Correlation of Noninvasive Electrocardiography with Invasive Electrophysiology in Syncope of Unknown Origin: Implications from a Large Syncope Database

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Background: The evaluation of syncope can be expensive, unfocused, and unrevealing yet, failure to diagnose an arrhythmic cause of syncope is a major problem. We investigate the utility of noninvasive electrocardiographic evaluation (12-lead ECG and 24-hour ambulatory electrocardiographic recordings) to predict electrophysiology study results in patients with undiagnosed syncope.

Methods: We evaluated 421 patients with undiagnosed syncope who had an electrocardiogram (ECG), an electrophysiology study, and 24-hour ambulatory monitoring. Noninvasive testing was used to predict electrophysiology testing outcomes. Multivariable logistic regression analysis adjusting for age, sex, presence of heart disease, and left ventricular ejection fraction (LVEF) was used to assess independent predictors for sinus node disease, atrioventricular node disease, and induction of ventricular tachyarrhythmias.

Results: Patients were divided into four groups: group 1, abnormal ECG and ambulatory monitor; group 2, abnormal ECG only; group 3, abnormal ambulatory monitor; and group 4, normal ECG and ambulatory monitor. The likelihood of finding at least one abnormality during electrophysiologic testing among the four groups was highest in group 1 (82.2%) and lower in groups 2 and 3 (68.1% and 33.7%, respectively). In group 4, any electrophysiology study abnormality was low (9.1%). Odds ratios (OR) were 35.9 ($P < 0.001$), 17.8 ($P < 0.001$), and 3.5 ($P = 0.064$) for abnormal findings on electrophysiology study, respectively (first three groups vs the fourth one). ECG and ambulatory monitor results predicted results of electrophysiology testing.

Conclusion: Abnormal ECG findings on noninvasive testing are well correlated with potential brady- or/and tachyarrhythmic causes of syncope, in electrophysiology study of patients with undiagnosed syncope.

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syncope; electrophysiology; ECG; Holter monitor

Syncope, due to a cardiac cause, is associated with an adverse long-term prognosis and may be associated with increased risk of sudden arrhythmic death.^{1,2} Additionally, brady- and tachyarrhythmias can cause syncope. Syncope, whose cause is unknown after an initial assessment, has an uncertain prognosis^{3–5} yet, it is critical to identify patients at highest risk who may require a pacemaker or defibrillator and to identify the cause of recurrent syncope to prescribe proper therapy.^{1–7}

However, evaluation of undiagnosed syncope can be expensive, complex, unrevealing, and nonproductive.⁸

Invasive electrophysiologic testing has been used to evaluate patients with undiagnosed syncope.^{9–18} Indirect evidence, small-series, meta-analysis, and anecdotal reports suggest that such testing may be useful to evaluate syncope patients who have abnormal electrocardiographic findings, regardless of the presence of ventricular dysfunction.^{19–21} Use of

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electrophysiological studies have been advocated for diagnostic purposes^{22,23} to help define the prognosis and to identify effective treatment.^{12-16,24} We suspected that data derived from noninvasive testing could identify which patient would benefit from an electrophysiology study and therefore tested the hypothesis that noninvasive evaluation predicts which patient with undiagnosed syncope could benefit from electrophysiology study.

METHODS

This was a study of 454 consecutive patients referred to cardiology for further investigation from September 1993 to April 2005. All patients had undiagnosed syncope despite a complete history and physical examination (syncope of unknown origin [SUO]). Complete data were available for 421 patients, the final study population. Until December 1998, available data were retrospectively collected in 137 patients, while since then the rest of the data were prospectively collected in additional 284 patients. The study was approved by the Hospital Ethics committee.

As part of our initial assessment, all patients were evaluated with a careful physical examination, complete personal and family history, and neurological assessment. Routine laboratory testing included an electrocardiogram, at least one 24-hour ambulatory monitor, and two-dimensional echocardiography.

12-Lead Electrocardiography

Standard 12-lead ECGs at rest were analyzed for the presence of any of the abnormal variables appearing in Table 1. An abnormal ECG was defined when one or more abnormal ECG findings, as identified in Table 1, were present on the admission record.

24-Hour Ambulatory Monitor

At least one 24-hour ambulatory monitor using standard techniques was performed usually on an outpatient basis or in an inpatient basis when the admission was processed through the emergency room. The 24-hour ambulatory monitor recordings were analyzed for the variables appearing in Table 2. The presence of any one or more than one of the six identified 24-hour ambulatory monitor variables, defined an abnormal 24-hour recording.

