

# Predicting the outcome in patients with unexplained syncope and suspected cardiac cause: Role of electrophysiologic studies

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## ABSTRACT

**Objective:** Unexplained syncope is a challenge facing electrophysiologists. The prognosis varies widely depending on underlying causes, specially, cardiac ones. We sought to determine the abnormal electrophysiologic (EP) study results as predictors of prognosis in syncope patients with suspected cardiac cause and risk factors associated with mortality.

**Methods:** A total of 227 consecutive patients with unexplained syncope were prospectively enrolled in this study. EP study was performed in 177 patients in base of inclusion criteria. These patients, in whom a cardiac cause of syncope was suspected, underwent EP study and if negative, head-up tilts test (HUTT). Complete follow-up was obtained for 132 patients for 20.0±10.8 months.

**Results:** A cardiac cause of syncope was established in 35%, a neurally mediated syncope in 35.6%, and in the rest 29.4% the cause of syncope remained unexplained despite a throughout neurologic and cardiologic evaluation. Logistic analysis revealed that the significant predictors of a cardiac cause of syncope were the absence of prodromal symptoms, left bundle branch block (LBBB), sever left ventricle (LV) dysfunction and male gender. At logistic analysis, the presence of LBBB (OR=6.63; 95% CI: 1.09-40) was significantly associated with outcome of death.

**Conclusion:** The present study provides evidence that presence of LBBB, abnormal EP study result and structural heart disease (SHD) have prognostic value in patients with suspected cardiac cause of syncope. The patients with SHD and unexplained syncope who had a negative EP study have a good long-term prognosis even in the presence of LV dysfunction. (*Anatol J Cardiol* 2015; 15: 213-7)

**Keywords:** syncope, left bundle branch block, electrophysiologic study

## Introduction

Syncope is a problem that can be caused by different etiologies ranging from benign self-limiting to malignant recurrent and potentially fatal events. Individuals presenting with syncope comprise 3% to 5% of emergency department visits and 1% to 3% of hospital admissions (1-4). Nearly 50% of the population may have at least a syncopal event during their life. In about 25% of patients with syncope, the history in combination with physical examination is sufficient to establish a diagnosis. Whereas in 40% of patients, the cause of syncope remains unknown after extensive clinical workup (5, 6). The disappointing results of ambulatory ECG monitoring are well known, since the heart rhythm of the patient is seldom monitored during an event (7, 8). The major difficulties to diagnosis are the unpredictable and uncommon nature of events and the high spontaneous recovery. Because of the transient nature of these episodes, the underlying causes may remain undi-

agnosed. An electrophysiologic study (EP) study is often performed to elucidate the potential arrhythmic basis for unexplained syncope; especially in patients with underlying structural heart disease (9, 10). While the EP study is a potent method to diagnose arrhythmias and help to guide therapy, it has several limitations. Some subgroups of patients did not benefit from an EP study, meaning that the EP results were non-diagnostic. Identification of these patients is important so that the risk and expense of EP study could be avoided (11-13). Prognosis of syncope varies widely and 1-year mortality may range from 0% in the case of vasovagal events up to 30% in the presence of heart disease (7, 14, 15).

The primary aim of this study was to determine the role of abnormal EP study in prediction of outcome in syncope patients with suspected cardiac cause. The second aim of this study was to assess the rate of long-term adverse outcome in terms of mortality and to determine the risk factors associated with mortality in this group.

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## Methods

### Study population

From 2008 to 2010, 227 consecutive patients presented with syncope referred to our electrophysiology and pacing Department of Pacemaker and Electrophysiology, Rajaie Cardiovascular Research and Medical Center, Tehran-Iran. Patients were recruited if they have a syncopal episode in the previous two months. All patients underwent standard workup including history, physical examination, 12-lead ECG, 24-hour Holter monitoring, echocardiography, carotid sinus massage and neurological evaluation.

