

## Selective Use of Diagnostic Tests in Patients With Syncope of Unknown Cause

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<b>OBJECTIVES</b>	We sought to prospectively assess the diagnostic yielding of a protocol in which electrophysiologic studies (EPS), tilt-table tests (TTTs), and loop recorder implantation are selectively used.
<b>BACKGROUND</b>	The optimal strategy in the diagnosis of patients with syncope of unknown cause has not been defined.
<b>METHODS</b>	A total of 184 consecutive patients with syncope of unknown cause were classified into two groups. Group A consisted of 72 patients fulfilling any of the following criteria: 1) presence of structural heart disease or family history of sudden death; 2) abnormal electrocardiogram; 3) significant non-symptomatic arrhythmia on Holter monitoring; and 4) paroxysmal palpitations immediately before or after syncope. These patients initially underwent an EPS and, if this study was negative, TTT. In the remaining 112 patients (group B), TTT was performed.
<b>RESULTS</b>	The EPS was positive in 32 patients (44%) in group A. The TTT was positive in 80 patients (71%) in group B. An additional patient had carotid sinus hypersensitivity. In patients of group A with a negative EPS, the TTT was positive in 23 (57%). A loop recorder was implanted in 15 patients from group A with negative conventional testing, and diagnostic activation was obtained in seven patients. Overall, a positive diagnosis was achieved in 143 patients (78%).
<b>CONCLUSIONS</b>	In patients with syncope of unknown cause, selective use of EPS or TTT leads to a positive diagnosis in >70% of the cases. An implantable loop recorder can be useful in non-diagnosed cases. (J Am Coll Cardiol 2003;41:787-90) © 2003 by the American College of Cardiology Foundation

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The etiology of syncope is difficult to establish in patients with syncope of a non-apparent cause after the initial clinical assessment. These patients are frequently referred for an electrophysiologic study (EPS) (1-3) and tilt-table testing (TTT) (2-4). Although the isolated value of these tests has been assessed in several studies, there is a lack of information about the diagnostic value of a protocol that

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selectively uses both tests. However, this information is important because, as has been suggested recently, a diagnostic strategy with initial use of an implantable loop recorder (ILR) can be superior to conventional testing (5). This study prospectively assessed the diagnostic yielding of a protocol in which EPS, TTT, and ILR were selectively used.

### METHODS

**Patients.** We studied 184 consecutive patients (113 men and 71 women; mean age  $54.5 \pm 17.4$  years) with syncope

of unknown cause after an initial clinical examination. Patients were referred by the Emergency Department or the general practitioner to the Cardiology Outpatient Clinic for an initial clinical evaluation. All patients had at least a syncopal episode in the previous two years. The initial clinical assessment included a careful history, a physical examination, an electrocardiogram (ECG), a carotid sinus massage, postural blood pressure testing, and 24-h ambulatory monitoring. Other tests were performed if clinically indicated.

**Study protocol.** Based on the results of a previous retrospective study (6), a two-step diagnostic protocol was developed and approved at our institution.

1. In accordance with the results of the initial evaluation and after giving informed, written consent, patients were classified into two groups. Group A consisted of 72 patients fulfilling any of the following criteria: 1) the presence of structural heart disease or family history of sudden death; 2) an abnormal ECG; 3) significant non-symptomatic arrhythmia on Holter monitoring (sinus pause >2 s, second-degree atrioventricular [AV] block, asymptomatic supraventricular or ventricular tachycardia); and 4) paroxysmal palpitations before or immediately after the episode. These patients initially

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Manuscript received July 2, 2002; revised manuscript received October 11, 2002, accepted October 31, 2002.

**Abbreviations and Acronyms**

- ATP = adenosine triphosphate
- AV = atrioventricular
- ECG = electrocardiogram, electrocardiographic
- EPS = electrophysiologic study/studies
- ILR = implantable loop recorder
- TTT = tilt-table test(s)/testing

underwent EPS. Group B comprised the remaining 112 patients in which TTT was performed.

2. All patients from group A with a negative EPS underwent TTT; and, if this was negative, an ILR (Reveal, Medtronic Inc., Minneapolis, Minnesota) was implanted, and the patients were instructed to activate the device after every episode of syncope or presyncope.

**EPS.** An EPS was performed as previously described (6) and was considered diagnostic in the presence of: 1) an abnormal sinus node recovery time; 2) baseline HV interval  $\geq 70$  ms, or second- or third-degree His-Purkinje block, as demonstrated during incremental atrial pacing or elicited by intravenous administration of procainamide (10 mg/kg over 10 min); 3) induction of sustained monomorphic ventricular tachycardia; and 4) induction of a rapid supraventricular arrhythmia that reproduced hypotensive or spontaneous symptoms.

