Influence of the Mode of Management of Acute Myocardial Infarction on the Inducibility of Ventricular Tachyarrhythmias with Programmed Ventricular Stimulation after Myocardial Infarction

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ABSTRACT: **Background:** Programmed ventricular stimulation (PVS) is a technique for screening patients at risk for ventricular tachycardia (VT) after myocardial infarction (MI), but the results might be difficult to interpret.

Objectives: To investigate the results of PVS after MI, according to date of completion.

Methods: PVS results were interpreted according to the mode of MI management in 801 asymptomatic patients: 301 (group I) during the period 1982–1989, 315 (group II) during 1990–1999, and 185 (group III) during 2000–2010. The periods were chosen based on changes in MI management. Angiotensin-converting enzyme (ACE) inhibitors had been given since 1990; primary angioplasty was performed routinely since 2000. The PVS protocol was the same throughout the whole study period.

Results: Group III was older (61 ± 11 years) than groups I (56 ± 11) and II (58 ± 11) ($P < 0.002$). Left ventricular ejection fraction (LVEF) was lower in group III (36.5 ± 11%) than in groups I (44 ± 15) and II (41 ± 12) ($P < 0.000$). Monomorphic VT < 270 beats/min was induced as frequently in group III (28%) as in group II (22.5%) but more frequently than in group I (20%) ($P < 0.03$). Ventricular fibrillation and flutter (VF) was induced less frequently in group III (14%) than in groups I (28%) ($P < 0.0004$) and II (30%) ($P < 0.0000$). Low left ventricular ejection fraction (LVEF) and date of inclusion (before/after 2000) were predictors of VT or VF induction on multivariate analysis.

Conclusions: Induction of non-specific arrhythmias (ventricular flutter and fibrillation) was less frequent than before 2000, despite the indication of PVS in patients with lower LVEF. This decrease could be due to the increased use of systematic primary angioplasty for MI since 2000.

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KEY WORDS: myocardial infarction (MI), programmed ventricular stimulation (PVS), ventricular flutter (VF), revascularization

Programmed ventricular stimulation was the most effective technique for screening patients at risk for ventricular tachycardia and VT-related sudden death during the period 1986–1995 [1-3]. At that time, PVS was used less for risk stratification in coronary heart disease since a number of landmark trials showed the benefit of prophylactic implantable cardioverter defibrillators in patients with only low left ventricular ejection fraction [4-6]. However, a pro-arrhythmic effect of ICD and other complications were reported [7]. Moreover, inducible VT remains an important and independent factor of cardiac mortality [8]. Recently, some papers reported the important role of the technique for risk stratification [9]. The management of acute myocardial infarction has changed since the first studies of PVS after infarction [1-3]. The purpose of the present study was to evaluate the results of systematic PVS after MI according to the period of indication and management of the ischemic heart disease.

PATIENTS AND METHODS

The study group comprised 801 patients aged 23 to 84 years (mean 58 ± 11); 715 men and 86 women without syncope or symptomatic sustained ventricular arrhythmias were studied between 1 and 3 months after the acute phase of an MI that occurred during the period April 1982 to December 2010:

- group I – 301 patients between 1982 and 1989
- group II – 315 patients between 1990 and 1999
- group III – 105 between 2000 and 2010.

These periods were chosen because angiotensin-converting enzyme inhibitors were introduced after 1990, and routine

VT = ventricular tachycardia
PVS = programmed ventricular stimulation
ICD = implantable cardioverter defibrillator
MI = myocardial infarction

acute primary angioplasty during acute MI has been performed in our department since 2000.

Patients in groups I and II were included if they had at least one risk factor for arrhythmia, a left ventricular ejection fraction < 40%, non-sustained ventricular tachycardia at Holter monitoring, or late potentials at signal-averaged electrocardiography. Patients in group III were included if they had the following: a) low LVEF (< 30%/35%) and advanced age (> 75 years), b) non-sustained VT, or c) late potentials and a decreased LVEF (< 40%).

Patients were excluded if they had: a) unstable angina, b) recent acute myocardial infarction (< 1 month), c) recent coronary angioplasty or coronary bypass surgery (< 6 weeks), d) paroxysmal second or third-degree atrioventricular block, e) sustained supraventricular or ventricular arrhythmia, e) clinical heart failure not controlled by furosemide, f) electrolytical abnormalities, g) end-stage non-cardiac disease, or h) were chronically treated with amiodarone.

