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The Efficacy of Implantable Cardioverter-Defibrillators in Heart Transplant Recipients

Results From a Multicenter Registry

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Background—Sudden cardiac death among orthotopic heart transplant recipients is an important mechanism of death after cardiac transplantation. The role for implantable cardioverter-defibrillators (ICDs) in this population is not well established. This study sought to determine whether ICDs are effective in preventing Sudden cardiac death in high-risk heart transplant recipients.

Methods and Results—We retrospectively analyzed the records of all orthotopic heart transplant patients who had ICD implantation between January 1995 and December 2005 at 5 heart transplant centers. Thirty-six patients were considered high risk for sudden cardiac death. The mean age at orthotopic heart transplant was 44±14 years, the majority being male (n=29). The mean age at ICD implantation was 52±14 years, whereas the average time from orthotopic heart transplant to ICD implant was 8 years ±6 years. The main indications for ICD implantation were severe allograft vasculopathy (n=12), unexplained syncope (n=9), history of cardiac arrest (n=8), and severe left ventricular dysfunction (n=7). Twenty-two shocks were delivered to 10 patients (28%), of whom 8 (80%) received 12 appropriate shocks for either rapid ventricular tachycardia or ventricular fibrillation. The shocks were effective in terminating the ventricular arrhythmias in all cases. Three (8%) patients received 10 inappropriate shocks. Underlying allograft vasculopathy was present in 100% (8 of 8) of patients who received appropriate ICD therapy.

Conclusions—Use of ICDs after heart transplantation may be appropriate in selected high-risk patients. Further studies are needed to establish an appropriate prevention strategy in this population. **(*Circ Heart Fail*. 2009;2:197-201.)**

Key Words: sudden death ■ implantable cardioverter-defibrillator ■ orthotopic heart transplant

Reports of sudden cardiac death (SCD) after cardiac transplantation are limited. Several small studies report widely varying numbers of patients (0.5% to 15%) experiencing SCD after cardiac transplantation.[1–15] The cause of sudden death after heart transplantation is multifactorial with possible contributions from graft injury and ischemic triggers.[16] In the first year after transplantation, SCD usually occurs in the setting of acute rejection. In the years after, SCD often occurs in patients with established allograft vasculopathy. Limited reports from the literature suggest that ventricular tachyarrhythmias may be a common mechanism of sudden death in either setting.[2,17–20]

Clinical Perspective on p 201

The use of implantable cardioverter-defibrillators (ICDs) is well established in patients with ischemic and nonischemic cardiomyopathy and decreased left ventricular ejection fraction (LVEF <35%).[21–24] Unlike the general population, there is little documented experience on the use of ICDs in cardiac transplant recipients.[25] Although clinical experience suggests that ICDs may be useful in certain patients with allograft vasculopathy, its role in heart transplantation has not been well established.

In this multicenter retrospective study, we sought to determine whether ICDs are effective in a group of patients considered at high risk for sudden death after cardiac transplantation.

Methods

The study was approved by the Investigational Review Boards of all participating institutions. We retrospectively analyzed the records of all adult orthotopic heart transplant (OHT) survivors at the Cleveland Clinic Foundation, Columbia University, Massachusetts General

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Hospital, University of Pennsylvania, and Stanford University. Only patients who had undergone ICD implantation between January 1995 and December 2005 after OHT were included in the study. Nine patients included in this study were previously described,[25] and all patients considered for ICD implant had survived at least 1 year post transplant. Patients within 6 months of a severe rejection episode were excluded from the study.

Adult patients selected for ICD implantation were considered high risk for SCD by experienced clinicians. The indications for ICD implantation were history of cardiac arrest, severely decreased LV systolic function (LVEF <35%), severe allograft vasculopathy, or unexplained syncope. "Severely decreased LV systolic function" was defined as LVEF ≤35%. LV dysfunction was defined as LVEF ≤45%. "Severe allograft vasculopathy" was defined as ≥70% stenosis in the proximal left anterior descending artery or left main artery, ≥70% stenosis in ≥2 epicardial vessels or by severe diffuse vasculopathy. "Allograft vasculopathy" was defined as ≥50% stenosis in ≥1 epicardial artery.

