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Original Article

What is The Utility of Electrophysiological Study in Elderly Patients with Syncope and Heart Disease?

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Abstract

Background: Syncope in elderly patients with heart disease is a growing problem. Its aetiological diagnosis is often difficult. We intended to investigate the value of the electrophysiological study (EPS) in old patients with syncope and heart disease.

Methods: EPS was performed in 182 consecutive patients with syncope and heart disease, among whom 62 patients were ≥75 years old and 120 patients <75.

Results: Left ventricular ejection fraction was 43.9±11.7% in patients ≥75 and 41.1±12.6% in patients <75. During EPS, induced sustained ventricular arrhythmias were as frequent in both groups (27.4% in patients ≥75 versus 27.5% in patients <75, p=0.99) whereas AV conduction abnormalities were more frequent in older patients (37.1% in patients ≥75 versus 18.3% in patients<75, p<0.005). Syncope remained unexplained in 35.5% of patients ≥75 and in 51.7% of patients <75 (p<0.04). ICD was more likely to be implanted in younger patients than in patients ≥75 years (37.5% vs 21% respectively, p<0.009). During a mean follow-up period of 3.3±3 years, the 4-year-survival rate was 66.9±6.8 % in patients ≥75 and 75.9±6.2 % in patients <75 years. The main cause of death was heart failure in both groups. The factors related to a worse outcome in a multivariate analysis were low LVEF and higher age.

Conclusion: Complete EPS allows the identification of treatable causes in a high proportion of elderly patients with syncope and heart disease. Yet, the prognosis of these patients is mainly related to LVEF and age.

Keywords: syncope, heart disease, electrophysiological study, elderly

Introduction

Syncope is a transient loss of consciousness due to a global cerebral hypo-perfusion characterized by a rapid onset, short duration, and spontaneous complete recovery. [1] Structural heart disease is a major risk factor for sudden cardiac death and overall mortality in patients with syncope. [1-4] The poor outcome in these patients appears to be related to the severity of their underlying heart disease (HD) rather than to syncope itself. [5,6]

Syncope is a common problem in elderly, especially in patients aged 70 years or older. [7] Aetiologic diagnosis is often difficult because of the frequent coexistence of several causes. The most common causes of syncope in the elderly are orthostatic hypotension, reflex syncope - especially micturition syncope and carotid sinus syndrome - and cardiac arrhythmias. [8,9] Cardiac origin accounts for more than 30% of the cases [1,10] whereas the syncope remains of unknown origin (SUO) in one out of three cases. The therapeutic goals in these patients are prevention of recurrences, treatment of underlying HD and reduction of cardiac mortality.

Electrophysiology study (EPS) can help to achieve these goals in selected patients. Indeed, EPS has a better yield in patients with HD. [11] Yet, indications for EPS are currently scarce, being only recommended in patients with HD and LVEF > 35%. [1] As a consequence, it is performed in less than 2 % of patients with syncope [1] and very infrequently in patients with advanced age. Importantly, the benefit of a prophylactic implantation of an implantable Cardioverter defibrillator (ICD) in elderly is believed to be less [12].

The objectives of the present study were, therefore, to evaluate the yield of EPS in elderly (≥75 years) with HD and SUO for the identification of an underlying possible cause. In addition, we intended to assess the risk factors for cardiac death in these patients who underwent EPS.

Patients and methods

All patients with HD (ischemic, dilated cardiomyopathy) and SUO were included between 2003 and 2013. These patients were allocated to two groups according to their age.

Group A with 62 patients aged 75 years and above, included 48 males and 14 females. The mean age was 79 ± 3.6 years. 50 of them (80.6%) presented with coronary HD and 12 (19.3) with dilated cardiomyopathy. The mean LVEF was 43.9% ± 11.7, 44.5±12% in patients with coronary HD and 40±9.5 % in patients with dilated cardiomyopathy. Patients with coronary HD generally had a previous history of myocardial infarction. In this group left anterior hemiblock was present in 5 patients, right bundle branch block associated (n=10 or not n=3) was present in 13 patients and left bundle branch block was noted in 15 patients. Group B with 120 patients younger than 75 years old, included 105 males and 15 females. There was a tendency for a lower number of females. The mean age was 60.1 ± 11.4 years. 78 of them (65%) presented with coronary HD and 42 (35%) with dilated cardiomyopathy. The mean LVEF was 41.1% ± 12.6. In this group left anterior hemiblock was present in 11 patients, right bundle branch block associated (n=8 or not n=6) was present in 14 patients and left bundle branch block was noted in 15 patients.