STUDY PROTOCOL

The patients underwent several investigations in the absence of anti-arrhythmic drugs after giving informed consent. They were treated with ACE inhibitors from 1990. Beta-blockers and digoxin were stopped before PVS.

The following non-invasive studies were performed between 1 and 3 months after acute myocardial infarction:

- surface ECG
- 24 hour Holter monitoring (Elatec™, Sorin, Italy)
- thallium exercise scintigraphy or exercise testing in patients able to perform the exercise
- two-dimensional echocardiography and/or left ventricular angiography for the determination of LVEF at the time of investigations and signal-averaged ECG including the measurement of QRS duration.

The following invasive studies were performed:

- coronary angiography in all patients < 80 years old and > 80 years in case of abnormal thallium exercise scintigraphy
- complete electrophysiological study including the PVS according to a previously reported protocol. The protocol included assessment of sinoatrial conduction function, atrioventricular conduction, and programmed atrial stimulation. Programmed right ventricular stimulation using one ventricular extrastimulus and double ventricular extrastimuli were introduced during sinus rhythm and paced cycle lengths (600 and 400 ms), at right ventricular apex and subsequently at right ventricular outflow tract. The decrement was 10 ms from 350 ms until the ventricular effective refractory period or 200 ms. When two extrastimuli were used, the first extrastimulus was delivered 20 ms above the ventricular effective refractory period. A third extrastimulus was added if a sustained VT or fibrillation was not induced. Short coupling intervals (< 200 ms) were not used in our study.

PVS was considered abnormal when a sustained ventricular tachyarrhythmia lasting at least 30 seconds or requiring termination before 30 seconds due to hemodynamic intolerance was induced. Induced ventricular tachyarrhythmias were categorized as monomorphic VT when the rate was < 275 beats/min or ventricular flutter when the rate of monomorphic VT was > 270 bpm or polymorphic VT/ventricular fibrillation. The duration of the follow-up varied from 2 months to 20 years (mean 9.48 ± 13 years).

STATISTICAL ANALYSIS

Data are expressed as means ± standard deviation. For categorical variables the chi-square test was performed. The independent sample *t*-test procedure was used for continuous variables. The stepwise logistic regression was used to analyze the relationships between the results of PVS as dependent variables and possible predictors (age, gender, LVEF, non-sustained VT at Holter monitoring, revascularization, date of inclusion) as independent variables. A P value < 0.05 was considered statistically significant. All statistical analyses were performed with the SPSS package for Windows (version 17. 0.1, SPS, USA).

RESULTS

CLINICAL DATA [Tables 1 and 2]

Age was higher in group III (61 ± 11 years) than in groups I (56 ± 11) and II (58 ± 11) (P < 0.002). Gender was similar in the

Table 1. Comparison of clinical and electrophysiological data between groups I and II

	1982–1989	1990–1999	*P*
No. of patients	301	315	
Age (yr)	56 ± 11	58 ± 11	0.01
Male gender	266 (88%)	287 (91%)	NS
LVEF (%)	44 ± 15	41 ± 12	0.007
QRS duration (ms)	115 ± 27	119 ± 23	NS
Non-sustained VT Holter	79 (26%)	149 (47%)	0.0000
Negative PVS	158 (52%)	148 (47%)	NS
Induced VT	59 (20%)	71 (22.5%)	NS
Induced V Fl/VF	84 (28%)	96 (30%)	NS
Induced V Fl	46 (25%)	62 (20%)	NS
Induced VF	38 (13%)	34 (11%)	NS
Revascularization	80 (26.5%)	84 (27%)	NS

LVEF = left ventricular ejection fraction, PVS = programmed ventricular stimulation, VT = ventricular tachycardia, V FL= ventricular flutter, VF = ventricular flutter/fibrillation

LVEF = left ventricular ejection fraction
ACE = angiotensin-converting enzyme

Table 2. Comparison of the clinical and electrophysiological data between groups II and III

