SIGNIFICANCE OF INDUCIBLE VENTRICULAR FLUTTER - FIBRILLATION AFTER MYOCARDIAL INFARCTION.

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Summary

The significance of induced ventricular flutter or fibrillation (V fl/VF) remains debatable especially in patients with myocardial infarction and relatively preserved ejection fraction.

The purpose of this study was to determine the factors associated with the induction of V fl/ VF and its prognostic significance in post-myocardial infarction.

Among a consecutively recruited population of 1446 patients who had a history of myocardial infarction (>1 month) and an indication of a programmed ventricular stimulation, V Fl/VF was induced by stimulation in 283 patients. V fl/VF was induced as frequently in patients with syncope (50/271, 18 %) than in asymptomatic patients (186/810, 23 %), less frequently in patients with spontaneous ventricular tachycardia (VT) (26/303, 13 %) than in other groups and more frequently in those with resuscitated cardiac arrest (21/62, 34 %) than in other patients. In this last group an ischemic factor was more frequent than in other patients (28. 5 vs 11 %).

During the follow-up, 39 patients (14%) died from a cardiac cause (21 from an arrhythmic death, 11 from heart failure). Ventricular flutter, but no ventricular fibrillation was a predictor of cardiac mortality and sudden death. The number of extrastimuli used to induce V fl/VF was not predictive of death. Nonsustained VT's on Holter monitoring were more frequent in patients who died than in alive patients (61 % vs 39 %). The cardiac mortality and sudden deaths were more frequent in patients with spontaneous VT than in other patients (26 vs 6.5 %). As expected, in patients without spontaneous ventricular arrhythmias, VF and LVEF were predictors of total cardiac mortality, but only LVEF < 40 % predicted sudden death.

In conclusion, the significance of inducible V fl/VF after myocardial infarction depends on the clinical data of the population. If the arrhythmia is pathological in patients with resuscitated cardiac arrest and those with spontaneous VT, the arrhythmia does not indicate a risk of sudden death in patients without documented arrhythmias: in patients with preserved LVEF, induced V fl/VF has no clinical significance; in patients with low LVEF, the induction of V fl/VF is associated with a higher mortality by heart failure; therefore, when the patient has the criteria for MADIT II and an indication of ICD, he should be carefully followed.

Key-Words : Myocardial infarction, Programmed ventricular stimulation, Ventricular flutter

The interest of electrophysiological study in post myocardial infarction (1-5) and in patients with syncope (6-12) was reported in many studies. The high mortality in patients with coronary artery disease, low ejection fraction and inducible monomorphic ventricular tachycardia (VT) was demonstrated in all studies (13-17). Therefore, programmed ventricular stimulation was considered as the reference technique of evaluation after myocardial infarction (18). However, in the era of implantable cardioverter defibrillator (ICD) (19, 20, 21) and resynchronization therapy, electrophysiological studies seem have lost their prognostic value; a non specific treatment without evaluation outside the measurement of left ventricular ejection fraction (LVEF) could be enough to manage the patient. More, an analysis of MADIT II (22) reports that electrophysiological study was not useful to identify the patients who benefit from ICD implantation: in these asymptomatic patients with a previous myocardial infarction and advanced left ventricular dysfunction, there was no correlation with the efficacy of defibrillator and the induction of a VT. However in some recent studies, the proarrhythmic effect of ICD (23, 24) or the occurrence of increased risk of heart failure in the MADIT II population (25) was reported. More, the beta blockers reduce the risk of ventricular arrhythmias and improve survival of the same population (26).

Therefore, we have to take carefully the most recent studies. More, it is frequently difficult to evaluate correctly the LVEF or the LVEF changes with the medical therapies or with the treatment of coronary ischemia. In clinical practice, the indications of electrophysiological studies remain important at least in ischemic heart disease and syncope (27). Although programmed ventricular stimulation is performed since 30 years, the significance of inducible ventricular flutter/fibrillation remains debatable in some studies, considered as without clinical significance in asymptomatic patients in post myocardial infarction (1-5, 2.8-31) and in those with syncope and coronary artery disease by Mitall et al (30). In 1996, ICD was indicated in patients with low ejection fraction, nonsustained VT on Holter monitoring and with inducible monomorphic VT or ventricular flutter (18).

Therefore, the significance of induced ventricular flutter or fibrillation remains debatable especially in patients with myocardial infarction and relatively preserved ejection fraction.

