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Implantable Cardioverter Defibrillator Discharge Rates in Patients with Unexplained Syncope, Structural Heart Disease, and Inducible Ventricular Tachycardia at Electrophysiologic Study

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Summary

Background and hypothesis: The implantable cardioverter defibrillator (ICD) is the best available strategy to protect patients from life-threatening ventricular arrhythmia. Although unproven, it is commonly utilized to treat subjects with syncope, a negative clinical workup, structural heart disease, and inducible sustained monomorphic ventricular tachycardia (VT) on programmed electrophysiologic stimulation (EPS). The purpose of this paper was to validate this approach.

Methods: We retrospectively identified 36 subjects who received primary ICD therapy for syncope in the setting of structural heart disease with inducible sustained monomorphic VT on EPS. The cohort was predominantly male (32/36) with underlying coronary artery disease (29/36). The mean left ventricular ejection fraction was 31 ± 12%, and a third of the patients (12/36) had undergone bypass surgery.

Results: The study group was followed for a mean of 23 ± 15 months (range 3–81 months) and experienced an ICD event rate of 22% at 3 months, which increased to 55% at 36 months. This event rate was comparable with the 66% event rate seen in a group of patients with primary ICD therapy for spontaneous life-threatening VT treated during the same time period. No future predictors of ICD events in the study group could be identified.

Conclusion: Syncope patients with negative workup, structural heart disease, and sustained monomorphic VT at EPS are at high risk for future tachyarrhythmic events. Based on present evidence, primary ICD therapy in this group appears warranted and justified.

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Introduction

A proven cardiac etiology for syncope places the patient at high risk of subsequent fatal cardiac events.[1–3] The unpredictable, sporadic, and transient nature of the clinical event, however, eludes electrocardiographic (ECG) documentation for diagnosis and makes establishment of a rational therapeutic program difficult. As self-terminating paroxysmal arrhythmia is common, patients with syncope often undergo provocative electrophysiologic stimulation (EPS) as part of diagnostic evaluation, particularly in subjects who have underlying structural heart disease and ventricular dysfunction. The goal in these patients is to provoke symptoms and arrhythmias under controlled laboratory conditions to duplicate the spontaneous clinical event. While a negative EPS indicates a low risk for sudden cardiac death, a significant proportion of patients with structural heart disease will have inducible sustained monomorphic ventricular tachycardia (VT), a potentially fatal arrhythmia. Inducible VT is considered a likely surrogate for the subsequent spontaneous event and treatment is typically initiated. Retrospective studies have revealed that successful pharmacologic suppression in subjects who test positive at EPS [4–11] appeared to confer a lower mortality and recurrence rate. Hence, based on largely inferential data, various antiarrhythmia strategies have been adopted to combat sustained monomorphic VT when patients present with unexplained syncope.

The justifiable concern of undertreatment has prevented a randomized and placebo-controlled trial assessing the possible benefit of an antiarrhythmic intervention. As a result, the natural history of patients with syncope and inducible VT with structural heart disease remains poorly defined. With the introduction and frequent use of implantable cardioverter defibrillators (ICDs), it has become feasible to identify and treat a high-risk group while still being able to establish what the incidence of recurrent VT/ventricular fibrillation (VF) would be. The ability of these devices to store ECG data and rate characteristics of spontaneous tachyarrhythmia apart from delivering therapy creates a unique opportunity for studying such patients, in many without the confounding effects of

pharmacotherapy. Enhanced understanding may ultimately influence the way these patients are managed. Furthermore, analysis of the prognosis of these patients may in turn validate the current wide use of an ICD in a population of patients defined by a presentation of unexplained syncope, significant structural heart disease, and inducible sustained monomorphic VT. The objectives of this study were (1) to assess the frequency of spontaneous ventricular tachyarrhythmia events based on treatment delivered by ICD, and (2) to identify which clinical variables, if any, would predict an increased risk for subsequent tachyarrhythmic events.

Methods

Patient Selection

The data for this retrospective analysis were derived from 36 patients recruited from four participating centers of the Antiarrhythmics versus Implantable Defibrillator (AVID) Trial prior to AVID enrollment: (1) St. Luke's-Roosevelt Hospital Center, New York, N.Y., (2) University of Rochester Medical Center, Rochester, N.Y., (3) Hahnemann University, Philadelphia, Penna., and (4) University of Oklahoma, Oklahoma City, Okla. All patients met inclusion criteria of (1) hospital admission for an index syncopal event that had no established clinical diagnosis for the index syncope after routine clinical evaluation, that is, unexplained syncope; (2) presence of underlying structural heart disease, defined as presence of coronary artery disease (CAD), prior myocardial infarction, congestive heart failure, valvular heart disease, or hypertrophic cardiomyopathy; (3) electrophysiologic evaluation demonstrating inducible sustained monomorphic VT with cycle length ≥ 180 ms; and (4) subsequent ICD implantation for presumptive syncopal VT as the cause of the index event. Patients who manifested spontaneous documented sustained VT/VF prior to ICD implantation were considered ineligible for the study.

