Implantable cardioverter-defibrillator therapy improves long-term survival in patients with unexplained syncope, cardiomyopathy, and a negative electrophysiologic study

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OBJECTIVES The purpose of this study was to evaluate the long-term outcomes of patients with unexplained syncope, ischemic or nonischemic cardiomyopathy, and a negative electrophysiologic study (EPS).

BACKGROUND EPS is frequently performed to evaluate syncope in patients with left ventricular dysfunction. Limited long-term data evaluating all-cause mortality in patients with no inducible arrhythmia or examining the potential benefits from implantable cardioverter-defibrillator (ICD) therapy are available.

METHODS We evaluated 102 consecutive patients with unexplained syncope, cardiomyopathy, and a negative EPS from September 1996 to December 2000. A blinded matched case-control analysis utilized 51 of these patients (19 treated with an ICD and 32 matched controls treated with conventional therapy). We compared primary endpoint of death and documented cardiac arrest of patients treated with ICD therapy to matched controls.

RESULTS Baseline characteristics were similar between groups. There were 14 primary events among the study population during a follow-up period of 44.3 $\pm$ 20 months: 2 in the ICD group and 12 in the conventional therapy group. The hazard ratio for the risk of event in the ICD group compared with the conventional therapy group was 0.18 (95% confidence interval, 0.04–0.85; $P = .04$). Other comorbid conditions, including age, sex, ischemic etiology of heart failure, ejection fraction, and antiarrhythmic use, did not predict outcome. Appropriate ICD shocks occurred in 26% of patients at 2 years.

CONCLUSIONS This study suggests that empiric ICD therapy improves long-term outcomes in patients with unexplained syncope, ischemic or nonischemic cardiomyopathy, and negative EPS.

KEYWORDS Syncope; Implantable cardioverter-defibrillator; Negative electrophysiologic study; Cardiomyopathy; Long-term outcome; Cardiac arrest

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Introduction

Unexplained syncope is a common diagnosis, accounting for approximately 3% of emergency room visits and 1% to 6% of hospital admissions.[1,2] In patients with structural heart disease, this symptom may herald a life-threatening arrhythmia.[3] Mortality is increased in persons with cardiac syncope and in persons with syncope from unknown cause.[4] Risk stratification with electrophysiologic studies (EPS) has been used to determine the need for implantable cardioverter-defibrillator (ICD) placement. Although data exist that support such treatment in patients with ischemic cardiomyopathy and inducible ventricular arrhythmias,[5,6] patients with negative EPS also may be at high risk for sudden

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death.[7] Results of EPS have especially poor predictive value in patients with nonischemic cardiomyopathy.[8] ICD therapy may improve survival in these patients with a prior history of syncope.[9] Knight et al[10] demonstrated that the incidence of appropriate ICD shocks in patients with nonischemic cardiomyopathy, unexplained syncope, and negative EPS was comparable to the incidence of patients with documented sustained ventricular arrhythmia. Debate continues as to whether patients with unexplained syncope, ischemic or nonischemic cardiomyopathy, and a negative EPS benefit from ICD therapy.[11–14] There are few studies evaluating the long-term outcomes of ICD therapy in these patients. The purpose of this study was to evaluate the long-term outcomes of patients with unexplained syncope, ischemic or nonischemic cardiomyopathy, and a negative EPS.

Methods

Study population

We retrospectively evaluated 102 consecutive patients from September 1996 to December 2000 who presented with unexplained syncope, depressed left ventricular function, regardless of etiology, and negative EPS. Patients with recent myocardial infarction within 4 weeks of symptoms, percutaneous coronary intervention or coronary artery bypass graft surgery within 2 months of EPS, New York Heart Association functional class IV for congestive heart failure, history of seizure, life-threatening malignancy, or no objective assessment of ejection fraction by echocardiography, left ventriculography, radionucleotide ventriculography, or nuclear cardiac imaging were excluded from the study. Patients with a history of sustained ventricular tachycardia (VT), those resuscitated from sudden cardiac death, and those with prior positive EPS were excluded. Patients with obvious neurocardiogenic syncope or vasovagal syncope also were excluded.

