

An "Aggressive" Protocol of Programmed Ventricular Stimulation for Selecting Post-Myocardial Infarction Patients with a Low Ejection Fraction who may not Require Implantation of an Automatic Defibrillator

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ABSTRACT: **Background:** The predictive value of electrophysiologic studies depends on the aggressiveness of the programmed ventricular stimulation protocol.

Objectives: To assess if non-inducibility with an "aggressive" protocol of PVS identifies post-infarction patients with low ejection fraction ($EF \leq 30\%$) who may safely be treated without implantable cardioverter defibrillator.

Methods: We studied 154 patients during a 9 year period. Our aggressive PVS protocol included: a) stimulus current five times the diastolic threshold (≤ 3 mA) and b) repetition of double and triple extrastimulation at the shortest coupling intervals that capture the ventricle.

Results: Sustained ventricular tachyarrhythmias were induced in 116 patients (75.4%) and 112 (97%) of them received an ICD (EPS+/ICD+ group). Of the 38 non-inducible patients, 34 (89.5%) did not receive an ICD (EPS-/ICD-group). In comparison to the EPS+/ICD+ group, EPS-/ICD-group patients were older (69 ± 10 vs. 65 ± 10 years, $P < 0.05$), had a lower EF ($23 \pm 5\%$ vs. $25 \pm 5\%$, $P < 0.05$) and a higher prevalence of left bundle branch block (45.5% vs. 20.2% , $P < 0.005$). Follow-up was longer for EPS+/ICD+ patients (40 ± 26 months) than for EPS-/ICD- patients (27 ± 22 months) ($P = 0.011$). Twelve EPS+/ICD+ patients (10.7%) and 5 EPS-/ICD-patients (14.7%) died during follow-up ($P = 0.525$). Kaplan-Meier survival curves did not show a significant difference between the two groups ($P = 0.18$).

Conclusions: The mortality rate in patients without inducible VTAs using an aggressive PVS protocol and who did not undergo subsequent ICD implantation is not different from that of patients with inducible arrhythmias who received an ICD. Using this protocol, as many as one-fourth of primary prevention ICD implants could be spared without compromising patient prognosis.

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KEY WORDS: programmed ventricular stimulation, post-myocardial infarction, ejection fraction, implantable cardioverter defibrillator

For editorial see page 552

A MUSTT sub-study [1] and MADIT-II [2] showed that in post-myocardial infarction patients with low left ventricular ejection fraction ($\leq 30\%$) and no prior sustained ventricular tachyarrhythmias, non-inducibility of sustained VTAs on electrophysiologic study does not necessarily predict a low arrhythmic risk. Consequently, these patients are now considered for prophylactic implantation of an automatic cardioverter defibrillator without further risk stratification with EPS [3]. However, on behalf of the MADIT-II investigators, Daubert et al. [2] pointed out that their findings on the predictive value of EP testing are specific to the protocol of programmed ventricular stimulation used. They suggested that more aggressive protocols, which may induce VTAs in a greater proportion of patients, could lead to different conclusions. Daubert and investigators [2] also noticed that MUSTT, the largest prospective study that included EP testing for risk stratification, used a virtually identical PVS protocol as that of the MADIT-II study [4,5].

For the last 20 years we have used a PVS protocol that is more aggressive than that used in most EP laboratories. This protocol includes higher stimulus current and repetition of extrastimulation at the shortest coupling intervals that capture the ventricles. That protocol has been very effective for increasing PVS sensitivity for induction of sustained VT in patients with spontaneous ventricular tachyarrhythmias [6]. In the present study, we report the use of this aggressive PVS protocol for risk stratification of post-MI patients with an ejection fraction $\leq 30\%$. We theorized that by reducing the proportion of patients with negative EP testing, we would reduce the number of MADIT-II-like patients requiring ICD implantation without compromising safety. We therefore

PVS = programmed ventricular stimulation
EF = ejection fraction
ICD = implantable cardioverter defibrillator
EPS = electrophysiologic study
VTA = ventricular tachyarrhythmias
MI = myocardial infarction

compared the all-cause mortality of patients with positive EPS who underwent ICD implantation to that of patients with negative EPS who were treated conservatively.