Table 1. Twelve-Lead ECG Criteria for Abnormality

1. Sinus bradycardia ≤ 60 bpm
2. Complete right (RBBB) or left (LBBB) bundle branch block
3. Left anterior (LAHB) or posterior (LPHB) hemiblock
4. First-degree atrioventricular (AV) block (PR ≥ 200 msec)
5. Bifascicular block (first AV block with RBBB or LAHB or LPHB, and RBBB with LAHB or LPHB)
6. Trifascicular block (first AV block with LBBB and first AV block with RBBB and LAHB or LPHB)
7. Right ventricular repolarization such as ST-T changes in leads V₁ through V₃
8. Delta waves
9. Q waves or poor R-wave progression indicative of an old myocardial infarction

Electrophysiology Study

A standard approach was used for electrophysiology testing²⁴ to assess the corrected sinus node recovery time, the sinoatrial conduction time, the chronotropic response to atropine and/or isoproterenol, the intrinsic heart rate, atrioventricular (AV) nodal conduction, His purkinje function and the point of Wenckebach, and 2:1 AV block.²⁵ Right atrial stimulation (≤ 2 premature extrastimuli) and right ventricular stimulation (from two sites, ≤ 3 premature extrastimuli and at 2 cycle lengths) generally before and after isoproterenol infusion were delivered. Carotid sinus massage was performed. Abnormal findings are listed in Table 3.

Based on noninvasive assessment, four groups of patients were considered and compared: group 1, patients with abnormal findings on ECG and 24-hour ambulatory monitor; group 2, patients with abnormal findings only on ECG; group 3,

Table 2. Ambulatory Monitor Criteria for Abnormality

1. Mean 24-hour (day and night) heart rate ≤ 60 bpm (persistent sinus bradycardia)
2. Runs of supraventricular tachycardia at rates ≥ 140 bpm
3. Complex ventricular ectopy (frequent premature ventricular contractions ≥ 30 /hour with pairs or/and runs of nonsustained ventricular tachycardia, namely, ≥ 3 beats at rates > 120 bpm)
4. Sinus pauses of 2.0 to 2.5 seconds
5. Episodes of second-degree atrioventricular (AV) block, either type I or type II
6. Blocked premature atrial beats

Table 3. Abnormal Values and Findings for the Detected Parameters

Sinus node function	CSNRT $\geq$ 525 msec	SACT $\geq$ 140 msec	Chronotropic response to atropine or isoproterenol $\leq$ 90 bpm	IHR IHR = $118.1 - (0.57 \times \text{age}) \pm \text{SD}$		
AVN and HIS bundle function	HV interval $\geq$ 60 msec	Wenckebach CL $\geq$ 500 msec and 2:1 AVB CL $\geq$ 400 msec	ERP of the AVN $\geq$ 450 msec	Presence of split HIS activity	Presence of sub-Hisian block with atrial stimulation	Appearance of bifascicular or trifascicular block on atrial stimulation
Ventricular stimulation		Sustained ventricular tachycardia or ventricular fibrillation (VT/VF)				
Supraventricular stimulation		Symptomatic sustained supraventricular tachycardia (SVT)				
Apparent bypass tract			Antegrade BT ERP $\leq$ 250 msec			
Carotid sinus message			Symptomatic pauses >3 seconds			

CSNRT = corrected sinus node recovery time; ERP = effective refractory period; IHR = intrinsic heart rate; SACT = sinoatrial conduction time; VT/VF = either ventricular tachycardia or fibrillation; SVT = supraventricular tachycardia with hemodynamic collapse or loss of consciousness.

patients with abnormal findings only on 24-hour ambulatory monitor; and group 4, patients without abnormal findings on ECG or 24-hour ambulatory monitor.

Statistical Analysis

Continuous variables are presented as mean values $\pm$ standard deviation, while qualitative variables are presented as absolute and relative frequencies. Univariate analysis was initially applied to test the associations between abnormal ECG findings and specific electrophysiology study abnormalities. Comparisons between normally distributed continuous variables and categorical variables were made using the Student's *t*-test. Chi-squared or Fisher's exact tests were used as appropriate to analyze categorical data. Among the four patient subgroups, values of numerical parameters were compared by analysis of variance (ANOVA). The Bonferroni post hoc test was used to locate the pairwise differences. One-way ANOVA method was applied in order to test subgroups of continuous variables as appropriate. The associations between an abnormal electrophysiology study and ECG findings were also tested through multinomial logistic regression analysis.