Patient outcomes were followed with a primary endpoint of survival free of death or documented cardiac arrest. Death was determined by accessing the national Social Security Death Index. A documented cardiac arrest did not include appropriate ICD shocks for VT or ventricular fibrillation (VF).

Appropriate ICD therapy was examined. The number of patients who had both appropriate and inappropriate ICD discharges was compared to rates in a registry group of consecutive patients during the same time period with unexplained syncope, inducible monomorphic VT on EPS, and left ventricular dysfunction.

Electrophysiologic evaluation

Informed consent was obtained prior to all procedures. Programmed ventricular stimulation was performed using single, double, and triple extrastimuli. Sustained monomorphic VT was the only endpoint considered a positive response to programmed ventricular stimulation. Patients with ventricular rhythms other than monomorphic VT were considered noninducible.

Definitions

Unexplained syncope was defined as the transient interruption of cerebral perfusion manifested by loss of consciousness and an inability to maintain postural tone with spontaneous recovery and no clear identifiable cause determined by careful history, physical examination, or testing (i.e., ECG, telemetry, laboratory data). *Ischemic cardiomyopathy* or *ischemic etiology of heart failure* was defined as angiographic evidence of $\geq$75% luminal occlusion of at least one of the major epicardial coronary arteries resulting in left ventricular systolic dysfunction.[15] *Nonsustained ventricular tachycardia* was defined as $\geq$3 consecutive ventricular beats at a rate $\geq$100 bpm. *Sustained ventricular tachycardia* was defined as VT lasting $>$30 seconds or associated with hemodynamic collapse requiring countershock. *Monomorphic VT* was defined as any well-defined ventricular QRS complex with constant axis and morphology on 12-lead ECG, with a VT cycle length $>$200 ms.[16] *Polymorphic VT* was defined as VT with variable ventricular QRS morphology and axis from beat to beat on at least one ECG lead. *Ventricular fibrillation* was defined as an arrhythmia of ventricular origin with a cycle length $<$200 ms requiring cardioversion. Definitions of sudden cardiac death, cardiac death, and noncardiac death were standardized per Kim et al.[17] Reported shocks were confirmed for sustained VT or VF by analysis of stored electrograms. *Appropriate ICD therapy* was defined as an ICD discharge for a VT that meets programming criteria for VT or VF zone of device.

Treatment

Treatment was not specified by the protocol. The decision for ICD placement was based on the response to programmed ventricular stimulation and the judgment of the attending physician.

Clinical follow-up

Follow-up of patients who received an ICD was performed in the arrhythmia clinic at intervals of 3 to 6 months. Patients who did not receive ICD therapy were followed by the referring physician. The national Social Security Death Index was accessed to determine date of death (available at *http://www.ancestry.com/search/rectype/vital/ssdi/main.htm).* Chart review of patients who received an ICD to determine evidence of ICD therapy was performed on all ICD patients. No patients receiving an ICD were lost to follow-up. The last day of follow-up was the date of death for patients who died and was

Table 1 Baseline characteristics of patients with unexplained syncope, cardiomyopathy, and negative electrophysiologic study