Data of the population are summarized in **Table 1**.

Table 1: Clinical data of the population

	Group A (≥75 yrs) N=62	Group B (<75 yrs), N =120	P value
Age (years)	79 ± 3.6	60.1 ± 11.4	<0.001
Female	22.6%	12.5%	0.08
LVEF	43.9 ± 11.7 %	41.1 ± 12.6%	0.15
Ischemic	80.6%	65%	0.03
LVEF < 0.35	33.5%	40.8%	0.48
QRS (ms)	135 ± 33.7	119.4 ± 37.9	0.01

Patients were excluded from the study if they had unstable angina, recent acute myocardial infarction (<1 month), recent coronary angioplasty or coronary bypass surgery (< 6 weeks), stenosis of the left main coronary artery or three-vessel disease , paroxysmal second or third degree AV block, sustained supraventricular or ventricular arrhythmia, clinical heart failure not controlled by furosemide, uncontrolled electrolyte abnormalities, significant non-cardiac comorbidities, received chronic amiodarone treatment, and if they were lost to follow up.

Protocol of the study

Personal and familial clinical history, list of drugs taken at the time of syncope and clinical examination were initially noted in all patients. They underwent several investigations in the absence of antiarrhythmic drugs after giving informed consent. These included surface ECG, 24-hour ambulatory ECG (Elatec), transthoracic echocardiogram, Thallium exercise scintigraphy or coronary angiography to exclude an ischemic origin and signal averaged ECG (Cardionics, QRS duration was measured by this method). The syncope was considered to be of unknown origin when no clear explanation was found after this conventional workup. The studies were performed only in patients in stable clinical and haemodynamic condition after treatment.

Complete EPS was performed according to a procotol previously reported. [6,13,14] A multichannel oscilloscope and a programmable stimulator were used for this purpose. The patients were in a fasting non sedated state and informed and written consent was obtained. All antiarrhythmic drugs, digoxin and drugs having an effect on cardiac electrophysiological properties were stopped since at least 5 half-lives. Most of the patients received ACE inhibitors.

The electrophysiological protocol included assessment of sinoatrial conduction time, sinus node recovery time, atrioventricular conduction using measurement of AH, HV intervals and intraatrial conduction time, and atrial pacing at progressively faster rates until atrioventricular block occurred. Programmed atrial stimulation with 1.8 ms rectangular pulses at twice diastolic threshold was systematically performed during sinus rhythm and atrial pacing at two cycle lengths, 600 and 400 ms. One (S2) and then second premature stimulus (S3) were delivered. Right ventricular pacing was performed at an incremental rate up to 200 beats/min or till ventricular refractoriness. Programmed right ventricular premature stimulation using a single premature ventricular extrastimulus (S2) and double ventricular extrastimuli (S2 and S3) were introduced during sinus rhythm and during paced cycle lengths (600 and 400 ms), at the right ventricular apex initially and subsequently at the right ventricular outflow tract. A third extrastimulus was added if a sustained ventricular tachycardia or fibrillation was not induced. Triple extrastimuli (S2, S3, S4) were introduced during sinus rhythm and during paced cycle lengths (600 and 400 ms) at the right ventricular outflow tract and the apex. Short coupling intervals (< 200 ms) were not used in the present study. Interruption of the induced VT was initially attempted with different protocols of anti-tachycardia pacing, followed by cardioversion. If the study remained negative, the protocol was repeated after isoproterenol infusion : a dose of 2 to 4 μg /min was administered to decrease the sinus cycle length by at least 15% and the infusion was continued until the completion of atrial and ventricular stimulation for 15 to 25 minutes. [13,14] Arterial blood pressure was continuously monitored by an external sphygmomanometer (Baxter, Japan). Carotid sinus massage was performed except in patients with known carotid atheroma.

