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# Prevalence and Prognostic Significance of Atrial Arrhythmias After Orthotopic Cardiac Transplantation

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***Objectives.*** **We studied the duration and prognostic significance of atrial arrhythmias in the denervated transplanted heart, specifically the occurrence of atrial fibrillation in the absence of vagal modulation.**

***Background.*** **Substantial animal data indicate that vagally induced dispersion of atrial refractoriness plays a central role in the induction and maintenance of atrial fibrillation.**

***Methods.*** **We studied the occurrence of atrial arrhythmias in the denervated hearts of 88 consecutive orthotopic transplantations in 85 patients by means of continuous telemetry and all available electrocardiographic tracings.**

***Results.*** **Fifty percent of recipients (44 of 88) developed at least one atrial arrhythmia. Atrial fibrillation occurred 23 times (21 recipients), atrial flutter 39 times (26 recipients), ectopic atrial tachycardia 3 times (3 recipients) and supraventricular tachycardia 18 times (11 recipients). The number of atrial fibrillation and atrial flutter episodes did not differ (23 vs. 39, p = 0.072), but the mean duration of atrial flutter was longer than that of atrial fibrillation (37.0 ± 10 vs. 6.6 ± 3.6 h, p = 0.014). Atrial fibrillation was associated with an increased risk of subsequent death (10 of 21 recipients with vs. 15 of 67 without atrial fibrillation, risk ratio 3.15 ± 0.18, p = 0.005 by Cox proportional hazards model). All 5 recipients who developed "late" atrial fibrillation (>2 weeks after transplantation) died versus 5 of 16 who developed atrial fibrillation within the first 2 weeks (p = 0.007). Causes of death included rejection (three recipients), allograft failure (two recipients), infection (three recipients) and multiorgan failure (two recipients). Atrial fibrillation was not associated with age, gender, ischemic time, reason for transplantation, echocardiographic variables, invasive hemodynamic variables or biopsy grade. Mean time from atrial arrhythmia to echocardiography was 2.7 ± 3.3 days; that to biopsy was 4.8 ± 6.3 days. Atrial flutter was not associated with subsequent death. Only 7 (15.9%) of 44 recipients demonstrated moderate or severe allograft rejection at the time of the arrhythmia.**

***Conclusions.*** **Atrial arrhythmias occur frequently in the denervated transplanted heart, often in the absence of significant rejection. Late atrial fibrillation may be associated with an increased all-cause mortality.**

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Substantial clinical and experimental evidence suggests that vagal tone and acetylcholine play a crucial role in the genesis of atrial fibrillation (1–9). This profibrillatory influence may be due to the inhomogeneous effects of vagal stimulation on different parts of the atria (10), the effects being more pronounced in the right than in the left atrium in the canine model (11). Vagal tone shortens the atrial refractory period, and this effect, distributed unequally over the two atria, may also contribute to ease of induction of atrial fibrillation. Vagal modulation thus increases the inhomogeneity or dispersion of atrial refractoriness, resulting in nonuniform wavefront propagation, and thereby facilitates atrial fibrillation (6).

In humans, atrial fibrillation has been induced by direct injection of acetylcholine into the carotid artery (12) and by simple carotid sinus massage (13). Whether atrial fibrillation can be sustained in a normal heart in the absence of vagal tone is unclear, although some investigators (14) have documented atrial fibrillation after transplantation and concluded that autonomic innervation of the heart is not a prerequisite for the development of cardiac arrhythmias. Orthotopic cardiac transplantation affords a unique model for studying the behavior of denervated human atria. Published studies (14–19) have suggested that the occurrence of atrial arrhythmias may be a marker of underlying allograft rejection. Thus, in the clinical setting the new onset of an atrial arrhythmia frequently prompts endomyocardial biopsy and two-dimensional echocardiography. However, other studies (20–22) have found that arrhythmias can occur in the absence of histologically documented rejection. The aim of this study was to examine the prevalence, duration and prognostic significance of atrial arrhythmias after orthotopic cardiac transplantation.