**TTT.** A TTT was performed to 60° during 20 min. If the passive tilt phase did not induce syncope, 0.4 mg of sublingual nitroglycerin spray was administered, and the tilt continued for 15 min (7). The TTT was considered positive if a syncopal episode associated with a rapid fall in blood

pressure with or without associated bradycardia was induced.

**Statistical analysis.** Data are presented as the mean value  $\pm$  SD and as group percentages. Group comparisons were performed by using the Mann-Whitney *U* test for continuous variables and the Fisher exact test for dichotomous variables. A *p* value  $<0.05$  was considered statistically significant.

**RESULTS**

The clinical characteristics of patients in groups A and B are shown in Table 1. The results of EPS and TTT are shown in Figure 1. In group A, the EPS was positive in 32 patients (44%). The diagnoses in these patients included paroxysmal AV block in 14 (43%), ventricular tachycardia in nine (28%), supraventricular tachycardia in five (16%), sinus node dysfunction in three (9%), and a previously unrecognized carotid sinus hypersensitivity in one patient.

In group B, a syncopal episode was induced in 80 patients (71%) during TTT, and carotid sinus hypersensitivity was detected in one patient of this group.

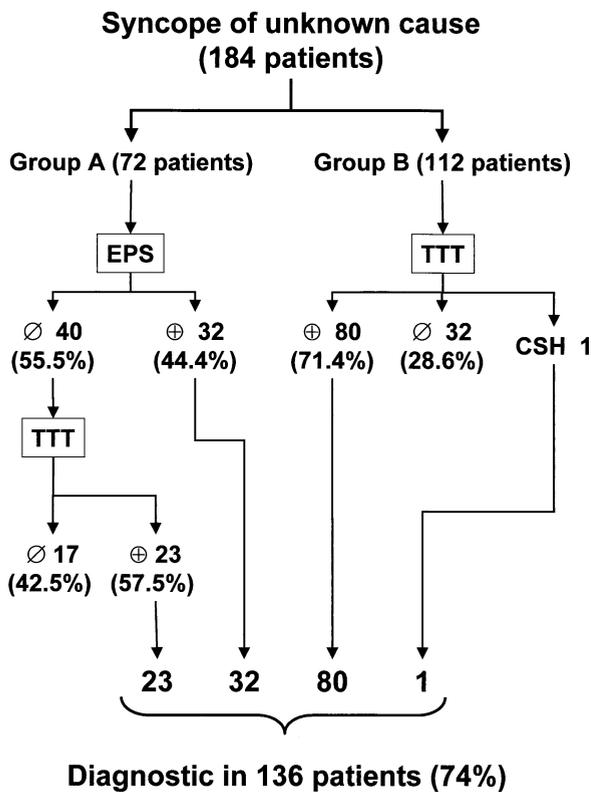
Of the 40 patients of group A with a negative EPS, the TTT was positive in 23 (57%). Therefore, with the selective use of EPS, TTT, and repeated carotid sinus massage, a positive diagnosis was found in 136 patients (74%).

An ILR was implanted in 15 patients of group A with negative conventional testing, whereas the remaining two patients refused implantation. During the follow-up period of  $7.8 \pm 4.7$  months, an ILR-documented syncopal event occurred in eight patients after a mean period of 81.3  $\pm$  96.4 days. The mechanism of syncope was paroxysmal AV

**Table 1.** Characteristics of Patients in Groups A and B

	Group A (n = 72)	Group B (n = 112)	p Value
Mean age (yrs)	59 $\pm$ 14	51 $\pm$ 18	0.002
Mean age at first episode of syncope (yrs)	54 $\pm$ 18	44 $\pm$ 21	0.001
Male gender	52 (72%)	61 (54%)	0.02
History of syncope			
No. of episodes last year	4.6 $\pm$ 7	3.9 $\pm$ 9	NS
No. of episodes in last 3 months	2.4 $\pm$ 5	1.4 $\pm$ 2	NS
No. of presyncopal episodes last year	3.8 $\pm$ 8	2.6 $\pm$ 5	NS
Patients with trauma	26 (36%)	46 (41%)	NS
Patients with severe trauma	7 (10%)	14 (13%)	NS
Associated structural heart disease	35 (49%)	—	
Ischemic	17	—	
Hypertrophic	8	—	
Dilated	4	—	
Valvular	2	—	
Others	4	—	
Heart failure	8 (11%)	—	
Abnormal ECG	52 (72%)	—	
Intraventricular conduction defect	27	—	
Abnormal Holter recording	22 (31%)	—	
Palpitations in episode	17 (24%)	—	
Family history of sudden death	1 (1.4%)	—	

Data are presented as the mean value  $\pm$  SD or number (%) of patients.  
ECG = electrocardiogram; NS = not significant.