Patient demographic data were collected, including age, sex, race, cause of transplantation, diabetes mellitus, hypertension, presence of allograft vasculopathy, year of cardiac transplantation, age at cardiac transplant, and LVEF at time of ICD implant. Device data were collected, including year of ICD implantation, timing of ICD implant after cardiac transplantation, indications for ICD implant, type of ICD implanted, delivery of shocks after ICD implant, rhythm at time of ICD implant, defibrillation threshold testing, and complications associated with ICD implant. Outcome data were collected, including death or retransplantation.

Statistical Analysis

Statistical analysis was performed using SPSS software, (SPSS 12.0, version 2003 for Windows). For univariate analysis, a Student *t* test was used to compare the differences in continuous variables, and the χ^2 test was used to compare the distribution of discrete variables. Variables with *P* values <0.05 were then subject to further analysis by multivariate logistic regression analysis. Patient and device characteristics were compared between patients who received ICD therapy, versus those who did not.

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Population

A total of 2612 orthotopic heart transplantations were performed at the 5 transplant centers from 1995 to 2005, of which 2299 patients (88%) survived at least 1 year after transplant. Of these patients, 36 individuals (1.5%) received ICDs (the Cleveland Clinic Foundation, 3; Columbia University, 7; Massachusetts General Hospital, 1; The University of Pennsylvania, 8; and Stanford University, 17). Table 1 summarizes the baseline characteristics of the patients included.

Patient and Device Characteristics

The average age at OHT was 44±14 years, whereas the mean age at ICD implantation was 52±14 years. The average time from OHT to ICD implantation was 8±6 years. Most patients (61%) who received ICD implants had survived at least 5 years after OHT (Figure 1). Twenty-nine (81%) patients were male. At the time of ICD implantation, 12-lead electrocardiograms revealed normal sinus rhythm in 94% (33 of 35) patients, whereas 2 (6%) patients had ventricular pacing. Most patients (34 of 36, 94%) had ICDs implanted after their first cardiac transplant, whereas 2 individuals (6%) had ICDs implanted after their second transplant. Of the ICDs implanted, 20 (65%) were dual chamber, 10 (28%) were single chamber, and the remaining 6 (17%) were biventricular. The median time from diagnosis of allograft vasculopathy to ICD implantation was 1.5 months, and the median time from diagnosis of severe allograft vasculopathy to ICD implantation was 46 days. 65% patients received ACE inhibitors, 65% β-blockers, 47% calcium channel blockers, and 15% an antiarrhythmic after cardiac transplant.

Table 1. Baseline Characteristics of OHT Patients Receiving ICD Implants

Variable	No. of Patients (n=36) n (%)
Sex	
Male	29 (81)
Female	7 (19)
Mean age at OHT, years	44±14
Mean age at ICD implantation, years	52±14
Mean time from OHT to ICD implantation, years	8±6
Comorbid conditions	
Precardiac transplant	
Diabetes	5 (33)
Hypertension	8 (27)
Coronary artery disease	17 (50)
Postcardiac transplant	
Diabetes	15 (42)
Hypertension	25 (69)
LVEF	45±12%
Electrocardiographic features	
Normal sinus rhythm	33 (94)
First degree AV block	7 (19)
Right bundle-branch block	12 (34)
Left anterior fascicular block	3 (25)
Left posterior fascicular block	1 (8)
QRS interval (ms)	123±36
QT interval (ms)	382±44
Defibrillation threshold (J)	
All patients	21±9
W/graft atherosclerosis	20±8

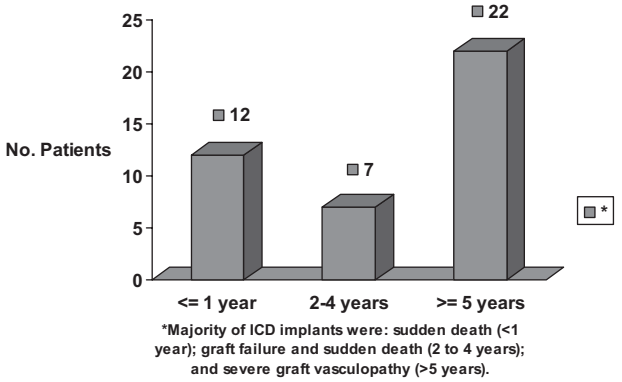

Figure 1. Timing of ICD implantation from OHT.