Abnormal electrophysiological findings were categorized as sinus node dysfunction, conduction disturbances, hypervagotonia, inducible supraventricular tachyarrhythmias (SVTA), or inducible ventricular tachyarrhythmia (VT) according to the following diagnostic criteria :

a. Sinus node dysfunction was considered as present if the corrected sinus node recovery time (sinus recovery time - mean sinus cycle length) was > 550 ms.
b. Conduction disturbances were considered as present, if AV Wenckebach block occurred at a pacing rate of < 90 bpm, or the HV interval was > 60 ms in the case of RBBB, > 70 ms in the case of LBBB or if the His bundle potential duration was > 40 ms, or a split His bundle potential was recorded in control state, and if infrahisian second degree AV block occurred at a pacing rate less than 150 bpm.
c. Carotid sinus hypersensitivity was present if right and then left carotid sinus massage performed in supine position at the beginning of electrophysiological study, produced asystole with an RR interval of > 3000 ms.
d. Inducible SVT was defined as a sustained (> 3 min), spontaneously terminating but reproducible or permanent SVT, provokng a drop of arterial blood pressure and symptoms similar to spontaneous dizziness, which could be a paroxysmal junctional tachycardia or an atrial tachyarrhythmia (atrial fibrillation, flutter or fibrillation). The induction of a relatively slow atrial fibrillation without symptoms or changes in blood pressure was considered as non-pathological. When a sustained ventricular tachycardia also was induced, the presumed cause for syncope was categorized in ventricular tachyarrhythmias.
e. Inducible ventricular tachyarrhythmia were categorized into 1) monomorphic VT (< 270 bpm) lasting more than 30 sec or requiring termination because of haemodynamic intolerance, or lasting between 10 and 30 seconds and responsible for syncope 2) ventricular flutter (>270 bpm) or ventricular fibrillation requiring cardioversion to stop it.

Follow-up

A pace maker was implanted in patients in whom syncope was attributed to conduction disturbances. In those with inducible VT and conduction disturbances, a pacemaker or a defibrillator was implanted depending on the 1 year expected survival - patients with life expectancies shorter than one year being implanted with pacemakers rather than defibrillators. The total cardiac deaths were deaths related to heart failure and sudden deaths. Sudden death was defined as an unexpected death from a cardiac cause within a short time period (< 1 hour); deaths in relationship with the development of a spontaneous sustained VT were classified as sudden deaths. Most of deaths occurred in our hospital; for those who died at home or in another hospital, we contacted both the last doctor who saw the patient and the family in order to classify the cause of death.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation and categorical variables as percentages. Differences in continuous and categorical variables were evaluated with unpaired t test and chi square test respectively. Survival probabilities were calculated using Kaplan Meier product-limit method and compared by log-rank test. Variables associated with survival were then evaluated with Cox survival analysis. Age, gender and all variables associated with a p-value <0.20 on univariable analysis were considered as candidate variables in the multivariable models. Backward selection was performed to identify variables independently associated with survival. These Cox models were performed in the whole population and in subsets of the population according to age. All statistical tests were performed using SPSS 21.0 for Windows. A p value < 0.05 was considered as significant.

Results

Results of electrophysiology study (**Table 2**)

A sustained monomorphic VT < 270 bpm or syncopal non-sustained VT (frequency from 220

to 240 bpm) was induced in 14/62 (22.6%) group A patients and in 25/120 (20.8%) group B patients but the difference was not statistically significant. Ventricular flutter or fibrillation was induced in 3/62 group A patients (4.8%) and in 8/120 (6.7%) group B patients (NS). Conduction abnormalities were significantly higher in the group A (23/62 patients, 37.1%) compared to group B (22/120, 18.3%, $p < 0.005$). Three group A patients and 4 group B patients had both conduction abnormalities and inducible VT. Atrial tachyarrhythmia (atrial tachycardia or paroxysmal junctional tachycardia) with a rapid ventricular rate (>130 bpm) was induced in 5 of 62 (8.1%) group A patients and in 8 of 120 (6.7%) group B patients (NS). The electrophysiological study remained negative in 62 of 120 (51.2%) group B patients and in 22 of 62 (35.5%) group A patients ($p < 0.04$).