## Methods

**Patients.** We retrospectively reviewed the medical records of 88 consecutive orthotopic cardiac transplantations performed in 85 patients at our institution between November

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1985 and January 1994. Indications for cardiac transplantation included heart failure due to ischemic heart disease (49%), dilated cardiomyopathy (37%), valvular heart disease (7%), congenital heart disease (6%) and hypertrophic cardiomyopathy (1%). Hemodynamic monitoring with pulmonary artery catheters was discontinued within the first 2 to 8 days after transplantation. Electrolytes and acid-base status were closely followed and any abnormalities aggressively treated. Atrial and ventricular pacing wires were removed as soon as pacing was not required for hemodynamic stability. All patients received triple-drug immunosuppressive therapy with prednisone, azathioprine and cyclosporine. Routine surveillance right ventricular endomyocardial biopsy was performed weekly for the first postoperative month, biweekly for the next 8 weeks and monthly for the remainder of the first year. Biopsies were also performed for any change in clinical status judged to be indicative of allograft rejection. Moderate (International Society of Heart and Lung Transplantation [23] grade 2 or 3A) cellular rejection not associated with hemodynamic compromise was treated with methyl prednisolone (24). Additional cytolytic therapy (antithymocyte globulin or OKT3) was used for hemodynamically significant allograft rejection of any histologic severity.

**Arrhythmia analysis.** All patients underwent continuous electrocardiographic (ECG) telemetric monitoring for the entire duration of their initial hospital stay and during all subsequent hospital readmissions. Routine 12-lead ECGs were recorded daily for all patients during the first week after transplantation and before hospital discharge. All available ECG tracings (including telemetry strips, surface ECGs, intracardiac electrograms recorded from temporary atrial pacing wires and Holter recordings) were reviewed to establish the presence or absence, and mechanism of, any atrial arrhythmia. All physician notes and nursing flow sheets were studied to accurately determine the timing and duration of each atrial event.

Atrial arrhythmias that developed within the first 2 weeks after transplantation were defined as *early* atrial arrhythmias; those that developed after the first 2 weeks were defined as *late* atrial arrhythmias. *Atrial fibrillation* was diagnosed when there was either no discernible or completely unorganized atrial activity, associated with an irregularly irregular ventricular response. *Atrial flutter* was diagnosed when there was clearly discernible atrial activity at a fixed atrial cycle length between the rates of 250 and 350 beats/min. *Ectopic atrial tachycardia* was defined as a rhythm, regular or irregular, where a p wave with an axis and configuration different from normal sinus rhythm preceded each QRS complex. *Supraventricular tachycardia* was defined as a regular, narrow complex arrhythmia without obvious p waves, that could not be categorized in to any of the previous groups.

Time to atrial arrhythmia after transplantation and duration of each episode were recorded. Invasive hemodynamic, two-dimensional echocardiographic and biopsy findings data were recorded for each patient from studies performed closest to the time of the atrial arrhythmia. These data were then compared with those obtained from the group of patients without any atrial arrhythmia (control transplant recipients) at matched times after transplantation. All variables (age, gender, length of index hospital stay, ischemic time, echocardiographically measured atrial dimensions, semiquantitative degree of tricuspid regurgitation, right ventricular function score, left ventricular ejection fraction, rest filling pressure and cardiac output measured at right heart catheterization, histologic grade of rejection) that could potentially influence the occurrence of atrial arrhythmias were recorded. Tricuspid regurgitation was scored as follows: *trace* = 1; *mild* = 2; *moderate* = 3; *severe* = 4. For statistical comparison, right ventricular function was scored as follows: *normal* = 1; *mild hypokinesia* = 2; *moderate hypokinesia* = 3; *severe hypokinesia* = 4.

**Statistical analysis.** Statistical analysis was performed with Kaplan-Meier survival analysis to assess the univariate impact of atrial fibrillation on mortality; stepwise multiple logistic regression to seek determinants of atrial fibrillation, atrial flutter, ectopic atrial tachycardia and supraventricular tachycardia; and stepwise Cox hazards regression models to test potential multivariate predictors of mortality. The BMDP Statistical Software package, release 7, (Dixon, WJ, editor. Berkeley [CA]: University of California Press) was used for these calculations. A p value $< 0.05$ was considered statistically significant. Results are expressed as the mathematical mean ± SE. If the first allograft did not survive and the patient required retransplantation, then the failure of the first heart was counted as a "death," even if the patient survived after receiving the second allograft. For the purpose of statistical analysis and simplicity in discussion, the three patients who underwent retransplantation, were counted as six "recipients"; the total number of recipients in this study was therefore 88.

