CARDIOVASCULAR MEDICINE

Comparative follow up of patients with implanted cardioverter-defibrillators after induction of sustained monomorphic ventricular tachycardias or ventricular fibrillation by programmed stimulation

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Heart 2003;89:629–632

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Accepted
6 December 2002

Objective: To investigate the prognostic value of induced monomorphic ventricular tachycardia (VT) and ventricular flutter or fibrillation (VF) during programmed electrical stimulation in patients with a high risk for sudden arrhythmogenic cardiac death.

Design: Prospective cohort study.

Patients: 102 patients at high risk for arrhythmogenic sudden cardiac death who received an automated implantable cardioverter-defibrillator (AICD) were evaluated. 56 patients received the AICD for primary prevention and 46 for secondary prevention. 58 patients had induction of a monomorphic VT (VT group) and 44 had induction of a polymorphic VT, ventricular flutter, or ventricular fibrillation (VF group) during programmed electrical stimulation. Average follow up was 20 months in both groups.

Main outcome measures: Appropriate AICD protocol.

Results: In patients who received the AICD for primary prevention, 16 of 32 patients in the VT group, compared with only four of 24 patients in the VF group, received an appropriate AICD protocol ($p = 0.02$). In the entire study population, 479 appropriate AICD protocols were recorded in 28 (48%) patients in the VT group and 28 appropriate protocols in 11 (25%) patients in the VF group. Cumulative Kaplan-Meier event-free survival curves were significantly different ($p = 0.02$).

Conclusion: Induction of VF during programmed electrical stimulation is of no prognostic value even in high risk patients without previously documented ventricular fibrillation.

A survival benefit of using an automated implantable cardioverter-defibrillator (AICD) in patients at high risk for sudden cardiac death has been documented by several recent studies. This includes patients with cardiac arrest caused by a ventricular tachyarrhythmia without a transient or reversible cause¹ and patients with coronary artery disease, left ventricular dysfunction, non-sustained ventricular tachycardia (VT), and inducible sustained VT or ventricular flutter or fibrillation (VF) during programmed electrical stimulation.^{2–3} While induction of VT indicates a specific arrhythmogenic anatomic substrate,⁴ induction of VF increases greatly with the aggressiveness of the stimulation protocol and therefore may be an unspecific response.⁵ As has been shown in several previous studies, the induction of VF in patients without prior documentation of sustained ventricular tachyarrhythmia and with preserved left ventricular function,^{6–8} even when induced with one or two extrastimuli,⁹ is not useful in the prediction of clinically relevant tachyarrhythmias. However, the value of induced VF during programmed stimulation in patients at high risk for arrhythmogenic sudden cardiac death is controversial.^{10–12} Studies to evaluate the predisposition to spontaneous ventricular arrhythmias, particularly in patients after myocardial infarction, found that both VT and VF induction are predictive.^{13–14} This has led to inclusion of these patients in treatment groups in recent trials that investigated the value of AICD implantation.^{2–3} We therefore conducted a prospective cohort study in which all high risk patients who had induction of a sustained ventricular arrhythmia during programmed electrical stimulation received an AICD and we related their outcome to the type of induced arrhythmia.

METHODS

Study population

During a period of 15 months, 694 patients without an AICD underwent programmed electrical stimulation at our institution. The decision to refer the patients to electrophysiological testing and to AICD implantation was not part of the study and was based on the clinical practice of the institution. Sustained ventricular tachyarrhythmia was induced in 186 patients, and 122 with impaired left ventricular function received an implantable cardioverter defibrillator. Twenty patients had their follow up at foreign institutions and therefore were not eligible for this study. The 102 patients studied here consisted of 56 who had received their AICD for primary prevention and 46 for secondary prevention (fig 1). To be eligible for primary prevention, patients who received an AICD must have had coronary heart disease with a left ventricular ejection fraction below 40% and documented non-sustained VT. Inclusion criteria for secondary prevention were cardiac arrest caused by VT or VF without a transient or reversible cause and syncope of undetermined origin. All data were obtained during routine three month clinical follow up visits (table 1).

Electrophysiological testing

After written consent was obtained, the procedure was performed with the patient in the fasting state. Patients were

Abbreviations: AICD, automated implantable cardioverter-defibrillator; MADIT, multicenter automatic defibrillator implantation trial; MUSTT, multicenter unsustained tachycardia trial; VF, ventricular flutter or fibrillation; VT, ventricular tachycardia