Brugada syndrome, mitral valve prolapse, long QT syndrome, severe aortic stenosis, and atrial myxoma were excluded. Uniform testing protocol was considered for all patients with suspected cardiac cause of syncope. According to the results of the initial evaluation, 177 patients (70.1% male; mean age  $61.3 \pm 16.0$  years) with one or some of the following criteria were included: 1) the presence of structural heart disease (coronary artery disease, ventricular dysfunction, severe mitral or aortic valve regurgitation, hypertrophic cardiomyopathy) 2) family history of sudden cardiac death 3) abnormal ECG or significant cardiac arrhythmia in 24-hour Holter monitoring. These patients, in whom a cardiac cause of syncope was suspected, underwent EP study and if negative, a head-up tilt test (HUTT).

The presence of bundle branch block, first degree atrioventricular block (AVB), Q wave on 12-lead surface ECG were considered as ECG abnormalities. Frequent non-sustained ventricular tachycardia (VT) (more than two episodes) during 24-hour Holter monitoring was considered significant. Major trauma during episodes defined as any fractures, head injury, internal organ damage or syncope leading to an car crash. Minor trauma defined as soft tissue injury.

All patients had been asked if they had prodromal symptoms including cold sweating, nausea and/or vomiting, lightheadedness, impending doom, visual blurring, non-paroxysmal palpitation, weakness and abdominal or chest discomfort.

Syncope was defined as sudden transient loss of consciousness and postural tone with spontaneous recovery caused by global cerebral hypoperfusion. A vasovagal or neurally mediated response to HUTT was defined as reproduction of syncope or presyncope in association with hypotension, bradycardia or both (decrease in systolic blood pressure  $>50\%$  and decrease in heart rate  $>30\%$  of the maximal value observed in upright position). Given a lack of a well described definition of near syncope, these patients were not included. The protocol of the study was approved by our Research Ethical Committee and the informed written consents were taken from the all patients.

### Electrophysiological study

The electrophysiological study (EP) study included measurement of corrected sinus node recovery time, HV interval at baseline and incremental pacing, inducibility of ventricular arrhythmia by means of programmed ventricular stimulation in

two drive cycle lengths (600 ms, 400 ms) with up to three extra-stimuli and programmed atrial stimulation. EP study was considered diagnostic in the presence of: 1- an abnormal sinus node recovery time; 2- baseline HV interval  $\geq 100$  ms, second or third degree His-Purkinje block demonstrated by incremental atrial pacing or elicited by intravenous procainamide (10 mg/kg over 10 min) 3-induction of sustained monomorphic ventricular tachycardia or rapid supraventricular tachycardia that reproduced symptoms.

### Head-up tilt test

HUTT test was performed in all patients with unexplained syncope if EP study was negative based on standard protocol. The patients received no oral intake for more than 6 hr before HUTT. An intravenous line was placed for fluid administration. At least 20 minute resting period after intravenous line placement, the patient was elevated to  $70^\circ$  until syncope occurred. Sublingual nitroglycerin (400  $\mu$ g) was used for drug provocation if passive phase had been negative. Drug provocation phase duration was 15 minute. The test was considered positive in case of bradycardia, hypotension (systolic blood pressure  $<70$  mm Hg) and syncope.

### Outcome measures

All enrolled patients had at least one episode of syncope meeting the above definition to be eligible for enrollment. Severe outcome was assessed by evaluating mortality. Outcomes were determined by inpatient diagnosis, follow-up phone call, and subsequent medical records.

### Statistical analysis

Continuous variables were expressed as mean  $\pm$  SD. The data were tested for normal distribution via the Kolmogorov-Smirnov (K-S) test. Logistic regression analysis was used to identify variables that increased the probability of a positive response. Potential predictors of mortality were first individually evaluated and then analyzed by binary logistic regression analysis with a stepwise backward selection strategy. P value  $<0.05$  was considered statistically significant. Analysis of data was performed using SPSS 15 statistical software (SPSS Inc, Chicago, IL, USA).

## Results

### Characteristics of patients

The characteristics of patients are shown in Table 1. Seventy percent of patients were male. Mean age of patients was  $61.3 \pm 16.0$  years. Fifty-three percent of patients had coronary artery disease, 4.5% dilated cardiomyopathy and 3.9% valvular heart disease. ECG abnormalities including right bundle branch block and left bundle branch block (LBBB) found in 15% and 5% and old myocardial infarction in 26% and 3.6% of patients with abnormal and normal EP study, respectively. Twenty-eight percent of patients had a history of physical injury during syncopal attack. Syncope occurred in upright position in 76.6%, in supine position in 8.5% and in sitting position in 14.9% of the patients.