Electrophysiologic Stimulation and Programmed Stimulation Protocol

After obtaining informed consent, patients were studied in the fasting state. All antiarrhythmic drugs were discontinued for ≥5 half lives prior to study. Two or three quadripolar catheters were inserted into the femoral vein and positioned in the high right atrium, across the tricuspid valve, to record the His-bundle electrogram, and in the right ventricle. Pacing was accomplished by means of a programmable stimulator with pulse duration of 2 ms at two times diastolic threshold. Attempts to provoke VT were then accomplished using one to three ventricular extrastimuli delivered after an eight-beat drive train performed at two or three paced cycle lengths. If VT was not induced at the right ventricular apex, the catheter was repositioned in the right ventricular outflow tract and programmed electrical stimulation was repeated. Sustained monomorphic VT was defined as VT lasting ≥ 30 s or requiring termination due to hemodynamic compromise. Patients with only inducible nonsustained VT or sustained VF were not included in the study. Additional electrophysiologic evaluation included assessment of sinus node, atrioventricular (AV) node and His-Purkinje function, and inducibility of supraventricular tachycardia.

Follow-Up

The defined endpoint was analyzed from ICD interrogation or chart review, and included at least one event that resulted in therapy being delivered by ICD. This was defined as the delivery of low- or high-energy shock, or antitachycardia pacing when the ICD programmed rate detection criteria for VT or VF were met. The events were further characterized by review of the external ECG recording (if available), by review of ICD-stored RR intervals or electrogram data, and by the presence of symptoms.

Statistics

All continuous variables are reported as mean value ± standard deviation. To assess predictors of ICD events in our study population, a Cox proportions hazards model was used to estimate relative risk with various clinical variables. The group receiving ICD therapy for cardiac syncope was also compared with a randomly selected group of 36 patients from the St. Luke's - Roosevelt Hospital Center database of patients treated with ICD therapy for documented, spontaneous, hemodynamically significant VT. A Kaplan- Meier survival curve was constructed to show ICD event-free survival in the study population during the follow-up period, and this was compared with the survival curve obtained from the control group described above.

Results

Patient Profile

Thirty-six patients were enrolled into the study after chart review (Table I). All patients presented with syncope and had no established cause for their syncope prior to EPS. The group was predominantly male, with a mean age of 65 ± 10 years and a left ventricular ejection fraction (LVEF) of 31 ± 12% (range 15–57%). Of the 36 patients, 29 had documented CAD, and 12 of these had undergone prior coronary artery bypass surgery (CABG). Another five patients had dilated cardiomyopathy of unknown etiology and one patient had hypertrophic obstructive cardiomyopathy.

Electrophysiologic Stimulation Results and Implantable Cardioverter Defibrillator Selection

All patients underwent EPS using the protocol described above and had sustained monomorphic VT induced with three or fewer extrastimuli. The VT cycle length was 262 ± 45 ms (range 180–384 ms). No other potential cause for syncope was identified. Subsequently, ICD implantation was performed and 16 (44%) patients had first- or second-generation ICD generators inserted that did not have electrogram recall capability. The remaining patients had third-generation de-

