

# Differences in Mechanisms and Outcomes of Syncope in Patients With Coronary Disease or Idiopathic Left Ventricular Dysfunction as Assessed by Electrophysiologic Testing

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<b>OBJECTIVES</b>	This study evaluated the causes of syncope and the significance and differences in left ventricular (LV) dysfunction, coronary disease, and idiopathic dilated cardiomyopathy (DCM).
<b>BACKGROUND</b>	Risk stratification of and indications for an automated defibrillator could differ according to the cause of LV dysfunction.
<b>METHODS</b>	Electrophysiologic study, including atrial and ventricular programmed stimulation, was performed in 119 patients with coronary disease (group I) and 61 patients with DCM (group II) with an left ventricular ejection fraction (LVEF) <40% and syncope. Patients were followed from one to six years (mean $4 \pm 2$ years).
<b>RESULTS</b>	Sustained monomorphic ventricular tachycardia (VT) was induced in 44 group I patients (37%) and 13 group II patients (21%); ventricular flutter (>270 beats/min) or ventricular fibrillation (VF) was induced in 24 group I patients (19%) and 9 group II patients (15%); and various other arrhythmias were identified. Syncope remained unexplained in 34 group I patients (30%) and 16 group II patients (27%). Prognosis depended on the heart disease: VT or VF induction was a predictive factor of mortality in coronary disease and identified a group with high cardiac mortality (46%), compared with patients with a negative study, who had a lower mortality (6%; $p < 0.001$ ) than in other studies. Cardiac mortality was only correlated with LVEF in DCM.
<b>CONCLUSIONS</b>	Various causes could explain syncope in 70% of patients with coronary disease and DCM, but differences were noted: VT was frequent in coronary disease with a bad prognosis, and ischemia could explain syncope; in DCM, different causes such as atrial tachycardia could be responsible for syncope, but the prognosis only depended on LVEF. (J Am Coll Cardiol 2004;44:594-601) © 2004 by the American College of Cardiology Foundation

Syncope is reported as a clinical sign of high risk of sudden death in patients with left ventricular (LV) dysfunction (1,2). In the era of the implantable cardioverter-defibrillator (ICD) (3-5), establishing the etiology of syncope is particularly important. We know that the causes of syncope are multiple (6) and that the implantation of an ICD does not resolve all causes of syncope and cardiac death (7). Studies on the prognosis of patients with syncope and heart failure (HF) have generally included patients with several etiologies. According to the nature of heart disease, the mechanism of syncope, its prognosis, and the methods used to evaluate risk stratification could differ. If indications for ICD now are clear in coronary disease and decreased LV ejection fraction (LVEF), they are still debatable in idiopathic dilated cardiomyopathy (DCM) (8). Electrophysiologic study (EPS) actually remains the best means to stratify patients with heart disease (9,10).

Therefore, the purposes of the study were to evaluate: 1)

the possible mechanisms of syncope; 2) the results of EPS; and 3) the prognosis of patients, according to the mechanism of LV dysfunction (i.e., idiopathic DCM or coronary disease).

**Study population.** All patients with coronary disease and LV dysfunction and those with idiopathic DCM who had an LVEF <40%, unexplained syncope ( $n = 121$ ), or dizziness and at least one episode of syncope ( $n = 98$ ), defined as a short loss of consciousness, were systematically recruited between 1985 and the beginning of 2000.

Patients were excluded from the study if they had: 1) unstable angina; 2) recent acute myocardial infarction (MI) (<1 month); 3) recent coronary angioplasty or coronary bypass surgery (<6 weeks); 4) paroxysmal second- or third-degree atrioventricular (AV) block on presentation; 5) sustained supraventricular or ventricular arrhythmia on presentation; 6) clinical HF not controlled by furosemide; 7) uncontrolled electrolytical abnormalities; 8) significant non-cardiac disease; or 9) received long-term amiodarone treatment.

During the period of study, 219 patients were recruited, of whom 37 had at least one exclusion criterion. Two additional patients were excluded because they were lost to follow-up.