PATIENTS AND METHODS

All patients with previous MI (≥ 1 month) and left ventricular ejection fraction $\leq 30\%$ undergoing EPS for the purpose of risk stratification in our laboratory between March 1998 and December 2007 were included. At the beginning of the study, patients were referred for EP consultation following an ambulatory Holter recording showing high grade ventricular arrhythmias and/or non-sustained ventricular tachycardia. As the limited value of Holter recordings for predicting spontaneous sustained ventricular arrhythmias was recognized, patients without such documented arrhythmias were also referred. Patients were excluded from the study if they had a history of syncope or cardiac arrest or documented sustained VT. Because of the controversial predictive value of spontaneous VT or ventricular fibrillation occurring in the setting of acute MI, we also excluded patients who had VT/VF at any time during hospitalization for acute MI.

ELECTROPHYSIOLOGIC STUDIES

As in MUSTT and MADIT, our protocol included single, double and triple ventricular extrastimulation delivered from two right ventricular sites (right ventricular apex and right ventricular outflow tract) at two basic cycle lengths (600 and 400 msec). However, our protocol differs from MUSTT and MADIT regarding: a) the stimulus current, b) the use of repetition of extrastimulation at the shortest coupling intervals, and c) the end-point definitions used.

We used a stimulus current of 2 msec duration at five times the diastolic threshold (but always ≤ 3 mA). In contrast to MADIT-I [7] and MADIT-II [2] protocols, in which the coupling intervals of the second and third extrastimuli were never shorter than 200 and 180 msec respectively, we used no pre-specified minimal coupling interval. Instead, the coupling interval of the second extrastimulus was decreased at 10 msec steps until ventricular refractoriness precluded ventricular capture. The coupling interval was then increased by 10 msec, and repetition of double extrastimulation using the shortest coupling intervals that captured the ventricle was performed 10 times [6]. This sequence of events was performed at each of the two ventricular sites and during the two basic cycle lengths. In a similar fashion, repetition of triple extrastimulation at the shortest coupling intervals that captured the ventricle was performed five times at each ventricular site and basic cycle length. Induction of *any* induced sustained ventricular tachyarrhythmia (lasting more than 30 seconds or

requiring rapid overdrive pacing or DC shock termination), regardless of the arrhythmia morphology and/or cycle length, was considered a "positive EPS."

DEFINITIONS

Monomorphic VT was a VT with a uniform stable QRS morphology with a cycle length > 230 ms. Polymorphic VT had a changing QRS morphology and almost always a very short cycle length (< 200 msec). VF was defined as a rapid disorganized rhythm without consistently identifiable complexes. Sustained polymorphic VT and VF were grouped together as "VF." Ventricular flutter was defined as sustained monomorphic VT with a very short cycle length (≤ 230 msec).

PATIENT MANAGEMENT

All patients received optimal medical therapy with beta-blockers, angiotensin-converting enzyme inhibitors, aspirin and statins unless contraindicated. In addition, as a matter of policy, all patients with positive EPS underwent ICD implantation, whereas all patients with negative EPS received only optimal medical therapy. There were a few exceptions to this rule: four patients with positive EPS did not receive an ICD due to personal preference ($n=3$) or because only a slow monomorphic VT (118/min) was the tachycardia induced ($n=1$). On the other hand, four patients with a negative EPS underwent ICD implantation due to positive T-wave alternance test ($n=2$), requirement of cardiac resynchronization therapy for severe heart failure ($n=1$), and participation in the MADIT-II trial ($n=1$).

FOLLOW-UP

Follow-up was conducted at our arrhythmia clinic at 3–6 month intervals for patients with ICDs and at 6–12 month intervals for patients without ICDs. In addition, the survival status of all patients was verified on 1 February 2008 using the National Citizens Registry. During the same month, all patients reported to be alive by the Registry were contacted by phone or seen at our arrhythmia clinic. The relatives of all deceased patients were contacted to ascertain the mode of death. The cause of death was classified as sudden cardiac death (instantaneous death without prodrome or occurring during sleep), non-sudden cardiac death (including those occurring in patients with end-stage heart failure or those occurring in the hospital following complications of non-cardiac illness or surgery), or non-cardiac death.