Table 2: EPS results and device therapy

	Group A (≥75 yrs) N=62	Group B (<75 yrs) N=120	P value
Conduction abnormalities	37.1%	18.3%	0.005
Ventricular tachycardia	22.6%	20.8%	0.78
Ventricular fibrillation or flutter	4.8%	6.7%	0.62
Supraventricular tachycardia	8.1%	6.7%	0.73
Negative study	35.5%	51.7%	0.04
Pacemaker (PM)	25.8%	10.8%	0.02
Implantable cardioverter defibrillator (ICD)	21.0%	37.5%	0.02
ICD with atrial lead	9.7%	7.5%	0.61

Follow-up of the patients **(Tables 2, 3)**

During a mean follow up of 3.3 ± 3 years, 35 cardiovascular deaths occurred (29 in hospital and 6 at home). Non cardiovascular deaths occurred in hospital in 7 patients. A pacemaker was implanted in 16 of 62 (25.8%) group A patients and in 13 of 120 (10.8%) group B patients ($p<0.009$). In remaining patients with conduction abnormalities ICD implantation was preferred either because a ventricular tachycardia was induced (n= 3 in group A, n= 4 in group B) or because left ventricular ejection was < 35%. Supraventricular tachycardia ablation was performed in 2 group A patients and none of group B patients ($p<0.05$). ICD implantation was significantly more frequent in group B (37.5%) compared to group A (21%) ($p<0.009$), conforming to the present recommendations. In group A, 4 patients refused ICD due to their age, 4 patients had an ICD implanted with a negative EPS but a low LVEF and 1 patient refused a pacemaker.

Table 3: Events during follow-up according to age

	Group A (≥75 yrs) N=62	Group B (<75 yrs) N=120	P value
Cardiovascular death	20	15	0.01
Sudden death	1	1	1.00
Death from heart Failure	19	14	0.01
Non cardiovascular deaths	9	1	<0.001

In group A, 8 patients among 13 implanted with an ICD presented an arrhythmic event at follow-up, 2 with a negative EPS and 6 with a positive EPS. All of them had ischemic heart disease and the LVEF was lower than 35% in 6 patients and higher than 35% in two patients. Two patients with dilated cardiomyopathy and a positive EPS, implanted with an ICD did not show any arrhythmic event on the same follow-up period as 3 patients with an ischemic cardiomyopathy and positive EPS. In elderly patients implanted with an ICD, 61.5 % had appropriate shocks and almost 63 % of patients having had an appropriate shock died of heart failure within 8 months to 7 years. The mean survival after ICD implantation was 4.5 years in elderly.

In group B, implantation of an ICD was performed when the LVEF < 35% as it is actually recommended, or when the EPS was positive. The death rate was significantly higher in the group A, (29 of 62) (47%) compared to the group B (16 of 120) (13 %) ($p< 0.01$). In both groups the major cause of death was cardiovascular but there was significantly higher rate of non cardiovascular mortality in the group A. There was one sudden death in group A: the patient presented a positive EPS, but was refused the implantation of the ICD due to a poor general state. There was also one sudden death in the group B, the patient had a negative EPS and a LVEF > 40%. Two patients in group A underwent a SVT ablation. There was no recurrence of syncope at follow-up in both groups.

Analysis of the factors associated with events

In a univariate analysis the survival curves of both groups showed a significant correlation between cardiac mortality and inducible VT at EPS. (**Figures 1** and **2**). Low LVEF and inducible VT at EPS were associated with a poor prognosis in group A and B (**Figures 3**, **4**). In a multivariate analysis, only a low LVEF and an older age were significantly correlated to a worse outcome in both groups. (**Table 4**)

