Author's Accepted Manuscript

http://www.jhltonline.org

Catheter Ablation of Organized Atrial Arrhythmias in Orthotopic Heart TransplantationAtrial tachycardia ablation after heart transplantation

Yamina Mouhoub, Mikael Laredo, Shaida Varnous, Pascal Leprince, Xavier Waintraub, Estelle Gandjbakhch, Jean-Louis Hébert, Robert Frank, Carole Maupain, Alain Pavie, Françoise Hidden-Lucet, Guillaume Duthoit

PII: S1053-2498(17)31924-1
DOI: http://dx.doi.org/10.1016/j.healun.2017.07.022
Reference: HEALUN6574

To appear in: *Journal of Heart and Lung Transplantation*

Cite this article as: Yamina Mouhoub, Mikael Laredo, Shaida Varnous, Pascal Leprince, Xavier Waintraub, Estelle Gandjbakhch, Jean-Louis Hébert, Robert Frank, Carole Maupain, Alain Pavie, Françoise Hidden-Lucet and Guillaume Duthoit, Catheter Ablation of Organized Atrial Arrhythmias in Orthotopic Heart TransplantationAtrial tachycardia ablation after heart transplantation, *Journal of Heart and Lung Transplantation,* http://dx.doi.org/10.1016/j.healun.2017.07.022

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting galley proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

ACCEPTED MANUSCRIPT

CATHETER ABLATION OF ORGANIZED ATRIAL ARRHYTHMIAS IN ORTHOTOPIC HEART TRANSPLANTATION

Authors:

Yamina Mouhoub, MD[1]*; Mikael Laredo, MD[1]*; Shaida Varnous, MD[2]; Pascal Leprince, MD,PhD[2]; Xavier Waintraub, MD[1]; Estelle Gandjbakhch, MD,PhD[1]; Jean-Louis Hébert, MD,PhD[1]; Robert Frank, MD[1]; Carole Maupain, MD[1]; Alain Pavie, MD[2]; Françoise Hidden-Lucet, MD[1]; Guillaume Duthoit, MD[1].

*: These authors contributed equally to this paper (to be cited in the above order).

Affiliations

[1]: Unité de Rythmologie, Institut de Cardiologie, Hôpital Pitié-Salpêtrière, 47-83 Boulevard de l'Hôpital, 75013 Paris, France.

[2]: Service de Chirurgie Thoracique et Cardiovasculaire, Institut de Cardiologie, Hôpital Pitié-Salpêtrière, 47-83 Boulevard de l'Hôpital, 75013 Paris, France.

Corresponding author

Yamina Mouhoub, MD. Institut de Cardiologie, Groupe Hospitalier Pitié-Salpêtrière, 47-83 boulevard de l'Hôpital, 75013 Paris. Email : mouhoubyamina@yahoo.fr; Phone: +33 1 42 16 30 54; Fax: +33 1 42 16 30 56

Short title

Atrial tachycardia ablation after heart transplantation.

Accepted manuscript

ACCEPTED MANUSCRIPT

Key words

Atrial flutter

Atrial tachycardia

Electroanatomical mapping

Orthotopic heart transplantation

Radiofrequency catheter ablation

Abbreviations

AFL: atrial flutter

AF: atrial fibrillation

CAD: coronary artery disease

CTI: cavotricuspid isthmus

EAM: electro-anatomical mapping

FAT: focal atrial tachycardia

LA: left atrium

OAA: organized atrial arrhythmia

OHT: orthotopic heart transplantation

RA: right atrium

RFCA: radiofrequency catheter ablation

Accepted manuscript

ACCEPTED MANUSCRIPT

Structured abstract

Background: Organized atrial arrhythmias (OAAs) are common after orthotopic heart transplantation (OHT). Some controversies remain about the clinical presentation, its relations to atrial anastomosis and their electrophysiological features. The objectives of this retrospective study were to determine the mechanisms of OAAs after OHT and describe the outcomes of radiofrequency catheter ablation (RFCA).

Methods: Thirty consecutive transplanted patients (mean age 48±17 years, 86.6% male) underwent 3D electroanatomical mapping and RFCA of OAA from 2004 to 2012 in our center.

Results: Twenty-two patients had biatrial and 8 bicaval anastomosis. Mean time from OHT to OAA was shorter for patients with bicaval than biatrial anastomosis (3.1±6 vs. 15.3±10 years respectively, p<0.0001). Macro-reentry was the arrhythmia mechanism for 96% of patients. The electrophysiogical diagnosis was: cavotricuspid isthmus (CTI)-dependent atrial flutter (AFL) for 93% of patients (n=28), perimitral AFL for 3% (n=1), and focal atrial tachycardia (FAT) for 3% (n=1). In 5 patients with biatrial anastomosis, a right FAT was inducible. Primary RFCA success was obtained in 93% of patients. Mean follow-up time was 39±26.8 months. Electrical repermeation between recipient and donor atria, present in 20% of patients (n=6), did not account for any OAA. Survival without OAA relapse at 12, 24 and 60 months was 93%, 89% and 79%, respectively.

Conclusions: CTI-dependent AFL accounted for most of the OAA cases after OHT, regardless of anastomosis type. Time from transplantation to OAA was shorter with bicaval than biatrial anastomosis. RFCA was safe and provided good long-term results.