Table 2. Characteristics of the Groups of Patients Who Underwent ICD Implant

Indications	No. of Patients, n (%)	Avg LV Ejection Fraction, %	LV Dysfunction (LVEF ≤45%); n (%)	Graft Atherosclerosis; n (%)	Appropriate ICD Therapy; n (%)
Severe graft atherosclerosis	12 (33)	52±6	1 (8); LVEF: 35	12 (100)	4 (33); LVEF: 54±3; Athero: 4 (100)
Unexplained syncope	9 (25)	48±12	3 (33); LVEF: 33±5	5 (55)	0; LVEF: NA; Athero: NA
Cardiac arrest	8 (22)	46±12	4 (50); LVEF: 36±4	5 (63)	1 (13); LVEF: 55; Athero: 1 (100)
Severe LV dysfunction	7 (19)	28±5	7 (100); LVEF: 28±5	4 (57)	3 (43); LVEF: 28±5; Athero: 3 (100)

Indication for ICD Implantation

The indications for ICD implantation were severe allograft vasculopathy (n=12), unexplained syncope (n=9), history of cardiac arrest (n=8), and severe LV dysfunction (n=8). Table 2 summarizes the characteristics of patients according to main indication of ICD implantation.

Of the 12 patients with severe allograft vasculopathy, the average LVEF was 52±6%, with one patient displaying LV dysfunction. Most patients (73%) who had ICDs implanted for allograft vasculopathy had 3-vessel disease, whereas the remainder had significant 1-vesel disease in the left anterior descending artery (18%) or 2-vessel disease (9%). Of the 9 patients who experienced unexplained syncope, the average LVEF was 48±12%. Of these patients, 3 (33%) had LV dysfunction and 5 (55%) had underlying graft atherosclerosis. Of the 8 patients with history of cardiac arrest, the average LVEF was 46±12%. Four patients had LV dysfunction and 5 had underlying graft atherosclerosis. Finally, in the group of 7 patients who had ICDs implanted for severe LV dysfunction, the average LVEF was 28±5%, and 4 (57%) had underlying graft atherosclerosis.

An electrophysiology study was conducted in 13 patients who were considered stable for the procedure. Of these 13 studies, 3 showed inducible VT, and 1 both inducible VT and VF. The decision to undergo an electrophysiological study was based on the hemodynamic stability of the patient and decision by the treating physician.

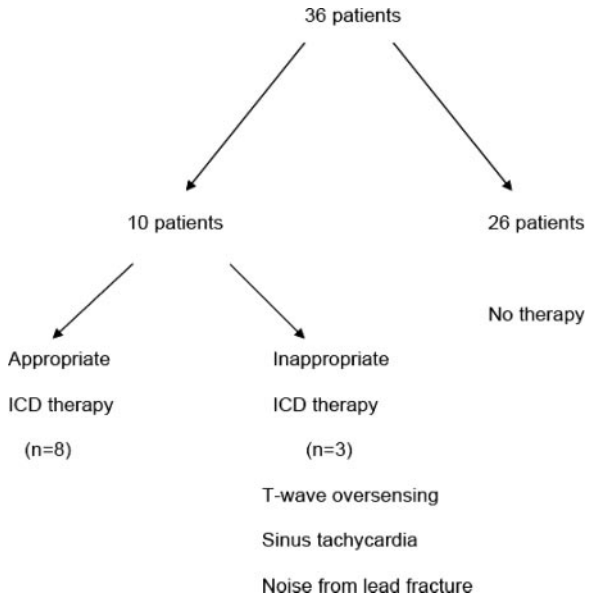

Figure 2. Distribution of ICD therapy among the ICD recipients.