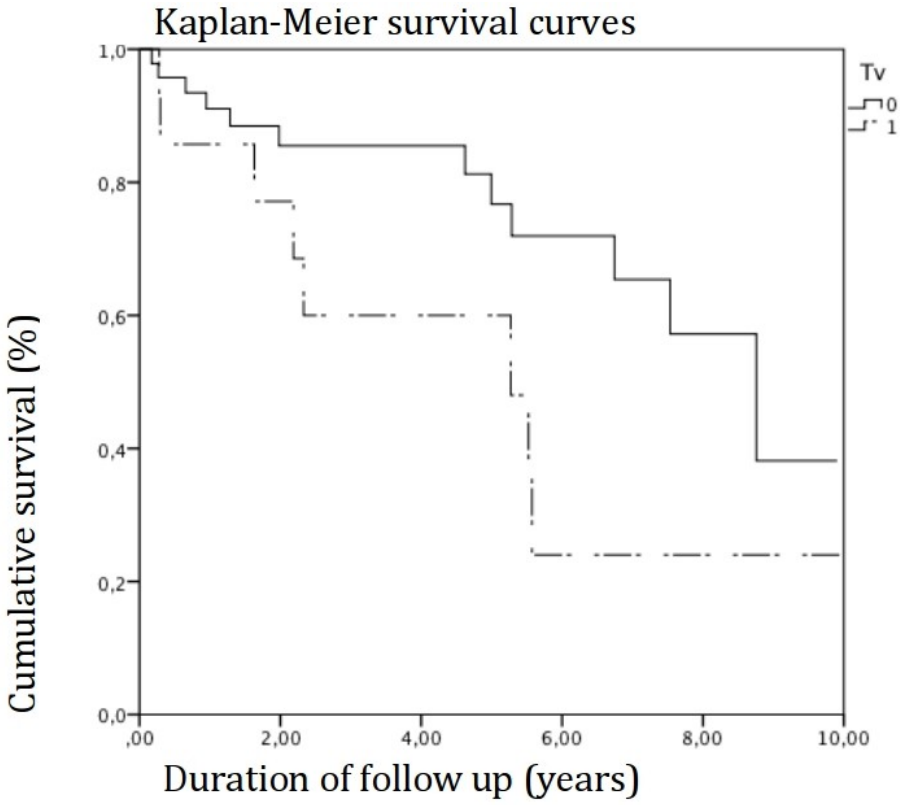

Figure 1: Survival in group A with and without inducible VT

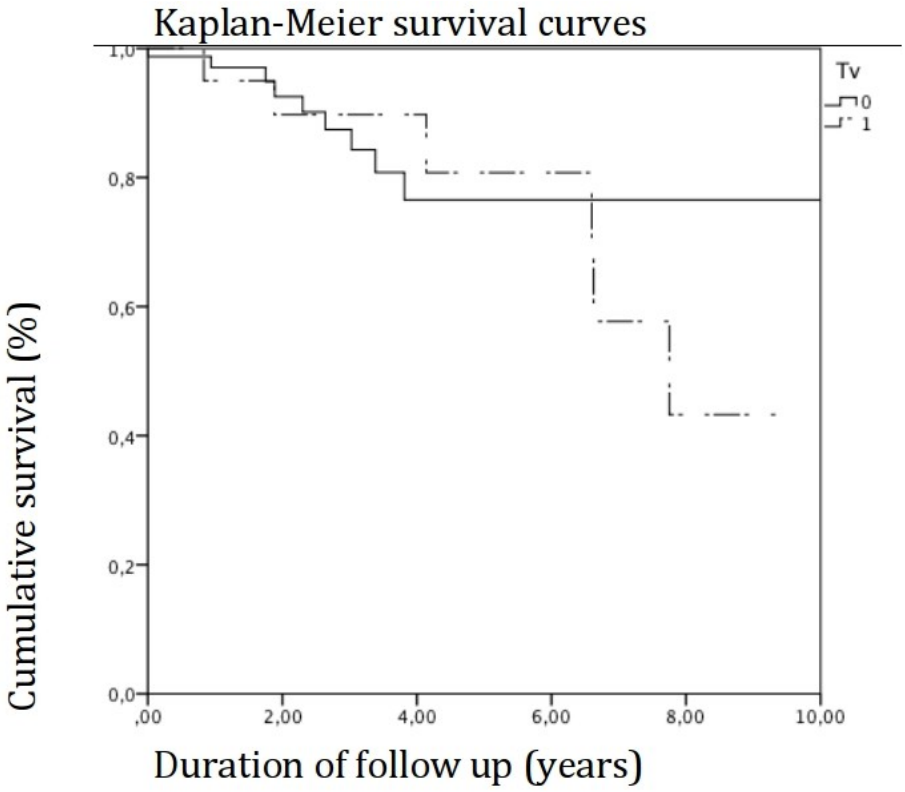

Figure 2: Survival in group B with and without inducible VT

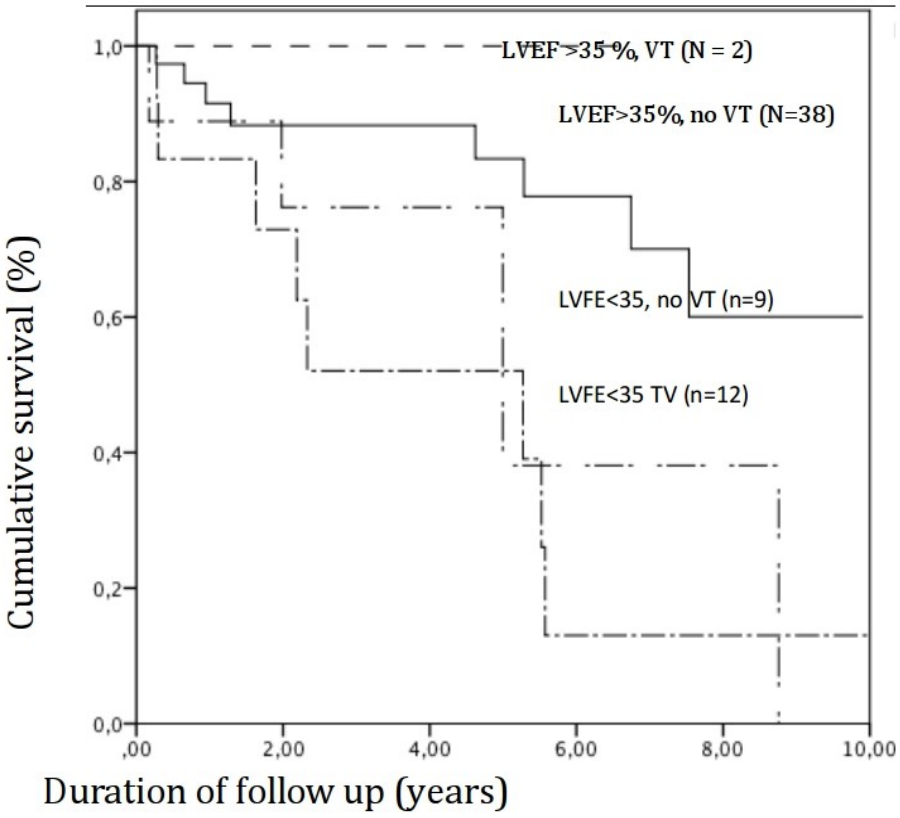

Figure 3: Survival in group A according to the LVEF and inducible VT

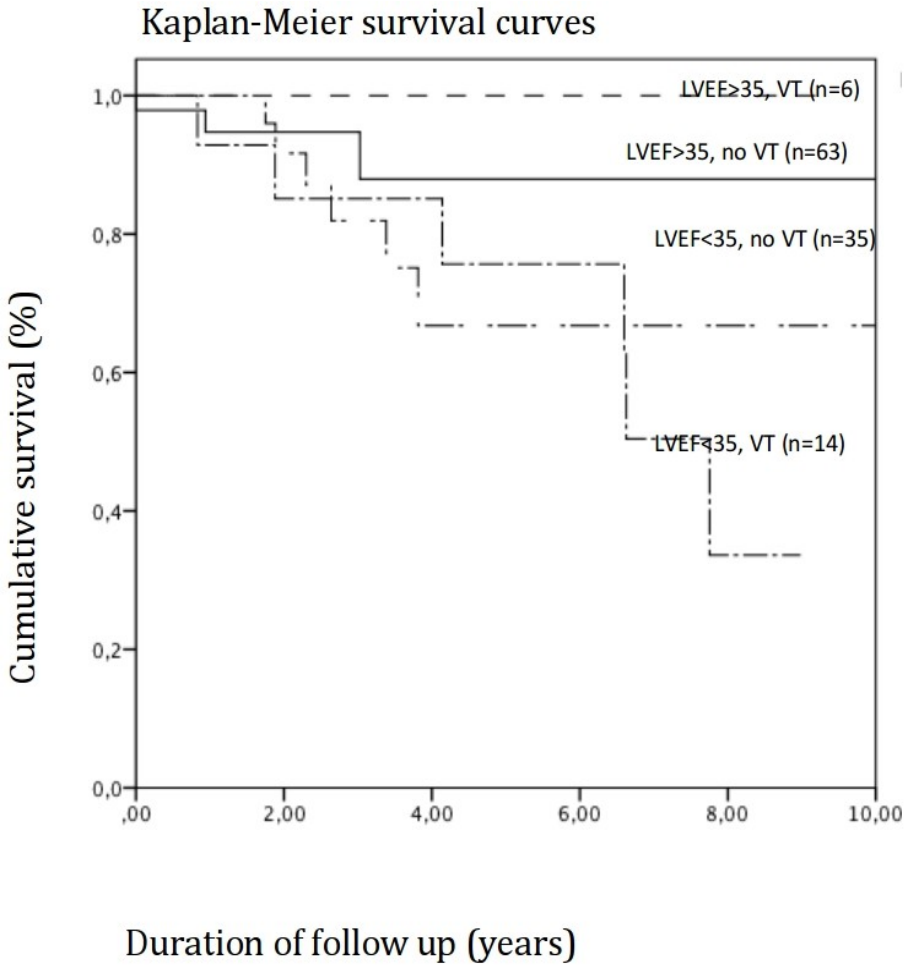

Figure 4: Survival in group B according to the LVEF and inducible VT

Table 4: Multivariate analysis in each group

Group A

	HR	95,0% CI Inferior Superior	p value	
VT	1,129	,355	3,587	,837
Age	1,217	1,041	1,424	,014
LVEF < 35 %	3,862	1,187	12,567	,025

Group B

	HR	95,0% CI Inferior Superior	p value	
VT	,844	,283	2,517	,761
Age	1,067	1,008	1,129	,026
LVEF < 35 %	3,870	1,034	14,475	,044

Discussion

In the large randomized clinical trials that evaluated the benefit of ICD, elderly were poorly represented. The mean age of the patients included in the three major ICD trials were less than

65 (62±9 years in the MADIT trial, 64±10 in the MADIT II trial and 60±9 years in the SCD-HeFT trial). In addition, in the Multicenter Unsustained Tachycardia (MUST) Trial, median age of patients treated with electrophysiologically guided therapy was 67 years (IQR 60-72 years). [15-18] The current knowledge regarding ICD treatment effect in elderly is mostly based on some sub-studies and meta-analysis. [21]