From the Department of Cardiology, CHU of Brabois, Vandoeuvre Les Nancy, France. This study was presented at the 75th Scientific Sessions of the American Heart Association, November 2002, Chicago, IL.

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#### Abbreviations and Acronyms

AV	=	atrioventricular
BP	=	blood pressure
DCM	=	dilated cardiomyopathy
EPS	=	electrophysiologic study
HF	=	heart failure
ICD	=	implantable cardioverter-defibrillator
LV	=	left ventricular
LVEF	=	left ventricular ejection fraction
MI	=	myocardial infarction
SVTA	=	supraventricular tachyarrhythmia
VF	=	ventricular fibrillation
VT	=	ventricular tachycardia

The remaining 180 patients were classified into two groups according to their history and results of coronary angiography: 1) Group I comprised 119 patients who had coronary disease with a history of MI and/or multiple coronary stenoses on coronary angiography and an LVEF <40% (range 10% to 40%, mean  $29 \pm 7\%$ ). There were 101 males and 18 females (age range 25 to 80 years, mean  $65 \pm 11.5$  years). 2) Group II comprised 61 patients who had idiopathic DCM confirmed by a normal coronary angiogram. The angiographic LVEF varied from 10% to 40% (mean  $27 \pm 10\%$ ;  $p = \text{NS}$ ). There were 52 males and 9 females (age range 27 to 78 years, mean  $62 \pm 10$  years).

**Study protocol.** Patients underwent several investigations in the absence of anti-arrhythmic drugs after giving written, informed consent. A personal and familial clinical history, list of drugs taken at the time of syncope, and clinical examination were noted.

The studies were performed in patients in stable clinical conditions after adaptation of their treatment. Most patients received angiotensin-converting enzyme inhibitors. Beta-blockers and digoxin were stopped before EPS.

The following noninvasive studies were performed: 24-h Holter monitoring (Elatec, France), two-dimensional echocardiography, thallium exercise scintigraphy in patients with ischemic heart disease and no recent coronary angiography ( $n = 10$ ) or with significant coronary artery stenosis on coronary angiography ( $n = 16$ ), and head-up tilt testing without provocative drugs in 30 patients with a negative EPS or inducible ventricular flutter or ventricular fibrillation (VF).

The following invasive studies were performed: right and left angiography, coronary angiography, and a complete EPS study according to a protocol previously reported (11,12).

The protocol included assessment of sinoatrial function, AV conduction using measurement of the AH and HV intervals and intra-atrial conduction time, and atrial pacing at progressively faster rates until AV block occurred.

Programmed atrial stimulation was performed during sinus rhythm and paced cycle lengths (600 and 400 ms). One and two extrastimuli were delivered. Right ventricular pacing was performed up to 200 beats/min. Programmed

right ventricular stimulation using one and two extrastimuli were introduced during sinus rhythm and paced cycle lengths (600 and 400 ms) at the apex and subsequently at the outflow tract. A third extrastimulus was added if sustained ventricular tachycardia (VT) or VF was not induced. Short coupling intervals (<200 ms) were not used.

If the study remained negative, the protocol was repeated after isoproterenol infusion at a dose of 2 to 4  $\mu\text{g}/\text{min}$  to decrease the sinus cycle length by at least 15% (13).

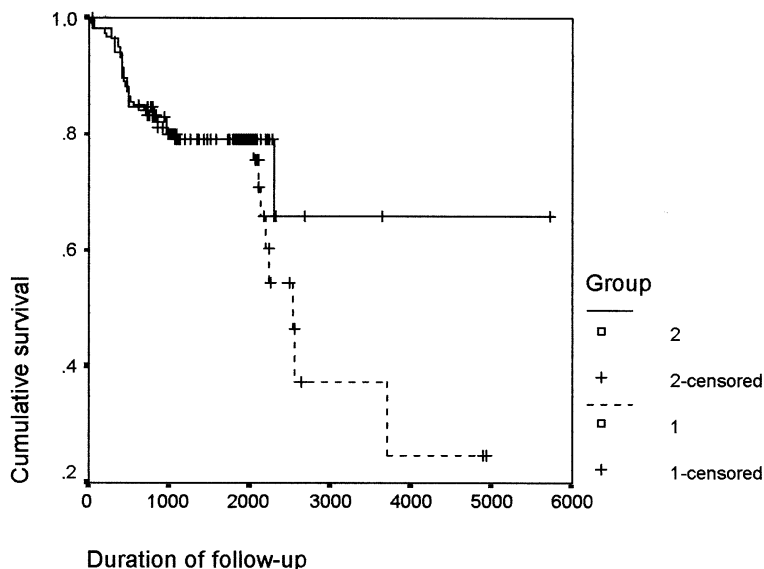
Arterial blood pressure (BP) was continuously monitored by an external sphygmomanometer (Baxter, Hayashikomaki, Japan). Carotid sinus massage was performed until the development of the head-up tilt test (1992).