	1990–1999	2000–2010	*P*
No. of patients	315	185	
Age (yr)	58 ± 11	61 ± 11	0.0009
Male gender	287 (91%)	1627 (89%)	NS
LVEF (%)	41 ± 12	36.5 ± 11	0.00000
QRS duration	119 ± 23	118 ± 26	NS
Non-sustained VT Holter	149 (47%)	120 (65%)	0.0001
Negative PVS	148 (47%)	107 (58%)	0.01
Induced VT	71 (22.5%)	52 (28%)	NS
Induced V Fl/VF	96 (30%)	26 (14%)	0.0001
Induced V Fl	62 (20%)	14 (8%)	0.002
Induced VF	34 (11%)	12 (6.5%)	NS
Revascularization	85 (27%)	89 (48%)	0.0000

LVEF = left ventricular ejection fraction, PVS = programmed ventricular stimulation, VT = ventricular tachycardia, V FL= ventricular flutter, VF = ventricular flutter/fibrillation

three groups, with a male predominance in group I (88%), II (91%) and III (89%) (not significant). Left ventricular ejection fraction was lower in group III (36.5 ± 11%) than in groups I (44 ± 15) ($P < 0.0000$) and II (41 ± 12) ($P < 0.0000$). QRS duration was similar in the three groups with a mean value of 115 ± 27 msec in group I, 119 ± 23 in group II and 119 ± 26 msec in group III (NS). Non-sustained VT at Holter monitoring was more frequent in group II than in group I ($P < 0.0000$) and more frequent in group III than in group II ($P < 0.0001$).

DATA OF CORONARY ANGIOGRAPHY

Total revascularization defined as the recanalization of occluded coronary artery and angioplasty or coronary artery bypass grafting of associated significant coronary stenoses was obtained more frequently in group III (48%) than in groups II (27%) and I (26.5%) ($P < 0.0000$). The changes could be related to primary angioplasty with recanalization of the occluded coronary artery, which has been performed in our department routinely since 2000 when MI occurs within 6 hours.

Table 3. Data of patients according to the period of study (I, II, III) and the results of PVS

	I VT-	II VT-	III VT-	I VT+	II VT+	III VT+	I VF	II VF	III VF
No. of patients	158	148	107	59	71	53	84	96	26
Age (yr)	56 ± 11	58 ± 11	60 ± 11	57 ± 11	59 ± 12	63 ± 10**	54 ± 11	57 ± 10	61 ± 9
Female gender	13%	11%	14%	12%	13%	9%	8%	3%*	4%
LVEF	45 ± 15	43 ± 12	38 ± 12	35 ± 12	37 ± 12	32 ± 10**	49 ± 13	41 ± 11	37 ± 11
Holter+	26%	47%	61%	36%	48%	77%***	20%	48%	42%
Revasc+	33.5%	34%	51%	37%	35%	64%	20%	9%	4%

*$P < 0.05$

**$P < 0.01$

VT- = negative PVS, VT+ = induction of a monomorphic VT, VF = induction of a ventricular flutter or fibrillation, Holter = presence of non-sustained VT at Holter monitoring, Revasc + = total revascularization

ELECTROPHYSIOLOGICAL DATA [Tables 1 and 2]

PVS was positive less frequently in group III (42%) than in group II (53%) ($P < 0.01$), but was as frequently positive as in group I (48%). Monomorphic VT < 270 bpm was induced as frequently in group III (28%) as in group II (22.5%), but more frequently than in group I (20%) ($P < 0.03$). Ventricular fibrillation and flutter was induced less frequently in group III (14%) than in groups I (28%) ($P < 0.0004$) and II (30%) ($P < 0.0001$). Ventricular fibrillation alone was induced less frequently in group III (6.5%) than in group I (13%) ($P < 0.03$) but tended to be less frequent than in group II (11%) ($P < 0.1$). Ventricular flutter alone was induced less frequently in group III (8%) than in groups I (15%) ($P < 0.0003$) and II (20%) ($P < 0.0002$). The induction of both ventricular flutter and fibrillation was similar in groups I (28%) and II (30%) but was significantly rarer in group III (14%) ($P < 0.0001$).

PREDICTORS OF VT OR VF INDUCTION

A lower LVEF was found to be associated with VT inducibility in all patient groups by univariate analysis [Table 3]. LVEF was also significantly lower in group III. The presence of non-sustained VT at Holter monitoring was not associated with a risk of VT induction except in group II. In the latter group the prevalence of non-sustained VT at Holter monitoring was higher in group III except in patients with inducible ventricular flutter or fibrillation. Surprisingly, total revascularization was performed as frequently in patients with inducible VT as in those with a negative study, but was rarer in patients with inducible VF in all groups.