## Results

The clinical characteristics and ischemic times for the entire transplantation cohort, as well as for those patients who developed an atrial arrhythmia, and are shown in Table 1.

**Atrial arrhythmias.** A total of 44 (50%) of the 88 recipients had at least one episode of atrial arrhythmia. Atrial fibrillation occurred 23 times in 21 recipients (24% of the total number of recipients), atrial flutter 39 times in 26 recipients (30%), ectopic atrial tachycardia 3 times in 3 recipients (3%) and supraventricular tachycardia 18 times in 11 recipients (13%). Nine patients had episodes of both atrial flutter and atrial fibrillation, two of whom also had episodes of supraventricular tachycardia (Fig. 1). The number of episodes of atrial flutter (39) was greater than that for atrial fibrillation (23), but the difference was not statistically significant ($p = 0.072$). The shortest duration of atrial fibrillation recorded in the present study was 3 min, and that for atrial flutter was 90 min. Mean duration of atrial flutter was 37 ± 10 h (range 90 min to 9 days), significantly greater than that for atrial fibrillation (6.6 ± 3.6 h, range 3 min to 3 days, $p = 0.014$ for comparison of arrhythmia duration). Four episodes of atrial flutter were either pace terminated or electrically cardioverted to normal

**Table 1.** Clinical Characteristics of the Study Group by Atrial Arrhythmia Type

| | Entire Group (n = 88) | Recipients With Atrial Fibrillation (n = 21) | Recipients With Atrial Flutter (n = 26) | Recipients With EAT (n = 3) | Recipients With SVT (n = 11) | Recipients Without Atrial Arrhythmias (control transplant recipients) (n = 44) |
|---|---|---|---|---|---|---|
| Age | 52 ± 10 | 50 ± 2 | 53 ± 2 | 51 ± 4 | 57 ± 2 | 52 ± 2 |
| Gender | | | | | | |
| Male | 74 (87%) | 18 (86%) | 23 (89%) | 2 (67%) | 8 (73%) | 40 (91%) |
| Female | 11 (13%) | 3 (14%) | 3 (11%) | 1 (33%) | 3 (27%) | 4 (9%) |
| Reason for transplantation | | | | | | |
| CAD | 42 (49%) | 5 (24%) | 11 (42%) | 1 (33%) | 6 (55%) | 25 (57%) |
| DCM | 31 (37%) | 10 (48%) | 10 (38%) | 2 (67%) | 2 (18%) | 14 (32%) |
| Congenital disease | 5 (6%) | 4 (19%) | 3 (12%) | 0 | 2 (18%) | 2 (4%) |
| Valvular disease | 6 (7%) | 2 (9%) | 1 (4%) | 0 | 1 (9%) | 3 (7%) |
| HCM | 1 (1%) | 0 | 1 (4%) | 0 | 0 | 0 |
| Ischemic time (min) | 162 ± 5 | 170 ± 14 | 162 ± 5 | 149 ± 7 | 168 ± 9 | 160 ± 7 |

Data presented are mean value ±SEM or number (%) of patients. CAD = coronary artery disease; DCM (HCM) = dilated (hypertrophic) cardiomyopathy; EAT = ectopic atrial tachycardia; SVT = supraventricular tachycardia.

sinus rhythm. Table 2 summarizes the characteristics of each type of atrial arrhythmia.

Early atrial fibrillation occurred in 16 (76%) of 21 recipients (mean time of onset 5.9 ± 1.3 days, range 0 to 14); the remaining 5 recipients (24%) had late atrial fibrillation (mean time of onset 322 ± 224 days, range 31 to 1213). Nineteen of 26 recipients (73%) had early atrial flutter (mean time of onset 4.1 ± 0.7 days, range 0 to 13); the remaining seven recipients had late atrial flutter (mean time of onset 84.6 ± 28.4 days, range 20 to 180). Two of the 3 recipients with ectopic atrial tachycardia and 8 of the 11 recipients with supraventricular tachycardia had the arrhythmia during the first 2 weeks. Overall, early atrial arrhythmias were recognized in 30 (34%) of 88 recipients, late arrhythmias in 10 (11%) of 88 and both early and late arrhythmias in 4 (5%) of 88.