Abnormal electrophysiologic findings were categorized according to the following diagnostic criteria:

- Sinus node dysfunction was considered as present if the corrected sinus node recovery time (sinus recovery time – mean sinus cycle length) was  $>550$  ms.
- Conduction disturbances were present if AV Wenckebach block occurred at a pacing rate of  $<90$  beats/min, if the HV interval was  $>60$  ms in the case of right bundle branch block and  $>70$  ms in the case of left bundle branch block, and if infrahisian second-degree AV block occurred at a pacing rate  $<150$  beats/min.
- Hypervagotonia was present if carotid sinus massage produced an asystole with an RR interval of  $>3,000$  ms.
- Inducible supraventricular tachyarrhythmia (SVTA) was defined as a sustained ( $>3$  min), either spontaneously regressive but reproducible or permanent SVTA provoking a drop in arterial BP ( $>30\%$ ) and symptoms similar to dizziness, which could be a paroxysmal junctional tachycardia or atrial tachyarrhythmia (atrial tachycardia, flutter, or fibrillation). The induction of a relatively slow atrial fibrillation without symptoms or changes in BP was considered as not pathologic. When sustained VT was also induced, the presumed cause of syncope was categorized as ventricular tachyarrhythmias.
- Inducible ventricular tachyarrhythmias were categorized as: 1) monomorphic VT ( $<270$  beats/min) lasting more than 30 s or requiring termination because of hemodynamic intolerance or lasting between 10 and 30 s and responsible for syncope; or 2) ventricular flutter ( $>270$  beats/min) or VF requiring cardioversion to stop it.

**Follow-up.** Patients were followed from one to six years (mean  $4 \pm 2$ ) or until heart transplantation ( $n = 6$ ). The patient was examined by the referent doctor every month and one of our cardiologists every three months. The follow-up was stopped at six years, because the hemodynamic and coronary status may have changed after this period.

A pacemaker was implanted in patients with conduction disturbances. In those who also had inducible VT, anti-arrhythmic therapy was introduced after pacemaker implantation, or since 1998, a pacemaker and defibrillator were implanted.



**Figure 1.** General Kaplan-Meier survival curves for groups I (1) and II (2) (p = NS).

Patients with induced SVTA or VT were treated with a combination of 200 mg amiodarone and small doses of a beta-blocker. This treatment was electrophysiologically guided. In the last recruited patients and in those with still rapid inducible VT, an ICD was placed. Before 1998, VT radiofrequency catheter ablation was performed in five patients; in patients receiving anti-arrhythmic drugs, the VT became not inducible or slowed and was hemodynamically well tolerated.

In patients with a non-arrhythmic cause of syncope such as ischemia, a specific treatment was indicated.

We considered the total cardiac mortality, including deaths related to HF and sudden deaths. "Sudden death" was defined as an unexpected death from a cardiac cause within a short period (<1 h); deaths associated with the development of spontaneous VT were classified with sudden deaths. Two deaths occurring during the night in stable patients were classified as sudden deaths. Some deaths occurred in our hospital; for those who died at home or in another hospital, we contacted the last medical doctor and the family to classify the mode of death.