Characteristic	ICD (n = 19)	No ICD (n = 32)	*P* value
Age (yr)	59.9 ± 15.9	60.9 ± 12.7	.80
Male	15 (79%)	26 (81%)	.84
Race (Caucasian)	14 (74%)	24 (75%)	.92
Ischemic cardiomyopathy	9 (47%)	19 (59%)	.41
Revascularization	6 (32%)	9 (28%)	.79
Diabetes mellitus	6 (32%)	10 (31%)	.98
Hypertension	10 (53%)	21 (66%)	.36
Dyslipidemia	**8 (42%)**	**5 (16%)**	**.04**
Tobacco	11 (58%)	19 (59%)	.92
Family history of coronary artery disease	7 (37%)	7 (22%)	.25
Ejection fraction	0.27 ± 0.07	0.27 ± 0.06	1.00
Serum sodium	139.1 ± 3.0	138.9 ± 2.9	.79
Serum BUN	25.2 ± 24.7	28.4 ± 17.4	.63
Serum creatinine	1.3 ± 0.3	1.6 ± 1.4	.35
Other sustained ventricular arrhythmias	**6 (31%)**	**2 (6.25%)**	**.02**
Aspirin	17 (89%)	24 (75%)	.21
Beta-blocker	5 (26%)	11 (34%)	.55
Angiotensin-converting enzyme/angiotensin receptor blocker	17 (89%)	25 (78%)	.30
Digoxin	8 (42%)	15 (47%)	.74
Diuretic	11 (58%)	19 (59%)	.92
Antiarrhythmic drug	3 (15%)	2 (6%)	.27
AH interval (ms)	107 ± 33	92 ± 26	.11
HV interval (ms)	59 ± 12	55 ± 14	.28

March 30, 2003 for patients who were not listed as having died on or before this date.

Statistical analysis

While blinded to survival status and length of follow-up, we matched patients who received an ICD to patients undergoing conventional therapy who did not. We compared categorical variables using the Chi-square test (or Fisher exact test for expected counts <5) and the (non-paired) Student's t-test for continuous variables.

Using a logistic regression model, we developed a propensity score using key variables (beta-blocker use, antiarrhythmic use, ejection fraction, and ischemic etiology of heart failure) to predict the likelihood that the patient would have received an ICD.[18] This score was used to match two cases per one control. If only one control was available for a case, we chose to keep the case-control pair rather than exclude the data.

Kaplan-Meier survival curves[19] were compared using the log rank test. Covariate-adjusted analyses of outcomes were performed using a Cox proportional hazards model.[20] Predictor variables (e.g., ischemic etiology of heart failure) with $P < .15$ were entered into a left to right multivariate Cox proportional hazards model. For all analyses, $P < .05$ was considered significant. All tests of significance were two tailed. Analyses were performed using the SPSS for Windows statistical software package (version 10.0.5; SPSS, Chicago, IL, USA) and SAS for windows statistical software package (version 6.12; SAS, Cary, NC, USA).

Results

Patients

Of the 102 patients evaluated, 21 patients received ICD therapy and 81 patients did not. All patients had decreased left ventricular systolic function, unexplained syncope, no prior documented sustained ventricular arrhythmia, and no inducible monomorphic VT on EPS. Two of 21 ICD patients had no match and were excluded. The 19 remaining ICD patients were blindly matched to 32 conventional therapy patients by previously stated method. Appropriateness of matching was confirmed by comparing the ICD (n = 19) and conventional therapy (n = 32) on all relevant variables. The clinical characteristics of the 51 matched patients are given in Table 1. Baseline characteristics and the prevalence of cardiac medications used were similar in the two groups, except for the number of patients with dyslipidemia ($P = .04$) and the number of patients with sustained inducible ventricular arrhythmia other than monomorphic VT ($P = .02$).

Noninvasive evaluation

Patients underwent baseline ECG measurement and blood work upon admission. Left ventricular ejection fraction was obtained by echocardiography, left ventriculography, nuclear imaging, or radionucleotide ventriculography. Mean left ventricular ejection fraction was 27% in the ICD group and the control treatment group ($P = 1.0$).