The results obtained from the regression models are presented as odds ratios and the 95% con-

fidence intervals (CI) of them. All models were adjusted for age, sex, left ventricular ejection fraction (LVEF), and evidence of organic heart disease. STATA 8.0 software (Stata Corporation 2003, Texas, USA) was used for all statistical calculations.

RESULTS

Clinical Characteristics

The mean patient age was 60 ± 16 years and 267 (64%) patients were males. The mean LVEF was $51 \pm 16\%$. Of those enrolled, 217 (52%) patients had no structural heart disease. Coronary artery disease was present in 105 (25%) patients, hypertrophic cardiomyopathy in 46 (11%) patients, dilated cardiomyopathy in 35 (8%) patients, valvular heart disease in 29 (7%) patients, and arrhythmogenic right ventricular cardiomyopathy was present in 5 (1%) patients. The number of syncopal or presyncopal episodes/patient was 2.3 (range 1–11). Clinical characteristics are presented in Table 4.

Correlation of Noninvasive Electrocardiographic Findings with Electrophysiology Test Results

The frequency of at least one abnormal electrophysiology test finding was significantly higher in

Table 4. Clinical Characteristics in the Four Patient Groups

	Group I ECG + HOLTER+ N = 202	Group II ECG + HOLTER- N = 94	Group III ECG - HOLTER+ N = 92	Group IV ECG - HOLTER- N = 33	*P Value
Age	60.18 ± 15.49	56.17 ± 19.28	50.13 ± 17.76 [†]	50.74 ± 17.77 [†]	0.084
LVEF	50.88% ± 15.68%	56.37% ± 14.1% [†]	58.37% ± 9.7% [†]	62.57% ± 6.01% [†]	<0.001
Male sex	130 (64.36%)	69 (73.40%)	47 (51.09%) [‡]	21 (63.64%)	0.017
No OHD	85 (42.08%)	42 (44.68%)	67 (72.83%) [‡]	23 (69.70%) [‡]	<0.001
CAD	64 (31.68%)	33 (35.11%)	6 (6.52%) [‡]	2 (6.06%) [‡]	<0.001
HCM	22 (10.89%)	17 (18.09%) ^{¶4}	3 (3.26%) [§]	4 (12.12%)	<0.014
DCMP	24 (11.88%)	4 (4.26%) [§]	6 (6.52%) [‡]	1 (3.03%)	<0.001
VHD	11 (5.45%)	8 (8.51%)	7 (7.69%)	3 (9.09%)	NS
ARVC	2 (1%)	0	3 (3.26%)	0	NS

No OHD = no organic heart disease; CAD = coronary artery disease; HCM = hypertrophic cardiomyopathy; DCMP = dilated cardiomyopathy; VHD = valvular heart disease; ARVC = arrhythmogenic right ventricular cardiomyopathy.

*P value after one-way ANOVA with Bonferroni correction for continuous variables and after chi-square test for discrete ones.

[†]P < 0.05 versus group I.

[‡]P < 0.05 versus group I or versus group II.

[§]P < 0.05 versus group I.

[¶]P < 0.05 versus group III.

the first, second, and third patient groups, that is, those with at least one abnormal finding on ECG, or/and on the ambulatory monitor compared to the fourth patient group in which ECG and ambulatory

monitor results were normal (Fig. 1, all P < 0.001 of the first three groups vs the fourth one).

Using multiple logistic regression analysis, after adjustment for age, sex, heart disease, and

Figure 1. Results of electrophysiology study (EPS) in the four patients groups.

*P value after chi-square test of each group with the fourth one.

Table 5. Independent Predictors of Abnormal EPS, after Logistic Regression

	OR	CI	P Value
ECG + Holter+	35.94	10.14–127.36	<0.001
ECG + Holter–	17.83	4.82–65.87	<0.001
ECG – Holter+	3.45	0.92–12.88	0.064
ECG – Holter–	0.07	0.02–0.23	<0.001
Age	1.02	1.007–1.033	0.002
LVEF	0.97	0.95–0.99	0.013
OHD	3.13	1.52–6.46	0.002

After adjustment for age, sex ejection fraction, and organic heart disease.

LVEF = left ventricular ejection fraction; OHD = organic heart disease.