Accepted manuscript

ACCEPTED MANUSCRIPT

Introduction

Supraventricular tachycardias are frequent after orthotopic heart transplantation (OHT). They are mainly represented by atrial flutter (AFL) and atrial fibrillation (AF), with incidence among OHT estimated at 7% and 9%, respectively[1]. While AF is mostly encountered with graft rejection, coronary artery disease (CAD) and in the post-operative period, AFL occur mostly in stable patients with normal graft function[1]. Although cavotricuspid isthmus (CTI)-dependent AFL has been reported as the most frequent OAA in OHT recipients, regardless of the type of atrial anastomosis[1–3], a recent study conducted in the era of electro-anatomical mapping (EAM) reported a majority of non-CTI-dependent AFL depending on a surgical substrate or recipient-to-donor electrical repermeation[4]. In this study, the electrocardiogram (ECG) aspect of the OAA failed to identify CTI-dependent AFLs. Moreover, the relation between the type of arrhythmia and type of atrial anastomosis is controversial[4,5].

Thus, despite a number of reports showing high success of radiofrequency catheter ablation (RFCA), several critical issues remain and may account for the reluctance of physicians to refer transplanted patients for RFCA.

The objective was to analyze the electrophysiogical mechanisms of these arrhythmias, their relation to the type of atrial anastomosis and to report the long-term outcomes of EAM-guided RFCA in the largest observational study of transplanted patients with OAA.

Accepted manuscript

Methods

Patients

Among the 774 patients who underwent OHT at our institution, we retrospectively selected 30 consecutive adults with persistent OAA referred to our arrhythmia unit between July 2004

ACCEPTED MANUSCRIPT

and April 2012 for electrophysiological study (EPS) and 3D EAM system guided RFCA. All patients had symptomatic OAA despite anti-arrhythmic drug therapy with at least one drug (amiodarone, sotalol or flecainide). Three patients (10%) had undergone electrical cardioversion. Endomyocardial biopsy (EMB) was performed both for acute rejection suspicion and after OAA onset

Electrophysiological study and RFCA

Antiarrhythmic drugs were discontinued for at least 5 half-lives before the procedure. Typical atrial flutter was defined by a P-wave morphology suggesting counterclockwise right atrial flutter as previously described[6,7], including (1) a dominant negative polarity following a down-sloping "plateau" segment, (2) a positive flutter deflection in lead V_1 with transition to a negative deflection in lateral leads, and (3) an atrial rate of 250 to 350 bpm. Electrophysiological study followed by RFCA was performed with the patient under light sedation with midazolam and fentanyl. All procedures were performed in clinical OAA. 3D mapping of the OAA involded use of the EAM systems EnSite (NavX or Velocity, St. Jude Medical, St. Paul, MN) or CARTO (Biosense Webster, Diamond Bar, CA). Electrograms were filtered with a 30-Hz high-pass and a 500-Hz low-pass filter. A quadripolar (when the 12-lead ECG was suggestive of CTI-dependent AFL) or decapolar steerable catheter was placed in the coronary sinus. To stabilize the EnSite 3D maps, we screwed a bipolar catheter on the donor's right atrium (right atrial appendage or free wall), which served as the spatial and temporal reference catheter. For the CARTO system, no intracardiac reference catheter was needed and the coronary sinus catheter was selected as the temporal reference. For spontaneous OAA occurring in the EP laboratory, a 3D activation map was performed with the quadripolar ablation catheter. If the rhythm was sinus, the atrial arrhythmia was induced by standard programmed atrial stimulation, atrial bursts and/or isoproterenol infusion maintained during the procedure (0.2 to 0.9 mg/h). Diagnosis of macro-reentrant tachycardia was established by standard criteria: induction by pacing, pace-termination, entrainment, and

Accepted manuscript

ACCEPTED MANUSCRIPT

non-inducibility after ablation at the slow-conduction isthmus[8].

Radiofrequency ablation involved a power output of 50 to 100W with maximum temperature 60-65°C for non-irrigated catheters. For redo procedures, atypical or left AFL, following failure of non-irrigated RFCA or when using the CARTO system, an open-irrigated 4-mm catheter with power setting 25 to 40W and maximum temperature of 43°C was used. Primary RFCA success was defined by OAA termination during RF pulses and non-inducibility despite infusion of isoproterenol and burst atrial pacing, maintained for 30 min after ablation. For macroreentrant tachycardia, bidirectional block across the line of ablation performed within the critical isthmus was also required to confirm procedural success.

Recipient-to-donor electrical repermeation was suspected when the recipient atria was activated at the same cycle length as the clinical tachycardia with a consistent local activation time regarding to the adjacent atrial myocardium and confirmed after OAA termination by capture of the donor atrium when pacing at the recipient atrium.

Atrioventricular node physiology and retrograde conduction was not systematically assessed after mapping and ablation of the clinical OAA.

Accepted manuscript

Follow-up

Patients underwent 24h Holter-ECG monitoring between 1 and 2 months after RFCA and consulted an electrophysiologist 3 months after RFCA. All patients were followed by the heart transplantation team with physical examination, ECG and echocardiogram every 6 months. Holter-ECG recordings were performed at 1 year and repeated depending on symptoms during follow-up. For stable patients, endomyocardial biopsy was performed monthly in the first year after OHT then annually for 9 years. It was always performed with newly-diagnosed heart failure, abnormal echocardiography or suspected acute rejection. Coronary artery angiography was performed every 2 years or annually with known graft CAD. After 10 years of stable follow-up, no systematic endomyocardial biopsy was

performed.