We have a large experience of programmed ventricular stimulation and the purpose of the present study was to report the clinical data of patients with inducible ventricular flutter or fibrillation and its prognostic significance in patients with history of myocardial infarction.

POPULATION

The study patients were identified from a consecutively recruited population of 1446 patients between 1985 and 2005. The criteria of recruitment were:1) a history of myocardial infarction (>1 month) and 2) the indications of a programmed ventricular stimulation.

Programmed ventricular stimulation was performed either systematically in asymptomatic patients (n= 810), for unexplained syncope (n=271), for the occurrence of a spontaneous VT (n=303) or after a resuscitated cardiac arrest (n=62). Among the 1446 patients, antiarrhythmic drug therapy guided by repeated electrophysiological studies was indicated in 351 patients. Asymptomatic patients were studied between 6 and 8 weeks after acute myocardial infarction. Until 1994, programmed ventricular stimulation was systematic (5) and after this date, was indicated either in patients with low ejection fraction, or late potentials or salvos of ventricular premature beats on Holter monitoring. Patients with syncope were studied between 6 weeks and 10 years after myocardial infarction (mean 3±1 years).

Patients were excluded, if they had (1) unstable angina, (2) recent acute myocardial infarction (< 1 month), (3) recent coronary angioplasty or coronary bypasses surgery (< 6 weeks), (4) presented a paroxysmal second or third degree AV block, (5) clinical heart failure not controlled by furosemide, (6) not controlled electrolytical abnormalities, (7) significant noncardiac disease or (8) a syncope related to an explained cause.

Among this population, a ventricular flutter (n=174) (figure 1) or fibrillation (n=109) (figure 2) was induced in 283 patients; they represent the study population.

METHODS

I) <u>Protocol</u> :

The patients underwent several investigations, approved by our review committee, in the absence of antiarrhythmic drugs, beta-blockers and digoxin, after giving informed consent. Personal and familial clinical history, list of drugs taken at the time of syncope and clinical examination were initially noted.

The following noninvasive studies were performed ; 24 hour Holter monitoring (Elatec) and 2D echocardiogram were recorded; thallium exercise scintigraphy was indicated in patients with no recent coronary angiography or with significant coronary artery stenosis at coronary angiography ; left ventricular ejection fraction (LVEF) was measured by radionuclide studies at the time of programmed ventricular stimulation.

The following invasive studies were performed; the coronary angiography was systematic except in those with a recent angiography (< 6 months). Complete electrophysiologic study according to a procotol previously reported (5): sinoatrial function and atrioventricular conduction were assessed. Programmed atrial stimulation was performed during sinus rhythm and atrial pacing at two cycle lengths, 600 and 400 ms. One (S2) and 2 premature stimulus (S3) were delivered. Right ventricular pacing was performed at an incremental rate up to 200 beats/min. Programmed right ventricular stimulation using one extrastimulus (S2) and 2 extrastimuli (S2 and S3) were introduced during sinus rhythm and ventricular pacing, 600 and 400 ms, at the right ventricular apex and ventricular outflow tract. A third extrastimulus was added if a sustained ventricular tachycardia (VT) or VF was not induced. Triple extrastimuli (S2, S3, S4) were introduced during sinus rhythm and paced rhythms at the right ventricular outflow tract and the apex. Short coupling intervals (< 200 ms) were not used.

II) The following definitions were used to express the results of programmed ventricular stimulation :

- monomorphic ventricular tachycardia (< 270 beats/min) lasting more than 30 sec or requiring termination because of haemodynamic intolerance
- ventricular flutter : monomorphic ventricular tachycardia >270 b/min requiring pacing or more frequently cardioversion to stop it
- ventricular fibrillation : polymorphic VT, requiring cardioversion to stop it.

Patients were followed from 1 to 6 years or until heart transplantation (n = 7) (mean 4±2)

III) follow-up :

The follow-up was stopped at 6 years, because the hemodynamic and coronary status may have changed after this period.