LVEF, the abnormal ECG and/or ambulatory monitor findings were highly correlated with abnormal electrophysiology study results (Table 5). The odds ratio of groups 2 and 1 of abnormal ECG without or with abnormal findings to predict abnormal electrophysiology study results ranged from 17.8 to 35.9, respectively ($P < 0.001$). In the absence of 12-lead ECG abnormalities, there was a trend for an association between 24-hour ambulatory monitor abnormalities and abnormal electrophysiology study findings (OR 3.45; $P = 0.064$).

Additional independent predictors of abnormal findings on electrophysiology study were age (OR = 1.02; $P = 0.002$), LVEF ≤ 0.40 (OR = 0.97; $P = 0.013$), and structural heart disease (OR = 3.13; $P = 0.002$). The detected abnormalities by electrophysiology testing were AV nodal disease (32%), induced ventricular arrhythmias (26%), sinus node disease (21%), supraventricular tachycardia (8%), high-risk Wolff-Parkinson-White syndrome (2%), and hypersensitive carotid sinus syndrome (2%).

More than one electrophysiology study abnormality was detected in 65 patients. Specifically, 37 patients had sinus node and AV nodal disease, 15 had AV nodal disease and induction of ventricular tachycardia/ventricular fibrillation, 8 had sinus node disease and induction of ventricular tachycardia/ventricular fibrillation, and 5 had sinus node disease, AV nodal disease, and induction of ventricular tachycardia/ventricular fibrillation.

Correlation of Specific 12-Lead ECG Findings with Electrophysiologic Study Results

Conduction Defects on 12-Lead ECG

Figure 2 describes the probability of finding evidence for AV nodal disease on electrophysiology

Figure 2. Proportion of patients with electrophysiologic study (EPS) evidence of atrioventricular node disease (AVND) among the syncope of unknown origin (SUO) patients with different conduction defects.

Table 6. Results of Multiple Logistic Regression Analysis for EPS Evidence of AVND among SUO Patients with Different Conduction Defects

	OR	95% CI	P Value
Any AVCD	6.06	3.75–9.78	<0.001
First-degree AV block	3.07	1.54–6.10	0.001
LAHB	0.56	0.17–1.81	NS
LPHB	2.22	0.43–11.45	NS
LBBB	2.83	1.10–7.22	0.029
RBBB	1.58	0.52–4.79	NS
Bifascicular	4.63	1.84–11.63	0.001
Trifascicular	8.63	3.01–24.71	<0.001
Age (for each year)	1.022	1.008–1.036	0.002

AVND = atrioventricular node disease; AVCD = atrioventricular conduction defect on 12-lead ECG; LBBB = left bundle branch block; RBBB = right bundle branch block; LAHB = left anterior hemiblock; LPHB = left posterior hemiblock; EPS = electrophysiologic study; SUO = syncope of unknown origin.

test among the patients with various forms of conduction defects on the 12-lead ECG. There was a significantly higher proportion of patients with any conduction defect pattern on 12-lead ECG who had also evidence of AV nodal disease on the electrophysiology test. After multivariate logistic regres-

sion analysis adjusted for age, sex, and structural heart disease, the electrocardiographic findings associated with any abnormal electrophysiology test result consistent with AV nodal disease are presented in Table 6. The highest odds ratio (8.63) was observed in the presence of trifascicular block, followed by bifascicular block (4.63), first-degree AV block (3.07), and left bundle branch block (LBBB) (2.83). Sex, ejection fraction, and structural heart disease were not independent predictors, whereas age, as a continuous variable, first-degree AV block, LBBB, and bifascicular or trifascicular block were independent predictors of electrophysiology test evidence of AV nodal disease (all $P < 0.05$).

Sinus Bradycardia on 12-Lead ECG

Sinus bradycardia was present on the electrocardiogram or ambulatory monitor in 141 patients, 76 of whom (54%) had evidence of sinus node disease on electrophysiology test. Among 68 patients with sinus bradycardia observed only on the electrocardiogram, 30 (44%) had electrophysiology test evidence of sinus node disease (OR = 3.9; CI = 2.2–7.0; $P < 0.001$). Among 56 patients with sinus bradycardia seen on the electrocardiogram and the ambulatory monitor, 46 (82%) had

Figure 3. Proportion of syncope of unknown origin (SUO) patients with either instantaneous sinus bradycardia (SB) on electrocardiogram (ECG), or combined SB on both ECG and 24-hour Holter monitoring (HM) who had electrophysiologic study (EPS) evidence of sinus node disease (SND).

electrophysiology test evidence of sinus node disease (OR = 36.0; CI = 16–78.5; $P < 0.001$) (Fig. 3).