ACCEPTED MANUSCRIPT

Statistical analysis

Quantitative data are expressed as mean±SD. Student's unpaired t-test and ANOVA were used to compare quantitative variables with normal distribution and the Mann-Whitney test for non-normal distribution variables. The exact Fisher's test or the chi-square test were for qualitative variables. Correlation between two continuous variables with non-normal distribution was calculated with the Spearman coefficient. Two-sided $P<0.05$ was considered statistically significant. Survival curves were built with the Kaplan-Meier method, with comparision by Log-Rank test. Univariate analyses involved a binary logistic regression test. All statistical analysis were performed with IBM SPSS Statistics v23 (IBM Corp., Armonk, N.Y., USA). This study was approved by our institutional review board.

Results

Patients

Baseline characteristics of patients are in Table 1 and descriptions of each patient are in Supplemental table 1. OHT was performed between October 1986 and April 2010 for end-stage heart disease. The last surgical procedure using biatrial anastomosis was performed in 2001. Mean time from OHT to arrhythmia onset was 133±78 months with two peaks of incidence, at a mean of 40 and 200 months following OHT. Seven patients (23.3%) had a history of AF: 1 during a documented acute rejection, 2 during the post-operative period (within 1 year post-OHT) and 4 who had significant graft CAD. At initial presentation, ECG suggested counterclockwise right AFL in 83.3% of patients. Two patients showed a 2:1

Accepted manuscript

ACCEPTED MANUSCRIPT

ventricular conduction which impaired interpretation of the P-wave morphology. All patients received triple-drug immunosuppressant therapy, including corticosteroids, calcineurin inhibitors and a maintenance agent (Supplemental Table 3). Overall, 2 patients were diagnosed with severe graft rejection during presentation for OAA. They both had a long history of moderate tissular rejection and showed severe tissular rejection at the time of OAA for 1 patient and 1 year earlier for the other. Side-by-side comparison of clinical characteristics and EPS results between biatrial and bicaval anastomosis is available in Supplemental Table 3.

Electrophysiological findings and RFCA

Sites of clinical and induced arrhythmias at initial and redo procedures in bicaval and biatrial anastomosis are shown in Figure 1. At the time of the initial procedure, macro-reentry was the arrhythmia mechanism for all patients except in 1, who had right focal atrial tachycardia (FAT) (Table 2). Macro-reentry depended on the CTI for most patients (93.3%). Description of electrophysiological study and RFCA for each patient is in supplemental table 2. Six patients (20%) had documented electrical repermeation between recipient and donor atria, but none was responsible for the initial clinical tachycardia.

One patient (patient 5, bicaval anastomosis) had left perimitral AFL as the initial OAA. This patient underwent transseptal puncture and left atrium (LA) mapping during tachycardia. The pulmonary veins were already disconnected from the LA and were identified as electrical scars by EAM. This perimitral AFL depended on a slow-conduction zone at the anterior LA wall and was subsequently ablated at a anteroseptal mitral isthmus. In another patient presenting perimitral AFL after successful CTI-AFL ablation (patient 27), pulmonary veins were disconnected from the donor atria but were connected to the native LA and adjacent native right atrium (RA) (biatrial anastomosis, Figure 2). This perimitral flutter was ablated at the usual left inferior mitral isthmus.

The initial FAT in patient 10 was related to local reentry, without repermeation, at the anterior

Accepted manuscript

ACCEPTED MANUSCRIPT

RA suture line of the biatrial anastomosis, without repermeation. The recipient RA was in sinus rhythm, dissociated from the donor's RA in tachycardia. In 5 patients (4 at the first RFCA procedure and 1 at a redo CTI-AFL ablation), electrophysiological study at the end of the procedure induced a FAT in the donor heart. These FAT were related to local reentry and arose from the anterolateral RA anastomosis (suture line, 4 patients) or from the anteroseptal RA (parahisian, patient 10).

Retrospectively, when 12-lead ECG suggested typical atrial flutter, this diagnosis was always confirmed by 3D mapping. Only three patients with CTI-dependent AFL did not have typical 12-lead ECG: 2 with rapid ventricular conduction (impairing p-wave interpretation) and 1 with ECG suggesting of a left AFL. The 2 perimitral AFL cases and the FAT case were correctly identified by the 12-lead ECG preceding electrophysiological study.

Primary success was obtained in 28 patients (93.3%). The two failures were CTI ablation failures due to complicated CTI anatomy in biatrial hearts. One underwent a successful redo CTI ablation with the use of a steerable sheath. The other received medical treatment alone because of left atrial appendage thrombus. We observed no major adverse events. One minor groin hematoma and 1 rapidly recovering acute respiratory distress due to volume overload were observed.

Accepted manuscript

Follow-up

Mean follow-up after the first RFCA procedure was 48±4.3 and 46±2.4 months for the biatrial and bicaval groups, respectively (supplemental Table 3). Four patients died during follow-up (Table 2): 2 from ischemic cardiomyopathy resulting from severe graft CAD, 1 from the complications of end-stage chronic kidney disease and 1 from lung adenocarcinoma. Five patients had OAA relapse (Table 2), which was successfully ablated by redo RFCA, except in one patient who required 3 procedures. Two were related to initial failure of CTI ablation, 2 to perimitral AFL (initial OAA: perimitral AFL and CTI-dependent AFL) and 1 to right FAT

ACCEPTED MANUSCRIPT

recurrence (see supplemental Table 2). Kaplan-Meier-estimated survival without OAA relapse at 12, 24 and 60 months' follow-up was 93%, 89% and 79%, respectively. AF occurred in 20% (n=6) of patients during follow-up and was not associated with any variable including left ventricular ejection fraction and donor age.