**Determinants of arrhythmia.** Stepwise multiple logistic regression demonstrated that the occurrence of *atrial fibrillation* was not associated with age; gender; length of index hospital period; donor ischemic time; two-dimensional echocardiographic variables including left atrial size, right ventricular function score, semiquantitative degree of tricuspid regurgitation and left ventricular ejection fraction; right heart hemodynamic variables, including right atrial pressure, pulmonary artery pressure, pulmonary capillary wedge pressure and cardiac output; or the grade of rejection on endomyocardial biopsy (all p = NS) (Table 3). Mean time from onset of atrial arrhythmia to echocardiography was 2.7 ± 3.3 days (range 0 to 12.5) and that for endomyocardial biopsy was 4.8 ± 6.3 days (range 0 to 33.5). Only 7 (16%) of 44 recipients had a biopsy grade ≥2 (i.e., at least moderate) rejection at the time of the arrhythmia. One patient demonstrated severe (grade 3B) rejection. Four (9%) of the 44 recipients without any atrial arrhythmias (i.e., control transplant recipients) had moderate rejection at matched times after transplantation (p = 0.41 for comparison of number of biopsies that showed moderate rejection in patients with and without any atrial arrhythmia).

*Episodes of atrial flutter, ectopic atrial tachycardia and supraventricular tachycardia* were also not associated with any of the clinical, echocardiographic, hemodynamic or histologic variables examined.

**Deaths.** Actuarial survival for all transplant recipients was 79%, 73% and 57% at 1, 3 and 5 years, respectively. There were a total of 25 deaths during follow-up, which averaged 777 ± 71 days.

*Atrial fibrillation and death.* Atrial fibrillation was documented in 10 (40%) of the 25 recipients who subsequently died during this study. The occurrence of atrial fibrillation was associated with an increased risk of death (10 [48%] of 21 recipients with recognized atrial fibrillation did not survive vs. 15 [22%] of 67 without atrial fibrillation; risk ratio 3.15 ± 0.18, p = 0.005 by Cox proportional hazards modeling). The risk ratio for death in recipients with versus without recognized atrial fibrillation was 3.5 ± 0.18. Figure 2 shows the Kaplan-Meier survival plots for recipients with and without recognized atrial fibrillation. All 5 recipients (100%) with recognized late atrial fibrillation died compared with 5 (31%) of 16 recipients who developed early atrial fibrillation (p = 0.007). Mean time

**Figure 1.** Venn diagrammatic representation of numbers of patients (not recipients) with atrial arrhythmias. EAT = ectopic atrial tachycardia; FIB = atrial fibrillation, FLU = atrial flutter; SVT = supraventricular tachycardia.

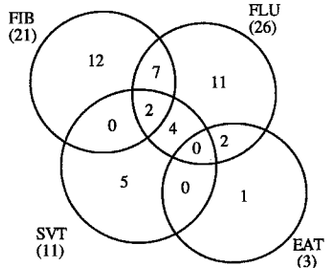

**Table 2.** Characteristics of Observed Atrial Arrhythmias

| | No. of Recipients | No. of Episodes | Mean (±SEM) Duration of Each Episode (min) | Mean (±SEM) Time From Transplantation to First Episode (days) |
|---|---|---|---|---|
| Atrial fibrillation | 21 | 23 | 393 ± 215 | 81 ± 57 |
| Atrial flutter | 26 | 39 | 2,219 ± 600 | 26 ± 10 |
| EAT | 3 | 3 | <1 | 8 ± 6 |
| SVT | 11 | 18 | 3 ± 1 | 88 ± 78 |

Abbreviations as in Table 1.

from occurrence of the first atrial fibrillation episode to death was 77 ± 57 days, and that for atrial flutter to death was 271 ± 230 days (p = 0.40).

*Causes of death.* Twelve of the 25 recipients who died during this study had a previous episode of atrial arrhythmia. Of these 12 patients, 5 died of cardiac-related causes, 5 of infectious complications and 2 of multiorgan failure. Rejection-related mortality did not appear to be increased in the atrial fibrillation group (three recipients had biopsy-proved moderate rejection in the atrial fibrillation group vs. one recipient in the atrial flutter group, p = NS) (Table 4). Of 13 patients without any documented atrial arrhythmia, 7 died of cardiac-related and 6 of non–cardiac-related causes.