ICD Therapy

Twenty-two shocks were delivered to 10 (28%) patients, of whom 8 (80%) received 12 appropriate shocks for 11 episodes of either rapid ventricular tachycardia or ventricular fibrillation (Figure 2). Three (8%) patients received 10 inappropriate shocks on 3 occasions. These patients are described in Table 3. The inappropriate shocks resulted from T-wave oversensing, sinus tachycardia, and noise resulting from a lead fracture. Allograft vasculopathy was present in 100% (8 of 8) of the patients who received appropriate ICD therapy, versus 64% (18 of 28) of patients who did not receive appropriate ICD therapy ($P=0.05$). In the small group of patients who underwent electrophysiological study, ventricular inducibility was not associated with arrhythmic events. The characteristics of the patients who received appropriate ICD therapy versus those who did not receive therapy are summarized in Table 4.

Complications After ICD Placement

Six (17%) of 36 patients experienced complications from ICD placement, which included infection at the pocket site (5%), displaced leads (5%), pocket hematoma (3%), and lead fracture (3%).

Outcomes After ICD Implantation

The average follow-up time for the patient cohort was 51 months ±26 months. At the end of the study, 32 (89%) patients were alive, of which 3 (8%) had undergone a second cardiac transplantation. Of the 4 deaths, 3 patients died from end-stage heart failure, and 1 from sepsis. A total of 88% (7 of 8) of the patients who received appropriate ICD therapy were alive at the end of the study.

Discussion

This multicenter study is the first to document the efficacy of ICD implantation in high-risk heart transplant recipients.

Table 3. Characteristics of the Group of Patients Who Received Inappropriate ICD Therapy

Patient No.	Age at OHT, Years	ICD Indication	LV Ejection Fraction	Allograft Vasculopathy
1	64	Syncope	55	Yes
2	24	Graft atherosclerosis	55	Yes
3	48	Syncope	40	Yes

Table 4. Characteristics of Patients Who Received ICD Therapy

Variable	Appropriate ICD Therapy (n=8) n (%)	No ICD Therapy (n=28) n (%)
Graft vasculopathy (≥50% stenosis in >1 vessel)*	8 (100)	18 (64)
Average ejection fraction	44±13	45±12
LVEF ≤35%	3 (38)	8 (29)
Severe graft vasculopathy (≥70% stenosis)	4 (50)	8 (29)
Hx cardiac arrest	1 (13)	7 (25)
Unexplained syncope	0	9 (32)
Electrocardiographic features		
Normal sinus rhythm	6 (75)	27 (96)
First degree AV block	1 (13)	6 (21)
Right bundle-branch block	2 (25)	10 (36)
Left anterior fascicular block	0	3 (11)
Left posterior fascicular block	0	1 (4)
QT interval (ms)	362±40	384±39
Average defibrillation threshold (J)	25±9	20±8

*P-value 0.05. No significant different in age, sex, and comorbid conditions were otherwise noted between the 2 groups. Small sample size may limit the generalizability of some of the results.

Almost one third of recipients received therapy, of which the majority (80%) was appropriate. Only 8% of the total shocks delivered were inappropriate. When compared with conventional ICD recipients, a relatively high percentage of the OHT group benefited from ICD therapy. This finding seems to suggest that in patients with allograft vasculopathy, sustained ventricular arrhythmias in the OHT population are not uncommon. Indeed, there seems to be a group of patients after cardiac transplant who are at significant risk for arrhythmic death, and in whom ICD therapy would be beneficial.