**Statistical analysis.** Data are expressed as the mean value  $\pm$  SD. Statistical analysis was performed using the unpaired Student *t* test for quantitative data and the chi-square test for discrete variables and ordinal tests. A p value <0.05 was considered as significant. Stepwise logistic regression analysis was performed to identify the independent variables predictive of cardiac death. The predictive negative and positive values of the data of programmed ventricular stimulation to predict cardiac death were calculated. Survival curves were calculated using the Kaplan Meier product-limit method and compared by the log-rank test.

**RESULTS**

**Results of EPS.** Sustained monomorphic VT (from 160 to 269 beats/min, mean 210) or syncopal nonsustained VT (frequency from 220 to 240 beats/min) was induced in 44 group I patients (37%) and 13 group II patients (21%; p = NS). There was no bundle branch tachycardia.

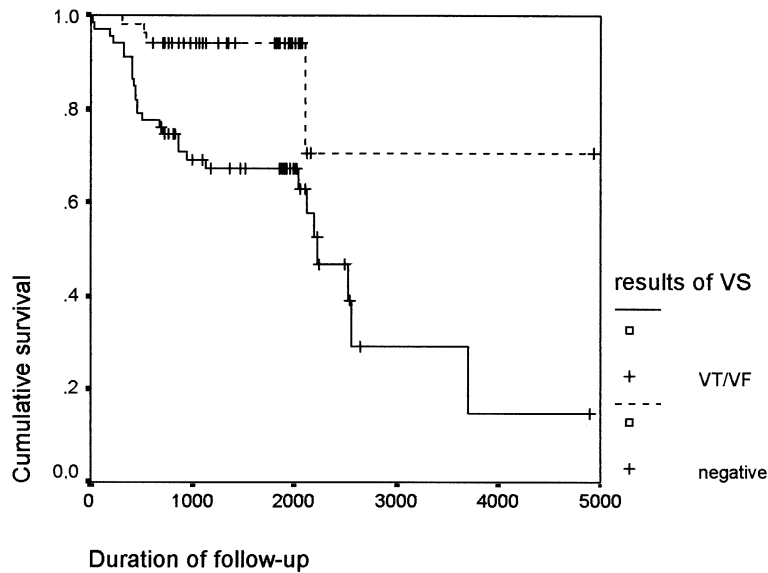
Ventricular flutter or fibrillation was induced in 24

**Table 1.** Clinical and Electrophysiological Data on Group I

	HF Death (n = 18)	Sudden Death (n = 16)	Total Deaths (n = 34)	Alive (n = 85)
Age (yrs)	70 $\pm$ 13	65 $\pm$ 10	68 $\pm$ 12	65 $\pm$ 12
Female gender	3 (17%)	1 (6%)	4 (12%)	14 (16%)
NSVT/Holter monitor	9 (50%)	9 (56%)	18 (53%)	30 (35%)
LVEF (%)	29 $\pm$ 7	29 $\pm$ 7	29 $\pm$ 7	30 $\pm$ 7
Induced monomorphic VT/VF (n = 68)	16 (23.5%)	15 (22%)	31* (91%)	37 (43.5%)
Induced monomorphic VT (n = 44)	10 (55.5%)	13† (81%)	23‡ (68%)	19 (22%)
Induced VF (n = 24)	6 (33%)	2 (12.5%)	8 (23.5%)	16 (19%)
Negative study (n = 51)	2 (11%)	1 (6%)	3 (9%)	48 (56%)

Comparisons with alive patients: \*p < 0.05. †p < 0.01. ‡p < 0.001. Data are presented as the mean value  $\pm$  SD or number (%) of patients.

HF = heart failure; LVEF = left ventricular ejection fraction; NSVT = nonsustained ventricular tachycardia; VF = ventricular flutter/fibrillation; VT = ventricular tachycardia <270 beats/min.



**Figure 2.** Kaplan-Meier survival curves for group I patients according to the results of programmed ventricular stimulation (VS) ( $p < 0.0009$ ) (**upper line** = patients with a negative study; **lower line** = patients with induced ventricular tachycardia [VT] and ventricular fibrillation [VF]).

group I patients (19%) and nine group II patients (15%;  $p = \text{NS}$ ).