*Atrial flutter, ectopic atrial tachycardia, supraventricular tachycardia and death.* Atrial flutter was not associated with an increased likelihood of death (9 [35%] of 26 patients with atrial with and 16 [26%] of 62 without atrial flutter died, p = 0.41). Further, seven of nine patients in the atrial flutter group who subsequently died also had an episode of atrial fibrillation. Ectopic atrial tachycardia (no deaths) and supraventricular tachycardia (2 [18%] of 11 patients with supraventricular vs. 23 [30%] of 77 without tachycardia died, p = 0.42) were also not associated with an increased risk of death.

**Other variables and death.** Death was not associated with duration of atrial fibrillation, reason for transplantation, echocardiographic variables measured at the time of the arrhythmia (left atrial size, right ventricular size, right ventricular function score, amount of tricuspid regurgitation), hemodynamic variables measured at the time of the arrhythmia (right atrial pressure, pulmonary artery pressure, pulmonary capillary wedge pressure), or biopsy grade (all p = NS). Death was significantly associated with a decreased left ventricular ejection fraction measured at the time of the arrhythmia (0.55 ±

**Table 3.** Clinical, Echocardiographic, Hemodynamic and Histologic Variables in Recipients With and Without Atrial Fibrillation

| Variable | Recipients With Atrial Fibrillation (n = 21) | Recipients Without Atrial Fibrillation (n = 67) | p Value |
|---|---|---|---|
| Clinical | | | |
| Age (yr) | 47 ± 2.5 | 51 ± 1.3 | 0.20 |
| Gender (M/F) | 18/3 | 58/9 | 0.92 |
| Ischemic time (min) | 170 ± 4.9 | 160 ± 13.7 | 0.43 |
| Hospital stay (days) | 23.6 | 24.4 | 0.39 |
| Echocardiographic | | | |
| LA size (mm) | 47.2 ± 2.6 | 46.3 ± 1.31 | 0.32 |
| Amount of TR | 2.6 ± 0.25 | 2.3 ± 0.12 | 0.23 |
| RV Size | 2.1 ± 0.2 | 1.6 ± 0.11 | 0.06 |
| RV Function | 1.8 ± 0.24 | 1.5 ± 0.01 | 0.17 |
| LV EF | 58.2 ± 3.6 | 62.6 ± 1.34 | 0.16 |
| Hemodynamic | | | |
| RA pressure (mm $H_2O$) | 8.1 ± 1.06 | 8.2 ± 0.67 | 0.91 |
| PA pressure (mm Hg) | 35.3 ± 1.6 | 34.5 ± 1.0 | 0.68 |
| PCW pressure (mm Hg) | 11.5 ± 1.11 | 12.5 ± 0.66 | 0.48 |
| Cardiac output (liters/min) | 5.6 ± 0.65 | 4.9 ± 0.18 | 0.17 |
| Histologic findings | | | |
| Grade 0 | 12 (57.1%) | 47 (70.1%) | NS |
| Grade 1A or 1B | 5 (23.8%) | 14 (20.9%) | NS |
| Grade 2 or 3 | 4 (19.1%) | 6 (9.0%) | 0.19 |

Data presented are mean value ± SEM or number (%) of recipients. EF = ejection fraction; F = female; Histologic findings = International Society for Heart and Lung Transplantation grading system (0, 1A, 1B, 2, 3A, 3B, 4); LA (RA) = left (right) atrial; LV = left ventricular; M = male; PA = pulmonary artery; PCW = pulmonary capillary wedge; RV function = right ventricular function (1 = normal, 2 = mild hypokinesia, 2 = moderate hypokinesia, 3 = moderate hypokinesia, 4 = severe hypokinesia); RV size = right ventricular size (1 = normal, 2 = mild dilation, 3 = moderate dilation, 4 = severe dilation); TR severity = tricuspid regurgitation severity (1 = trace, 2 = mild, 3 = moderate, 4 = severe).

**Figure 2.** Kaplan-Meier survival curves in patients with **(dashed line)** and without **(solid line)** atrial fibrillation.