TABLE I Profile of 36 patients enrolled in the study

Subject	Age (years)	Gender	SHD	EF %	Beta Rx	CABG	VTCL	F/U	First event (months)
1	44	M	CAD	40	Y	Y	330	50	
2	77	M	CAD	39	Y	Y	220	21	3
3	55	M	CAD	20	Y	N	300	23	1
4	75	M	CAD	20	Y	N	200	17	
5	66	M	CAD	30	N	N	240	20	1
6	70	M	DC	15	N	N	210	37	1
7	65	M	CAD	36	Y	Y	280	79	1
8	77	M	CAD	40	N	N	280	18	4
9	67	M	CAD	20	N	N	226	48	
10	54	M	DC	28	N	N	240	36	36
11	69	M	DC	20	N	N	250	27	
12	70	M	CAD	37	Y	Y	290	30	1
13	72	M	CAD	20	Y	Y	230	36	
14	70	F	CAD	45	N	N	340	8	
15	74	M	CAD	60	Y	Y	280	19	7
16	80	M	CAD	30	N	N	300	11	7
17	66	M	CAD	45	Y	N	210	15	
18	58	F	HCM	57	Y	N	270	32	
19	69	M	DC	15	N	N	240	17	12
20	58	M	CAD	35	Y	Y	245	6	
21	65	M	DC	30	N	N	240	41	
22	79	M	CAD	45	N	Y	250	12	
23	83	M	CAD	45	Y	N	240	12	
24	61	M	CAD	16	N	Y	350	8	
25	71	M	CAD	50	N	Y	240	26	
26	58	M	CAD	18	N	N	225	6	
27	59	M	CAD	45	Y	N	260	7	
28	79	M	CAD	30	N	N	280	14	
29	63	M	CAD	30	N	N	180	17	
30	65	M	CAD	20	Y	N	230	3	
31	67	F	CAD	20	N	Y	322	36	
32	57	F	DC	15	Y	N	384	36	12
33	49	M	CAD	28	Y	Y	270	10	1
34	72	M	CAD	22	N	N	220	22	13
35	36	M	CAD	30	N	N	310	11	1
36	50	M	CAD	35	N	N	240	18	6

Abbreviations: Beta Rx = treatment with beta blockers, CABG = coronary artery bypass grafting, EF = ejection fraction, F/U = follow-up in months, SHD = structural heart disease, VTCL = ventricular tachycardia cycle length in ms, M = male, F = female, CAD = coronary artery disease, DC = dilated cardiomyopathy, HCM = hypertrophic cardiomyopathy, Y = yes, N = no.

vices with transvenous leads able to store electrograms or RR intervals of events that triggered ICD discharge.

Follow-Up and Implantable Cardioverter Defibrillator Therapy

Subjects were followed for a mean period of 23 ± 15 months (range 3–81 months). During this period, 16 patients (44%) experienced ICD intervention: 13 patients experienced one or more shocks and 3 patients experienced one or more episodes of antitachycardia pacing that were followed by ICD discharge. In five patients (32%), ICD shock was preceded by syncope. When event-free survival was graphically analyzed (Fig. 1), the likelihood of ICD intervention during the follow-up was high. At 3 months, 22% of the study group had had an ICD event; this rate gradually increased over time to 55% at 36 months. It was significant that no instances of sudden cardiac death were documented during the study. Three patients, however, died of progressive congestive heart failure and another patient died of hepatic failure during the follow-up period.

Correlation of Induced and Clinical Ventricular Tachycardia Rate

We compared the cycle length of the ICD-detected VT with that induced in the electrophysiology laboratory. Electrograms

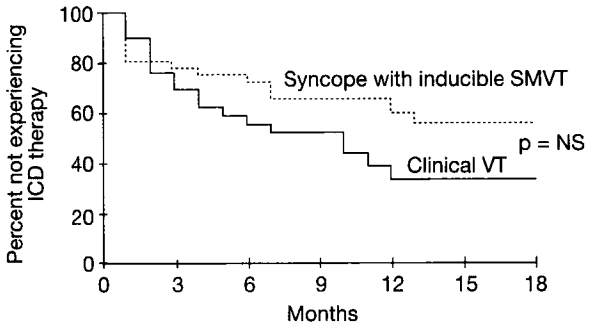

FIG. 1 Implantable cardioverter defibrillator (ICD) event-free survival for subjects with syncope, structural heart disease, and inducible sustained monomorphic ventricular tachycardia (SMVT) is illustrated here. Event rates in this study group are also compared with those seen in a group of patients treated with ICD therapy for documented hemodynamically significant clinical ventricular tachycardia.

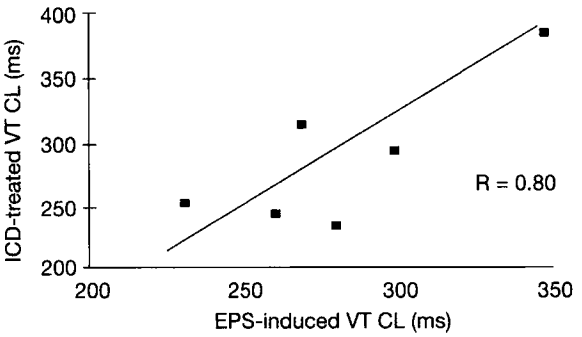

FIG. 2 In six patients, the induced ventricular tachycardia (VT) cycle length correlated well with the spontaneous VT cycle length based on an analysis of electrograms (n = 3) and RR intervals (n=3). CL = cycle length, EPS = electrophysiologic stimulation, ICD = implantable cardioverter defibrillator.

