Journal of the American College of Cardiology
© 2008 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 51, No. 23, 2008
ISSN 0735-1097/08/$34.00
doi:10.1016/j.jacc.2008.02.065

Supraventricular Tachycardia After Orthotopic Cardiac Transplantation

Marmar Vaseghi, MD,* Noel G. Boyle, MD, PHD,* Rohit Kedia, MD,* Jignesh K. Patel, MD, PHD,† David A. Cesario, MD, PHD,* Isaac Wiener, MD,* Jon A. Kobashigawa, MD,† Kalyanam Shivkumar, MD, PHD*

Los Angeles, California

Objectives The purpose of this study was to define the incidence, mechanisms, and management, including catheter ablation, of supraventricular tachycardia (SVT) in a large series of patients after orthotopic heart transplantation (OHT).

Background Supraventricular arrhythmias are frequently encountered after OHT, but their characteristics in this population have not been well established.

Methods We analyzed the incidence, clinical course, and management of SVTs in a cohort of 729 adult patients who underwent OHT. Furthermore, the mechanisms of arrhythmias among the patients referred for electrophysiological study (EPS) and ablation were also characterized.

Results The most common arrhythmia was atrial flutter, which occurred in 9% of this cohort. Persistent or paroxysmal atrial fibrillation occurred in 7%, the majority (57%) in the perioperative period. Persistent or paroxysmal atrial fibrillation was observed in OHT patients, beyond the post-operative period, only in the presence of rejection or transplant vasculopathy. Other persistent or paroxysmal SVTs were seen in 47 stable OHT patients (7%). Of these, 24 patients (4%) underwent EPS. Accessory and dual atrioventricular nodal pathways in the donor heart caused SVT in 3 patients. Macro-reentrant atrial tachycardia was seen in 7 patients, and isthmus-dependent atrial flutter occurred in 14 patients.

Conclusions The majority of SVTs in stable OHT patients can be attributed to macro-reentrant tachycardias (flutter and scar reentry). Catheter ablation is effective in management of these SVTs. Atrial fibrillation was never encountered in stable patients in our series, and its occurrence should prompt an evaluation for acute rejection and/or vasculopathy. (J Am Coll Cardiol 2008;51:2241–9) © 2008 by the American College of Cardiology Foundation

The incidence, clinical course, and management of supraventricular tachycardias (SVTs) in orthotopic heart transplant (OHT) patients have not been well characterized. Transplanted hearts provide a unique model to study the management of these arrhythmias, because of the relative autonomic denervation and the pro-arrhythmic characteristics of surgical scars. Previous studies have reported atrioventricular nodal (AVNRT) and atrioventricular reentrant tachycardias (AVRT) in transplanted patients due to pre-existing accessory pathways and dual atrioventricular nodal physiology in the donor hearts (1–5). Macro-reentrant atrial tachycardias (ATs) from pro-arrhythmic substrates originating at surgical anastomotic sites have also been reported (6–9).

Atrial flutter (AFL) and atrial fibrillation (AF) are known to occur in patients with acute rejection, transplant vasculopathy, or in the immediate post-operative period (10–13). Whereas AFL has also been described in stable transplant patients (14–18), the mechanisms and occurrence of AF in patients without the aforementioned conditions are not clear. In fact, in 1 study, heart transplantation was an independent predictor of freedom from post-operative AF when compared with patients with other cardiac surgeries (19). Nevertheless, a rare case of AF in the absence of rejection or vasculopathy has been described (20).

The purpose of this study was to quantify the incidence of AF and AFL, to define the mechanisms of SVT in post-transplant patients, and to evaluate the role of catheter ablation.

From the *UCLA Cardiac Arrhythmia Center and the †UCLA Heart Transplant Program, Division of Cardiology, Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, California. This work was supported by grants from the American Heart Association, National Affiliate (grant #0430287N), and the National Heart, Lung, and Blood Institute, R01HL084261, to Dr. Shivkumar. This report was presented in part at the American Heart Association Annual Scientific Sessions, November 9–12, 2003, Orlando, Florida.

Manuscript received November 19, 2007; revised manuscript received January 29, 2008, accepted February 5, 2008.

JACC Vol. 51, No. 23, 2008
June 10, 2008:2241–9

Abbreviations and Acronyms

AF = atrial fibrillation
AFL = atrial flutter
AT = macro-reentrant atrial tachycardia
AVNRT = atrioventricular nodal reentrant tachycardia
AVRT = atrioventricular reentrant tachycardia
EPS = electrophysiological study
HRV = heart rate variability
OHT = orthotopic heart transplant
RFA = radiofrequency ablation
RMSSD = root-mean-square of successive normal sinus RR interval difference
SDANN = standard deviation of the averaged normal sinus RR intervals for all 5-min segments
SDNN = standard deviation of all normal sinus RR intervals over 24 h
SVT = supraventricular tachycardia

Methods

Study cohort. A total of 729 patients who underwent OHT between January 30, 1994, and January 1, 2006, at our center were screened. Retrospective review of patient data was approved by our Institutional Review Board. These patients were divided into 3 groups. The first group included patients with benign atrial premature complexes or transient SVT that resolved without intervention. The second included those with persistent or paroxysmal SVT occurring during the immediate post-operative period or concurrent with acute rejection or transplant vasculopathy, as documented by symptoms, right ventricular endomyocardial biopsy, echocardiography, and right and left heart catheterization. The third group, defined as stable OHT patients, included those with recurrent persistent or paroxysmal SVT without clinical signs or symptoms of rejection or severe vasculopathy, defined as at least 1 coronary artery with >70% stenosis. The second and third groups were the primary focus of this study, and the third group served as the population in whom the underlying mechanism of their arrhythmia was confirmed via electrophysiological study (EPS). Patients with AF and AFL had biopsies performed to rule out rejection. All patients received triple-drug immunosuppression therapy with systemic steroids, cyclosporine or tacrolimus, and mycophenolate mofetil or rapamycin. Patients who died in the immediate post-operative period were excluded.