Multivariate analysis showed that low LVEF was the only significant predictor of VT induction in group I ($P < 0.0001$). Three independent predictors of VF inducibility were found: a low LVEF ($P < 0.003$), the presence of non-sustained VT at Holter monitoring ($P < 0.043$), and the absence of revascularization ($P < 0.0001$). In group II, a low LVEF was also the only significant predictor of VT induction ($P < 0.04$). There were only two significant predictors of VF inducibility: the absence of revascularization ($P < 0.0001$) and male gender ($P < 0.013$). In group III, there were two significant and independent predictors of VT inducibility: a low LVEF ($P < 0.01$) and the presence of non-sustained VT at Holter monitoring ($P < 0.009$). Only older age was a predictor of VF inducibility. We then analyzed the possible role of the date of inclusion.

Multivariate analysis of age, gender, LVEF, non-sustained VT at Holter monitoring, and revascularization showed that a low LVEF was the only significant predictor of VT inducibility

VF = ventricular flutter and fibrillation

Table 4. Follow-up in the study population

	Sudden death	Death (heart failure)	Alive/non-cardiac death
No. of patients	35	79	689
Age (yr)	55 ± 12	58 ± 11	58 ± 11
Female gender	4 (11%)	8 (10%)	64 (9%)
LVEF (%)	35 ± 12	43 ± 12	43 ± 12**
VT	13 (37%)	31 (39%)	138 (20%)**
VF	11 (31%)	18 (23%)	177 (26%)
Negative PVS	11 (31%)	30 (38%)	374 (54%)***
QRS duration (ms)	124 ± 31	116 ± 32	116 ± 23

**$P < 0.01$

***$P < 0.001$

in groups I and II compared to group III ($P < 0.0001$). Three independent factors were associated with the induction of a ventricular flutter or fibrillation: male gender ($P < 0.007$), low LVEF ($P < 0.025$), and, mainly, the date of the PVS before 2000 ($P < 0.0001$) in groups I and II compared to group III.

The comparison of data for group I with those for groups II and III showed that a low LVEF was the only significant predictor of VT inducibility ($P < 0.0001$) and VF inducibility ($P < 0.004$).

FOLLOW-UP [Table 4]

Thirty-five patients died suddenly, 79 died from heart failure and 13 died from a non-cardiac cause. A defibrillator (ICD) was implanted in 83 patients. Comparing patients who are alive with those who died from a non-cardiac death (n=689) indicated that the induction of a monomorphic VT was the only univariate predictor of sudden death (37%) ($P < 0.01$) or heart failure-related death (39%) ($P < 0.0001$ compared to alive patients (20%). A low LVEF was more frequently observed in patients who died suddenly (35 ± 12%) than in patients who remained alive (43 ± 13%) ($P < 0.01$). Age, gender and QRS duration did not differ significantly. The induction of a ventricular flutter or fibrillation was not significantly associated with sudden death (31%) or heart failure-related death (23%); this arrhythmia was induced in 26% of alive patients. ICD implantation has most likely changed the cause of cardiac mortality, namely, increased risk of death from heart failure: in our study 29% of patients who died from heart failure had received a defibrillator compared to 5% of patients who are alive ($P < 0.0001$); 11% of patients who died suddenly had received a defibrillator (NS).

DISCUSSION

We report a significant decrease in ventricular flutter and fibrillation inducibility due to PVS since 2000, which is possibly associated with our program of acute coronary interventional procedures during acute MI in our institution. In the last decade the role of PVS was criticized because the technique was not capable of predicting sudden death unrelated to a monomorphic VT [10]. Sudden death has multiple causes, such as VT degenerating into ventricular fibrillation (20–30%), asystole associated or not with a complete atrioventricular block (25%), and primary VF. In asymptomatic patients, the induction of a monomorphic VT is always pathological and associated with a risk of VT-related sudden death and spontaneous VT [1-3]; only ICD implantation decreases the risk of sudden death in these patients [4]. Interest in the method declined after the MADIT II study [11], where a low LVEF (less than 30%) was only used for the indication of ICD, resulting in a lower death rate.