In group I, ventricular tachyarrhythmia was induced by one extrastimulus ( $n = 13$ ) and two ( $n = 35$ ) and three extrastimuli ( $n = 20$ ) in the control state in 64 patients and after isoproterenol in four patients. In group II, ventricular tachyarrhythmia was induced by two ( $n = 10$ ) or three extrastimuli ( $n = 12$ ) in the control state in 18 patients and after isoproterenol in four patients. In addition, SVTA was induced in 11 group I patients (9%) and 15 group II patients (25%;  $p < 0.001$ ).

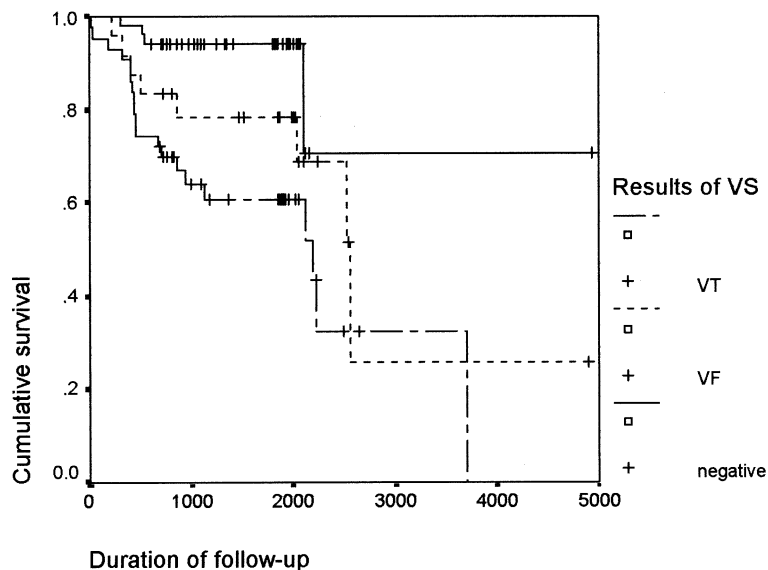
Conduction disturbances were noted in three group I patients (2.5%) and five group II patients (8%). Intrafascicular

conduction abnormalities were also noted in association with inducible VT in seven group I patients (6%) and one group II patient (2%).

Carotid sinus massage was positive in three group I patients and two group II patients, but other arrhythmias were noted, and hypervagotonia was not retained as the cause of syncope.

The EPS remained negative in 43 group I patients (36%) and 20 group II patients (33%;  $p = \text{NS}$ ).

**Results of other investigations.** 24-H HOLTHER MONITORING. Ventricular arrhythmias (couplets or nonsustained VT) were present in 54 group I patients (45%) and 25 group II patients (41%;  $p = \text{NS}$ ).



**Figure 3.** Kaplan-Meier survival curves according to the results of programmed ventricular stimulation (VS) in group I (log-rank 13.92,  $p < 0.0009$ ) (**upper line** = patients with a negative study; **middle line** = patients with induced ventricular fibrillation [VF]; **lower line** = patients with induced ventricular tachycardia [VT]).

**Table 2.** Positive and Negative Predictive Values of the Induction of Monomorphic Ventricular Tachycardia <270 beats/min and Ventricular Fibrillation to Predict All Cardiac Deaths, Sudden Death, and Death Related to Heart Failure in Group I

	PPV			NPV		
	CD	SD	HF	CD	SD	HF
VT	52%	29.5%	23%	85%	96%	89%
VF	33%	8%	25%	73%	85%	87%

CD = cardiac death; HF = heart failure; NPV = negative predictive value; PPV = positive predictive value; SD = sudden death; VF = ventricular fibrillation/flutter; VT = ventricular tachycardia.

**HEAD-UP TILT TEST.** In 30 patients, this test reproduced the syncope in four group I patients with a negative EPS and two group I patients with inducible ventricular flutter. Syncope was reproduced in three group II patients with a negative EPS.