Figure 1 Patient selection protocol. Patients were recruited from 694 consecutive patients who underwent programmed electrical stimulation. An automated implantable cardioverter defibrillator was implanted in 122 of 186 patients with induction of a sustained ventricular tachyarrhythmia and impaired left ventricular function, and they were eligible for the study. Follow up data were obtained from all 102 patients who had their follow up at the study centre. AICD, automated implantable cardioverter-defibrillator; EF, ejection fraction; PES, programmed electrical stimulation; PP, primary prevention; SP, secondary prevention; VF, ventricular flutter or fibrillation; VT, ventricular tachycardia

sedated with 5–10 mg diazepam orally. With the exception of amiodarone, all antiarrhythmic drugs were discontinued for at least five half lives before the study. Amiodarone was discontinued for at least 10 days before testing. Under local anaesthesia, standard quadripolar catheters were advanced through the right femoral vein to the right atrium, His bundle, and right ventricle. Standard 12 lead surface ECGs and bipolar endocardial electrograms were recorded. Programmed right ventricular stimulation was undertaken at up to three basic drive rates (550, 400, and 330 ms) with up to three extrastimuli at twice diastolic threshold (1–4 mA, impulse duration 1 ms). Stimulation was from the right ventricular apex. The shortest coupling interval was 150 ms. Coupling intervals were shortened in 10 ms steps until refractoriness or 150 ms was reached. The study was terminated after induction of any sustained ventricular arrhythmia or, if no

Table 2 Numbers of automated implantable cardioverter-defibrillator (AICD) protocols that were appropriate in patients with coronary heart disease, impaired left ventricular function (ejection fraction <40%), and documented non-sustained VT

	Number of patients*	Overdrive pacing	Cardioversion
VT group	16 (50%)	206	87
VF group	4 (17%)	4	3

*p=0.02.

arrhythmia was induced, at the end of the complete protocol. Patients were considered to have no inducible arrhythmia if ventricular extrasystole lasted < 10 seconds. All ventricular tachyarrhythmias with a polymorphic appearance at onset and throughout the episode and ventricular flutter (cycle length < 230 ms) that did not terminate spontaneously were classified as VF.

Patient follow up

All patients had a prehospital discharge test (start of the follow up time) for the implanted device and were evaluated every three months. Antitachycardia protocols of the defibrillators were programmed in at least two zones, including empirical antitachycardia pacing in the first zone and shock treatments in the VF zone. The incidence and number of AICD protocols were assessed. A protocol was classified as appropriate if sinus tachycardia or atrial fibrillation could be ruled out by the morphology of the intracardiac electrograms, by analysis of the RR intervals, and on the basis of the response to the protocol.

Statistical analysis

Continuous variables are expressed as mean (SEM) and were compared by Student's *t* test. Nominal variables were compared by Fisher's test or a χ^2 test, when appropriate. To compare Kaplan-Meier survival curves, a log rank test was performed.

RESULTS

Primary prevention group

As outlined above, 56 of the 102 patients received their AICD for primary prevention. The induced ventricular arrhythmia

Table 1 Patient baseline characteristics

	VT group (n=58)	VF group (n=44)	p Value
Age (years)	65.8 (10.9)	62.54 (10.9)	0.14
Men (%)	91.3	81.8	0.23
Follow up (months)	22.1 (11.1)	19.9 (11.6)	0.33
LV ejection fraction (%)	30.1 (8.6)	32.8 (8.0)	0.13
β Blocker (%)	72.4	72.7	1.0
Antiarrhythmic medication (%)	32.8	22.7	0.19
Coronary heart disease (%)	81.0	81.8	1.0
Idiopathic dilated cardiomyopathy (%)	15.5	11.4	0.77
Other cardiac disease (%)	3.4	6.8	0.65
Diabetes (%)	22.4	22.7	1.0
Induction with one to two ES (%)	50	34.1	0.1
Induction with three ES (%)	50	65.9	
Reason for ICD implantation (%)			
Primary prevention	55.2	54.5	1.0
History of cardiac arrest	13.8	31.8	0.02*
History of syncope	8.6	11.4	0.74
History of sustained VT	22.4	2.3	0.003*

Continuous data are mean (SEM).

*The only significant differences.

ES, ventricular extrastimuli delivered at programmed electrical stimulation; LV, left ventricle; VF, ventricular flutter or fibrillation; VT, ventricular tachycardia.

Table 3 Numbers of AICD protocols that were appropriate in all patients of the study (primary and secondary prevention)

	Number of patients*	Overdrive pacing	Cardioversion
VT group	28 (48%)	387	92
VF group	11 (25%)	9	19

*p=0.04.

Patients at risk

MVT	58	34	23	6	1	0
PVT/VF	44	33	16	8	3	2

Figure 2 Kaplan-Meier curves of event-free survival in patients with induced ventricular tachycardia and ventricular flutter or fibrillation during programmed electrical stimulation. MVT, monomorphic ventricular tachycardia; PVT/VF, polymorphic ventricular tachycardia/fibrillation.

was a monomorphic VT in 32 patients (VT group) and ventricular flutter (n=15) or fibrillation (n=9) in 24 patients (VF group). Sixteen (50%) patients in the VT group and four (17%) patients in the VF group received 293 versus 7 appropriate AICD protocols, respectively (table 2). The 293 protocols in the VT group consisted of 206 overdrive pacing

protocols and 87 cardioversion shocks compared with four overdrive pacing protocols and three cardioversion shocks in the VF group. Three of the four patients who received protocols in the VF group had a left ventricular ejection fraction below 25%.