Discussion

To date, this study is the largest series of patients with OAAs undergoing electrophysiological study and RFCA after heart transplantation. Our main result is that CTI-dependent AFL is the most frequent atrial arrhythmia after OHT, regardless of the type of atrial anastomosis. This finding is consistent with most retrospective series of OHT patients referred for EPS for atrial arrhythmia[1,2,9,10]. In contrast, Nof et al., in a series of 15 OHT patients referred for EPS of persistent atrial arrhythmia, CTI-dependent flutter was found in only 33% of the cases, whereas non-CTI macroreentrant arrhythmia was found in 22%, focal atrial tachycardia in 22%, local reentry at the site of recipient-to-donor atria conduction in 22% and atrioventricular nodal reentrant tachycardia in 6%[4]. In this study, some patients were in sinus rhythm at the time of EPS and underwent programmed atrial stimulation, which is likely to induce OAA in cicatricial atria that may not be related to the clinical OAA.

We found no case of typical AFL on 12-lead ECG that did not depend on CTI. Atypical AFLs or FATs accounted for only 6.6% of the inital OAAs. However, non-CTI-dependent OAAs could be associated with CTI-dependent AFL and present as a relapse or be induced at the end of the initial procedure. Overall, 17% of the patients had other types of OAA induced by the final electrophysiological study, which were mostly FAT arising from the graft, near the atrio-atrial anastomosis suture line. Previous studies[1,11,12] also described arrhythmias arising from this region. In our study, these cases were exclusive to hearts with biatrial anastomosis, with scarred and low-voltage areas of slow conduction that can be substrates for local reentry[8]. Although 4 out of 5 OAA relapses were related to left OAAs or right FATs in biatrial hearts, we could not statistically demonstrate that the bicaval anastomosis protected against

Accepted manuscript

ACCEPTED MANUSCRIPT

OAA relapses because 1 bicaval recipient presented initial perimitral AFL and underwent 3 procedures. By avoiding local reentry due to the absence of atrio-atrial anastomosis suture line, we assume that bicaval anastomosis might have a protective effect on OAA relapse. However, our population with bicaval anastomosis was too small to demonstrate this hypothesis.

One of our patients who underwent successful RFCA for CTI-dependent AFL was referred for perimitral AFL 1 year later. This single observation among our population should be considered. LA tachycardia in OHT has rarely been described[1,4,12,13]. Conceptually, the connection between the remnant pulmonary veins/posterior LA wall and the donor LA remains the same for both anastomosis types and provides pulmonary vein isolation and a potential perimitral circuit anterior to the suture line.

Our retrospective study was not designed to compare the incidence of OAAs between biatrial and bicaval OHT. Bicaval anastomosis is associated with less atrial scarring as compared with biatrial anastomosis and might reduce the risk of late OAA. Brandt et al. found a 12-fold higher risk of developing AFL with biatrial than bicaval anastomosis[5], despite an unknown follow-up time in each group that might be substantially different considering that bicaval anastomosis is an evolution in OHT technique. Nevertheless, we found that bicaval anastomosis does not prevent from CTI-dependent AFL and may be associated with other arrhythmias such as perimitral AFL that may be related to the surgical anastomosis between donor LA and recipient pulmonary veins.

Electrical repermeation between the graft and the native atrium has been reported in several studies of catheter ablation in OHT[4,8] and is thought to occur through anatomical reconduction or electromechanical coupling. In our series, electrical repermeation was present in 20% of the initial procedures but was not responsible for any clinical tachycardia. This is in contradiction with previous studies finding atrio-atrial conduction between the remnant atrium and the graft responsible for a high number of arrhythmias[8,14]. In our study, repermeation was a bystander phenomenon at the time of the clinical arrhythmia. Studies reporting arrhythmias related to repermeation include patients with paxoxysmal arrhythmias

Accepted manuscript

ACCEPTED MANUSCRIPT

refered for RFCA while in sinus rhythm and undergoing programmed atrial stimulation. In OHT, stimulation of the cicatricial atria is likely to induce atypical macroreentrant and focal atrial tachycardia, which may rely on donor-to-recipient repermeation and may not be linked to the clinical arrhythmia. A longer follow-up including a larger proportion of OAA reccurences should enlight this issue.

AF incidence after OHT is low despite surgical scars and atrial remodeling and strongly associated with specific conditions such as graft CAD, rejection of the graft, and the post-operative period[1,2,9]. AF is more common after lung transplantation even without graft rejection or cardiac dysfunction[15,16]. OHT, by its nature, provides surgical pulmonary veins isolation, a well-known AF source. Also, cardiac autonomic denervation and reduced critical excitable mass of atrial tissue may prevent AF. In our population, AF developped in 1 patient during acute rejection, in 4 who had CAD and in 2 during the post-operative period. Among patients who underwent transseptal puncture, we always observed pulmonary-vein electrical disconnection. An increased risk of early post-operative AF after OHT with presence of pre-operative AF has been reported[16]. The prevalence of AF among patients with end-stage heart disease undergoing OHT is high, whereas the OAA incidence years after OHT is less than 10%[1]. Also, OAAs occurring late after OHT depend on anatomical substrates unrelated to the pre-operative disease. Therefore, we think it is very unlikely that pre-operative AF could predict late OAA occurrence.