Notable is that patients who received ICD therapy for rapid ventricular arrhythmias survived, indicating the possibility of resuscitating OHT patients from sudden death in certain clinical settings. Although there is limited data regarding the types of arrhythmias associated with sudden death in heart transplant recipients, clinical experience seems to suggest that pulseless electric activity is more common after hemodynamically compromising rejection. This observation has led many physicians to question the efficacy of ICDs among OHT patients, and subsequently, had led to a nonuniform pattern of ICD implantation among OHT patients who may be at risk for sudden death. Our study included patients who had survived several years post cardiac transplant (average, 8 years). Among the patients who had received appropriate ICD therapy, all of the individuals had underlying graft vasculopathy, and none were in acute rejection. This observation confirms that ventricular arrhythmias may account for a proportion of the sudden deaths in OHT recipients who survive several years after cardiac transplant, and suggests ICDs would be effective in certain clinical settings after cardiac transplant.

An important finding of this study was the association between graft vasculopathy and shock delivery. All of the patients who received appropriate ICD therapy had underlying graft atherosclerosis. This association between ICD therapy and graft atherosclerosis suggests that allograft vasculopathy may be a trigger for arrhythmias in this high risk population. Allograft vasculopathy may also lead to the development of areas of scarring due to myocardial infarction that may act as a substrate for ventricular arrhythmias.[26,27] In addition to epicardial disease, microvascular disease, which was not studied in these patients, could play a role in the potentially fatal cardiac arrhythmias experienced in this group of patients. Recent studies have suggested its value in predicting long term outcomes after heart transplantation.[28–30]

The study also emphasized the higher rate of complications related to ICD implant in the OHT population than the general population.[31] Seventeen percent of patients experienced infection, pocket hematoma, displaced leads, or lead fractures. This finding illustrates the challenge of placing ICDs in immunocompromised hosts; these patients are more susceptible to infections and may have more challenging vascular access.

Limitations

This study is limited by its retrospective nature. In addition, the number of patients in this study is small, even with the participation of multiple high volume heart transplant centers. The population also reflects a highly select group of patients who were considered high risk for sudden death, and the findings of this study should be cautiously extended to the general OHT population. Despite the small numbers, this study represents the largest experience to date of ICD use in the transplant population. Future studies will need to further characterize those patients at high risk for sudden death, to devise a proper prevention strategy for this patient population.

Conclusions

ICD therapy in patients after cardiac transplantation may appropriately treat ventricular tachyarrhythmias and prevent sudden death in certain OHT patients. Graft atherosclerosis is associated with lethal ventricular tachyarrhythmias, and ICD therapy should be considered in these individuals at high risk for sudden death. However, given the immunocompromised nature of this population, the significant rate of possible complications related to ICD implant should be considered before implant and weighed against the potential benefits of ICD therapy. Future multicenter studies are needed to improve risk stratification for sudden death after heart transplantation.

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Disclosures

Drs Al-Ahmad, Cooper, and Natale received honorario from Medtronic, St Jude, and Boston Scientific. Dr Hsia is a speaker for, received research grant support from, and is on the advisory board for Medtronic; is a speaker for Boston Scientific and St Jude Medical; and received research and fellowship support and is a speaker for Biosense-Webster and Johnson and Johnson. Dr Wang received an educational grant, a fellow grant, and honoraria from and serves on the advisory board for Medtronic, St Jude Medical, and Boston Scientific. Dr Zei is a consultant for Biosense-Webster and a speaker for Medtronic. The remaining authors have no disclosures.

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CLINICAL PERSPECTIVE

Sudden cardiac death is an important mechanism of death after cardiac transplantation. Although the benefits of implantable cardioverter-defibrillators have been well established in patients with heart failure, its role in heart transplantation is not as well defined. In this multicenter cohort study, we demonstrated that a significant proportion of heart transplant patients at high risk of sudden death received appropriate implantable cardioverter-defibrillator therapy. These shocks were effective in terminating ventricular arrhythmias in all cases. A minority of patients received inappropriate shocks. Underlying allograft vasculopathy was present in all of the patients who received appropriate implantable cardioverter-defibrillator therapy. Use of implantable cardioverter-defibrillators may be appropriate in a selected group of high-risk heart transplant recipients. However, more studies are needed to establish an appropriate prevention strategy in this population.