The induction of a ventricular flutter in patients with MI is more controversial [12,13] and was considered pathological in the MADIT I study only [4]. Generally, polymorphic VT (VF) induction was considered not significant except after resuscitated sudden death [1-3] in post-myocardial infarction [12,13] and in those with syncope and coronary artery disease [14,15]. It was considered pathological in other series [16,17], including patients with spontaneous VT. The induction of these non-specific arrhythmias was reported to occur in almost 30% of asymptomatic patients with MI [1-3].

Several studies have reported a favorable prognosis of patients with negative PVS [1-3,8] except in a sub-study of MADIT II: patients with a negative study had a higher rate of VF than those with inducible VF [11]. Today, PVS is used for risk stratification after MI in the case of LVEF 40–30/35% when non-sustained VT is noted at Holter monitoring (MADIT I) [18]. The limits of the prognostic value of LVEF were demonstrated [19,20], with a higher risk of sudden death in patients with LVEF > 30% and another risk factor than in patients with LVEF < 30% alone and no other risk factor. The sub-analysis of the MUSTT [8] and MADIT 2 studies [11] found more VT in patients with inducible VT. The prognosis was worse in patients with inducible VT in the MUSTT study in the first 6 months [9]. Furthermore, PVS performed soon after MI (day 9) could identify individuals at risk or not [21,22]. The prospective study of early ICD implantation 6 to 40 days post-MI (DINAMIT) [23] and a retrospective analysis of data from the MADIT II trial [11] failed to show a survival benefit for patients with ICD implantation in the early post-MI period. Recent studies have suggested that patients may benefit from an ICD if they have an inducible ventricular tachyarrhythmia in the early post-MI period. A large majority of patients with a negative PVS were at significantly lower risk of arrhythmic events without a defibrillator [22]. Analysis of the PVS results according to the years of indication demonstrates a decrease in non-specific arrhythmia induction. PVS was easier to interpret when only VT was induced. Mainly, low LVEF and also the presence of non-sustained VT at Holter monitoring remained the predictors of VT induction.

Furthermore, the present study confirms that the induction of a sustained monomorphic VT was the only predictor of sudden death or heart failure-related death, whereas a low LVEF was only a predictor of sudden death. The induction of a ventricular flutter or fibrillation was not significantly associated with sudden death or heart failure-related death.

LIMITATIONS

The first group (group I) referred between 1982 and 1989 included all patients seen for acute MI. This was followed by a bias in recruitment related to the introduction of ICD and the MUSTT and MADIT 2 studies. The bias begins in group II and is evident in group III. The indications of PVS were not routinely performed and were reserved for patients older than 70–75 years, patients with low LVEF, or patients with intermediate LVEF and non-sustained VT at Holter monitoring. This explains the lower LVEF in groups II and III and the larger number of patients with abnormal Holter monitoring than in group I. The differences increased between groups II and III. However, these data did not influence the results of PVS. Relatively young patients with low LVEF were excluded because ICD was indicated.

Some changes in the management of post-myocardial infarction have occurred since 1982. The influence of beta-blockers was not studied because this drug was always stopped before PVS. ACE inhibitors were introduced in groups II and III. The changes could be related to primary angioplasty with recanalization of the occluded coronary artery, which has been performed routinely since 2000 when the mean duration of MI is less than 6 hours. The induction of a ventricular flutter or fibrillation was more frequent in patients without revascularization. However, we cannot demonstrate an independent role of this factor in the risk of induction of a ventricular flutter or fibrillation. At least the delay of reperfusion is lacking. This fact could explain a similar incidence of revascularization in patients with inducible VT or in those with a negative study. These results differ from those of Kumar et al. [24], who reported that reperfusion time is a critical determinant of post-infarct ventricular electrical instability early and late after STEMI treated with primary percutaneous coronary intervention. The development of a non-invasive method that could also predict the risk of adverse events after MI seems associated with a similar prognostic value [25].

CONCLUSIONS

The induction of two poorly specific arrhythmias, ventricular fibrillation and flutter, in asymptomatic patients after myocardial infarction is rarer today than before 2000, although PVS was indicated in patients with lower LVEF. This decrease could be related to the routine practice of primary revascularization during acute myocardial infarction. The interpretation of PVS became easier. Only induction of monomorphic VT correlated with higher risk of sudden cardiac death or heart failure-related death.

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