Anti-arrhythmic therapy. All patients with confirmed persistent or paroxysmal SVT were initially treated with cardioversion and antiarrhythmic drugs, including beta-blockers, sotalol, or amiodarone. Of these patients, 24 had persistent drug-resistant SVTs; they were referred for EPS and radiofrequency catheter ablation and therefore had the underlying mechanism of their arrhythmias identified.

AF and AFL in OHT patients. Because AF was not seen in any patient with SVT referred for EPS and AFL was the most common arrhythmia initially identified, a detailed chart review of all 729 patients transplanted between January 30, 1994, and January 1, 2006, was performed to quantify the incidence of these arrhythmias. Patients who died in the immediate post-operative period and those <18 years of age were excluded. For the remaining 657 patients, all clinic notes, electrocardiograms, echocardiograms, cardiac catheterization reports, stress tests, and Holter monitors were carefully reviewed for evidence of AF as well as AFL. Atrial fibrillation was defined with the American College of Cardiology/American Heart Association criteria (21).

Heart rate variability (HRV) analysis. To better delineate the mechanism potentially underlying paroxysmal or persistent AF in stable OHT patients, a retrospective review of transplant patients with HRV data available on 24-h Holter monitoring was performed. Patients with Holter monitors manifesting significant supraventricular or ventricular arrhythmias were excluded. Sixteen Holter monitors remained, and these were analyzed for HRV parameters, specifically standard deviation of all normal sinus RR intervals over 24 h (SDNN), standard deviation of the averaged normal sinus RR intervals for all 5-min segments (SDANN), SDNN index, and root-mean-square of successive normal sinus RR interval difference (RMSSD), and compared with age- and gender-matched references previously standardized in published reports.

EPS. Informed consent was obtained from all patients to undergo an EPS and possible radiofrequency ablation (RFA). Multipolar mapping catheters were inserted through femoral veins. Endocardial electroanatomic (CARTO, Biosense-Webster, Diamond Bar, California) or NavX (St. Jude Medical, Minnetonka, Minnesota) and entrainment mapping were performed during EPS. Scar was defined as myocardial regions with local electrograms <0.05 mV and/or regions where electrical capture could not be demonstrated. Viable muscle was defined as regions with local electrograms >0.05 mV. Areas of native myocardium were specially tagged as gray zones on the electroanatomic map. The presence of macro-reentrant tachycardia was established by standard criteria that included: induction by pacing, pace-termination, entrainment, and noninducibility after ablation of the slow-conducting isthmus.

Catheter ablation. Four- or 8-mm-tip catheters (Biosense-Webster) were used for RFA in 22 patients. Two patients had ablation performed with a 3.5-mm-tip open irrigated catheter. Successful RFA was defined as termination of SVT and noninducibility by pacing. Atrioventricular valve isthmus ablation on the right side involved creation of a bidirectional line of block between the tricuspid valve-inferior vena cava isthmus. The ablation for left-sided isthmus-dependent flutter involved creation of a line between the mitral annulus and the region of the suture site close to the left inferior pulmonary vein (these lines were not validated by pacing maneuvers). Sites of ablation were defined by electroanatomic mapping.

Statistics. The SAS software (version 9.1, SAS Institute, Cary, North Carolina) was used for all statistical analyses. Each variable was checked for normality of distribution with the Shapiro-Wilk test, although none required transformation. Values are presented as mean and SD for demographic variables. A 1-sample t test was used to compare clinical variables with standardized references based on published

means, SEMs, and SDs of healthy individuals (22,23). p values <0.05 were considered significant.

Results

AF and AFL in stable OHT patients. Of the 729 patients, 152 (23.1%) had died by January 1, 2006, and 24 of these (3.3%) died in the immediate post-operative period. Forty-four patients transferred care to other medical centers or were lost to follow-up. In the 657 adult patients who had not died in the post-operative period, the mean and median follow-up were 6.6 and 4.1 years, respectively. In 4,299 person-years of follow-up, 46 patients (7.0%) presented with AF. Of these, 26 patients (4.0%) had AF in the post-operative period, 16 patients (2.4%) had AF associated with acute rejection, 3 (0.5%) patients had AF associated with severe transplant vasculopathy, and 1 patient had AF associated with severe sepsis. In the absence of the aforementioned conditions, paroxysmal or chronic AF was not encountered (Fig. 1). In comparison, 60 patients (9.1%) presented with documented AFL. Of these, 16 patients (2.4%) had AFL in the post-operative period, 17 (2.6%) had AFL associated with acute rejection, 2 (0.3%) with severe vasculopathy, 1 with infection, and 1 in the setting of pulmonary emboli. Twenty-three stable patients presented with documented AFL without evidence of rejection or vasculopathy (Fig. 1). Therefore, the incidence of AFL not associated with the aforementioned conditions (cardioverted, treated medically, or with catheter ablation) was 3.5% during the same follow-up period. No patient was referred for ablation of AF, whereas 2.1% of the cohort (i.e., 43% of those presenting with AFL) required EPS and ablation for successful treatment of their arrhythmias.

Patients with post-operative AF associated with allograft rejection or vasculopathy were cardioverted, and the underlying rejection or vasculopathy was treated. Patients who were chemically cardioverted—either in the perioperative period or after successful treatment of allograft rejection, vasculopathy, or infection—had their anti-arrhythmic drug therapy discontinued within 3 months of discharge. None of these patients had recurrence of their arrhythmia during follow-up, unless in association with repeat acute rejection or severe transplant vasculopathy.