**THALLIUM-201 EXERCISE SCINTIGRAPHY.** This modality showed severe coronary ischemia (>40%) with a drop in arterial BP and/or development of polymorphic VT in three group I patients.

At the end of investigations, syncope remained unexplained in 34 group I patients (30%) and 16 group II patients (27%;  $p = \text{NS}$ ).

**Follow-up (1 to 6 years, mean  $4 \pm 2$  years).** The general survival was 65% at five years, similar in both groups (log-rank 0.76;  $p = \text{NS}$ ) (Fig. 1).

In group I, an ICD was placed in four patients. Heart transplantation was performed in three patients. Thirty-four patients died of a cardiac cause: 18 from HF and 16 suddenly; among the latter group, two were resuscitated but died of HF one year later. Sudden deaths occurred between two weeks and one year after the hospitalization for syncope. One sudden death occurring during Holter monitoring was related to VT degenerating into VF; this patient had inducible monomorphic VT. Deaths related to HF occurred between one month and five years after syncope.

Among alive patients, six had recurrent syncope and a second EPS. In four of them, both studies remained negative; they are alive. In two patients, sustained VT was induced on both studies; one patient died later from HF and an ICD was placed in the other one.

Among the 11 patients with SVTA, none died suddenly.

One patient developed AV node reentrant tachycardia, and three had paroxysmal rapid atrial fibrillation.

Table 1 reports the results of noninvasive and invasive studies in group I according to follow-up. The LVEF and presence of salvos of ventricular premature beats were similar in alive patients and those who died. There was a trend toward older age in patients who died compared with alive patients, but the differences were not significant. There was a higher total cardiac mortality (46%) in patients with inducible ventricular tachyarrhythmias than in those with a negative EPS (6%;  $p < 0.001$ ). Induced VT was significantly associated with death from HF ( $p < 0.05$ ) and sudden death ( $p < 0.01$ ). The significance of induced flutter/fibrillation remained unclear because the differences were not significant; linear logistic regression shows that it was only a significant predictor of total cardiac mortality (odds ratio 3.406), but it was not a significant predictor of sudden death. Survival curves indicated a high difference of mortality rates in patients with inducible ventricular tachyarrhythmias as compared with those with a negative study (Fig. 2) (log-rank 11.08,  $p < 0.0009$ ). Significant differences were noted in patients with inducible VT or those with inducible ventricular flutter/fibrillation, as compared with those with negative programmed stimulation (Fig. 3) (log-rank 13.92,  $p < 0.0009$ ).

The positive and negative values of the induction of VT or another arrhythmia for the prediction of death are reported in Table 2. The positive predictive value is relatively low, but the negative predictive value is high. The positive predictive value of a negative programmed ventricular stimulation to predict survival is high; its negative predictive value is lower.

In group II, an ICD was placed in three patients. Heart transplantation was performed in three patients. Ten patients died of a cardiac cause, HF ( $n = 5$ ), or sudden death ( $n = 5$ ). Among the patients who died suddenly, four had inducible ventricular arrhythmias, syncopal nonsustained VT ( $n = 1$ ), or ventricular flutter ( $n = 3$ ).

Two patients with a negative study but a positive head-up tilt test still had dizziness.

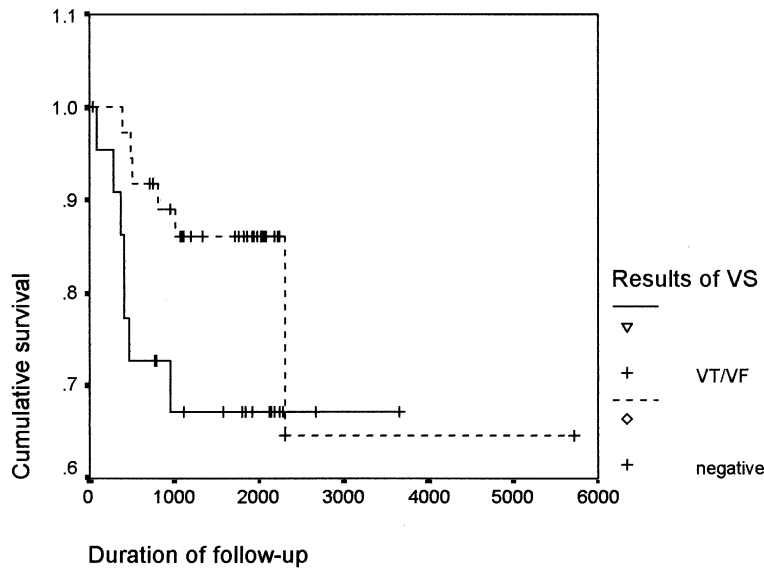
In the 15 patients with SVTA who are still alive, two developed AV node reentrant tachycardia, two had atrial flutter, and three developed chronic atrial fibrillation.