(n = 3) and RR intervals (n = 3) were available in six patients. In this small subset there was a strong relationship between induced and spontaneous VT cycle length with a correlation coefficient of 0.8 (Fig. 2).

Antiarrhythmic Drug Treatment

Twelve patients received class I or class III medications as adjunctive therapy at some point during follow-up. Antiarrhythmic treatment was begun after ICD event in seven of these patients (Table I). Among them, three patients were treated with amiodarone, two received procainamide, and one patient received sotalol. One patient with multiple shocks was treated with both amiodarone and procainamide. Of the 20 subjects without ICD therapy during follow-up, 5 were treated with a class I or class III agent: 2 were on amiodarone, 1 each was placed on sotalol and dofelitide, and 1 patient received brief treatment with quinidine. Sixteen patients (44%) were taking beta blockers during follow-up.

Predictors of Events

To determine which factors, if any, would predict future ICD events in this study population, Cox's regression analysis was performed. None of the variables including age, use of beta blockers, ejection fraction, history of CABG, or induced VT cycle length were able to predict the development of ICD therapeutic events successfully.

Comparison with Group with Documented Ventricular Tachycardia

The event rate in our study group was compared with ICD event-free survival in a group of 36 control patients chosen randomly from the ICD database at one of the participating institutions (St. Luke's-Roosevelt Hospital Center). All patients in the control group had documented hemodynamically significant spontaneous sustained monomorphic VT and were treated with primary ICD therapy. The mean age was 64.6 ± 11.7 years and patients were predominantly male (77%). The majority of the patients had CAD (87%) with an LVEF of 37.2 ± 13.0%. All patients had inducible sustained monomorphic VT in the electrophysiology laboratory with a VT cycle length of 273 ± 47.0 ms. The follow up was 24 ± 14 months. There was no significant difference in any of these measured variables between the study and control groups. During follow-up, patients in the syncope group had a risk and pattern of ICD therapy that was comparable to the group of patients with documented VT (Fig. 1). At 6 months, 28% of the syncope group versus 40% of the documented VT group experienced therapy. At 36 months, however, 55% of the syncope group and 66% of the VT group had ICD therapy at least once (p = NS).

Discussion

Natural History of Unexplained Syncope

Although available data suggest a 1-year mortality in excess of 10%, the pathogenesis of fatal events in patients with a history of unexplained syncope in the presence of structural heart disease remains unclear. While this high mortality seen following cardiac syncope may simply reflect the severity and progression of underlying structural heart disease, the reduction in mortality by various antiarrhythmic drug strategies shown in nonrandomized clinical trials appears to suggest that there may be a high risk of sudden cardiac death that can be modified. If this implied arrhythmogenic risk is indeed validated, the poor outcomes in patients with cardiac syncope may be potentially altered by appropriate and optimal therapeutic intervention. The ICD is presently the best antiarrhythmic therapy available to reduce sudden cardiac death and even all-cause mortality in defined patient subsets;[12,13] however, not all high-risk patients benefit.[14] Consequently, if VTs play a significant role in subjects with syncope and structural heart disease, it then seems prudent and rational to predict that ICD therapy will successfully impact on outcomes in this group of patients. While a large, prospective, multicenter randomized

trial may be necessary to determine ideal treatment strategies conclusively, this in turn may not be mandatory if strong unidirectional benefit can be proven by multiple clinical observations.[15, 16] However, before universally recommending primary ICD device therapy in patients with unexplained syncope and structural heart disease, the risk of VT in patients with inducible VT will have to be adequately quantitated and effectively validated. Much previous data are hampered by the absence of untreated controls and contaminated by treatment with predominantly class I drugs. The availability of the ICD facilitates assessment of ventricular tachyarrhythmic risk without introducing the confounding effects of drug therapy.

Main Findings

We have shown that patients with structural heart disease who experience clinical syncope and have inducible monomorphic VT at EPS are at high risk for future ventricular tachyarrhythmic events. This risk of 55% during the 36 months of follow-up was comparable with (Fig. 1) the risk encountered by patients whose VT was documented but who otherwise had similar clinical characteristics. The rate of ICD discharge is also comparable with that observed in other well-established, high-risk patient cohorts.[17–19] Our findings are also consistent with the recent report by Link *et al.*[20] who followed 50 consecutive patients with unexplained syncope, inducible ventricular arrhythmia, and primary ICD therapy. The actuarial probability of appropriate ICD therapy in this group was 22% at 1 year and 50% at 3 years, with a sudden cardiac death incidence of only 2%. Similarly, Militianu *et al.* studied 33 consecutive patients who received an ICD after electrophysiologic testing for unmonitored syncope.[21] Over a median follow-up of 17 months, 36% of the study population received appropriate ICD discharge.