HRV analysis. In this cohort, 34 Holter recordings were available for analysis. Of these, 4 were excluded secondary to multiple episodes of documented supraventricular and ventricular arrhythmias. Of the remaining 30, HRV data were available on 16 patients (10 men, 6 women, age 55 ± 16 years). The overall as well as the gender-based mean SDNN, SDANN, SDNN index, and RMSSD were compared with healthy age- and gender-matched historical control subjects (Table 1). Compared with age- (40 to 60 years) and gender-matched healthy adult references previously reported, SDNN, SDANN, and SDNN index were significantly depressed (22–24). Furthermore, the depression of HRV parameters was in the moderate-to-severe range, when compared with adults with coronary artery

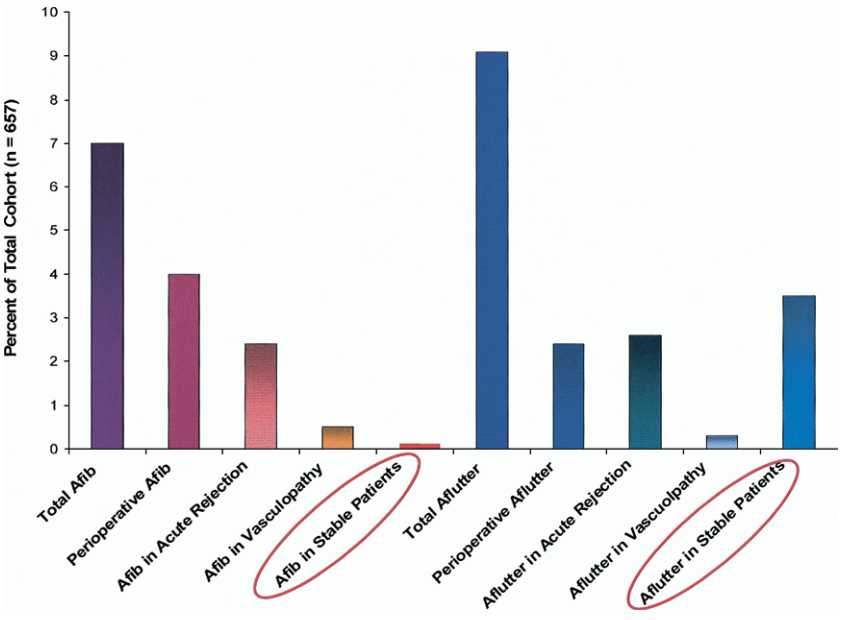

Figure 1 Incidence of Atrial Flutter Versus Atrial Fibrillation

In the cohort of cardiac transplant patients, the percentage of patients with any atrial flutter and fibrillation as well as the individual arrhythmias associated with the appropriate clinical setting are shown. Stable was defined as those without simultaneous severe transplant vasculopathy, sepsis, or acute rejection who are not in the immediate post-operative period while experiencing the arrhythmia as shown. Note that no atrial fibrillation was observed in stable cardiac transplant patients. In comparison, atrial flutter occurred in 4.6% of patients and, in 2.3%, required electrophysiological study and ablation. AFib = atrial fibrillation; Aflutter = atrial flutter.

JACC Vol. 51, No. 23, 2008
June 10, 2008:2241–9

Table 1 Heart Rate Variability Parameters

	OHT Patients	Control Subjects
Overall		
Age (yrs)	55 ± 15	50–59
Heart rate (beats/min)	95 ± 11*	76 ± 9
SDNN (ms)	47 ± 13*	121 ± 27
SDANN (ms)	41 ± 14*	106 ± 27
SDNN index (ms)	16 ± 11*	52 ± 15
RMSSD (ms)	19 ± 13	25 ± 9
Men		
Age (yrs)	63 ± 11	50–69
Heart rate (beats/min)	95 ± 11*	78 ± 11
SDNN (ms)	40 ± 11*	117 ± 30
SDANN (ms)	35 ± 12*	104 ± 28
SDNN index (ms)	14 ± 11*	46 ± 18
RMSSD (ms)	16 ± 13	22 ± 8
Women		
Age (yrs)	43 ± 14	30–49
Heart rate (beats/min)	86 ± 12	79 ± 7
SDNN (ms)	58 ± 9*	129 ± 30
SDANN (ms)	53 ± 9*	114 ± 31
SDNN index (ms)	19 ± 10.3*	58 ± 13
RMSSD (ms)	23 ± 14	31 ± 10

All parameters are given as mean ± SD. *Significantly depressed, $p < 0.05$, parameters in orthotopic heart transplant (OHT) patients compared with the healthy reference population.

RMSSD = root-mean-square of successive normal sinus RR interval difference; SDANN = SD of the averaged normal sinus RR intervals for all 5-min segments; SDNN = SD of all normal sinus RR intervals over 24 h; SVT = supraventricular tachycardia.

disease thought to be at high risk of sudden cardiac death (i.e., SDNN <50 for severely and SDNN <100 for moderately depressed) (24). This provides evidence supporting autonomic denervation in OHT patients.

Incidence of SVT in a stable heart transplant cohort. Of the 729 patients, we identified 47 adult OHT patients with paroxysmal, persistent, or chronic SVT (7.1%) who were not in the immediate post-operative period and whose arrhythmia was not complicated by acute rejection, vasculopathy, or sepsis. No patient presented with AF. Atrial flutter was the most common arrhythmia identified in the overall cohort, with 23 of 47 patients having documented AFL. Of the 47 patients with SVT, 24 (49%) had SVT refractory to medical therapy and required EPS and ablation for treatment, whereas the remaining patients were successfully treated either with medical therapy or cardioversion. The summary of mechanism of the arrhythmias found in the group referred to EPS is shown in Figure 2. Fourteen (58%) presented with palpitations, 7 (29%) with symptoms of heart failure (i.e., fatigue, shortness of breath, paroxysmal nocturnal dyspnea, edema), and 3 (13%) were asymptomatic. Patient characteristics are listed in Table 2.