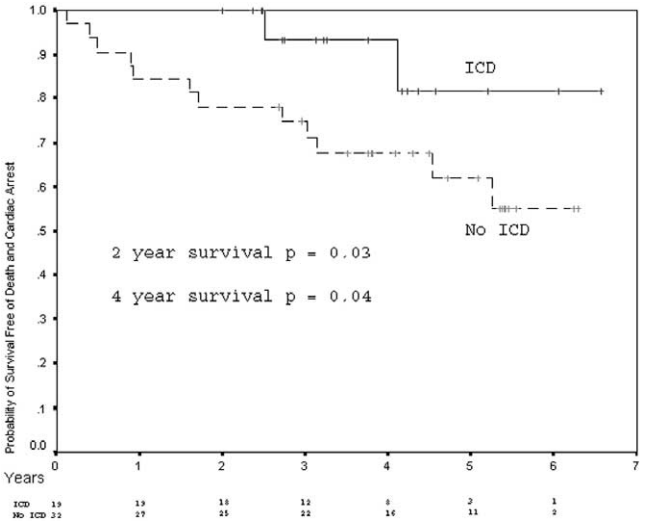

Figure 1 Kaplan-Meier analysis showing actuarial survival free of death or cardiac arrest of patients with unexplained syncope, ischemic or nonischemic cardiomyopathy, and a negative electrophysiologic study who received an implantable cardioverter-defibrillator (ICD) compared with those who did not.

Electrophysiologic evaluation

At the time of EPS, a standard protocol at Washington University Medical Center was used for evaluation of syncope for patients with structural cardiac abnormalities. Mean sinus node recovery time, AH interval, and HV interval were similar between both groups. An *inducible EPS* was defined as sustained monomorphic VT. All patients included in this study were noninducible for sustained monomorphic VT. Other sustained ventricular arrhythmias, such as sustained polymorphic VT and VF, were elicited: 6 in the ICD group and 2 in the conventional therapy group ($P = .02$, 30% vs 6.25%).

Outcome

Primary endpoint event occurred in 14 cases: 2 deaths in the ICD group and 10 deaths and 2 resuscitated cardiac arrests in the conventional therapy group during a follow-up of 44.3 ± 20 months. This finding excluded any appropriate or inappropriate ICD therapy delivered. Patients with unexplained syncope, cardiomyopathy, and a negative EPS treated with ICD therapy had an improved actuarial survival free of death or documented cardiac arrest compared to the conventional therapy group at 2 years ($P = .03$ by log rank, 100% vs 78.1%) and at 4 years ($P = .04$ by log rank, 94.7% vs 68%). Mean survival free of death or documented cardiac arrest was 73 ± 4.4 months for the ICD group and 55.9 ± 4.9 months for the matched conventional therapy group by Kaplan-Meier analysis (Figure 1).

The hazard ratio from a Cox regression analysis that compared the risk of death or cardiac arrest per unit of time in the ICD group with that in the conventional therapy group was 0.18 (95% confidence interval, 0.04–0.85; $P = .04$) The hazard ratio of 0.18 indicates an 82% reduction in the risk of death or documented cardiac arrest at any interval among patients in the ICD group compared with the conventional therapy group (Figure 2).

Beta-blocker use was associated with improved outcome, with a hazard ratio for death or documented cardiac arrest 0.08 (95% confidence interval, 0.01–0.73; $P = .03$.) In contrast, presence of diabetes mellitus was associated with worsened outcome, with a hazard ratio for death or documented cardiac arrest 4.1 (95% confidence interval, 1.8–12.5; $P = .01$). Cox regression analysis revealed no evidence that any of the other preselected baseline variables had a meaningful influence on the hazard ratio (Table 2). The presence of ischemic etiology of heart failure was not predictive of outcome by either univariate or multivariate analysis in this study. The presence of other sustained ventricular arrhythmias considered noninducible did not predict outcome. None of the eight patients with a sustained ventricular arrhythmia other than monomorphic VT suffered an adverse outcome event during follow-up. Antiarrhythmic use did not affect outcome of the primary endpoint.

ICD discharge rate

Appropriate ICD therapy was delivered in 5 of 19 patients (26.3%) with syncope, cardiomyopathy, and negative EPS. This rate was compared to the rate of a separate registry group of 19 cardiomyopathy patients who had unexplained syncope, were inducible for monomorphic VT, and subsequently underwent ICD placement during the same time period. Baseline characteristics between groups were similar, except that the number of