Patients with syncope and induced ventricular tachycardia < 270 b/min and ventricular tachycardia or fibrillation were treated with an association of 200 mg of amiodarone and small doses of beta-blocker until 1998/2000. The treatment was electrophysiologically-

guided. This treatment is actually still indicated in patients with inducible VT and LVEF > 40 %. A total of 351 electrophysiologically-guided studies was performed. The treatment was considered as effective if ventricular tachycardia was not inducible or a relatively slow and hemodynamically well-tolerated tachycardia was induced. In those with still inducible rapid ventricular tachycardia, several non medical treatments were discussed either heart surgery and ventriculotomy, or ventricular tachycardia catheter ablation or ICD implantation. This last indication was retained as the first choice since in the last recruited patients (1998/2000). Asymptomatic patients with negative study or inducible ventricular flutter or fibrillation only were treated by beta blockers. An ICD was indicated since end 2000 in those with induced ventricular flutter and low ejection fraction. ICD implantation was now systematic in patients with spontaneous VT and LVEF< 40 % or those with resuscitated cardiac arrest.

Coronary ischemia was specifically treated by coronary angioplasty or coronary artery bypass surgery.

We considered the total cardiac mortality including the deaths related to heart failure and the sudden deaths. Sudden death was defined as an unexpected death from a cardiac cause within a short time period (< 1 hour); deaths following the occurrence of a spontaneous sustained VT, generally related to the haemodynamic failure provoked by the tachycardia and or its treatment, and sudden deaths were classified as arrhythmic deaths.

IV) Statistical analysis

Statistical analysis of the data was expressed as mean ± standard deviation. Statistical analysis was performed with the Student's unpaired t test for quantitative data, with 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.

RESULTS

I) Incidence of ventricular flutter/fibrillation induction according to clinical data:

Ventricular flutter/fibrillation was induced in 283 patients, 21 women and 262 men, aged 59± 11 years; mean left ventricular ejection fraction was 42±13 %.

The ventricular arrhythmia was induced by ventricular pacing in one patient, atrial pacing in 2 patients, one extrastimulus in 5 patients, 2 extrastimuli in 131 patients and 3 extrastimuli in other 143 patients. In 5 patients a second programmed electrophysiologic study was performed between 2 and 3 years after the first study and ventricular/fibrillation remained inducible.

This ventricular arrhythmia was induced as frequently in patients with syncope (50/271; 18 %) than in asymptomatic patients (186/810, 23 %), less frequently in patients with spontaneous VT (26/303, 13 %) than in other groups and more frequently in those with resuscitated cardiac arrest (21/62, 34 %) than in other patients.

Significant coronary stenosis was identified in 35 patients, 16 asymptomatic patients (9%), 9 patients with syncope (18 %) (NS), 4 patients with spontaneous VT (15 %) and more frequently ($p< 0.05$) in 6 patients with resuscitated cardiac arrest (28.5 %) (table I).

The occurrence of a ventricular flutter /fibrillation in patients with inducible VT in control state and treated by antiarrhythmic drugs was a very rare finding; this effect was noted in 8 of 351 electrophysiologically-guided studies (2 %); ventricular fibrillation was provoked in 6 and ventricular flutter in only 2 patients. Among 12 patients with inducible ventricular flutter/ fibrillation, the association of amiodarone with beta-blockers prevented the induction of ventricular arrhythmia in 7 patients.

Table II reports the clinical data of each group. Patients with syncope and those with resuscitated cardiac arrest were older (64±11 years) than asymptomatic patients (57±10 years) ($p <0.001$) or those with spontaneous VT; Patients with syncope and those with spontaneous VT had a lower LVEF than asymptomatic patients.

Patients with syncope, spontaneous VT and resuscitated cardiac arrest differed from asymptomatic patients by the date of myocardial infarction (3±1 years vs 4±1 weeks).

In patients without documented arrhythmias, the ventricular arrhythmia was induced in 96 of 460 patients (21 %) with LVEF < 40 % and 137 of 621 patients (22 %) with LVEF > 40 % (NS).

II) Cardiac mortality:

Thirty -nine patients (14%) died from a cardiac cause: 21 died from an arrhythmic death and 11 died from heart failure; heart transplantation was performed in 2 patients; a cardioverter defibrillator was implanted in 16 patients. Total cardiac mortality was more frequent in

patients with spontaneous VT (38 %) and those with syncope (22 %) than in asymptomatic patients (8 %) or those with resuscitated cardiac arrest (14 %); in patients with syncope, the deaths were related to a higher incidence of death due to heart failure than in asymptomatic patients (14 % vs 2 %). In those with VT, the deaths were either sudden or related to heart failure. Ten other patients died from cancer (n=6), after a general surgery (n=2) or from a stroke (n=2).