Arrhythmias documented during EPS. Of the 47 stable patients with SVT, 24 underwent EPS and ablation. The mechanism of arrhythmias noted in these patients were: isthmus-dependent right or left AFL (n = 14); macro-reentrant intra-atrial tachycardia (n = 7; left atrial = 1, right atrial = 6); accessory pathway mediated tachycardia: atrioventricular reentry (AVRT) (n = 2); and atrioventricular nodal reentrant tachycardia (AVNRT) (n = 1) (Table 2, Fig. 2). Of note, 1 patient had 2 right atrial tachycardias and 1 left atrial tachycardia documented at the time of EPS. Persistent or paroxysmal AF was not identified in any stable post-transplant patient.

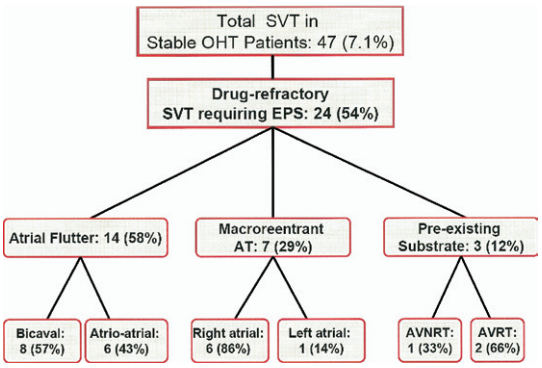

Figure 2 Classification of SVT in Stable OHT Patients

Incidence of the different types of drug refractory supraventricular tachycardia (SVT) in this cohort of orthotopic heart transplant (OHT) patients who underwent electrophysiological study (EPS) is shown. Note that isthmus-dependent atrial flutter was the most commonly observed SVT, followed by scar-related macro-reentrant tachycardia. AT = atrial tachycardia; AVNRT = atrioventricular nodal reentrant tachycardia; AVRT = atrioventricular reentrant tachycardia.

AVNRT. One patient with AVNRT had recurrent palpitations and poor response to beta-blockers. Electrophysiological study confirmed AVNRT. Radiofrequency modification of the slow atrioventricular nodal pathway was curative.

AVRT. Two patients had clinical tachycardia with AVRT as the underlying mechanism. There were no baseline electrocardiograms available from the donor hearts before

Table 2 Patient Characteristics of Stable OHT Patients Referred for EPS

Number of patients undergoing EPS	24
Mean age (yrs)	48 ± 18
Male	13
Female	11
Ejection fraction (%)	56 ± 7
Type of anastomoses	
Biatrial	10
Bicaval	14
Electrophysiological mechanisms	
Atrial flutter	15
Macro-reentry	
Atrial tachycardia	6
AVNRT	1
AVRT	2
Catheter ablation	
Effective	23
Repeat procedures	3

AVNRT = atrioventricular nodal reentrant tachycardia; AVRT = atrioventricular reentrant tachycardia; EPS = electrophysiological study; OHT = orthotopic heart transplant.

transplantation. The EPS confirmed their diagnoses, with 1 left-sided accessory pathway arising from the inferior aspect of the mitral annulus, requiring transseptal puncture for ablation, and 1 right-sided accessory pathway that was diagnosed after ablation of AFL in the same patient. Radiofrequency ablation was curative in both cases.

AT. Six patients were identified as having scar-related right atrial reentrant tachycardia with electroanatomical mapping. In all 6 cases, the reentrant circuit was identified at the upper right atrium, around the native and donor anastomotic suture line. Ablation along the suture line was curative in our patients. One of these patients had 2 right atrial and 1 left atrial tachycardias. The focus of 1 of the scar-related macro-reentrant right atrial tachycardias was successfully ablated with a plan to perform a second ablation if symptoms recurred. However, no further episodes of tachycardia were noted after the first ablation. A second patient had macro-reentrant tachycardia in his native right atrium with breakthrough conduction into the donor heart. The RFA was also curative. One patient had macro-reentrant left atrial tachycardia around the donor left atrial cuff. The RFA at the slow conduction site of the reentrant circuit resulted in a cure of the tachycardia (Fig. 3).

Isthmus-dependent AFL. A total of 14 patients were identified as having isthmus-dependent AFL as the underlying mechanism of their SVT. Six occurred in patients with bi-atrial anastomosis, and 8 occurred in patients with bicaval anastomosis. In 12 patients the reentrant circuits were tricuspid isthmus-dependent, and in 2 patients the reentrant circuits were in the left atrium around the mitral annulus, as confirmed by electroanatomic and entrainment mapping (Figs. 4 and 5). Regardless of the type of anastomosis, 12 of the 14 patients had tricuspid isthmus-dependent AFL. One patient with bi-atrial anastomosis had incessant AFL of the native right atrium with variable conduction to the grafted atrium. In the EP laboratory, the flutter was found to use 2 focal sites at the proximal and distal anastomosis for conduction into the graft atrium, which became 1:1 with isoproterenol infusion. Ablation at these 2 focal sites terminated the tachycardia. Although RFA was effective in all of these patients, 2 patients had a recurrent tachycardia (recurrent right AFL and right atrial macro-reentrant tachycardia), requiring a second EPS and ablation. One patient had associated left ventricular dysfunction with a decrease in ejection fraction from 50% to 55% at baseline to 30% to 35%. This subsequently improved after ablation of AFL.