Presence of Q Waves on 12-Lead ECG

Induction of sustained ventricular tachyarrhythmia on electrophysiology test was more frequent when Q waves were present on the electrocardiogram (OR 5.11; CI 2.78–9.39; $P < 0.001$) or/and when complex ventricular ectopy was identified on the ambulatory monitor (OR 5.59; CI 3.39–9.23). In a multivariate logistic regression analysis model, electrophysiology test results were associated with structural heart disease (OR = 2.8; CI = 1.5–5.1; $P = 0.001$), the LVEF (OR 0.96; CI 0.94–0.97; $P < 0.001$), and history of syncope versus presyncope (OR 1.7; CI 0.99–3.1; $P = 0.053$).

DISCUSSION

This study identifies a strong correlation between noninvasively derived abnormal electrocardiographic findings and electrophysiology test results in patients with otherwise undiagnosed syncope. Of importance, there were very few patients with abnormal electrophysiology test findings when abnormal noninvasive findings were not detected on the examination. The study indicates that for undiagnosed syncope patients, ambulatory monitor and electrocardiographic results contribute significantly to the diagnostic yield.

Detected Electrophysiology Test Abnormalities among SUO Patients

The most frequent electrophysiology test abnormality found was the atrioventricular conduction system disease, followed by sustained ventricular tachyarrhythmias and sinus node dysfunction. In a minority, supraventricular tachyarrhythmias and fast preexcited atrial fibrillation or hypersensitive carotid sinus syndrome were encountered.

One could argue that in our study protocol we used borderline abnormal electrophysiology test findings.^{11–13,15,16,20,21} However, it was our purpose to investigate the probability of abnormal noninvasive electrocardiographic findings to be associated with even “borderline” aberrations, as previously proposed in the electrophysiology literature, in a selected patient cohort with undiagnosed recurrent syncope. In these patients, indirect evidence for correct diagnosis would be a successful response to pacing or the recording of symp-

tomatic bradycardic episodes with implantable loop recorders.^{26,27}

It has been suggested that the long-term development of permanent complete heart block among asymptomatic or even symptomatic patients with different conduction defects is unusual, except for those cases with electrophysiology test evidence of subnodal block, or very prolonged His-ventricle (HV) interval.^{28–30} This cannot exclude the possibility of milder degrees of AV conduction defects on electrophysiology test among symptomatic patients with different conduction defects to be associated with temporary episodes of symptomatic bradycardia.^{31,32}

In other reports of syncope patients evaluated by electrophysiology testing, the reported incidence of sinus nodal disease was lower than seen in our study.^{6,9,14,15,33} There are no accessible data as far as the incidence of either instantaneous or persisting sinus bradycardia in the long-term recordings in these patient series. The sinus node function assessment was mostly limited to the sinus node recovery time, frequently ignoring other parameters such as the sinoatrial conduction time, the chronotropic response to atropine, or isoproterenol, or the estimation of the intrinsic heart rate. It is known that the detection of sinus nodal disease on electrophysiology test is significantly improved when these parameters are examined in combination. It is also possible that in previous SUO patient series addressed with electrophysiology test, a proportion of symptomatic bradycardia patients who were not included were driven to permanent pacing on a presumptive diagnosis of sinus nodal disease.^{12,16} In our SUO patient series, 141 patients presented with at least borderline documented sinus bradycardia without sinus pauses ≥ 2.5 seconds. It appears that a significant proportion of these patients had electrophysiology test evidence for sinus nodal disease. It has been suggested that even symptomatic bradycardia patients have a benign long-term prognosis as far as survival, regardless of initiation of permanent antibradycardia pacing.³⁴ Permanent pacing in these patients improves symptoms and frequently prevents recurrent syncope. Thus, it is likely for a significant proportion of SUO patients with even borderline sinus bradycardia to be improved clinically with permanent pacing. Such a therapeutic approach may limit the high recurrence syncope rate reported in SUO patients undergoing electrophysiology test.