In our series, 12-lead ECG successfully identified OAA related to CTI-dependent AFL with standard criteria. All but one atypical ECG patterns was related to non-CTI-dependent OAA or FAT. Neverthless, we discourage use of classical fluoroscopy-based RFCA even for typical AFLs. Indeed, 3D EAM systems were helpful to perform accurate anatomical ablation, localize the scar and ensure procedural safety considering the particular anatomy of biatrial anastomosis (in which the heart is often rotated leftward, leading to CTI ablation in a more septal position in left anterior oblique view) and the LA anastomosis in both surgery types. Another finding that indicates mandatory use of EAM systems is the frequency of induced FAT of the anastomosis region in the RA, not only in relapse situations but also during the

Accepted manuscript

ACCEPTED MANUSCRIPT

initial procedures. CTI was shorter in biatrial than in bicaval anastomosis. However, tricuspid annulus was markedly more anterior and at a greater distance from the IVC ostium, so achieving bidirectional CTI block was more challenging than in bicaval anastomosis. Therefore we encourage the use of large-curve ablation catheters and steerable sheaths to increase the contact force. Also, irrigated radiofrequency should be preferred over conventional radiofrequency, particularly in biatrial anaostomosis and in case of atypical AFL. As in native hearts, mitral isthmus ablation can be challenging, as epicardial ablation in the coronary sinus is often required to obtain a bidirectional block. Mitral isthmus ablation after OHT was not more complex than in native hearts. However, physicians should be aware that perimitral circuits always have a posterior boundary corresponding to the anastomosis between the native and donor left atrium.

After RFCA, most patients remained free of atrial arrhythmia recurrence and anti-arrhythmic drug therapy at the last evaluation. This is of importance in these patients, who are at risk of pharmacological interactions with immunosuppressive drugs, altered drug metabolism, frequent anti-arrhythmic drug toxicity and sick sinus syndrome[17–19]. For this reason, RFCA could be proposed as the first therapeutic option for OAA in OHT.

Study limitations

Our objective was not to determine the incidence of atrial arrhythmias or risk factors for OAA in OHT. We compared the timing of OAA occurrence depending on the type of atrial anastomosis, but because of the study's retrospective nature and the low number of bicaval anastomosis recipients, we cannot provide an estimation of its relative incidence in both groups. Also, comparisons between biatrial and bicaval anastomosis are cautioned by the different eras during which both anastomosis were performed. Second, we lacked precise echocardiographic assessment of graft function. Third, despite a long and close follow-up, some paroxysmal atrial arrhythmias may have been missed in this population, which is known to be less symptomatic than non-transplanted patients because of heart denervation[1].

Accepted manuscript

ACCEPTED MANUSCRIPT

Conclusions

CTI-dependent AFL was the most common OAA after OHT, regardless of the type of anastomosis, and was correctly identified by 12-lead ECG. OAA occurred earlier after OHT with bicaval than biatrial anastomosis. OAA relapses were mostly related to left-sided OAAs and occurred in the 2 types of atrial anastomosis. FATs were only found in biatrial anastomoss. RFCA guided by EAM systems was safe and was associated with a high rate of long-term freedom from OAA relapse. Electrical repermeation between the recipient and donor atria increased the risk of OAA relapse.

Source of funding

None

Disclosures

None

References

1. Vaseghi M, Boyle NG, Kedia R, et al. Supraventricular Tachycardia After Orthotopic Cardiac Transplantation. *J Am Coll Cardiol*. 2008;51(23):2241-2249. doi:10.1016/j.jacc.2008.02.065.

2. Ahmari SAL, Bunch TJ, Chandra A, et al. Prevalence, Pathophysiology, and Clinical Significance of Post-heart Transplant Atrial Fibrillation and Atrial Flutter. *J Heart Lung Transplant*. 2006;25(1):53-60. doi:10.1016/j.healun.2005.07.017.

3. Marine JE, Schuger CD, Bogun F, et al. Mechanism of Atrial Flutter Occurring Late After Orthotopic Heart Transplantation with Atrio-atrial Anastomosis. *Pacing Clin Electrophysiol*. 2005;28(5):412-420. doi:10.1111/j.1540-8159.2005.40019.x.

4. Nof E, Stevenson WG, Epstein LM, Tedrow UB, Koplan BA. Catheter Ablation of

Accepted manuscript

ACCEPTED MANUSCRIPT

Atrial Arrhythmias After Cardiac Transplantation: Findings at EP Study Utility of 3-D Mapping and Outcomes. *J Cardiovasc Electrophysiol*. 2013;24(5):498-502. doi:10.1111/jce.12078.

5. Brandt MD M, Harringer MD W, Hirt MD SW, et al. Influence of Bicaval Anastomoses on Late Occurrence of Atrial Arrhythmia After Heart Transplantation. *Ann Thorac Surg*. 1997;64(1):70-72. doi:10.1016/S0003-4975(97)82822-6.

6. Saoudi N, Cosio F, Waldo A, et al. Classification of Atrial Flutter and Regular Atrial Tachycardia According to Electrophysiologic Mechanism and Anatomic Bases: A Statement from a Joint Expert Group from the Working Group of Arrhythmias of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *J Cardiovasc Electrophysiol*. 2001;12(7):852-866. doi:10.1046/j.1540-8167.2001.00852.x.

7. Blomstrom-Lundqvist C. ACC/AHA/ESC Guidelines for the Management of Patients With Supraventricular Arrhythmias*--Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Supraventricular Arrhythmias). *Circulation*. 2003;108(15):1871-1909. doi:10.1161/01.CIR.0000091380.04100.84.

8. Saoudi N, Redonnet M, Anselme F, Poty H, Cribier A. Catheter ablation of atrioatrial conduction as a cure for atrial arrhythmia after orthotopic heart transplantation1. *J Am Coll Cardiol*. 1998;32(4):1048-1055. doi:10.1016/S0735-1097(98)00360-X.