Among the 10 asymptomatic patients with ICD, 3 deaths occurred 18 months after implantation, one was due to heart failure; one was related to a cardiovascular collapse and another one was due to recurrent ventricular fibrillation probably related to an ischemic event; in other patients, there was no arrhythmic event.

III) Predictive factors of prognosis (table II, III):

Patients who died from a cardiac cause were compared to other total patients.

Mean age was similar in patients who died (59±11 years) and in remaining patients (59±11 years) (NS).

Syncope was more frequent in patients who died (28%) than in other patients (16 %) ($p< 0.05$) ; among patients with syncope who died, 4 died from arrhythmic death and 7 died from heart failure : the differences of total cardiac mortality between patients with syncope who died and remaining patients without spontaneous VT were only related to a significant increase of deaths due to heart failure ($p<0.001$) and were not significant for arrhythmic deaths.

Patients with spontaneous VT had the higher total cardiac mortality and the sudden deaths were also more frequent than in other groups.

The mortality of patients with resuscitated cardiac arrest was similar to asymptomatic patients, probably because the ischemic factor was more frequent and was treated.

Left ventricular ejection fraction (LVEF) was 33±12.5 % in patients who died from a cardiac cause and 43±13 % in remaining patients ($p<0.0004$). Cardiac mortality was low in patients without documented arrhythmias (asymptomatic or with syncope) and with LVEF > 40 % and with induced ventricular flutter/fibrillation; 3 of 117 (2.5 %) asymptomatic patients had an arrhythmic death and 2 of 22 patients with syncope (9%) died from heart failure; in one of these last patients, the left ventricular ejection was preserved at the time of programmed

stimulation (68 %) and was very low at the time of admission for heart failure; another ischemic event could be suspected.

The presence of ventricular couplets or non sustained ventricular tachycardia on 24 hour Holter monitoring was predictive of cardiac mortality (51 % vs 39 %). In our precedent study in patients without documented arrhythmias (31), Holter monoitoring was not predictive of death.

The nature of ventricular arrhythmia (flutter or fibrillation) was also a predictor of cardiac mortality: 32 of 174 patients with induced ventricular flutter (22%) and 7 of 109 patients with induced ventricular fibrillation (6%) died from a cardiac cause ($p<0.01$). More, 19 of 174 patients with induced ventricular flutter (11%) and only 1 of 109 patients with induced ventricular fibrillation (1 %) died from an arrhythmic cause ($p < 0.001$). In our precedent study in patients without documented arrhythmias (31), the nature of ventricular arrhythmia (flutter or fibrillation) was not a significant predictor of cardiac mortality.

The number of extrastimuli required to induce the ventricular arrhythmia did not significantly modify the prognosis; 19 patients in whom the ventricular arrhythmia was induced by 2 extrastimuli, died (15 %), 19 patients in whom the ventricular arrhythmia was induced by 3 extrastimuli, died (13 %) (NS).

Linear logistic regression applied to the population without documented ventricular arrhythmia indicated that induction of ventricular flutter or fibrillation and LVEF < 40 % were predictors of total cardiac mortality (odds ratio respectively 3.406, 3.109), (95% CI respectively 1.28-9, 1.36-7.09), but only the LVEF < 40 % was predictor of arrhythmic death (odds ratio 9.34, 955% CI1.18-75.02). Figures 3 and 4 report the Kaplan-Meier curve of mortality in these groups.

DISCUSSION

The controversial data concerning the induction of ventricular flutter/fibrillation probably are due to the inhomogeneous studies populations. Some studies report the data of patients with heart diseases of various origin; other studies in post myocardial infarction include symptomatic and asymptomatic patients.

In post myocardial infarction, several groups should be differentiated.