STATISTICS

Categorical variables were compared between groups with the chi-square test. Continuous variables normally distributed were compared by *t*-test or ANOVA. Continuous variables

VT = ventricular tachycardia

VF = ventricular fibrillation

Figure 1. Effect of repetition of triple extrastimulation on VT inducibility. In this patient, no sustained ventricular tachyarrhythmia could be induced with single and double extrastimulation (including repetition) from two right ventricular sites at two basic cycle lengths. Also no arrhythmias could be induced with triple extrastimulation (including repetition) from the right ventricular apex (at two basic cycle lengths) or with triple extrastimulation from the right ventricular outflow tract at a basic cycle length of 600 msec. Shown are the effects of triple extrastimulation (S2/S3/S4) from the outflow tract delivered at a basic cycle length of 400 msec using the same shortest coupling intervals that allowed ventricular capture (S1S2=245 msec; S2S3=215 msec; S3-S4=200 msec). Two repetitive ventricular beats are induced at the first trial of triple extrastimulation (upper panel) while non-sustained VT (7 beats) are induced at the second repetitive trial (middle panel). At the third repetition a sustained monomorphic VT (cycle length ranging from 220 to 260 msec) is induced that will require direct current shock for termination (lower panel). Shown here are ECG lead V1 and intracardiac recordings from the atrioventricular junction (AV) and the right ventricular outflow tract (RVOT).



without a normal distribution were analyzed by the Mann-Whitney U test or Kruskal-Wallis H test. The study endpoint was death from any cause. The follow-up was measured from the EP study to death or last follow-up. Survival curves were plotted using the Kaplan-Meier method and analyzed by the

log rank test. All tests were two-sided and $P < 0.05$ was considered statistically significant. All analyses were done using the SPSS statistical package (SPSS Inc., Chicago, IL, USA).

RESULTS

PATIENT CHARACTERISTICS

The initial patient cohort consisted of 154 post-MI patients with an ejection fraction $\leq 30\%$ who underwent EPS for the purpose of risk stratification during a 9 year period. There were 142 (92.2%) males and 12 females aged 34 to 87 (66 ± 10 years old). Their left ventricular ejection fraction ranged from 8 to 30% (24.5 ± 4.6). In 97 patients (63%) the results of Holter monitoring were available. These recordings showed non-sustained VT in 65 patients (67%) and high grade ventricular arrhythmias in 32 patients (33%).

RESULTS OF EPS

Sustained VTAs were induced in 116 (75.4%) of the initial study cohort while the remaining 38 patients (24.6%) had a negative EPS [Figure 1]. In 112 (96.6%) of the 116 patients with inducible VTAs an ICD was implanted. These 112 patients, who had a positive EPS and therefore underwent ICD implantation, comprise the EP+/ICD+ group. In 34 (89.5%) of the 38 patients without inducible VTAs an ICD was not implanted. These 34 patients with negative EPS and no ICD comprise the EP-/ICD- group. The arrhythmias induced in the EP+/ICD+ group were sustained monomorphic VT, ventricular flutter and VF in 81 (72.3%), 16 (14.3%), and 15 (13.4%) patients, respectively [Table 1]. Patients with induced monomorphic VT were similar to those with inducible ventricular flutter and/or inducible VF in terms of ejection fraction and New York Heart Association functional class. Ventricular flutter and VF were more frequently induced with triple extrastimuli but the difference did not reach statistical significance ($P = 0.7$) [Table 1].

COMPARISON BETWEEN PATIENT GROUPS

Important characteristics that correlate with adverse prognosis (like older age, lower ejection fraction, bundle branch block, and need for diuretic therapy) were present more often in EP-/ICD- patients than among EP+/ICD+ patients [Table 2]. The time from last myocardial infarction to EPS was similar for the two groups [Table 2].

FOLLOW-UP

The mean follow-up duration of the study group was 36 ± 26 months. Follow-up periods were longer for EP+/ICD+ patients than for EP-/ICD- patients (40 ± 26 months vs. 27 ± 22 months) ($P = 0.011$). Follow-up was ≥ 2 years and ≥ 4 years for 74 (66%) and 44 (39.2%) EP+/ICD+ patients and for 19 (55.9%) and 5 (14.7%) EP-/ICD- patients, respectively.