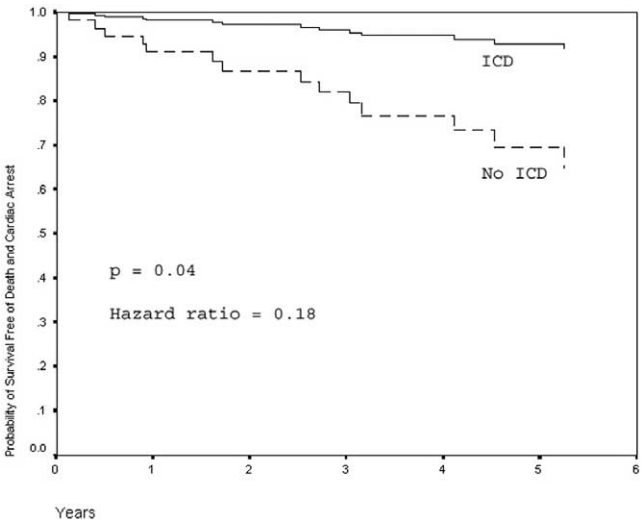

Figure 2 Cox regression analysis showing the risk of death or cardiac arrest per unit of time in patients with unexplained syncope, ischemic or nonischemic cardiomyopathy, and a negative electrophysiologic study who received an implantable cardioverter-defibrillator (ICD) compared with those who did not.

Table 2 Cox regression showing independent associations with primary endpoint

Variable	Univariate *P* value	Multivariate *P* value	Hazard ratio	Confidence interval
Age	.31	NS		
Gender	.94	NS		
Race (Caucasian)	.23	NS		
Ischemic cardiomyopathy	.59	NS		
Revascularization	.38	NS		
Diabetes mellitus	.12	**.02**	**4.1**	**1.80–12.5**
Hypertension	.21	NS		
ICD	.11	**.04**	**0.18**	**0.04–0.85**
Ejection fraction	.65	NS		
Other sustained ventricular arrhythmias	.31	NS		
Angiotensin-converting enzyme/angiotensin receptor blocker	.21	NS		
Antiarrhythmic	.40	NS		
Beta-blocker	.07	**.02**	**0.08**	**0.01–0.73**
Dyslipidemia	.60	NS		
Family history of coronary artery disease	.72	NS		
Tobacco use	.38	NS		

patients who had ischemic cardiomyopathy was greater in the registry group who were inducible for monomorphic VT (Table 3). This finding is not surprising, as most data supporting use of ICD therapy in this setting have occurred in patients with ischemic etiology of heart failure. Table 4 lists the number of patients receiving appropriate and inappropriate defibrillator discharges in patients with unexplained syncope, cardiomyopathy, and negative EPS compared with the registry group of patients with syncope and positive EPS. The number of patients receiving appropriate ICD therapy at 2 years was not statistically different between groups. Inappropriate ICD therapy rate also was similar.

Discussion

Main findings

Patients with unexplained syncope and severe left ventricular dysfunction are at a high risk for death.[21,22] Our findings indicate that patients with unexplained syncope, left ventricular dysfunction, and noninducible arrhythmia on EPS have improved long-term survival free of death and documented cardiac arrest if treated with ICD therapy. Compared with conventional medical therapy, ICD therapy was associated with an 82% reduction in the risk of death or

Table 3 Baseline demographics of patients compared for ICD discharge rate

Characteristic	Inducible registry (n = 19)	Noninducible (n = 19)	*P* value
Age (yr)	70.2 ± 9.6	59.9 ± 15.5	.10
Male	17 (89%)	15 (79%)	.25
White	18 (94%)	14 (74%)	.07
Ischemic cardiomyopathy	**16 (84%)**	**9 (47%)**	**.03**
History of revascularization	11 (58%)	6 (32%)	.1
Diabetes mellitus	10 (53%)	6 (32%)	.19
Hypertension	13 (68%)	10 (53%)	.21
Dyslipidemia	11 (58%)	8 (42%)	.33
Tobacco	10 (53%)	11 (58%)	.92
Family history of coronary artery disease	5 (26%)	7 (37%)	.50
Ejection fraction	0.28 ± 0.06	0.27 ± 0.07	.56
Serum sodium	40.2 ± 2.7	139.1 ± 3.0	.66
Serum BUN	26.2 ± 9.5	25.2 ± 24.7	.36
Serum creatinine	1.7 ± 1.7	1.3 ± 0.3	.08
Aspirin	17 (89%)	17 (89%)	1.00
Beta-blocker	9 (47%)	5 (26%)	.18
Angiotensin-converting enzyme/angiotensin receptor blocker	15 (79%)	17 (89%)	.85
Digoxin	9 (47%)	8 (42%)	.74
Diuretic	9 (47%)	11 (58%)	.33
Antiarrhythmic drug	5 (26%)	3 (15%)	.50
AH interval (ms)	110 ± 44.9	107.4 ± 33.4	.53
HV interval (ms)	55.1 ± 14.8	58.9 ± 12.0	.45