**Figure 1.** Results of electrophysiologic studies (EPS) and tilt-table testing (TTT) in groups A and B. Figures represent the number of patients, with group percentage in brackets. CSH = carotid sinus hypersensitivity.

block in three patients with an intraventricular conduction defect, sinus arrest in two patients, and polymorphic ventricular tachycardia in two patients. One patient showed sinus rhythm during the syncopal episode, so no positive diagnosis was obtained. None of the two patients with polymorphic ventricular tachycardia had structural heart disease. One patient had a family history of sudden death, and the other had borderline idiopathic QT prolongation (0.48 s). Eventually, a diagnosis was obtained in 143 patients (78%).

## DISCUSSION

The main finding of the present study is that selective use of conventional techniques (EPS and TTT) is associated with a high diagnostic yield in non-selected cases of syncope of unknown cause. The performance of a diagnostic protocol of syncope is clearly influenced by patient selection. In the present study, the presence of at least one syncopal episode in the previous two years and a negative initial clinical work-up were the only conditions for being included.

In our study, we assigned patients to group A or B in order to: 1) be sensitive in the detection of potential lethal arrhythmias without excessively increasing the number of EPS; 2) diagnose as many patients as possible; and 3) save time and costs.

The EPS is the most suitable test for the detection of potentially lethal arrhythmias. The yield of abnormal results with this technique varies between 11% and 75% in distinct series (1,2,8,9), mainly reflecting differences in patient selection. In one study (9), an LV ejection fraction  $\geq 40\%$ , the absence of structural heart disease, a normal 12-lead ECG, and the absence of significant arrhythmias on Holter monitoring were predictive criteria of a non-diagnostic EPS. On the other hand, palpitations were the only significant predictor of a cardiac cause of syncope in patients without heart disease (10). So, the clinical criteria used in the present study should define a group B in which the EPS had a low diagnostic yield and a group A in which most of the patients with arrhythmic syncope would be included.

The positive rate of EPS in this study was relatively low (44%). The EPS has a limited sensitivity to detect paroxysmal AV block (11). Some studies have shown that EPS has a poor predictive value in patients with dilated cardiomyopathy, poor LV function, and syncope, making advisable the implantation of an automatic defibrillator in those patients (12,13).

A TTT potentiated with sublingual nitroglycerin has showed a positive rate of 69% in patients with syncope of unknown cause and 8% in control subjects (7). In our study, the selection criteria made patients in group B have a high pre-test probability of vasovagal syncope. So, the high rate of positive TTT (71%) observed in this group is in accordance with the expected figure. In patients of group A with a negative EPS, a high TTT positivity rate was also found. This is in accordance with previous reports in which TTT was performed in patients with a previous negative EPS (2,14).

To get a maximal diagnostic yield in patients of group A, we implanted an ILR in patients of this group with negative conventional testing, and syncope recurred in 50%. Prolonged monitoring results suggest that this is a heterogeneous subgroup including patients with paroxysmal AV block, polymorphic ventricular tachycardia, and neuromediated syncope.

In patients of group B with a negative TTT, no more diagnostic tests were scheduled. There is general agreement that in this group of patients, EPS is not a useful strategy (3). In a similar subgroup, ILR monitoring has shown evidence of a very good prognosis, with 34% recurrence of syncopal episodes, suggestive of neurally mediated syncope in most cases (15). In the present study, we decided not to systematically implant an ILR in patients with isolated syncope, because we believed that the benign nature, the low recurrence rate, and the uniform type of response of these cases do not justify an invasive approach and the additional cost of an ILR.

**Comparison with previous studies.** There are no published data on the diagnostic value of a protocol similar to ours. In the study of Sra et al. (2), 86 consecutive patients with syncope of unknown cause underwent EPS that was positive in 29 (34%). A TTT was done in the remaining 57

patients and was positive in 34 (58%). So, the overall positive diagnosis with this protocol (74%) is similar to that obtained in the conventional phase of our protocol, in which an EPS was performed in only 39% of patients.

The results of the present study are markedly different from those obtained by Krahn et al. (5). In their study, 60 patients with unexplained syncope were randomized to conventional testing (EPS and TTT) or prolonged monitoring with an ILR. After crossover, a diagnosis was obtained in 55% of the patients with prolonged monitoring, compared with 19% in the conventional testing branch. However, young patients without structural heart disease and patients with significant structural heart disease were both excluded. The exclusion of patients with a high pre-test probability of vasovagal syncope or arrhythmic syncope was responsible for the low diagnostic yield of the conventional approach observed in that study.