Table 3 reports the results of studies in group II patients according to their follow-up. There was a trend toward a more frequent presence of salvos of ventricular beats on

**Table 3.** Clinical and Electrophysiologic Data on Group II

	HF Death (n = 5)	Sudden Death (n = 5)	Total Deaths (n = 10)	Alive (n = 51)
Age (yrs)	68 ± 6	49 ± 15	58.5 ± 14	62 ± 11
Female gender	1 (20%)	3 (60%)	5 (50%)	7 (14%)
NSVT/Holter monitor	4	3	7	17 (33%)
LVEF (%)	23 ± 8	25 ± 14	24 ± 11*	29 ± 7
Induced VT/VF (n = 22)	1(20%)	4 (80%)	5 (50%)	17 (33%)
Negative study (n = 39)	4 (80%)	1 (20%)	5 (50%)	34 (67%)

\* $p < 0.05$ . Data are presented as the mean value ± SD or number (%) of patients. Abbreviations as in Table 1.



**Figure 4.** Kaplan-Meier survival curves according to the results of programmed ventricular stimulation (VS) in group II (NS,  $p < 0.10$ ) (upper line = patients with a negative study; lower line = patients with induced ventricular tachycardia [VT] and ventricular fibrillation [VF]).

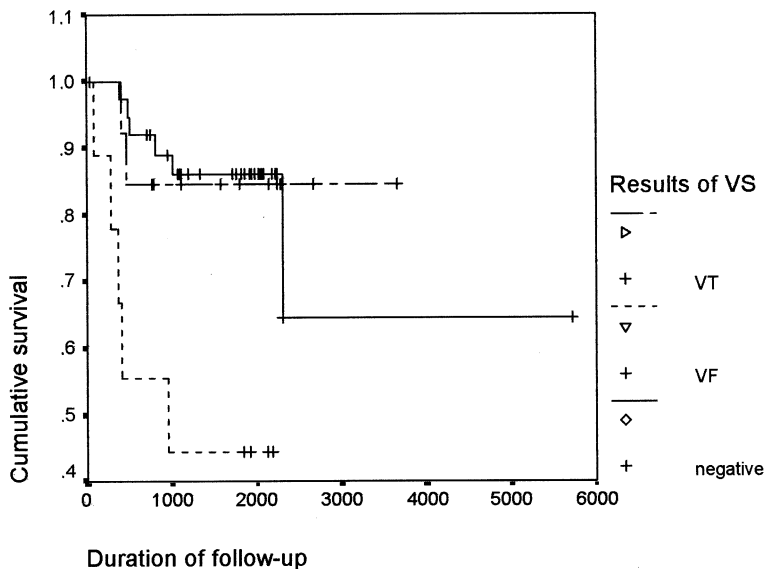
Holter monitoring in those who died than in alive patients, but the differences were not statistically significant. The only significant difference was LVEF, which was lower in patients dead from a cardiac cause than in alive patients ( $p < 0.05$ ). There is a trend for a higher frequency of inducible ventricular tachyarrhythmia to predict sudden death, but the cardiac mortality was statistically similar in patients with inducible VT or ventricular flutter (23%) and in those with a negative EPS (13%). Kaplan-Meier survival curves did not reveal significant differences of cardiac mortality according to the induction or not of ventricular tachyarrhythmias (log-rank 2.64,  $p = \text{NS}$ ) (Fig. 4). However, the survival curve of patients with inducible ventricular

flutter/fibrillation differed significantly from that of the remaining population (log-rank 11.13,  $p < 0.0038$ ) (Fig. 5).