Table 1. Clinical data of patients with positive electrophysiologic study

	VF N=15	VFL N=16	VT N=81	P value
Age (yrs)	67 ± 11	58 ± 11	66 ± 10	0.011
LVEF (%)	25 ± 4	27 ± 4	25 ± 5	0.08
CABPG	6 (40%)	4 (25%)	41 (51.3%)	0.139
NYHA (median)	II	II	II	0.58
LBBB	6 (40.0%)	2 (12.5%)	14 (17.9%)	0.106
Amiodarone	2 (13.3%)	3 (21.4%)	18 (22.2%)	0.738
Site of induction				0.004
RVA	7 (46.7%)	9 (56.3%)	66 (85.7%)	
RVOT	8 (53.3%)	7 (43.8%)	11 (14.3%)	
No. of extrastimuli				0.704
Single	0	0	2 (2.6%)	
Double	5 (33.3%)	5 (31.3%)	31 (40.3%)	
Triple	10 (66.7%)	11 (68.8%)	44 (57.1%)	
CL (msec)		206 ± 8	259 ± 35	< 0.0001

CABPG = coronary artery bypass graft surgery, CL = cycle length, LVEF = left ventricular ejection fraction, NYHA = New York Heart Association, RVA = right ventricular apex, RVOT = right ventricular outflow tract, VF = ventricular fibrillation, VFL = ventricular flutter, VT = ventricular tachycardia.

The mortality rate in the EPS+/ICD+ group (10.7%, 95% confidence interval 6.2–17.9%) was lower than in the EPS-/ICD- group (14.7%, 95% CI 6.3–30.8%) but the difference did not reach statistical significance ($P = 0.525$). With regard to all-cause mortality, 2 year, 4 year and 5 year rates, calculated by Kaplan-Meier methods, were 4.5%, 9.8% and 9.8%, respectively, for EPS+/ICD+ patients [Figure 2]. The corresponding rates for EPS-/ICD- patients were 8.8%, 14.7% and 14.7% ($P = 0.18$ by the log-rank test).

Of the 12 EPS+/ICD+ patients who died, 1 died from sudden cardiac death, 9 from non-sudden cardiac death and 2 from non-cardiac death. Of the five EPS-/ICD- patients who died, only one death was sudden and four patients died of non-cardiac causes. Importantly, none of the EPS-/ICD- patients required ICD implantation or any other intervention for spontaneous sustained ventricular arrhythmias during the follow-up period. Thus, the risk of fatal or non-fatal sustained ventricular arrhythmias for patients with negative EPS treated conservatively was only 3% (CI 0.4–18%): one sudden death and no cases of non-fatal arrhythmias among 34 patients.

Of the four patients who had a positive EPS and refused ICD implantation, one died from non-cardiac cause 8 months after the EPS. All four patients with negative EPS who received an ICD are alive after 6–90 months follow-up; none of them experienced an ICD discharge resulting from VT or VF.

CI = confidence interval

Table 2. Clinical and electrocardiographic data of patients with positive EPS treated with ICD (EPS+/ICD+ group) and patients with negative EPS treated without ICD (EPS-/ICD- group)