**Table 1. Patient's baseline characteristics**

Number of patients	177
Patients age, years	61.3±16.0
Sex, male (%)	70.1%
Underlying heart disease, n (%):	
Coronary artery disease	94 (53.1%)
Dilated cardiomyopathy	8 (4.5%)
Valvular heart disease	7 (3.9%)
Medications, n (%):	
Beta-blocker	78 (59.1%)
Diuretics	38 (28.8%)
Vasodilators	49 (37.1%)
ACE inhibitors	74 (56.1%)
Number of syncope	2.6±1.9
Patients with injury, %:	
major	6 (3.4%)
minor	43 (24.3%)
Time interval*, day	89.0±53.7
*Time interval between first and last episode of syncope (day) ACE inhibitors - angiotensin converting enzyme inhibitors	

The time interval between the first and last episode of syncope was 89.0±53.7 days and the number of syncopal attacks was 2.6±1.9. Twenty-five percent of patients cited prodromal symptoms.

### Electrophysiologic characteristics

A cardiac cause of syncope was established in 35.0% (n=62), a neurally mediated syncope in 35.6% (n=63), and in 29.4% (n=52) the remaining the cause of syncope remained unexplained despite a thorough neurologic and cardiologic evaluation. In all patients with a cardiac cause of syncope, the diagnosis was made during the EP study: AV block requiring pacemaker in 7 patients (11.3%), sinus node dysfunction in 6 (9.7%), VT in 47 (75.8%), supraventricular tachycardia in 3.2%. In patients with a negative EP study result, the diagnosis of neurally mediated syncope was made based on positive HUTT result in 35.6%. Mean ventricular ejection fraction was 31.28±12.96 percent in patients with a cardiac cause of syncope and 47.23±9.60 percent in patients with negative EP study (p<0.001).

### Predictors of cardiac cause of syncope

Logistic regression analysis revealed that the significant predictors of a cardiac cause of syncope were absence of prodromal symptoms, LBBB, severe left ventricular (LV) dysfunction and male gender (p=0.002, p<0.001, p<0.001 and p=0.010 respectively). Position of patients during syncope, number of syncopal attacks, the time interval between the first and the last episode of syncope, history of injury and age didn't have any relationship with cardiac cause (All p values >0.05). Of noted, we could not show any association between the presence of prodromal symptoms and cause of syncope (p=0.260).

**Table 2. Risk factors for outcome of death: Univariate analysis and binary logistic regression**

Univariate analysis:		P value	
LVEF<40%		0.009	
Use of diuretics		0.011	
History of MI		0.043	
Ventricular tachycardia		0.006	
Presence of LBBB		<0.001	
Abnormal EP result		0.007	
Binary logistic regression:			
		95%	
	Odds Ratio	Confidence Interval	
Presence of LBBB	6.63	1.09 to 40	<0.001
EP - electrophysiology; LBBB - left bundle branch block; LVEF - left ventricular ejection fraction; MI - myocardial infarction			

### Follow-up

The mean follow-up period was 20.0±10.8 months. Complete follow-up was obtained for 132 patients. Among these, 48 patients (36.4%) had a positive EP study result, 44 patients (33.3%) had a positive HUTT result and the remaining had no diagnosis. The 1-year overall mortality was 7.6%. At univariate analysis, the risk factors significantly associated with the long-term outcome of death were a history of myocardial infarction (MI), structural heart disease, LV dysfunction, abnormal ECG at presentation, use of diuretics, ventricular arrhythmias, and abnormal EPS result. At multivariate analysis, none of them were independent risk factors for the development of severe adverse outcome. In a subgroup analysis of patients with structural heart disease, the risk factors significantly associated with outcome of death included history of MI, use of diuretics, presence of bundle branch block (BBB), abnormal EP study result, ventricular arrhythmias, and LV dysfunction (Table 2). At logistic analysis, the presence of LBBB (OR 6.63; 95% CI 1.09 to 40) was significantly associated with outcome of death (Table 2). In patients without structural heart disease, severe outcome could not be predicted by clinical characteristics and or EP study result.