- The largest group concerns the induction of ventricular flutter/ fibrillation in asymptomatic patient. Programmed ventricular stimulation was largely used until 2000 to evaluate the prognosis of this patient and identify those at risk of VT and sudden death occurrence. The incidence of ventricular flutter/ fibrillation in this group was 18 to 23 % of patients after a myocardial infarction. The rate of induction was not related to the value of LVEF, but as known since more 20 years, the prognosis was related to LVEF. The prognosis of induced ventricular flutter/fibrillation was favourable in patients with preserved left ventricular ejection fraction and many studies have reported the good prognosis of induced ventricular flutter/fibrillation in post myocardial infarction (1- 5, 29). In those with decreased left ventricular ejection fraction, the cardiac mortality increased, but the differences with patients without induced arrhythmias (32) were not significant. However, the recent study of Gurewitz (33) reported a high risk of death in patients with decreased left ventricular ejection fraction and inducible ventricular flutter or inducible monomorphic ventricular tachycardia, but the population study included patients with heart diseases of various origins. In patients with only coronary disease and left ventricular dysfunction, we could not find not any clinical significance of inducible ventricular flutter/fibrillation, but our group could be too small to have a statistical significance. In clinical practice, the indication of a cardioverter defibrillator in asymptomatic patients clearly does not depend on the induction of a ventricular/fibrillation, but mainly on the left ventricular ejection fraction which is an important predictor of sudden death (1, 8-10, 34). Other predictor factors remain to be defined in these patients as QRS duration, heart rate variability, T wave alternans or other data.

- In patients with syncope, ventricular flutter or fibrillation was noted with a similar incidence to asymptomatic patients and was considered as without significance by Mittal (30). In a precedent study of our group (31) and in the present study, we found a less good prognosis than in asymptomatic patients but the differences were related to a higher incidence of deaths by heart failure. The patients with syncope were older and had a lower LVEF than asymptomatic patients. These data confirm previous studies which report higher mortality rates in patients with syncope and low left ventricular ejection fraction (15, 16). Therefore, in patients with low LVEF, several papers following the study MADIT II (1) are in favour of the systematic implantation of ICD (36-38); a study of our group (17) shows that electrophysiologic study remains indicated in patients with syncope to look for AV conduction

disturbances or supraventricular tachycardia which require specific treatment. However in the present study the induction of ventricular flutter/fibrillation did not probably explain the cause of syncope, but indicated a higher cardiac mortality than in patients without inducible ventricular arrhythmias. These patients should be carefully followed to avoid the high incidence of death by heart failure. More, in our short experience, ICD implantation seems not to change the prognosis of patients without documented arrhythmias.

- In patients with spontaneous VT, clearly, the induction of a ventricular flutter is less frequent than the induction of a monomorphic slower VT, but has a same prognostic value that a monomorphic VT with a high total cardiac mortality and risk of sudden death, mainly in patients with low LVEF. These data are similar to those reported by Viskin and coll (35); they noted a similar prognostic value of inducible ventricular flutter to that of inducible ventricular tachycardia with a high risk for ventricular tachycardia and VF in patients with old myocardial infarction, because most of their patients had previously presented spontaneous documented ventricular tachycardias.

- In patients with resuscitated arrest, it is frequent to induce a ventricular flutter/fibrillation, which clearly is always pathological. However, the prognostic was relatively good in our small group because cardiac arrest had several origins. LVEF was preserved, but ischemic factor was frequent and can be treated.

Limitations of the study: The patient population, recruited during several years and receiving different treatments, was heterogeneous. The number of patients in each group remains relatively limited, although a large number of programmed ventricular stimulations in our department. The indications of electrophysiological studies also have changed during these past years.

In conclusion, the significance of inducible ventricular flutter/fibrillation depends on the clinical data of the population. If the arrhythmia is clearly pathological in patients with resuscitated cardiac arrest and those with spontaneous ventricular tachycardia, the arrhythmia does not indicate a risk of sudden death in patients without documented arrhythmias. In patients with preserved LVEF, induced ventricular flutter/fibrillation has no clinical significance in asymptomatic patients and nor in those with syncope. The cause of syncope may not have been arrhythmic. However, in patients with low LVEF, the induction of this arrhythmia after myocardial infarction, mainly in the case of ventricular flutter induction, is

associated with a higher mortality by heart failure; therefore, when the patient has the criteria for MADIT II and has an indication of ICD, he should be carefully followed.

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Table I: Incidence of induction of ventricular flutter/ fibrillation (V fl/VF) in according to symptoms

(VT : spontaneous ventricular tachycardia, CA : resuscitated cardiac arrest;

comparisons with asymptomatic group : * $p<0.05$, ** : $p<0.01$, *** $p<0.001$)

	Total	asymptomatic	Syncope	VT	CA
Number	1446	810	271	303	62
V fl/VF	283	186 (23 %)	50 (18 %)	26 (13 %)**	21 (34 %)**

Table II :

Clinical data of each group (asymptomatic, patients with syncope, with VT, with CA)

(legends : VT : patients with spontaneous VT, CA : patients with resuscitated cardiac arrest; LVEF : left ventricular ejection fraction, , HF: heart failure)