Table 4 Incidence of ICD shocks in patients with inducible vs noninducible sustained ventricular tachycardia

	EPS +	EPS −	*P* value
Appropriate	7/19 (36.8%)	5/19 (26.3%)	.49
Inappropriate	2/19 (10.5%)	4/19 (21.1%)	.37

documented cardiac arrest over a follow-up of 44.3 months (range 24.3–64.3 months). Both groups were well matched and received similar cardiac medical therapy.

Although the exact reasons for ICD placement are unknown between groups, the ICD group had a statistically significantly higher proportion of patients with ventricular rhythms other than sustained monomorphic VT at the time of EPS ($P = .02$, 30% vs 6.25%). This finding on EPS may have influenced the decision to proceed to ICD placement in such a population. The other ventricular arrhythmias considered noninducible were not predictive of outcome in our analysis ($P = .31$), with no patient in this subgroup suffering a primary endpoint event. The presence of ischemic etiology of heart failure and the history of a previous revascularization were analyzed in both univariate and multivariate statistical analysis. Both failed to affect outcome in this patient population. Antiarrhythmic agents had no significant influence on the observed outcome.

Prior studies

The natural history of patients with unexplained syncope and nondiagnostic EPS has been examined in the literature.[23] Prior studies have examined ICD event rates in patients with syncope and structural heart disease. Andrews et al[24] demonstrated that time to first ICD therapy for these patients and those with documented history of sustained ventricular was not significantly different. Knight et al[25] prospectively compared the outcomes of patients with nonischemic cardiomyopathy, syncope, and a negative EPS treated with ICD therapy to patients with nonischemic cardiomyopathy and history of cardiac arrest treated with ICD. There was no significant difference in time to first shock, number of appropriate shocks, or mortality between patients with a history of nonischemic cardiomyopathy and syncope group compared with those who survived cardiac arrest. This finding suggested that patients with syncope and nonischemic cardiomyopathy are at substantial risk for sudden death and benefit from ICD therapy.

Brilakis et al[26] found that programmed ventricular stimulation was not a useful method for risk stratification in patients with idiopathic dilated cardiomyopathy and syncope and may delay necessary ICD implantation. Fonarow et al[9] concluded that patients with nonischemic advanced heart failure and syncope treated with an ICD had lower sudden cardiac death at 2 years.

The results of the current study are consistent with the results of preceding studies. Our study differs by its inclusion of patients with ischemic and with nonischemic etiology of heart failure and use of matched cases to compare patients who received ICD therapy with those who did not.

Study limitations

The limitations of our study include the retrospective evaluation of patient outcomes. Treatment determination was not standardized and therefore may be inherently subject to bias. We limited other confounding factors by using a propensity score to match cases to controls while blinded to the study's outcome and adjusting for covariates with multivariate analysis. Using a propensity score, which improved statistical power, limited our sample size. Lack of the cause of death prevented us from testing the hypothesis that ICD placement prevented sudden cardiac death. Although the cause of death could have been estimated from death certificates, these certificates are often erroneous.[27,28]

Conclusions

Patients with unexplained syncope, cardiomyopathy, and a negative EPS are at high risk for death. Empiric ICD therapy improves long-term outcome in patients with unexplained syncope and ischemic or nonischemic cardiomyopathy, even when EPS is negative.

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