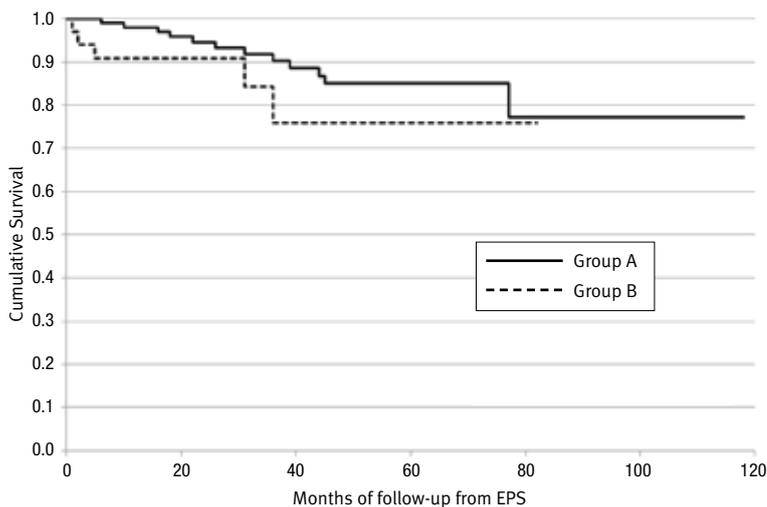
	EPS+/ICD+ N=112	EPS-/ICD- N=34	P value
Age (yrs)	65 ± 10 (34–85)	69 ± 10 (43–87)	0.024
Male gender	105 (93.8%)	29 (85.3%)	0.116
Date from MI (mos)	126 ± 92 (1–540)	113 ± 70 (3–216)	0.535
Median NYHA class II		II	0.966
LVEF (%)	25 ± 5	23 ± 5	0.027
Holter data			0.707
NSVT	49 (43.8%)	14 (41.2%)	
Multiple VPBs	25 (22.3%)	6 (17.6%)	
No Holter data	38 (33.9%)	14 (41.2%)	
ECG			
LBBB	22 (20.2%)	15 (45.5%)	0.004
RBBB	20 (18.3%)	2 (6.1%)	0.087
CABPG	51 (45.9%)	23 (67.6%)	0.027
Diabetes mellitus	19 (17.0%)	11 (32.4%)	0.052
Hypertension	17 (42.5%)	4 (33.3%)	0.570
Medications			
Anti-aggregants	77 (68.8%)	24 (70.6%)	0.839
Beta-blockers	85 (77.3%)	25 (75.8%)	0.856
Amiodarone	23 (20.9%)	3 (9.1%)	0.123
ACE / ARB	93 (83.0%)	25 (73.5%)	0.218
Calcium blockers	13 (11.8%)	2 (6.1%)	0.344
Other anti-arrhythmics	1 (0.9%)	1 (3.0%)	0.410
Digoxin	11 (10.0%)	4 (12.1%)	0.727
Diuretics	69 (62.7%)	29 (87.9%)	0.006
Statins	67 (60.9%)	19 (57.6%)	0.732
Follow-up duration (mos)	40 ± 26	27 ± 22	0.011
All-cause mortality	12 (10.7%)	5 (14.7%)	0.525
Sudden cardiac death	1 (0.9%)	1 (3%)	0.36

ACE = angiotensin-converting enzyme inhibitors, ARB = angiotensinreceptor blockers, CABPG = coronary artery bypass graft surgery, ECG = electrocardiogram, LBBB = left bundle branch block, LVEF = left ventricular ejection fraction, NSVT = non-sustained ventricular tachycardia, NYHA = New York Heart Association, RBBB = right bundle branch block, VPBs = ventricular premature beats.

DISCUSSION

We report a single-center experience with EPS-based risk stratification of post-MI patients with low ejection fraction ($\leq 30\%$). Our main goal was to evaluate whether a more aggressive protocol of PVS surpasses the main limitation of standard EPS protocols, namely, the unacceptable sudden death rate of patients left without ICD after a negative EPS (24% at 5 years in MUSTT) [5]. We found that one of four MADIT-II-like patients had a negative EPS and their long-term mortality

Figure 2. Kaplan-Meier estimates of the probability of survival in EPS+/ICD+ group (patients with inducible arrhythmias who received an ICD) and in EPS-/ICD- group (patients without inducible arrhythmias who did not receive an ICD). The difference in survival between the two groups was not significant (nominal $P = 0.18$, by the log-rank test).



without ICD was not different from the mortality rate of patients with positive EPS treated with ICD.

INDUCIBILITY RATES: COMPARISON WITH LANDMARK STUDIES

In our study, 75.4% of patients had inducible sustained ventricular arrhythmias. This figure is higher than the inducibility rate reported in MUSTT (34.8%) and the MADIT-II EPS sub-study (41%) [2,5]. The higher inducibility rate observed in our study could merely be due to differences in the definition of "positive EPS" used in the different studies. Patients in MUSTT and MADIT-II were classified as "negative EPS" if they had polymorphic VTAs induced with triple extrastimulation. In contrast, we counted all inducible sustained arrhythmias (regardless of morphology and mode of induction) as "positive EPS." However, extrapolating our definition of "positive EPS" to the MADIT-II and MUSTT population would increase their positive inducibility rate only moderately. For example, if all patients who had ventricular flutter or polymorphic VT induced by triple extrastimuli in MUSTT would have been counted as "positive EPS," their inducibility would have increased to 45.9%, which is still lower than our 75% inducibility rate. Therefore, we believe that the most plausible explanation for the discrepant results in arrhythmia inducibility rates between both MUSTT and MADIT-II and our study is that our PVS protocol was more aggressive than the "standard" protocol used in those studies. As shown by us [6] and others [10-15], use of high stimulus current, repetition of extrastimulation and no lower limitation in coupling intervals of the extrastimuli are factors that markedly increase arrhythmia inducibility rate.