Discussion

Major findings. This is the largest published study to date on the mechanism of arrhythmias in patients who have undergone heart transplantation. Atrial flutter was the most

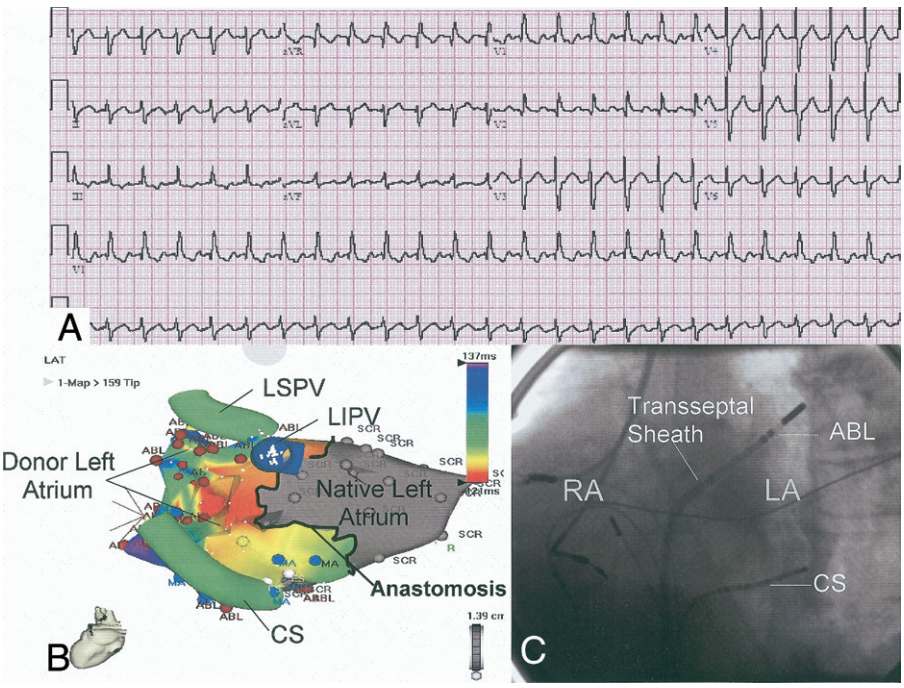

Figure 3 Left Atrial Macro-Reentrant Tachycardia

(A) Surface electrocardiogram demonstrates atrial tachycardia at a rate of 150 beats/min. **(B)** Activation maps demonstrate the tachycardia using an isthmus in the left atrium (LA), just anterior to the left superior pulmonary vein (LSPV), involving the donor, but not native **(gray)** left atrium (LA cuff tachycardia). **Red marks** represent ablation lesions. **(C)** Fluoroscopic left anterior oblique view: this tachycardia was mapped and ablated with transseptal catheterization. ABL = ablation catheter; CS = coronary sinus; LAT = left atrial tachycardia; LIPV = left inferior pulmonary vein; RA = right atrium; SCR = native atrium tagged as "scar" and shown in **gray**.

JACC Vol. 51, No. 23, 2008
June 10, 2008:2241–9

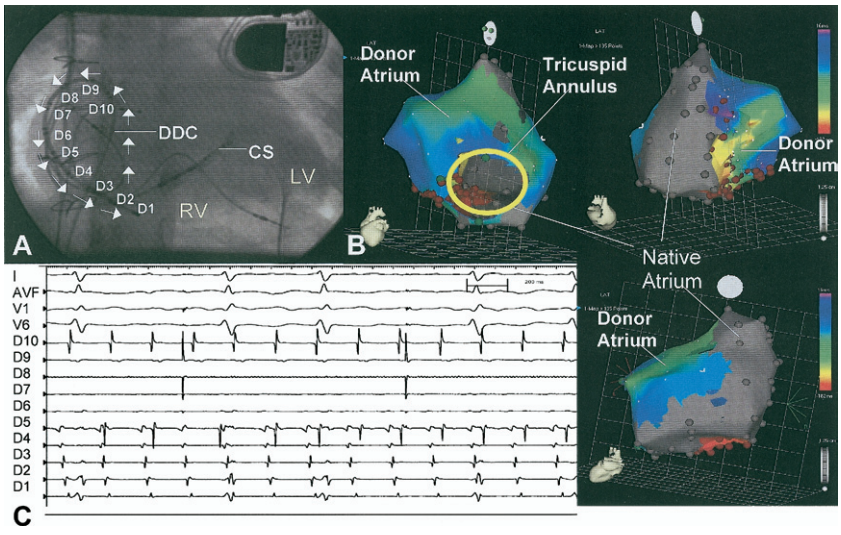

Figure 4 **Atrio-Atrial Anastomosis With Donor Isthmus Right Atrial Flutter and Dissociated Native Atrial Rhythm**

(A) Fluoroscopic right anterior oblique view shows the position of the duodecapolar catheter with the distal bipoles (D1 to D3) along the tricuspid valve isthmus and the proximal electrode (D10) along the superior aspect of the interatrial septum. **(B)** Electroanatomic maps of atrio-atrial anastomosis (**gray areas** identify native atrial tissue). The flutter wave-front involves the donor atrium only and is propagating in a counterclockwise fashion along the tricuspid annulus. **(C)** Intracardiac activation sequence in the donor atrium confirms counterclockwise activation. A critical isthmus was located near D5 in the lateral right atrium wall. The native atrium was in a dissociated atrial rhythm (D6 to D9) and did not conduct to the donor atrium. Therefore, ablation of the native atrium was not performed. CS = coronary sinus; D1 to D10 = duodecapolar bipoles 1 to 10; DDC = duodecapolar catheter; LV = left ventricle; RV = right ventricle.

common arrhythmia identified, regardless of clinical setting. No cases of paroxysmal or chronic AF were seen in our cohort of transplant patients in the absence of vasculopathy, rejection, severe infection, or the acute post-operative period. Supraventricular tachycardia occurred in 47 stable patients (7.1%) and required an EPS and catheter ablation in 24 patients (3.7%). The most common mechanism of arrhythmia in stable patients was isthmus-dependent AFL (58%) followed by scar-related AT (29%).