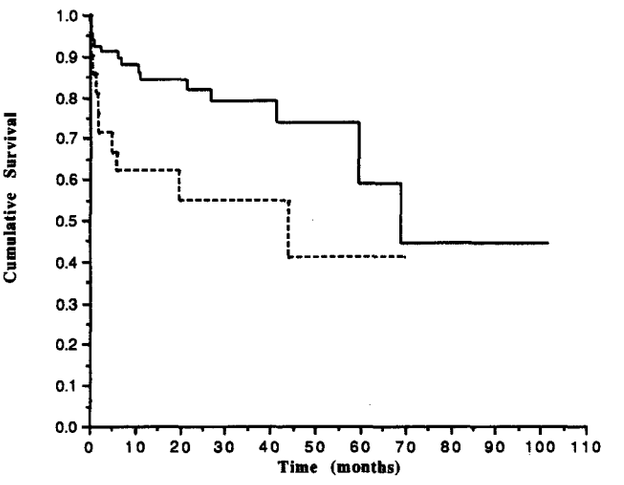

**Table 4.** Cause of Death by Atrial Arrhythmia

| | Atrial Fibrillation (10 deaths) | Atrial Flutter (9 deaths) | Supraventricular Tachycardia (2 deaths) | No Atrial Arrhythmia (13 deaths) |
|---|---|---|---|---|
| Cardiac etiology | Graft dysfunction<br>Rejection (3 recipients)<br>RV failure | Graft dysfunction*<br>Rejection*<br>RV failure* | Graft dysfunction* | Graft dysfunction<br>Rejection<br>RV failure (2 recipients)<br>Sudden death<br>Coronary atherosclerosis (2 recipients) |
| Noncardiac etiology | Fungal pneumonia<br>Sepsis (2 recipients)<br>Multiorgan failure<br>Hepatic failure | Fungal pneumonia*<br>Sepsis*<br>Multiorgan failure*<br>Hepatic failure*<br>Pneumonia<br>Pulmonary failure | Hepatic failure* | Hepatic failure<br>Pancreatitis<br>Lymphoma (3 recipients)<br>ARDS |

*Patients who also had atrial fibrillation. ARDS = adult respiratory distress syndrome; RV = right ventricular.

0.03 in patients who subsequently died vs. 0.64 ± 0.01 in survivors, p = 0.03 by Cox proportional hazards model).

Duration of atrial fibrillation was not significantly associated with the likelihood of subsequent death. Seven of 21 patients had atrial fibrillation that lasted <7 min. However, four of these seven patients died, and mean time from first occurrence of atrial fibrillation to death in these four patients was 35.2 ± 13.4 days (range 7 to 71). In the remaining six patients with atrial fibrillation who subsequently died, mean time to death from first episode of atrial fibrillation was 105.0 ± 97.2 days (range 1 to 591, p = 0.58 for mean time to death). Mean left ventricular ejection fraction was 0.62 ± 0.03 in the four patients with brief atrial fibrillation who subsequently died compared with 0.44 ± 0.07 in the six patients with more sustained atrial fibrillation who subsequently died; however, this difference did not reach statistical significance (p = 0.08).

## Discussion

**Animal data and background.** Substantial data from in vitro and in vivo animal experiments (1–9) have shown that the induction of sustained atrial fibrillation requires the presence of acetylcholine or vagal tone. Vagal stimulation and acetylcholine have been shown (1) to shorten both the action potential duration and the refractory period of canine atrial myocardium. Although it is difficult to sustain fibrillation in normal canine atria, acetylcholine can reproducibly induce at least transient atrial fibrillation when applied directly to the atrial surface (2). Atrial fibrillation can also be induced by delivering a single premature stimulus during continuous electrical stimulation of the vagus nerve (5,25), even with atria of normal size and in the tiny atria of puppies (5). Atropine-induced vagal blockade diminishes, but does not abolish, these effects on atrial refractoriness (2) and terminates acetylcholine-induced atrial fibrillation (4). Similarly, induced atrial fibrillation cannot be sustained in surgically vagotomized dogs (5).

This pro-fibrillatory influence of the vagus may be due to the inhomogeneous effects of vagal stimulation on different parts of the atria (10). There may be differential effects between stimulation of the right and the left vagus nerves; atrial fibrillation was reported to have been more easily induced during stimulation of the right rather than the left vagus nerve (5). Vagal modulation thus increases the inhomogeneity or dispersion of atrial refractoriness, resulting in nonuniform wavefront propagation, and thereby facilitates atrial fibrillation.