PROGNOSTIC VALUE OF A NEGATIVE EPS: MUSTT VS. THE PRESENT STUDY

In our study, the 2 and 5 year mortality rates in EPS-/ICD- patients were 8.8% and 14.7% respectively, and the risk for fatal or non-fatal spontaneous sustained ventricular arrhythmias was only 3%. These figures are markedly lower than those found in the MUSTT registry for patients with negative EPS treated conservatively (mortality rates 21.7% and 45%, and cardiac arrest rates 12% and 24%, at 2 and 5 years, respectively) [5]. Importantly, none of our EPS-/ICD- patients required ICD implantation during follow-up because of spontaneous non-fatal arrhythmias.

Several differences between the EPS-/ICD- patients of the MUSTT registry and our own EPS-/ICD- patients may explain the lower mortality observed in our study: a) beta-blockers were used in 76% of non-inducible patients in our study but in only 35% of non-inducible patients in MUSTT [5], b) 17% of patients in the MUSTT registry would have been classified as "EPS-positive" using our definitions, and c) the more aggressive character of our PVS protocol probably reduced the rate of false negative EPS.

Data from a MADIT-II sub-study showed that patients with a negative EPS who underwent ICD implantation hardly developed spontaneous sustained monomorphic VT but were at considerable risk for spontaneous rapid and polymorphic ventricular tachyarrhythmias [2]. Since the induction of rapid VT (ventricular flutter) and VF is facilitated by aggressive PVS protocols such as the one we used [6,10-15], one may speculate that a higher number of the clinically observed rapid and polymorphic VT in MADIT-II could have been induced with a more aggressive PVS protocol.

PROGNOSTIC VALUE OF A POSITIVE EPS: MADIT-II VS. THE PRESENT STUDY

In our study, the all-cause 2 year and 4 year mortality rates in EPS+/ICD+ patients were 4.5% and 9.8% respectively. These figures are slightly lower than those found in the "EP-positive" population in MADIT-II (mortality rates of 10% and 14%, respectively) [2]. In MADIT-II, the EPS+/ICD+ group comprised mainly patients with inducible monomorphic VT because inducible VF with triple extrastimulation was classified as "negative EPS." Patients with monomorphic VT generally have lower ejection fraction and may be at higher risk for cardiac death even with implanted ICD [16]. In fact, the significance of inducible polymorphic VT and VF in post-MI patients is controversial. While several studies, including MUSTT [5,16-18], showed that inducibility of such tachyarrhythmias has a significant clinical prognostic value and predicted a higher likelihood that a subsequent death would be caused by an arrhythmic mechanism, other studies including MADIT-II [2,19-21] support the notion that such inducibility, particularly with aggressive protocols, is non-

specific. In addition, the study by Brembilla-Perrot and co-authors [22] showed that the induction of these arrhythmias did not increase the risk of sudden death but increased the mortality related to heart failure.

MORTALITY RATES: THE EPS+/ICD+ GROUP VS. THE EPS-/ICD-GROUP

Our results showed a slightly lower mortality rate in the EPS+/ICD+ group (10.7%) as compared to EPS-/ICD- patients (14.7%) but the difference did not reach statistical significance. In addition, Kaplan-Meier survival curves also did not show significant differences in mortality rates between the two groups.

The mean follow-up duration in our study was 36 ± 26 months. It was longer in the EPS+/ICD+ group (40 ± 26 months) than in the EPS-/ICD- group (27 ± 22 months) because many of the EPS-/ICD- patients were referred to us by our Heart Failure Clinic during the last 4 years of our study. It should be noted, however, that the average follow-up duration in our study was similar to that in MUSTT (39 months) and markedly longer than in MADIT-II (20 months).

Likewise, the total mortality rate in our study cohort (including EPS+/ICD+ and EPS-/ICD- patients) was only 11.6%. This figure is slightly lower than the total mortality of patients treated with ICD in MADIT-II (14.2%) [8]. Such a result was achieved despite the fact that the follow-up in our study was much longer than in MADIT-II (36 months vs. 20 months). This observation suggests that reserving ICD implantation only for patients with inducible sustained VTAs using our EPS protocol does not compromise safety while preventing a substantial number of unnecessary ICD implantations.