AF. Atrial fibrillation in the transplant population is highly debated both in terms of onset and maintenance. Our current report suggests persistent AF is extremely rare in stable OHT patients. Three broad mechanisms have been associated with the initiation and maintenance of AF: 1) rapidly discharging triggers or foci, especially from the thoracic veins; 2) the autonomic nervous system, which might promote electrophysiological heterogeneity; and 3) substrate abnormalities promoting wavelet reentry. Interestingly, cardiac transplant patients by definition have complete surgical isolation of their pulmonary veins. Furthermore, they essentially lack cardiac innervation, which was further corroborated by HRV data in our population showing significantly depressed parameters. This supports both the autonomic and/or the pulmonary vein trigger hypothesis for genesis of AF. Transient episodes of AF have been reported in OHT patients in the immediate post-surgical period who were on vasopressors and had an altered hemodynamic and neurohormonal state. These episodes were also observed in our cohort of 729 patients. However, once cardioverted, these patients were not at an increased risk of developing persistent or chronic AF during follow-up. Furthermore, compared with historical control subjects in whom the incidence of post-operative AF ranges from 20% to 50% (19,25,26), the incidence of post-operative AF was extremely low (4%) in our OHT population, suggesting that heart transplantation with its denervation and pulmonary isolation might have a protective role in preventing post-operative AF.

Substrate abnormalities, such as myocarditis, abnormal hemodynamic status, and inflammation, can cause direct electrophysiological alteration of the atrial myocardium, atrial stretch, and interstitial fibrosis, permitting and promoting wavelet reentry. A prior study performed at our institution reported that patients experienced episodes of AF long after their transplants, but these episodes were associated with rejection or ischemia related to severe transplant vasculopathy, altering the normal atrial substrate (10).

It has been suggested that long-term cardiac transplant recipients develop sympathetic and parasympathetic reinnervation (27,28). It is well known that vagal tone and acetylcholine shorten activation recovery intervals, potentially playing a role in the genesis of AF (29,30). Atrial fibrillation in stable OHT patients has also been reported in 3 cases. Although the mechanism of the underlying AF in these reports was unclear, all 3 patients were affected 5 to 10 years after transplantation, suggesting a role for parasympathetic reinnervation (20). Furthermore, all were successfully cardioverted without recurrence.

Transplantation could also potentially reduce the likelihood of AF by resulting in a reduction of the "critical mass"

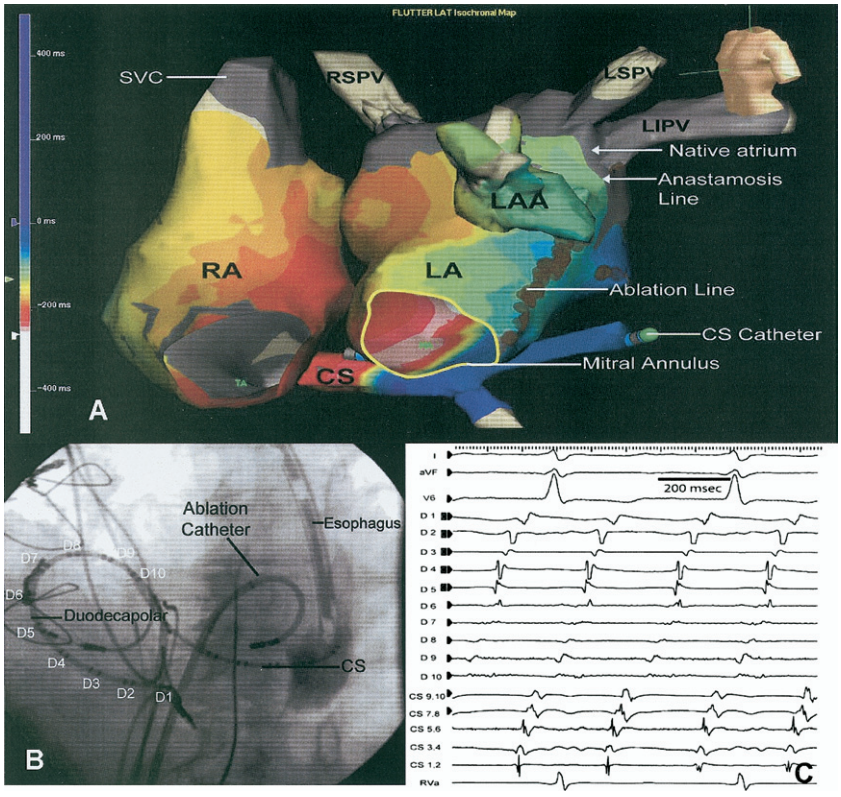

Figure 5 **LA (LIPV-Mitral Isthmus) Flutter**

(A) Activation map: the flutter circuit begins in the inferior wall of the LA **(pink)** close to the CS3-4 bipole and propagates across to the RA and around the tricuspid annulus as well as around and over the mitral annulus. The ablation line, shown, successfully terminated the arrhythmia without recurrence during follow-up. **(B)** Fluoroscopic left anterior oblique view: an ablation catheter was placed in the LA and duodecapolar catheter in the RA for mapping. **(C)** Intracardiac tracings corresponding to the activation map in **panel A** showing the earliest activation in the LA and extending to the RA. LAA = left atrial appendage; RSPV = right superior pulmonary vein; SVC = superior vena cava; other abbreviations as in Figure 3.

of atrial myocardium required for the maintenance of the arrhythmia (31,32).