### Discussion

The causes of syncope are often benign, but can sometimes be due to potentially life-threatening disorders. These patients are frequently referred for an EP study (16, 17). On the basis of the premise that most cardiogenic syncope is related to an arrhythmia, tachyarrhythmia, or bradyarrhythmia, electrophysiological testing makes sense. The performance of a diagnostic protocol of syncope is clearly influenced by patient selection (18, 19).

In this study, EP study abnormalities have been identified in 35.5% of patients with otherwise unexplained syncope, with ventricular tachycardia the most common abnormality (75.8%). EP study was performed in the hope of not only identifying

abnormalities, leading to therapy to prevent recurrent syncope, but also to determine prognosis. Therapy directed at treating the underlying abnormality (most commonly sustained ventricular tachycardia and conduction disorders) has been associated with a reduction in the risk of death and recurrent syncope. Based on our results, it appears that syncope in the face of structural heart disease and abnormal EP study results is associated with a poor outcome. There are some abnormalities at EP study that may reflect the true cause of syncope but have less prognostic meaning, e.g. supraventricular tachycardia, prolonged AV nodal refractory period. It is worthy to note that the use of EP study results, in order to guide therapy, is disease and stimulation protocol specific.

In this study, we also addressed the rate of deaths and what are the predictors of mortality in patients with unexplained syncope and suspected cardiac cause. Our investigation revealed that in patients with unexplained syncope in whom a cardiac cause is suspected, LBBB, severe LV dysfunction, absence of prodromal symptoms and male gender are predictive of a cardiac cause. An interesting new finding in our study was that the clinical features including the presence of prodromal symptoms, the time interval between the first and last episode of syncope, the number of syncope episodes, age, sex, and history of injury have a limited role in predicting a cardiac cause of syncope (4, 10, 20). Whereas, the finding of Moya et al. (10) shows clinical conditions suggestive of a serious cause of syncope include occurrence during either whilst supine or exertion. Prodromal symptoms of angina pectoris, acute dyspnea and sudden onset palpitation with lightheadedness may all suggest a serious cardiac cause.

Our data indicate that a history of MI, structural heart disease, LV dysfunction, abnormal ECG at presentation, use of diuretics, ventricular arrhythmias, and abnormal EP study result are associated with adverse outcome of death. Moreover, similar to that of Freedman et al. (21), our study suggests that the presence of LBBB is an independent risk factor associated with mortality. In a subgroup of patients without structural heart disease, severe outcome could not be predicted by clinical characteristics and/or EP study result.

Although individuals who present with syncope and are prone to sudden cardiac death, frequently have a history of structural heart disease along with clinical, echocardiographic or ECG characteristics suggestive of a serious arrhythmia however, it is noteworthy that presence of structural heart disease per se does not necessarily imply that the syncopal event is caused by the underlying heart disorder (22). Even for patients with cardiac disease in whom an arrhythmia is suspected as the cause of syncope, the etiology could be difficult to determine.

The prognosis of majority of patients is favorable, but varies widely depending on diagnosis; specifically cardiac causes (23-25). A number of studies have notified the prognosis of syncope, highlighted its remarkable variability according to the different causes that underlie the loss of consciousness (7, 26-28). In

particular, cardiac syncope had the worst prognosis compared to the absence of mortality at 12 months in neurally mediated syncope (14, 26). It is intriguing that the study concludes that the good prognosis associated with a negative EP study outweighs the implications of the LV dysfunction for a poor prognosis. Treatment guided by EP study diagnoses in syncope patient is associated with an improved prognosis. A normal or non-diagnostic study carries a favorable prognosis.

## Study limitations

There is no gold standard of reference for measuring the diagnostic tests. As such, there is no ideal pattern or set of criteria for diagnosing syncope. In this study, we employed the diagnostic criteria that most commonly used. We focused on a composite endpoint of mortality, and the rate of other severe adverse outcomes (i.e. major therapeutic procedures) was not assumed.

## Conclusion

The present study provides evidence that presence of LBBB, abnormal EP study result and structural heart disease have prognostic value in patients with suspected cardiac cause of syncope. The non-diagnostic EP study has an important implication: a patient with structural heart disease and unexplained syncope who has a negative EP study has a good long-term prognosis even in the presence of LV dysfunction.

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