Our results are particularly interesting considering that the EPS-/ICD- patients were actually older, had lower ejection fraction and had a higher prevalence of left bundle branch block than the EP+/ICD+ patients. These factors are known to be associated with increased mortality [23-25]. Thus it is tempting to speculate that the negative EPS using our protocol identified patients who lack the arrhythmic substrate to allow arrhythmic death despite their greater degree of left ventricular dysfunction and in whom the mode of cardiac death during follow-up may be heart failure rather than arrhythmic death.

STUDY LIMITATIONS

The most important limitation of our study is the relatively small size of the population, especially when compared with the landmark MUSTT and MADIT-II studies. On the other hand, it should be noted that MUSTT and MADIT-II involved 85 and 76 participating centers, respectively. Thus, on average, each participating center in MUSTT and MADIT-II studied only 39 and 13 patients, respectively. In contrast, this is a relatively large single-center experience (n=154) where

approximately 90% of the EPS were performed by the same operator (B.B.), which ensured an optimal uniformity of the PVS protocol. In addition, compared to data from MUSTT [1,5] and MADIT-II [2,8], the power of our trial was satisfactory and estimated to be approximately 55% for the 2 year mortality and 95% for the 4 year mortality.

Our study shares the limitations of retrospective studies. Although all EPS results were prospectively entered, electrocardiographic data such as QRS duration or left ventricular hypertrophy [24] were not systematically assessed and Holter recordings were not available for all patients.

We did not collect data on the number of EPS+/ICD+ patients who had appropriate ICD therapy during follow-up. Aggressive EPS protocols may increase the number of "false positive" results and reduce the number of patients who actually derived benefit (by means of appropriate therapy) from the ICD. However, our main goal was to reduce the number of unnecessary ICD implantations without compromising safety in terms of total mortality.

CLINICAL IMPLICATIONS

The results of our study suggest that EPS is still useful for risk stratification, provided that an aggressive PVS protocol is used. Based on the results of the present study, a randomized multicenter clinical trial comparing ICD therapy and no ICD therapy in patients without inducible sustained VTAs using our PVS protocol seems warranted. Further confirmation of our results might change current guidelines for prophylactic ICD therapy. As many as one-fourth of the ICD candidates (the patients with negative EPS) could be spared the implantation of a device without significantly raising their mortality risk. Taking into account the heavy economic burden of ICD therapy on health and medical systems along with its non-negligible risks of complications, we believe that this is a timely study.

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References

1. Buxton AE, Lee KL, Hafley GE, et al., for MUSTT Investigators. Relation of ejection fraction and inducible ventricular tachycardia to mode of death in patients with coronary artery disease: an analysis of patients enrolled in the multicenter unsustained tachycardia trial. *Circulation* 2002; 106: 2466-72.
2. Daubert JP, Zareba W, Hall WJ, et al., for MADIT II Study Investigators. Predictive value of ventricular arrhythmia inducibility for subsequent ventricular tachycardia or ventricular fibrillation in Multicenter Automatic Defibrillator Implantation Trial (MADIT) II patients. *J Am Coll Cardiol* 2006; 47: 98-107.