AVRT AND AVNRT AFTER TRANSPLANTATION. Although adult cases involving accessory pathways in post-OHT patients have been documented in published reports (3–5), only 2 cases reported a donor arrhythmia on electrocardiography, 1 SVT and another unspecified. In the remaining cases, as in our 2 patients, there was no prior knowledge of pre-excitation in the donor heart, on the basis of the pre-operative electrocardiography. Furthermore, although more than one-half of the reported cases required ablation within 1 month, RFA was curative in all cases.

Cases of AVNRT reported in post-OHT patients are rare (1,2,5). Once again, RFA with slow pathway modification was effective at treating AVNRT in all cases.

SCAR-RELATED AT. Surgical scars at atrial suture lines can create areas of slowed conduction predisposing to atrial tachycardia (33). This in part prompted the development of bicaval anastomosis, which is now a more widely used technique for OHT, resulting in a significant reduction of atrial arrhythmias after OHT (33,34). In our study 6 of the 7 ATs ablated—5 in right atrium and 1 in left atrium—were related to scar formation with the reentrant circuit involving the isthmuses created by surgical suture lines. Electroanatomic mapping helped to determine the boundary and circuit in these tachycardias. Entrainment mapping was performed to identify critical isthmuses and successful ablation.

ATRIOVENTRICULAR VALVE ISTHMUS-DEPENDENT TACHYCARDIA. Atrial flutter can be encountered in OHT patients in the immediate post-transplant period and during acute rejection; it has been shown that patients with acute rejection and severe transplant vasculopathy have lower left ventricular ejection fractions, increased left ventricular end-diastolic pressures, right atrial enlargement, and decreased tricuspid valve deceleration times, potentially contributing to the initiation and persistence of atrial arrhythmias (10,11). However, both clockwise and counterclockwise AFL also occur in post-transplant patients without symptoms and signs of acute rejection and normal left ventricular function (14–18). Bicaval anastomosis essentially preserves the integrity of the right atrium and avoids the formation of

right atrial scars, placing them instead in areas with negligible arrhythmogenicity (34). It has been suggested, therefore, that bicaval anastomosis reduces the risk of AFL post-transplantation when compared with atrio-atrial anastomosis (33). However, in our study, although this technique prevented reentry around the right atrial scar, it did not prevent tricuspid isthmus-dependent typical AFL from occurring. In fact, tricuspid isthmus-dependent AFL was the most common type of flutter, similar to nontransplanted patients. Eight of 14 patients with tricuspid-dependent AFL in our study had bicaval anastomoses. This is the first time this type of flutter has been reported in this group of patients. Given the size of our study, the prevalence of AFL in these patients in comparison with the general OHT population cannot be determined. However, the incidence of flutter in this transplanted population stayed the same regardless of the type of anastomosis.

Study limitations. Despite extensive review of patient charts, electronic documents, 24-h Holter monitors, echocardiograms, cardiac catheterizations, and electrocardiograms, it is possible that certain paroxysmal episodes of arrhythmia were not documented, and thus the incidence of arrhythmias depicted underestimates their impact. However, given regular and close monitoring of all of our cardiac transplant patients, we believe we have captured the large majority of the burden of arrhythmias requiring any form of intervention or treatment.

Conclusions

This is the largest study to date reporting the incidence and associated clinical setting of AFL and AF in a cohort of 729 cardiac transplant patients. Atrial flutter was the most common arrhythmia observed, regardless of clinical condition. Atrial fibrillation was seen in patients with severe vasculopathy, acute rejection, sepsis, or in the post-operative period. However, paroxysmal or chronic AF was not encountered in stable transplant patients, suggesting the existence of different mechanisms for AF under specific clinical conditions. This study also confirms earlier findings that pre-existing substrates (accessory pathways and dual atrioventricular nodal physiology) can cause SVT in the transplanted heart and can be treated effectively by RFA. Furthermore, surgical scars are central to AT and can cause arrhythmias in the transplanted heart. Bicaval anastomosis might reduce scar-related AT, but atrioventricular valve isthmus-dependent AFL can still occur in these patients.

Reprint requests and correspondence: Dr. Kalyanam Shivkumar, UCLA Cardiac Arrhythmia Center, Division of Cardiology, Department of Medicine, 47-123 CHS, David Geffen School of Medicine at UCLA, 10833 Le Conte Avenue, Los Angeles, California 90095-1679. E-mail: kshivkumar@mednet.ucla.edu.

