: body max index, EC: extracorporeal circulation, RS: rejection score.

or systemic infection. Patients with late AF were 87.9% male. The majority (60%) of these episodes occurred in patients treated with biatrial anastomosis, but without statistical significance. These patients did not show high grade of rejection (between 0 and 1B) in the biopsy obtained close to the AF episode; no significant correlation was found from univariate analysis and no correlation was found either with CAV or with graft failure. Late AF resulted not associated with higher 11-years mortality.

Kaplan Meyer analysis confirmed the difference in terms of survival between patients who experienced AF episodes and patients who maintained sinus rhythm (p Log-Rank < 0.0001, Fig. 1). The best model resulting from the multivariate Cox regression (Table 4) showed that the combination of the rate of AF episodes (Hazard ratio 2.00), the one-year RS (Hazard ratio 1.50) and old age of the recipient (Hazard ratio 1.04) has a statistically significant impact in the survival of the patient.

5. Discussion

The reported rate of AF in the transplanted heart ranges between 0.3%[15] and 24%[16] and this variation might be due to the methods used for arrhythmia detection. In a recent review, the overall estimated rate was 10% [8]. In this study, the total rate was 23.4%, similar to the results reported by Pavri et al. [16] with a comparable cohort. Most of arrhythmia episodes can be classified as post-operative AF. The rate of AF was shown to be lower after OHT rather than after other open-heart surgeries [17,18] and other organ transplantations[19]. This can be explained by the peculiar pathophysiology of the transplanted heart, since the presence of surgical electrical isolation from the thoracic veins and the total vagal denervation [15,16,20]. It is widely recognized that ectopic beats from PVs can initiate and promote AF and that vagal tone, shortening the atrial refractory period unequally over the atria, contributes to the induction and the maintenance of the arrhythmia [4,5]. Moreover, OHT could also potentially reduce the likelihood of AF episodes through a reduction of the "critical mass" required from the atrial myocardium for the maintenance of the arrhythmia [21]. In the absence of the most common triggers, other mechanisms play an important role promoting AF, like the graft status: young hearts are less prone to develop AF and the old age of donors was shown to be an important predictor of AF [20]. Previous studies looking at the rate of atrial arrhythmias after biatrial or bicaval anastomosis showed controversial results[22,23]; here, we observed a comparable rate of post-operative AF between the two techniques, with a higher rate of late AF in biatrial anastomosis (60% of total cases with biatrial anastomosis vs 40% with bicaval anastomosis), although not statistically significant. The bicaval anastomosis grants a better preservation of right atrial morphology and function together with the long-term maintenance of the physiological atrial pacing pathway [24]; and it was also shown that this approach leads to a more physiological left-ventricular filling[23].