The positive predictive value of the induction of ventricular tachyarrhythmia to predict all types of death is low, but its negative predictive value is high (Table 4). The positive value of a negative programmed ventricular stimulation to predict patient survival is high, but its negative predictive value is lower.

## DISCUSSION

The study confirms that syncope is a clinical sign of deleterious prognosis in patients with LV dysfunction and



**Figure 5.** Kaplan-Meier survival curves for group II patients according to the results of programmed ventricular stimulation (VS) ( $p < 0.0038$ ) (upper lines = negative study and inducible ventricular tachycardia [VT]; lower line = inducible ventricular fibrillation [VF]).

**Table 4.** Positive and Negative Predictive Values of Positive Programmed Ventricular Stimulation (VT and VF) to Predict Total Cardiac Death, Sudden Death, and Death Related to Heart Failure in Group II

	PPV			NPV		
	CD	SD	HF	CD	SD	HF
VT/VF	23%	18%	4.5%	87%	97%	90%

Abbreviations as in Table 2.

inducible monomorphic VT (14–16) In fact, this is a strong prognostic factor for mortality in coronary disease and a weaker factor in idiopathic DCM. The high mortality in coronary disease was previously reported (17). The significance of inducible ventricular flutter/fibrillation is more debatable. It is considered as without clinical significance in asymptomatic, post-MI patients (11,18) and in those with syncope and coronary disease, as reported by Mitall et al. (19). In the present study, we noted a higher cardiac mortality than in those with a negative study, but the deaths could be related to HF and the differences were not statistically significant. A negative EPS in patients with coronary disease, syncope, and LVEF <40% indicates a prognosis similar to that of a population without syncope (11). The relatively low mortality is probably explained by the date of MI, which is frequently old. Most sudden deaths occur during the first year after acute MI.

Menozi et al. (20) reported that the causes of syncope in coronary disease are multiple. Vagal hypertonia could be a frequent cause (21–23), and paroxysmal AV block was also frequent (24,25).

In patients with idiopathic DCM, abnormal electrophysiologic data were noted with a similar incidence as in patients with coronary disease, but SVTA could be a more frequent finding than VT. This cause remains difficult to prove; salvos of atrial premature beats on 24-h Holter monitoring are frequent and not specific, but the relationships between syncope and SVTA were previously demonstrated (26). The prognosis was independent of the results of the EPS and the presence of syncope; a control group without syncope had a cardiac mortality rate of 18% at three years (13). The mortality is lower than in epidemiologic studies of patients admitted for HF (27–29), because our patients were in a stable hemodynamic condition, as in asymptomatic patients (30). The present study indicated that a low LVEF was the only significant predictor of death in this disease.

**Study limitations.** The small number of patients with an ICD could explain the high mortality of patients with coronary disease, syncope, and induced ventricular tachyarrhythmia. This is explained by the period of recruitment, as the indications for ICD in France were rare. Antiarrhythmic drugs did not explain the high mortality, because we have used amiodarone, which has been demonstrated without a negative effect in MI, and beta-blockers, which have beneficial effects. The EPS was performed in the supine position; only the patients with rapid nonsustained monomorphic VT reproduced their syncope. The head-up

tilt testing was not systematic, and some neurocardiogenic syncope could have been missed. The number of patients with syncope and idiopathic DCM is relatively small, and some data have shown a low statistical significance.

**Conclusions.** The presumed causes of syncope were identified with the same frequency in patients with coronary disease and LV dysfunction and those with idiopathic DCM, but SVTA could be a more frequent cause of syncope in idiopathic DCM, and ventricular tachyarrhythmias could be more frequent in coronary disease. The prognosis differed and was dependent on the results of EPS principally in coronary disease with a high spontaneous cardiac mortality in patients with induced ventricular tachyarrhythmias. The prognosis mainly depended on LVEF in idiopathic DCM.

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