In the present study, as in previously published reports, [12,19,20] we observed higher rate of mortality in elderly patients compared to younger patients with syncope and HD. Heart failure was the main cause of mortality in both groups but a higher non-cardiovascular mortality rate was observed in elderly patients. The EPS helped identify a potential origin for the syncope in more than 60% of the patients ≥ 75 years old. Inducible VT was more frequent in patients with a low LVEF. [22] The results led to a higher number of PM implantation in this elderly population and to some ICD implantations. In our study ICD implantation was performed in elderly patients according to the expected survival. As a result, median survival in elderly ICD recipients was greater than 4 years [19,23,24]. Patients ≥ 80 years of age who meet current indications for ICD implantation were already reported to live long enough to warrant device implantation in most cases. [24] In contrast, those with an EF ≤ 20% were reported to have markedly elevated 1-year mortality without increased appropriate ICD therapy, thus reducing the net benefit of device implantation in this population. [24] Yet, based on previous reports and on our results, despite the presence of competing non-cardiovascular causes of deaths, the prognosis of selected elderly patients appears good enough to warrant ICD implantation in appropriate cases. We believe that ICD implantation should be encouraged in elderly patients with SUO, heart disease and positive EPS according to their expected 1-year survival. Importantly, special attention has to be paid to the evaluation of elderly with low ejection fraction given their high probability of death - either cardiac or non-cardiac.

If the treatment of underlying VT is troublesome in elderly patients, the treatment of conduction abnormalities or supraventricular tachycardia can be quite easily performed in elderly. As we diagnosed conduction abnormalities in a third of patients >75 undergoing EPS, the diagnostic yield of EPS in this elderly population appears very high. This aspect further encourages performing EPS in elderly patients with SUO and heart disease.

Limitations of the study

The number of patients is small. The study is retrospective and recruitment over a 10-year period during which the management of some situations changed. Head-up tilt test was only performed when the medical history suggested a vaso-vagal origin. The proportion of female gender was higher in patients >75 years, which was expected given the better female survival in our country. Brain CT, EEG, or Carotid Doppler were not performed in elderly group resulting in possible underdiagnosis of other syncope etiology.

Conclusions

EPS in elderly patients with structural heart disease and SUO helps to identify syncope cause. As we observed a good survival of selected elderly patients in whom VT was diagnosed during EPS, ICD implantation should be encouraged in elderly according to their expected 1-year survival. Importantly, special attention has to be paid to the evaluation of elderly with low ejection fraction given their high probability of death - either cardiac or non-cardiac.

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