Another striking feature is the clustering of events around the index clinical event. Thus, 56% of our study patients who experienced ICD events did so within 6 months of implantation and 20% within the first month. This is consistent with survival curves of both sudden cardiac death and total cardiac death, which show that the most rapid rate of attrition occurs during the first 1 to 7 months after the index clinical event.[22] This further implicates the role of arrhythmia in these patients and appears to confine the window of opportunity in treating these patients to the period immediately following clinical presentation.

Role of Electrophysiologic Stimulation

Sustained VT arising from a region of scar is the likely etiology in the majority of victims of sudden cardiac death with CHD and probably other forms of ventricular dysfunction as well. The mechanism of these arrhythmias is reentry, and consequently they can be reproduced by induced programmed electrical stimulation in the laboratory. As most arrhythmic events are both sporadic and transient, clinicians have resorted to EPS to stratify risk in various clinical settings. Syncope in the presence of structural heart disease may be a manifestation of a hemodynamically significant ventricular arrhythmia and consequently EPS is commonly employed. Our study shows that the inducibility of sustained monomorphic VT by EPS in this setting identifies a group of patients at high risk for future VT and both justifies and validates its use in this situation. A reasonable correlation between clinical and inducible VT was also found, albeit in a limited number of subjects. The apparent protection offered by ICD therapy in the study group appears to make this approach purposeful. Illustrating this is the absence of sudden cardiac death during the study period and in similar studies,[20, 21] which is in contrast to that seen in other patient groups unprotected by ICD and treated by pharmacotherapy alone. Bass *et al.* studied 37 patients with positive EPS for unexplained syncope (31 with inducible VT), and at 3 years the sudden cardiac death rate in this population was 48%.[23] Similarly, Click *et al.* reported a sudden cardiac death rate of 24% in 46 patients with inducible VT at EPS for unexplained syncope in the presence of bundle-branch block on surface ECG.[24] Further validation of EPS is evident by ICD event rates observed in our patients with syncope, which are comparable with event rates seen in our control group of high-risk patients with documented VT. As similar high-risk patients clearly benefited in the AVID trial,[12] it also appears reasonable to extrapolate possible ICD benefit to syncope patients.

Predictors of Events

While identification of subgroups of patients at higher risk for ICD events would be beneficial for stratification, none of the variables we measured were able to predict outcome. This is in contrast to earlier studies by Kelly *et al.* and Tebbenjohanns *et al.*[25, 26] in which a low ejection fraction (EF) was found to be a strong predictor of future ICD events. This discrepancy may arise from small sample sizes in this and previous studies and the overall low EF in our entire study group, which may have masked our ability to discern the impact of EF. Militianu *et al.*[21] reported sustained monomorphic VT on EPS and LVEF < 35% as independent predictors of ICD discharge. Our observations were restricted to patients all of whom had inducible sustained monomorphic VT on EPS. Unlike the study by Link *et al.*,[20] which reported a significantly greater event rate in patients with VT cycle length < 263 ms, a correlation between VT cycle length and future ICD events could not be elicited in our population.

Limitations

There are several limitations to our observations, including its small size and retrospective nature. A minority of patients were managed with antiarrhythmic agents that carried significant proarrhythmic potential and may have altered the natural history; however, medications were added after the first ICD shock in most patients and this would not affect survival calculations. In the early models of the ICDs, a number of shocks could only be assessed on clinical grounds alone. Furthermore, while documenting the expected low arrhythmic risk in a noninducible group of patients would strengthen our observations, these data are not available and ICD implantation was not routinely done.

Conclusions

Over the past decade, considerable strides have been made in ICD technology and implantation techniques. The efficacy of the device is now established and indications for its use are being expanded. A body of evidence, albeit retrospective, has now emerged that establishes VT risk in patients with unexplained syncope, structural heart disease, and inducible VT. These observations, while indicating risk for future ventricular arrhythmias, also appear to suggest, but not prove, a potential mortality benefit with ICD therapy. Prospective trials comparing ICD therapy with conventional treatment[27] and large observational studies (J.S. Steinberg for AVID investigators, personal communication) will also add clinically relevant information to guide treatment for syncope. In the absence of available randomized data, the present strategy of diagnostic EPS followed by ICD placement in patients with inducible VT and with unexplained syncope and structural heart disease appears both warranted and justified.

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