3. Epstein AE, Dimarco JP, Ellenbogen KA, et al. ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: Executive Summary A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) Developed in Collaboration With the American Association for Thoracic Surgery and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2008; 51: 2085-105.
4. Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley G. A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter Unsustained Tachycardia Trial Investigators. *N Engl J Med* 1999; 16; 341: 1882-90.
5. Buxton AE, Lee KL, DiCarlo L, et al. Electrophysiologic testing to identify patients with coronary artery disease who are at risk for sudden death. Multicenter Unsustained Tachycardia Trial Investigators. *N Engl J Med* 2000; 342: 1937-45.
6. Belhassen B, Shapira I, Sheps D, Laniado S. Programmed ventricular stimulation using up to two extrastimuli and repetition of double extrastimulation for induction of ventricular tachycardia: a new highly sensitive and specific protocol. *Am J Cardiol* 1990; 65: 615-22.
7. Moss AJ, Hall WJ, Cannom DS, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. *N Engl J Med* 1996; 335: 1933-40.
8. Moss AJ, Zareba W, Hall WJ, et al., Multicenter Automatic Defibrillator Implantation Trial II Investigators. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002; 346: 877-83.
9. Bigger JT Jr, Fleiss JL, Kleiger R, Miller JP, Rolnitzky LM, Multicenter Post-Infarction Research Group. The relationships among ventricular arrhythmias, left ventricular dysfunction, and mortality in the 2 years after myocardial infarction. *Circulation* 1984; 69: 250-8.
10. Morady F, DiCarlo LA Jr, Liem LB, Krol RB, Baerman JM. Effects of high stimulation current on the induction of ventricular tachycardia. *Am J Cardiol* 1985; 56: 73-8.
11. Morady F, DiCarlo LA Jr, Baerman JM, de Buitleur M. Comparison of coupling intervals that induce clinical and nonclinical forms of ventricular tachycardia during programmed stimulation. *Am J Cardiol* 1986; 57: 1269-73.
12. Cooper MJ, Hunt LJ, Richards DA, Dennis AR, Uther JB, Ross DL. Effect of repetition of extrastimuli on sensitivity and reproducibility of mode of induction of ventricular tachycardia by programmed stimulation. *J Am Coll Cardiol* 1988; 11: 1260-7.
13. Avital B, McKinnie J, Jazayeri M, Akhtar M, Anderson AJ, Tchou P. Induction of ventricular fibrillation versus monomorphic ventricular tachycardia during programmed stimulation. Role of premature beat conduction delay. *Circulation* 1992; 85: 1271-8.
14. Martinez-Rubio A, Shenasa M, Borggrefe M, Chen X, Benning F, Breithardt G. Electrophysiologic variables characterizing the induction of ventricular tachycardia versus ventricular fibrillation after myocardial infarction: relation between ventricular late potentials and coupling intervals for the induction of sustained ventricular tachyarrhythmias. *J Am Coll Cardiol* 1993; 21: 1624-31.
15. Koller BS, Karasik PE, Solomon AJ, Franz MR. Relation between repolarization and refractoriness during programmed electrical stimulation in the human right ventricle. Implications for ventricular tachycardia induction. *Circulation* 1995; 91: 2378-84.
16. Viskin S, Ish-Shalom M, Koifman E, et al. Ventricular flutter induced during electrophysiologic studies in patients with old myocardial infarction: clinical and electrophysiologic predictors, and prognostic significance. *J Cardiovasc Electrophysiol* 2003; 14: 913-19.
17. Gurevitz O, Viskin S, Glikson M, et al. Long-term prognosis of inducible ventricular flutter: not an innocent finding. *Am Heart J* 2004; 147: 649-54.
18. Greenberg SL, Mauricio Sánchez J, Cooper JA, et al. Sustained polymorphic arrhythmias induced by programmed ventricular stimulation have prognostic value in patients receiving defibrillators. *Pacing Clin Electrophysiol* 2007; 30: 1067-75.
19. Brembilla-Perrot B, de la Chaise AT, Briancon S, et al. Programmed ventricular stimulation in survivors of acute myocardial infarction: long-term follow-up. *Int J Cardiol* 1995; 49: 55-65.
20. Bourke JP, Richards DA, Ross DL, McGuire MA, Uther JB. Does the induction of ventricular flutter or fibrillation at electrophysiologic testing after myocardial infarction have any prognostic significance. *Am J Cardiol* 1995; 75: 431-5.
21. Andresen D, Steinbeck G, Bruggemann, et al. Risk stratification in the thrombolytic era. *J Am Coll Cardiol* 1999; 33: 131-8.
22. Brembilla-Perrot B, Suty-Selton C, Claudon O, et al. Significance of inducible ventricular flutter-fibrillation after myocardial infarction. *PACE* 2005; 28: 938-43.
23. Sesselberg HW, Moss AJ, Steinberg J, et al. Factors associated with ventricular inducibility in the MADIT-II study population. *Am J Cardiol* 2003; 91: 1002-4.
24. Zimetbaum PJ, Buxton AE, Batsford W, et al. Electrocardiographic predictors of arrhythmic death and total mortality in the Multicenter Unsustained Tachycardia Trial. *Circulation* 2004; 110: 766-9.
25. Buxton AE, Lee KL, Hafley GE, et al., the MUSTT Investigators. A simple model using the MUSTT database can stratify total mortality and sudden death risk of coronary disease patients. *J Am Coll Cardiol* 2004; 425A, abstract#889-6.