**How can atrial fibrillation occur in the absence of vagal modulation?** In the absence of vagal tone, there must be another mechanism responsible for the dispersion in atrial refractoriness that is required for the occurrence of atrial fibrillation. This dispersion in atrial refractoriness may be due to intrinsic myocardial disease or an abnormal neurohormonal or electrolyte milieu. Thus, inhomogeneity in atrial refractoriness may be provided by 1) the abnormally large surgical atrium of the transplanted heart (more likely to be an important factor for the occurrence of atrial flutter); 2) a diseased state of the atrial myocardium due to ischemic injury or surgical trauma; 3) abnormal intraatrial conduction due to altered anisotropy after atrial surgery; 4) a response to heightened catecholamine stimulation; or 5) increased sensitivity to catecholamine levels. The native (explanted) heart, after prolonged exposure to increased levels of circulating catecholamines, manifests catecholamine receptor down-regulation (26,27). However, the transplanted (donor) heart is derived from a more normal hormonal milieu and typically demonstrates normal or increased catecholamine receptor density. Several investigators (28,29) have shown that denervation increases the sensitivity of beta-adrenergic receptors to catecholamine levels in the transplanted human heart. Thus, the transplanted heart may now be exposed to, and indeed demonstrate enhanced sensitivity to, circulating catecholamine levels. The resultant increased dispersion in atrial refractoriness may facilitate the occurrence of atrial fibrillation. This is analogous to the proved increase in susceptibility to ventricular fibrillation during catecholamine stimulation (30,31).

**Published studies reporting atrial arrhythmias in transplant recipients.** Several published studies have reported that atrial arrhythmias do occur in cardiac transplant recipients but have generally failed to distinguished between atrial fibrillation and flutter. Pooled data from seven studies (14,16–18,20, 32,33) that did distinguish between the atrial arrhythmia types included 347 patients. These pooled data report a 12% incidence for atrial flutter and an approximate 5% incidence of atrial fibrillation. Only two studies (14,20) have reported a higher incidence of atrial arrhythmias in the posttransplant period. Hence, most of the published reports suggest that the occurrence of atrial arrhythmias, specifically atrial fibrillation, is an uncommon event in this population.

**Present study.** *Incidence of atrial arrhythmias.* Despite these earlier reports, our study demonstrates that atrial arrhythmias in general, and specifically atrial fibrillation, are a common occurrence in the denervated transplanted human heart. The overall incidence of all atrial arrhythmias (50%) was also higher in our study compared with most, but not all, of the previous reports. This may be due in part to the fact that we noted every instance of atrial arrhythmia, even if relatively short-lived. Thus, the mean duration of ectopic atrial tachycardia in this study was <1 min, and there were seven patients with atrial fibrillation that lasted <6 min. Although atrial flutter was more common than atrial fibrillation, this difference did not reach statistical significance.

*Atrial fibrillation and death.* An unexpected finding of this study was the observed association between the occurrence of late atrial fibrillation and subsequent mortality. The occurrence of atrial fibrillation was a marker of adverse outcome, especially when atrial fibrillation was documented after the first 2 weeks after transplantation. The occurrence of atrial fibrillation was not simply a preterminal event because it predated death by an average of 77 days. Even brief paroxysms of atrial fibrillation were associated with an adverse outcome.

The explanation for this association is not immediately evident. In the absence of vagal modulation, the required dispersion of atrial refractoriness for atrial fibrillation to occur may be provided by a diseased state of the myocardium or an abnormal neurohormonal milieu. Thus, atrial fibrillation in the denervated heart may simply be a marker of an underlying myocardial disease process and the observed increase in subsequent mortality a result of progression of that disease process. In support of this theory, mean left ventricular ejection fraction in the patients with atrial fibrillation tended to be less than that of patients without atrial fibrillation, but this difference did not reach statistical significance. This hypothesis is also consistent with the observations of Heinz et al. (32), who also postulated that there was more extensive electrical atrial abnormality in patients with atrial fibrillation than in those with atrial flutter. This same group of investigators (32) also noted that in patients with inducible atrial flutter, sinus node function (as assessed by measurement of sinus node recovery times and sinoatrial conduction times) was entirely normal. However, in patients with inducible atrial fibrillation, sinus node function was profoundly abnormal. The lack of association between the duration of atrial fibrillation and death is not necessarily inconsistent with this hypothesis. Whether atrial fibrillation is brief or sustained may simply be reflective of the degree of myocardial abnormality or the degree of endogenous catecholamine stimulation.

The proposed link between recognized atrial fibrillation (as a marker of myocardial disease) and death does not directly explain the deaths that occurred from noncardiac causes. However, it is possible, that the abnormal hormonal milieu in these patients with active infection or multisystem failure may have facilitated atrial fibrillation.