9. Li Y, Grönefeld G, Israel C, Lu S, Wang Q, Hohnloser SH. Radiofrequency catheter ablation in patients with symptomatic atrial flutter/tachycardia after orthotopic heart transplantation. *Chin Med J (Engl)*. 2006;119(24):2036-2041.

10. Rodríguez-Entem F, Expósito V, González-Enríquez S, García-Camarero T, Olalla J. Atrial Flutter after Heart Transplantation: Mechanism and Catheter Ablation. *Transplant Proc*. 2010;42(7):2697-2701. doi:10.1016/j.transproceed.2010.04.067.

11. Grant SC, Khan MA, Faragher EB, Yonan N, Brooks NH. Atrial arrhythmias and pacing after orthotopic heart transplantation: bicaval versus standard atrial anastomosis. *Br Heart J*. 1995;74(2):149-153. doi:10.1136/hrt.74.2.149.

12. D'Alto M, Lord S, Bourke J, et al. Orthotopic heart transplantation: two parts of the

Accepted manuscript

ACCEPTED MANUSCRIPT

heart with two different arrhythmias. *J Cardiovasc Med*. 2011;12(3):193-196. doi:10.2459/JCM.0b013e328336ecaf.

13. Makanjee B, Klein GJ, Derval N, Skanes AC. An Anterior Ablation Line Is Preferred for Perimitral Flutter After Heart Transplant. *J Cardiovasc Electrophysiol*. 2010;21(5):574-576. doi:10.1111/j.1540-8167.2009.01657.x.

14. Khan M, Kalahasti V, Rajagopal V, et al. Incidence of Atrial Fibrillation in Heart Transplant Patients: Long-Term Follow-Up. *J Cardiovasc Electrophysiol*. 2006;17(8):827-831. doi:10.1111/j.1540-8167.2006.00497.x.

15. Dizon J, Chen K, Bacchetta M, et al. A Comparison of Atrial Arrhythmias After Heart or Double-Lung Transplantation at a Single Center: Insights Into the Mechanism of Post-Operative Atrial Fibrillation. *J Am Coll Cardiol*. 2009;54(22):2043-2048. doi:10.1016/j.jacc.2009.08.029.

16. Noheria A, Patel SM, Mirzoyev S, et al. Decreased Postoperative Atrial Fibrillation Following Cardiac Transplantation: The Significance of Autonomic Denervation. *Pacing Clin Electrophysiol*. 2013;36(6):741-747. doi:10.1111/pace.12102.

17. Nicolau DP, Uber WE, Crumbley AJ, Strange C. Amiodarone-cyclosporine interaction in a heart transplant patient. *J Heart Lung Transplant Off Publ Int Soc Heart Transplant*. 1992;11(3 Pt 1):564-568.

18. Preuner JG, Lehle K, Keyser A, Merk J, Rupprecht L, Goebels R. Development of severe adverse effects after discontinuing amiodarone therapy in human heart transplant recipients. *Transplant Proc*. 1998;30(8):3943-3944. doi:10.1016/S0041-1345(98)01296-2.

19. Luebbert JJ, Lee FA, Rosenfeld LE. Pacemaker Therapy for Early and Late Sinus Node Dysfunction in Orthotopic Heart Transplant Recipients: A Single-Center Experience. *Pacing Clin Electrophysiol*. 2008;31(9):1108-1112. doi:10.1111/j.1540-8159.2008.01149.x.

Accepted manuscript

Figure 1. Sites of clinical and induced arrhythmias at initial and redo procedures. **A.** Biatrial anastomosis. Initial procedures (white rectangles): 21 CTI-dependent AFL (CTI), 1 clinical FAT (12-pointed star), 5 induced FAT (4-pointed star, 4 from the right anterosuperior anastomosis, 1 parahisian in the vicinity of His bundle), which were not ablated. Electrical repermeation between the graft and the native atrium was present in 6 patients but in no case related to the clinical tachycardia (bidirectional dashed arrow). Redo procedures (red rectangles): 3 CTI-dependent AFL (CTI), 1 clinical perimitral flutter (ILMI). Usual ablation lines were performed for CTI block (black line), between IVC and medial TA. Redo ablation lines are indicated by red lines: mitral isthmus block was performed between left inferior pulmonary vein and mitral annulus (ILMI). **B.** Bicaval anastomosis. 7 CTI-dependent AFLs (black line), 1 clinical perimitral AFL that was ablated twice at an anteroseptal site of slow conduction (ASMI; white and red lines).: 1 inducible perimitral AFL dependent on the ILMI in the same patient (4-pointed star), 1 clinical FAT (red 12-pointed star, local reentry originating from the CS ostium during a third procedure in the same patient). In both anastomoses, a pronounced 45° left oblique anterior view was used.

Abbreviations. AFL: atrial flutter; ASMI: asnteroseptal mitral isthmus; CS: coronary sinus; FAT: focal atrial tachycardia; IVC: inferior vena cava; ILMI: inferolateral mitral isthmus. LA: left atrium; MA: mitral isthmus; RA: right atrium; SVC: superior vena cava; TA: tricuspid annulus

Accepted manuscript

Figure 2. Catheter mapping and ablation of a perimitral flutter in a biatrial transplant recipient. **A.** Anteroposterior (left) and posteroanterior (right) views of the 3D activation map of a clockwise perimitral flutter depending on a posterolateral mitral isthmus (St. Jude Medical EnSite Velocity). Electrograms recorded within the mitral isthmus (white arrow) show fragmented delayed potentials suggesting slow diastolic conduction. The remnants of the recipient-heart left atrium and pulmonary veins (grey area) are an area of dense scar (bipolar