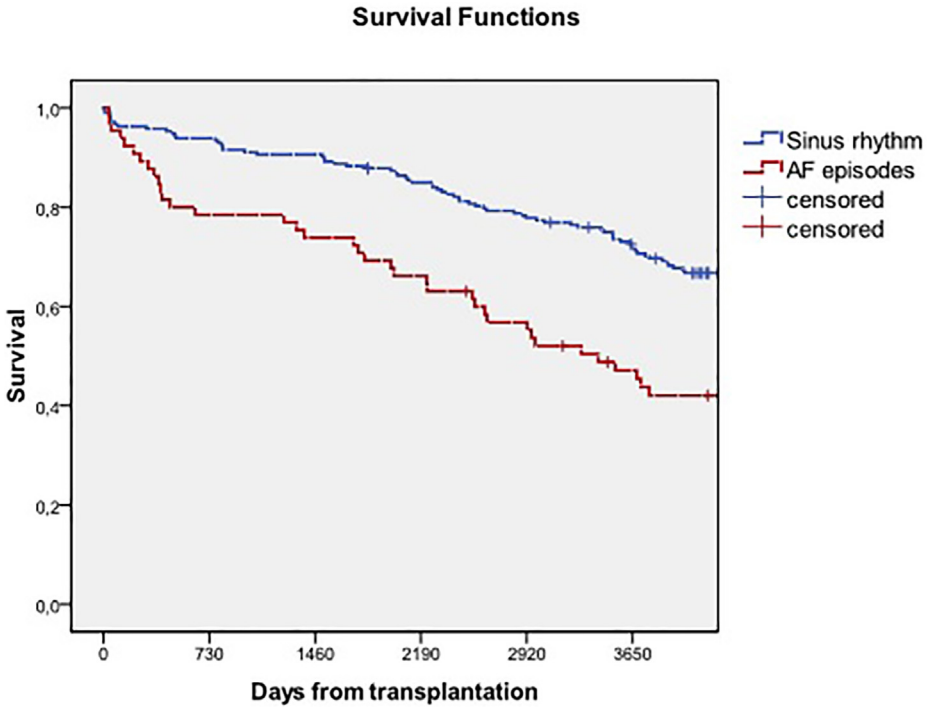

Fig. 1. Kaplan Meyer analysis between patients showing AF episodes and patients who maintained sinus rhythm.

Table 4
Cox analysis: predictors of 11-years mortality.

	Hazard ratio	95% CI	p-value
AF episodes	2.00	1.26 – 3.16	0.003
Age of recipient	1.04	1.01 – 1.07	0.005
1-year RS	1.50	1.02 – 2.18	0.039

AF: atrial fibrillation, RS: rejection score.

We observed a correlation between post-operative AF and acute rejection, in agreement with some previous studies[22,25]. In particular, most of the biopsies showed inflammation and myocites damage (rejection grading above 2), and in a third of the cases only inflammation. The inflammatory atrial substrate associated with the rejection can directly cause electrophysiological alteration, promoting and sustaining wavelet re-entry triggers[26]. Moreover, the association between AF and other inflammatory states as myocarditis had been described under different scenarios[27–29]. The grade of atria involvement during rejection is not well-known, since the atrial myocardium is not regularly sampled in either postmortem examination or in common surgical pathology practice [28].

In our cohort, 9 over 45 cases (20%) of post-operative AF episodes were not triggered by rejection and these events were recorded within 15 days after OHT. A proposed mechanism for these arrhythmic episodes is the increased sensitivity of the myocardial adrenergic receptors to circulating cathecolamines, which facilitate the autonomic imbalance [30] in association with others well-established arrhythmogenic mechanisms, such as the cardiac manipulation and the pericardial inflammation [17]. For cases with late AF, no clear associations with either chronic rejection or graft dysfunction were found in this study, but these episodes occurred frequently during hospitalization because of renal failure or systemic infection. The higher rate of late AF in male patients suggests that also classical AF predisposing factors can be involved; in addition, the control of artery blood pressure was found essential to reduce AF recurrences in these patients. Vaseghi et al. [21] suggested a potential involvement of parasympathetic re-innervation, but without reporting an objective demonstration, while a recent case report described PVs reconnection several years after OHT as a cause of atrial tachyarrhythmia [31]. As previously described[8,16,21,22], we observed a significantly higher mortality in patients with AF episodes, confirmed by Kaplan Meyer and Cox regression analysis. It is known that an old age recipient with rejection episodes has higher mortality, but if the patient experienced AF episodes, its outcome gets worse. Higher mortality can only be in part explained by myocardial disease, which does not justify non-cardiac deaths. As the alteration of the humoral state can promote AF, arrhythmia should be considered as a sign of patient's frailty and the worse outcome might represent a sign of the progression of a poor systemic condition.

6. Study limitation

This is a retrospective observational study where no patient selection was performed, and data were collected reviewing hospital and ambulatory databases. Some data, especially during long-term follow-up can be missed. In addition, lifestyle and patient's behavior can be confounding factors and the low number of cases of late AF can affect statistical accuracy. Some AF episodes could have been not recognized or recorded during follow-up while patients were kept on telemetry during hospitalization. As an example, long-term therapies, co-morbidities and causes of death were not disposable.

7. Conclusion

Our findings suggest that pulmonary vein isolation and vagal denervation lead to a low post-operative and late AF rate in OHT recipients. Acute rejection and graft status are the main AF triggers in the early period after OHT (i.e., within the first 60 days), while in the long term other systemic conditions act as arrhythmic triggers.

The incidence of AF episodes is associated with poor outcome and it should be considered as a marker of clinical frailty.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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