Event rate in all AICD patients with induced VT and VF

Twenty eight patients (48%) in the VT group and 11 patients (25%) in the VF group received 479 and 28 appropriate AICD protocols, respectively ($p = 0.04$) (table 3). In the VT group, patients received 387 overdrive pacing protocols and 92 cardioversions. In the VF group, nine overdrive pacing protocols and 19 cardioversion shocks were recorded. Seven of the 11 patients with protocols in the VF group had a cardiac arrest with documented ventricular fibrillation in their history. Kaplan-Meier curves for event-free survival were significantly different (fig 2).

Appropriate AICD protocols in patients with induced VT or VF

In patients with an induced VT during programmed stimulation, the incidence of appropriate AICD protocols was independent of the mode of induction (with one to two or three extrastimuli), the presence of a history of cardiac arrest, syncope or sustained VT, and the degree of left ventricular dysfunction (table 4).

Surprisingly, in the VF group, the aggressiveness of the stimulation protocol that led to induction of the index arrhythmia had no impact on the prognostic value with regard to future appropriate AICD protocols. In contrast, the presence of a history of cardiac arrest with documented ventricular fibrillation was predictive of appropriate AICD protocols. Only four of the 11 patients with appropriate AICD protocols in the VF group had no history of these events; three of them had severely impaired left ventricular function (ejection fraction < 25%). Severely depressed left ventricular function was another predictive value in this patient group, with a 55% incidence of appropriate AICD protocols compared with only a 15% incidence in the remaining patients ($p = 0.045$) (table 5). With a single exception, all patients in the VF group who received appropriate AICD protocols during a mean follow up of 20 months had either a positive history of cardiac arrest with documented ventricular fibrillation or severely impaired left ventricular function.

Table 4 Comparison of subgroups of patients with induced VT during programmed electrostimulation with appropriate AICD protocols

	Patients with appropriate protocols			p Value
One to two extrastimuli	59%	Three extrastimuli	37%	0.12
Primary prevention	50%	Secondary prevention	46%	0.79
LVEF ≤ 25%	48%	LVEF > 25%	49%	1.0

None of the parameters was predictive. LVEF, left ventricular ejection fraction.

Table 5 Comparison of subgroups of patients with induced VF during physiological electrostimulation with appropriate AICD protocols

	Patients with appropriate protocols			p Value
One to two extrastimuli	35%	Three extrastimuli	21%	0.47
Ventricular flutter induced	30%	Ventricular fibrillation induced	19%	0.49
Primary prevention	17%	Secondary prevention	33%	0.3
No history of cardiac arrest with VF	13%	History of cardiac arrest with VF	50%	0.02
LVEF ≤ 25%	55%	LVEF > 25%	15%	0.045

Severely impaired LVEF and a history of cardiac arrest with documented VF both were predictors of appropriate AICD protocols. The mode of VF induction was not predictive of events.

DISCUSSION

The only baseline characteristics that were significantly different were a higher incidence of a history of cardiac arrest in the VF group and of a history of sustained VT in the VT group. In accordance with this observation, a previous study had found that a polymorphic pattern of induced ventricular arrhythmia distinguished survivors of cardiac arrest from patients presenting with sustained VT.¹⁵ Both a history of cardiac arrest with documented VF and severely impaired left ventricular function were predictive of appropriate AICD protocols in patients with induced VF. Only one of the patients without a positive history or severe left ventricular dysfunction in this group had an appropriate AICD protocol. In contrast, in patients with induced VT, the incidence of an appropriate AICD protocol was the same, regardless of a history of documented severe VT or severe left ventricular dysfunction, indicating that induction of VT during programmed stimulation selects patients with future appropriate AICD protocols better than these clinical variables.

Patients with induced VT during programmed electrical stimulation had a more than 10-fold higher frequency of appropriate AICD protocols. More than twice as many patients in this group received appropriate protocols compared with the VF group.

More than 50% of the studied patients received an AICD for primary prevention based on the criteria derived from the MADIT (multicenter automatic defibrillator implantation trial) and MUSTT (multicenter unsustained tachycardia trial).^{2,3} This comprises patients with coronary heart disease, impaired left ventricular function, and non-sustained VT. In 24 patients with these characteristics in whom VF was induced during programmed stimulation, only four (17%), three of them with severely impaired left ventricular function, had an appropriate AICD protocol during follow up compared with 16 (50%) patients with these criteria in the VT group.

The present study is in line with previous reports on the prognostic value of VF induction during programmed electrical stimulation^{6,7,9,16} and extends the finding to the subgroup of high risk patients. The former studies excluded patients with severe cardiac disease and a history of cardiac arrest or severe ventricular tachyarrhythmias. The average left ventricular ejection fraction of patients with induced VF in these studies was about 40%, compared with 30% in the present study. Beyond the extension to high risk patients in the current study, medical treatment has progressed substantially over the past decade, particularly by avoidance of class I antiarrhythmic medication and the introduction of β blockers as a mainstay in the treatment of patients with left ventricular dysfunction. In the present study, nearly three quarters of all patients received a β blocker. Only one quarter received other antiarrhythmic drugs, mostly class III agents, whereas only four patients received a class I antiarrhythmic drug during the follow up period.

In summary, the present study provides evidence that induction of VF during physiological electrostimulation, perhaps with the exception of patients with previously documented VF, has no prognostic value for future ventricular tachyarrhythmias.

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