ACCEPTED MANUSCRIPT

voltage <0.05 mV). **B.** Radiofrequency applications on the endocardial and epicardial sides (brown spots and yellow dots, respectively) of the mitral isthmus terminated the arrhythmia (not shown). **C.** After ablation of the mitral isthmus and return to sinus rhythm, pacing from the LAA shows mitral isthmus block with CS activated from proximal (SC 3.4) to distal (SC 1.2) and a long, 176 ms, LAA to CS interval. RA electrograms of 2 dissociated activities: one with sharp electrograms concomitant with the paced P wave with 1:1 atrioventricular conduction (red arrows) corresponding to the donor heart's normal sinus rhythm, and a rapid regular activity with no atrio-atrial or atrioventricular conduction, corresponding to the recipient's remnant right atrial tachycardia (gray arrows). **D.** During the same procedure, activation mapping of this native atrial tachycardia demonstrated a focal source from the anterolateral native RA and conducting to the posterior native RA, interatrial septum, left atrium and pulmonary veins. Local electrograms show early fragmented potentials suggesting local reentry (white spot with yellow arrow).

Abbreviations. CS: coronary sinus; EPS: electrophysiological study; LAA: left atrial appendage; RA: right atrium.

Accepted manuscript

ACCEPTED MANUSCRIPT

Table 1: Characteristics of patients undergoing RFCA of OAA after OHT (n=30).

Age at OHT (years)	37±17
Male sex	26 (86.6)
Initial heart disease	
Dilated cardiomyopathy	14 (46.6)
Coronary heart disease	7 (23.3)
Hypertrophic cardiomyopathy	5 (16.6)
Toxic cardiomyopathy	2 (6.6)
Valvular heart disease	1 (3.3)
Congenital heart disease	4 (6)
Type of atrial anastomosis	
Biatrial	22 (73.3)
Bicaval	8 (26.6)
Donor age	39.9±15
Hypertension	14 (86.6)
Diabetes mellitus	11 (36.6)
NYHA class III-IV	4 (13.3)
Left-ventricular ejection fraction	49 (7)
Documented AF before OAA	4 (13.3)
Transplant CAD	6 (20)
Histological rejection*	2 (6.66)
ECG presentation	
Typical flutter	25 (83.3)
Atypical flutter	2 (7)
FAT	1 (3.33)
Undefined**	2 (7)

Data are number of patients (%) or mean ± SD.

Accepted manuscript

ACCEPTED MANUSCRIPT

*: at the time of OAA diagnosis. **: no p-wave due to 2:1 atrioventricular conduction.

Abbreviations. AF: atrial fibrillation; CAD: coronary artery disease; FAT: focal atrial tachycardia; NYHA: New York Heart Association; OAA: organized atrial arrhythmia; RFCA: radiofrequency catheter ablation.

Accepted manuscript

ACCEPTED MANUSCRIPT

Table 2: Electrophysiological findings and catheter ablation results.

Initial procedures	
Electrophysiological diagnosis	
CTI-dependent flutter	28 (93.3)
Perimitral flutter	1 (3.3)
Right-sided FAT	1 (3.3)
Recipient to donor electrical repermeation	6 (20)
RFCA	
Procedure duration (min)	180±69
Fluoroscopy time (min)	31±11
Primary success*	28 (93.3)
Induction of a second OAA at final EPS	5 (17)
Right-sided FAT	4
Perimitral flutter**	1
Follow-up	
Death	4 (13.3)
OAA relapse	6 (20)
CTI-dependent flutter	3
Perimitral flutter	2
Right-sided FAT	1
Need for redo catheter ablation	5 (16.6)
Anti-arrhythmic drug discontinuation	25 (83)
Atrial fibrillation	6 (20)

Data are number of patients (%) or mean ± SD.

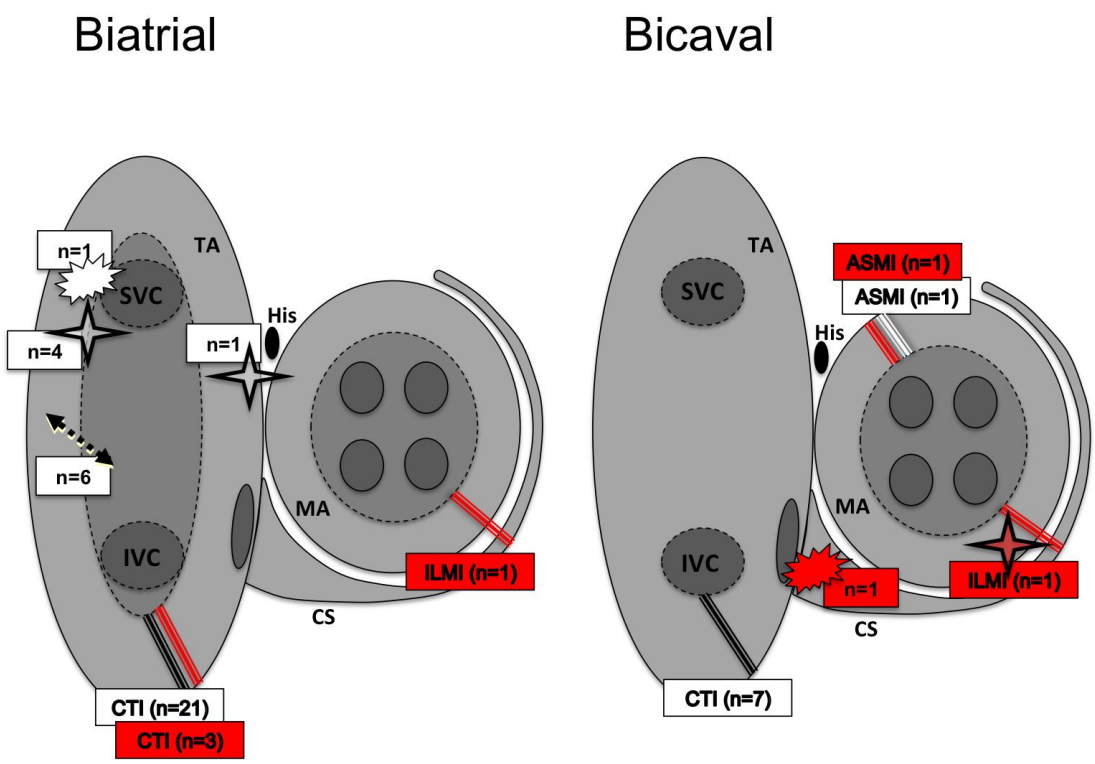
*: defined as arrhythmia termination by radiofrequency and non-inducibility at the end of the procedure. **: occurred during redo procedure.