REFERENCES

1. Padder FA, Wilbur SL, Kantharia BK, Lee A, Samuels F, Kutalek SP. Radiofrequency catheter ablation of atrioventricular nodal reentrant tachycardia after orthotopic heart transplantation. J Interv Card Electrophysiol 1999;3:283–5.
2. Rodriguez de Armas L, Dorantes M, Castro J, et al. Radiofrequency catheter ablation of atrioventricular nodal reentrant tachycardia in a patient with orthotopic heart transplantation by bicaval anastomosis. J Interv Card Electrophysiol 2006;15:171–4.
3. Gallay P, Albat B, Thevenet A, Grolleau R. Direct current catheter ablation of an accessory pathway in a recipient with refractory reciprocal tachycardia. J Heart Lung Transplant 1992;11:442–5.
4. Sharma PP, Marcus FI. Radiofrequency ablation of an accessory pathway years after heart transplant: a case report. J Heart Lung Transplant 1999;18:792–5.
5. Magnano AR, Garan H. Catheter ablation of supraventricular tachycardia in the transplanted heart: a case series and literature review. Pacing Clin Electrophysiol 2003;26:1878–86.
6. Birnie D, Green MS, Veinot JP, Tang AS, Davies RA. Interatrial conduction of atrial tachycardia in heart transplant recipients: potential pathophysiology. J Heart Lung Transplant 2000;19:1007–10.
7. Fournet D, Zimmermann M, Campanini C. Atrial tachycardia with recipient-to-donor atrioatrial conduction and isthmus-dependent donor atrial flutter in a patient after orthotopic heart transplantation. Successful treatment by radiofrequency catheter ablation. J Heart Lung Transplant 2002;21:923–7.
8. Rothman SA, Miller JM, Hsia HH, Buxton AE. Radiofrequency ablation of a supraventricular tachycardia due to interatrial conduction from the recipient to donor atria in an orthotopic heart transplant recipient. J Cardiovasc Electrophysiol 1995;6:544–50.
9. Strohmer B, Chen PS, Hwang C. Radiofrequency ablation of focal atrial tachycardia and atrioatrial conduction from recipient to donor after orthotopic heart transplantation. J Cardiovasc Electrophysiol 2000;11:1165–9.
10. Cui G, Tung T, Kobashigawa J, Laks H, Sen L. Increased incidence of atrial flutter associated with the rejection of heart transplantation. Am J Cardiol 2001;88:280–4.
11. Ahmari SA, 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;25:53–60.
12. Kaufman LJ, Kofalvi AE, Hong RA, Moreno-Cabral CE, Low LL. Cardioversion of atrial fibrillation with ibutilide in an orthotopic heart transplant patient. J Heart Lung Transplant 1999;18:1018–20.
13. Landolina M, De Ferrari GM, Cantu F, Campana C. Donor-to-recipient decremental conduction of atrial fibrillation following orthotopic heart transplantation: insights into the mechanism of atrioatrial conduction. J Cardiovasc Electrophysiol 2000;11:1043–7.
14. 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;28:412–20.
15. Hadian D, Leier CV. Electroanatomic and electrographic characterization of atrial flutter following cardiac transplantation: pre- and post-ablation. J Heart Lung Transplant 2004;23:1205–8.
16. Pinski SL, Bredikis AJ, Winkel E, Trohman RG. Radiofrequency catheter ablation of atrial flutter after orthotopic heart transplantation: insights into the redefined critical isthmus. J Heart Lung Transplant 1999;18:292–6.
17. Pitt MP, Bonser RS, Griffith MJ. Radiofrequency catheter ablation for atrial flutter following orthotopic heart transplantation. Heart 1998; 79:412–3.
18. Poty H, Saoudi N, Nair M, Anselme F, Letac B. Radiofrequency catheter ablation of atrial flutter. Further insights into the various types of isthmus block: application to ablation during sinus rhythm. Circulation 1996;94:3204–13.
19. Khan M, Kalahasti V, Rajagopal V, et al. Incidence of atrial fibrillation in heart transplant patients: long-term follow-up. J Cardiovasc Electrophysiol 2006;17:827–31.
20. Woo GW, Schofield RS, Klodell CT, Pauly DF, Hill JA, Aranda JM Jr. Atrial fibrillation as a cause of left ventricular dysfunction after cardiac transplantation. J Heart Lung Transplant 2006;25:131–3.
21. Fuster V, Ryden LE, Cannom DS, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: 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 Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation). J Am Coll Cardiol 2006;48:854–906.

22. Umetani K, Singer DH, McCraty R, Atkinson M. Twenty-four hour time domain heart rate variability and heart rate: relations to age and gender over nine decades. J Am Coll Cardiol 1998;31:593–601.
23. Ramaekers D, Ector H, Aubert AE, Rubens A, Van de Werf F. Heart rate variability and heart rate in healthy volunteers. Is the female autonomic nervous system cardioprotective? Eur Heart J 1998;19:1334–41.
24. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Eur Heart J 1996;17:354–81.
25. Daoud EG, Strickberger SA, Man KC, et al. Preoperative amiodarone as prophylaxis against atrial fibrillation after heart surgery. N Engl J Med 1997;337:1785–91.
26. Ommen SR, Odell JA, Stanton MS. Atrial arrhythmias after cardiothoracic surgery. N Engl J Med 1997;336:1429–34.
27. Bengel FM, Ueberfuhr P, Schiepel N, Nekolla SG, Reichart B, Schwaiger M. Effect of sympathetic reinnervation on cardiac performance after heart transplantation. N Engl J Med 2001;345:731–8.
28. Fitzpatrick AP, Banner N, Cheng A, Yacoub M, Sutton R. Vasovagal reactions may occur after orthotopic heart transplantation. J Am Coll Cardiol 1993;21:1132–7.
29. Euler DE, Scanlon PJ. Acetylcholine release by a stimulus train lowers atrial fibrillation threshold. Am J Physiol 1987;253:H863–8.
30. Hoffman BF, Siebens AA, Brooks CM. Effect of vagal stimulation on cardiac excitability. Am J Physiol 1952;169:377–83.
31. West TC, Landa JF. Minimal mass required for induction of a sustained arrhythmia in isolated atrial segments. Am J Physiol 1962; 202:232–6.
32. Garrey WE. The nature of fibrillary contraction of the heart—its relation to tissue mass and form. Am J Physiol 1914;33:397–414.
33. Brandt M, Harringer W, Hirt SW, et al. Influence of bicaval anastomoses on late occurrence of atrial arrhythmia after heart transplantation. Ann Thorac Surg 1997;64:70–2.
34. 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;74:149–53.