Comparisons with asymptomatic group : * $p<0.05$, ** : $p<0.01$, *** $p<0.001$)

	Total	asymptomatic	syncope	VT	CA
Number	283	183	50	26	21
Age (years)	59±11	57±10	64±10***	59±11	64±12**
LVEF (%)	42±13	43.5±13	39±14*	35±13***	43.5±10.5
Total cardiac death	39 (14 %)	15 (8 %)	11 (22%)**	10 (38 %)***	3 (14 %)
Arrhythmic deaths	21 (7 %)	11 (6 %)	4 (8 %)	5 (19 %)*	1 (5 %)
Death from HF	19 (7 %)	4 (2 %)	7 (14 %)**	5 (19 %)*	2 (10 %)
Other death	10	3	3	2	2

Table III:

Factors of prognosis

Legends : LVEF: left ventricular ejection fraction, NSVT Holter: presence of salvos of ventricular premature beats on Holter monitoring; V fl: ventricular flutter : inducible ventricular flutter; remaining patients had inducible ventricular fibrillation; syncope: patients admitted for syncope VT : patients with spontaneous VT, CA : patients with resuscitated cardiac arrest; S3: induction by 2 extrastimuli, S4: by 3 extrastimuli; remaining patients : Induction by one extrastimulus, atrial pacing or ventricular pacing.

	Cardiac mortality	Other patients	P
Number	39 (14%)	244 (66 %)	
Age	59±10.5	59±11	NS
Sex (male)	38 (97 %)	224 (92 %)	NS
Syncope	11 (28 %)	39 (16 %)	NS (< 0.06)
VT	10 (26 %)	16 (6.5 %)	P < 0.0o1
CA	3 (8 %)	18 (7 %)	NS
LVEF	33±12.5 %	43±13 %	P< 0.004
NSVT Holter	20 (51 %)	95 (39 %)	P < 0.05
V flutter	32 (82 %)	142 (58 %)	P <0.01
S3 vs S4	19/19	112/125	NS