Abbreviations. AF: atrial fibrillation; CTI: cavotricuspid isthmus; EPS: electrophysiological study. FAT: focal atrial tachycardia; LVEF: left ventricular

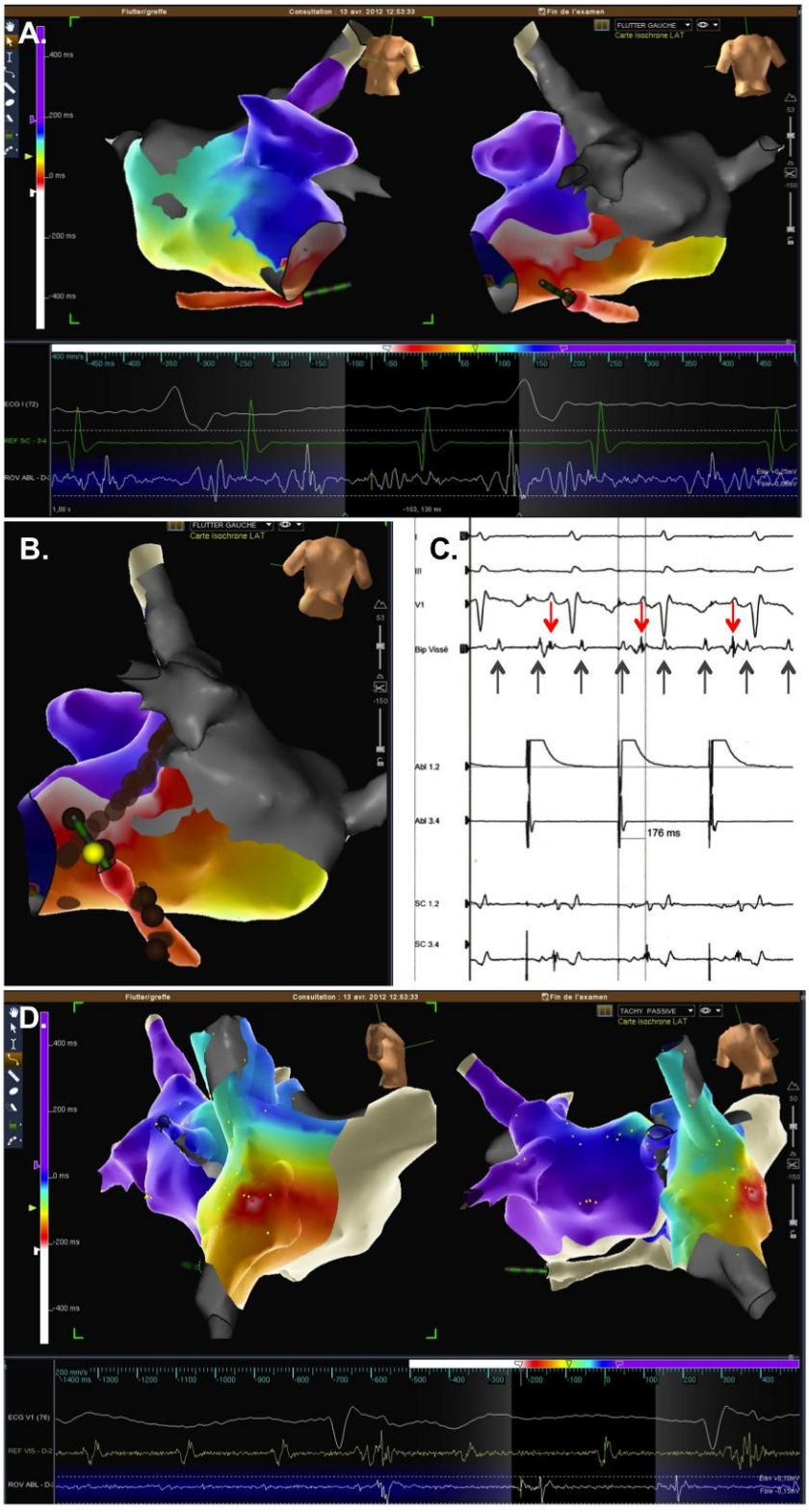
Accepted manuscript

ACCEPTED MANUSCRIPT

ejection fraction; NYHA: New York Heart Association; OAA: organized atrial arrhythmia; RFCA: radiofrequency catheter ablation.



Accepted M


A.
B.
C.
D.
176 ms