**Study limitations.** In our study, an adenosine triphosphate (ATP) test was not performed. It is possible that the addition of an ATP test to our protocol could increase the diagnostic yield (16,17).

As in other studies of syncope, an abnormal EPS or TTT response was considered to be a surrogate of the true cause of syncope. Although the diagnostic criteria used in the present study are commonly accepted, the significance of these criteria in a concrete subgroup of patients (for example, in patients of group A with a negative EPS and a positive TTT) would be clarified, in the future, by the results of long-term follow-up and by comparing them with the results of prolonged ILR monitoring (18).

**Conclusions.** In non-selected patients with syncope of unknown cause after the initial clinical evaluation, selective use of EPS or TTT guided by relatively simple clinical criteria leads to a positive diagnosis in more than 70% of cases. The use of an ILR in non-diagnosed cases increases the diagnostic success.

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## REFERENCES

1. Klein GJ, Gersh BJ, Yee R. Electrophysiological testing: the final court of appeal for diagnosis of syncope? *Circulation* 1995;92:13332-35.
2. Sra JS, Anderson AJ, Sheikh SH, et al. Unexplained syncope evaluated by electrophysiologic studies and head-up tilt testing. *Ann Intern Med* 1991;114:1013-9.
3. Brignole M, Alboni P, Benditt DG, et al. Task Force on Syncope, European Society of Cardiology: guidelines on management (diagnosis and treatment) of syncope. *Eur Heart J* 2001;22:1256-306.
4. Benditt DG, Ferguson DW, Grubb BP, et al. ACC Expert Consensus Document: tilt table testing for assessing syncope. *J Am Coll Cardiol* 1996;28:263-75.
5. Krahn AD, Klein GJ, Yee R, et al. Randomized assessment of syncope trial: conventional diagnostic testing versus a prolonged monitoring strategy. *Circulation* 2001;104:46-51.
6. García-Civera R, Sanjuán-Máñez R, Ruiz-Granell R, et al. Rendimiento diagnóstico de un protocolo de estudio del síncope de causa no aparente. *Rev Esp Cardiol* 2001;54:425-30.
7. Bartoletti A, Alboni P, Ammirati F, et al. 'The Italian Protocol': a simplified head-up tilt testing potentiated with oral nitroglycerin to assess patients with unexplained syncope. *Europace* 2000;2:339-42.
8. Gulamhusein S, Nacarelli GV, Ko PT, et al. Value and limitations of clinical electrophysiologic study in assessment of patients with unexplained syncope. *Am J Med* 1982;73:700-5.
9. Krol RB, Morady F, Flacker GC, et al. Electrophysiologic testing in patients with unexplained syncope: clinical and noninvasive predictors of outcome. *J Am Coll Cardiol* 1987;10:358-63.
10. Alboni P, Brignole M, Menozzi C, et al. Diagnostic value of history in patients with syncope with or without heart disease. *J Am Coll Cardiol* 2001;37:1921-8.
11. Brignole M, Menozzi C, Moya A, et al. Mechanism of syncope in patients with bundle branch block and negative electrophysiological test. *Circulation* 2001;104:2045-50.
12. Knight BP, Goyal R, Pelosi F, et al. Outcome of patients with nonischemic dilated cardiomyopathy and unexplained syncope treated with an implantable defibrillator. *J Am Coll Cardiol* 1999;33:1964-70.
13. Russo AM, Verdino R, Schorr RN, et al. Occurrence of implantable defibrillator events in patients with syncope and nonischemic dilated cardiomyopathy. *Am J Cardiol* 2001;88:1444-6.
14. Raviele A, Gasparini G, DiPede F, et al. Usefulness of head-up tilt test in evaluating patients with syncope of unknown origin and negative electrophysiologic study. *Am J Cardiol* 1990;65:1322-7.
15. Moya A, Brignole M, Menozzi C, et al. Mechanism of syncope in patients with isolated syncope and in patients with tilt-positive syncope. *Circulation* 2001;104:1261-7.
16. Flammang D, Church T, Waynberger M, et al. Can adenosine 5'-triphosphate be used to select treatment in severe vasovagal syndrome? *Circulation* 1997;96:1201-8.
17. Brignole M, Gaggioli G, Menozzi C, et al. Adenosine-induced atrioventricular block in patients with unexplained syncope: the diagnostic value of ATP testing. *Circulation* 1997;96:3921-7.
18. Brignole M, Menozzi C, Moya A, et al. Implantable loop recorder: towards a gold standard for the diagnosis of syncope? *Heart* 2001;85: 610-2.