Figure 1: induction of a ventricular flutter

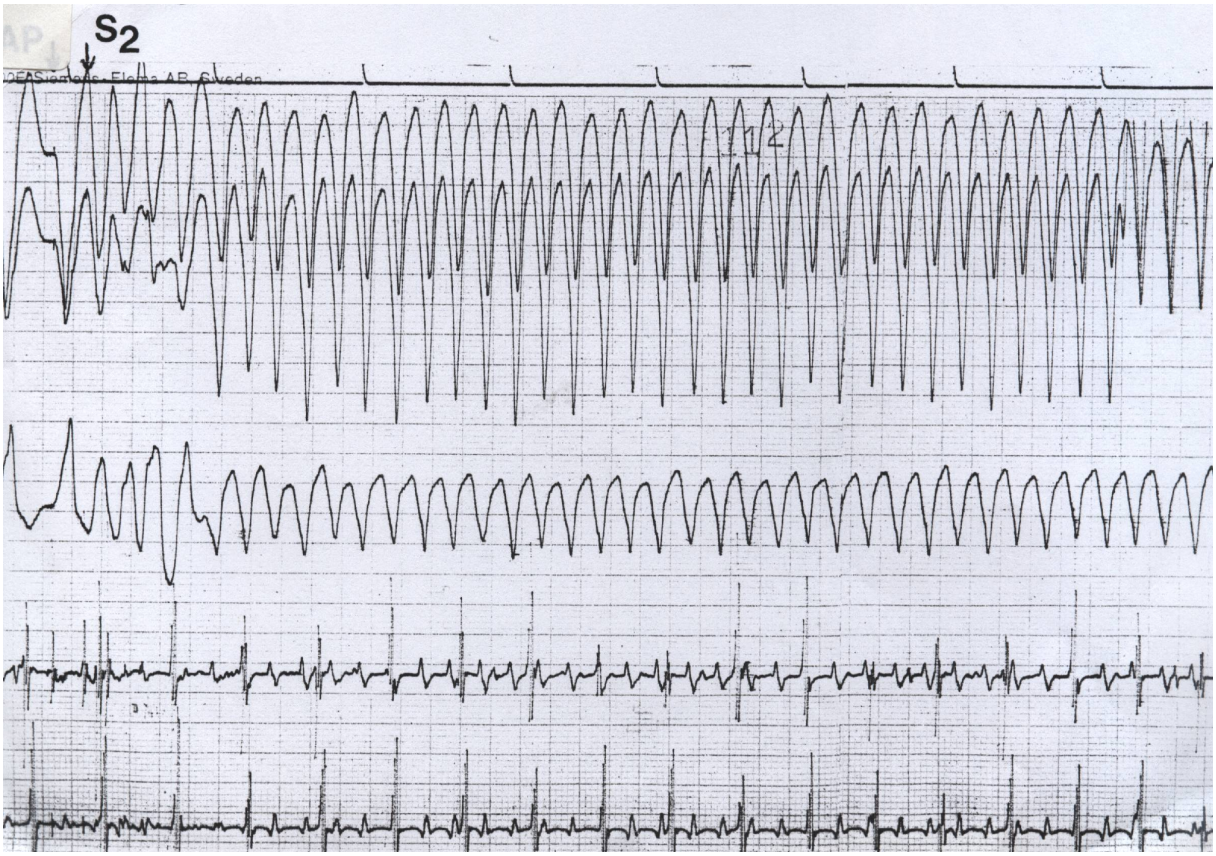

Figure 2: induction of a ventricular fibrillation

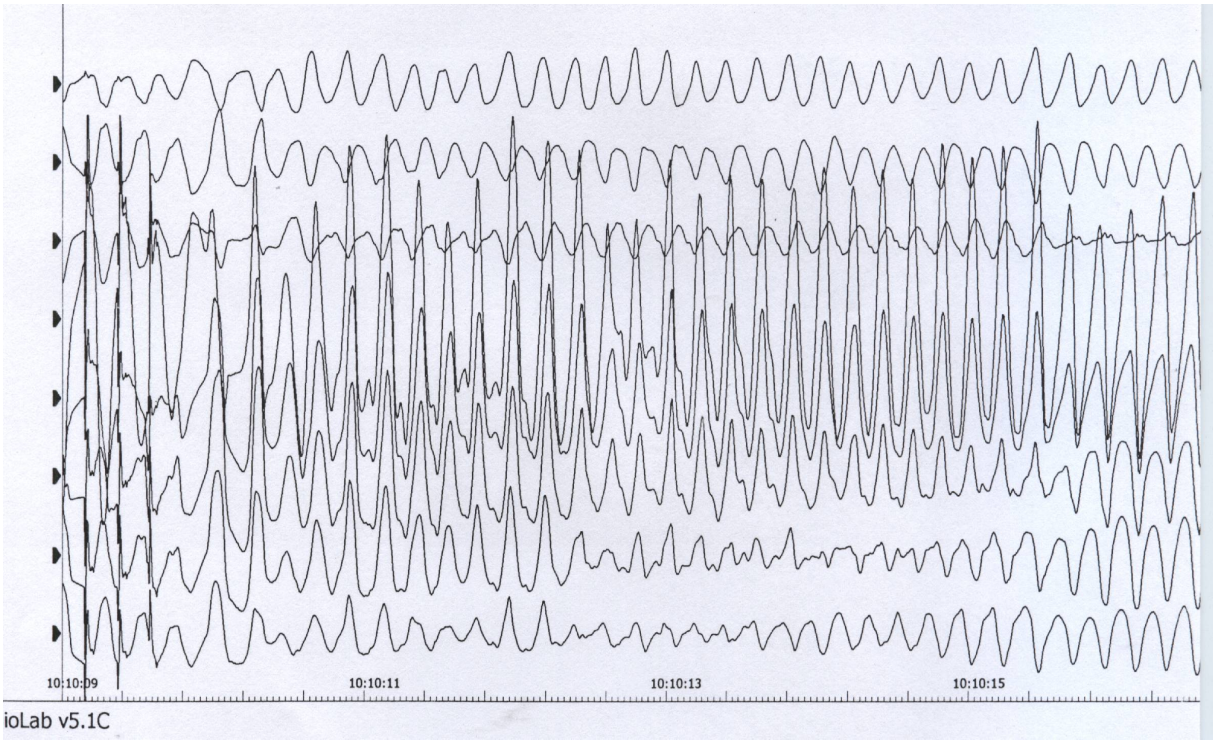

Figure 3 : Kaplan-Meier analysis curves comparing the patients with and without syncope.

Figure 4 : Kaplan-Meier analysis curves comparing the patients with preserved left ventricular ejection fraction (EF> 40 %)