*Atrial flutter.* Mean duration of atrial flutter was significantly greater than that of atrial fibrillation and might have been even greater had not four episodes of flutter been terminated by cardioversion or overdrive atrial pacing. It is possible that atrial flutter was more sustained in the present study simply because it may not be dependent on vagal modulation. It is not known whether denervation may have a "permissive" effect on the occurrence of atrial flutter. It has been suggested (34) that the exaggerated response of the denervated heart to endogenous adenosine (35) may play a role in the genesis of atrial flutter, particularly in situations associated with increased adenosine release, such as hypoxia and rejection. The maintenance of atrial flutter requires a critical zone of slow conduction (usually located in the anteroinferior portion of the interatrial septum, near the tricuspid annulus–inferior vena cava isthmus), as evidenced from the recent reports (36,37) on radiofrequency ablation for the common type of atrial flutter. This zone of slow conduction allows a reentrant circuit to be maintained around a zone of block. The long anastomotic suture line between the recipient and donor atria may provide another line of anatomic block that allows sustained reentry to occur in a "corridor" of excitable muscle between it and the tricuspid annulus. Thus, a minimal change in the electrophysiologic properties of the atria (possibly induced by denervation, mechanical handling during surgery, creation of an anatomic zone of block from the suture line or irritation from sutures) may be sufficient to allow atrial flutter to occur. However, for atrial fibrillation to occur, a far greater area of the atrium may need to be affected (32).

**Allograft rejection and atrial arrhythmias.** Several studies have reported an association between cardiac allograft rejection and atrial arrhythmias (15–18). However, in our study an analysis of the results of endomyocardial biopsy samples that were obtained within several days of the atrial arrhythmia, revealed that only a minority (16%) of patients with atrial arrhythmias had histologic evidence for moderate or severe rejection. Further, there was no significant difference in the incidence of rejection between the patients with and without an atrial arrhythmia. This is in keeping with the findings of Little et al. (20) who observed that in patients treated with cyclosporine, atrial arrhythmias were just as common in patients with rejection as in patients without rejection. Romhilt et al. (21) also noted a high prevalence of cardiac arrhythmias throughout the transplant period irrespective of acute rejection in the donor heart (21). A well recognized limitation of

endomyocardial biopsy in detecting histologic rejection is sampling error. Rejection may be patchy, and the biopsy site may not reflect ongoing rejection in other areas of the myocardium.

**Limitations of the study.** The acquisition of data in the present retrospective analysis was dependent on the degree of data entry into the hospital medical record of each patient. In the first 2 to 4 weeks after transplantation, patient monitoring in the intensive care and stepdown units was continuous, and all arrhythmias occurring during the posttransplant period were completely documented. However, ECGs were not recorded at all outpatient follow-up visits, and subsequent hospital admissions were either a result of scheduled annual evaluation and coronary angiography or were necessitated by intercurrent illness. Thus, late follow-up was more intense for the sicker patients, whereas the healthier patients may have had asymptomatic late arrhythmias as outpatients that were not recorded. Hence it was recognized "late" atrial fibrillation that was associated with increased mortality, and the reporting of arrhythmias in this study may have underestimated the incidence of late asymptomatic arrhythmias in healthy outpatients. For the same reason, the time from transplantation to the first occurrence of atrial arrhythmia may have been underestimated because some of the patients without any recognized arrhythmia may have had their first (unrecognized) arrhythmia episode as an outpatient.

Another potential limitation is the relatively small sample size of this retrospective study. Larger numbers of patients will need to be prospectively studied to confirm our preliminary observations.

**Conclusions.** Despite experimental data to the contrary, atrial arrhythmias do occur frequently in the denervated transplanted human heart. Further, atrial fibrillation is commonly seen in the transplanted heart in the absence of vagal modulation. Atrial fibrillation that is recognized after the first 2 weeks after transplantation may be a marker of an underlying disease process and is associated with an increased risk of all-cause mortality. The reasons for this increased risk of death remain unclear because <50% of the deaths were directly due to cardiac dysfunction. Atrial flutter, on the other hand, is a more stable and longer lasting arrhythmia in this population and is not associated with an increased risk of subsequent mortality. Finally, both atrial flutter and fibrillation can frequently occur in the absence of histologically significant rejection or hemodynamic abnormalities.

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