In prior reports of electrophysiology testing in those with SUO, the most important abnormal electrophysiology test finding was the induction of sustained monomorphic ventricular tachycardia.^{9–11,14–18} Findings such as the induction of polymorphic ventricular tachycardia or ventricular fibrillation were considered nonspecific without any prognostic significance.³⁵ In our SUO patient's series, among the abnormal electrophysiology test findings, we included these two forms of malignant ventricular arrhythmias.³⁶ In our database, independent predictors for the induction of sustained ventricular tachyarrhythmia in SUO patients were the presence of organic heart disease, a low LVEF $\leq 40\%$, and the history of syncope versus presyncope episodes. The electrocardiographic presence of scar tissue, right ventricular repolarization abnormalities, or the presence of nonsustained ventricular tachycardia on ambulatory monitor, were all associated with the induction of malignant ventricular arrhythmias, but were not independent predictors on logistic regression analysis. In the remote SUO patient's series managed with electrophysiology test, the coexistence of an underlying heart disease with left ventricular dysfunction was associated with induction of sustained ventricular tachycardia and an unfavorable long-term prognosis.^{9,15,16,18}

CONCLUSION

Noninvasive electrocardiographic and clinical assessment of undiagnosed syncope patients can help identify those with abnormal electrophysiology study findings suggesting a brady- and/or tachyarrhythmic cause of syncope. A simplified, inexpensive, and readily available, noninvasive diagnostic workup may help identify those patients who may benefit from an electrophysiologically guided arrhythmia treatment.

REFERENCES

- Day SC, Cook EF, Funkenstein H, et al. Evaluation and outcome of emergency room patients with transient loss of consciousness. *Am J Med* 1982;73:15–23.
- Kapoor W. Evaluation and outcome of patients with syncope. *Medicine (Baltimore)* 1990;69:160–175.
- Soteriades ES, Evans JC, Larson MG, et al. Incidence and prognosis of syncope. *N Engl J Med* 2002;347:878–885.
- Savage DD, Corwin L, McGee DL, et al. Epidemiologic features of isolated syncope: The Framingham Study. *Stroke* 1985;11:626–629.
- Kapoor WN, Karpf M, Wieand S, et al. A prospective evaluation and follow up of patients with syncope. *N Engl J Med* 1983;309:197–204.
- Gatzoulis KA, Toutouzas PK. Neurocardiogenic syncope. Aetiology and management. *Drugs* 2001;61:1415–1423.
- Gatzoulis K, Sideris S, Theopistou A, et al. Long-term outcome of patients with recurrent syncope of unknown cause in the absence of organic heart disease and relation to results of baseline tilt table testing. *Am J Cardiol* 2003;92:876–879.
- Kapoor WW, Karpf M, Maher Y, et al. Syncope of unknown origin. The need for a more cost-effective approach to its diagnostic evaluation. *JAMA* 1982;247:2687–2691.
- Krol RB, Morady F, Flaker GC, et al. Electrophysiologic testing in patients with unexplained syncope: Clinical and non-invasive predictors of outcome. *J Am Coll Cardiol* 1987;10:358–363.
- Bass EB, Elson JJ, Fogoros RN, et al. Long-term prognosis of patients undergoing electrophysiologic studies for syncope of unknown origin. *Am J Cardiol* 1988;62:1186–1191.
- Teichman SL, Felder SD, Matos JA, et al. The value of electrophysiologic studies in syncope of undetermined origin: Report of 150 cases. *Am Heart J* 1985;110:469–479.
- Gulamhusein S, Naccarelli GV, Ko PT, et al. Value and limitations of clinical electrophysiologic study in assessment of patients with unexplained syncope. *Am J Med* 1982;73:700–705.
- Kushner JA, Kai WH, Kadish AH, et al. Natural history of patients with unexplained syncope and a non diagnostic electrophysiologic study. *J Am Coll Cardiol* 1989;14:391–396.
- Doherty JK, Pembroke-Rogers D, Grogan EW, et al. Electrophysiologic evaluation and follow-up characteristics of patients with recurrent unexplained syncope and presyncope. *Am J Cardiol* 1985;55:703–708.
- Hess DS, Morady F, Scheinmann MM. Electrophysiologic testing in the evaluation of patients with syncope of undetermined origin. *Am J Cardiol* 1982;50:1309–1315.
- Moazzez F, Peter T, Simonson J, et al. Syncope of unknown origin: Clinical, non-invasive, and electrophysiologic determinant of arrhythmia induction and symptom recurrence during long-term follow-up. *Am Heart J* 1991;121:81–88.
- Sra JS, Anderson AJ, Sheikh, SH, et al. Unexplained syncope evaluated by electrophysiologic studies and head-up tilt testing. *Ann Intern Med* 1991;114:1013–1019.
- Olshansky B, Mazuz M, Martins JB. Significance of inducible tachycardia in patients with syncope of unknown origin. A long-term follow up. *J Am Coll Cardiol* 1985;5:216–223.
- Linzer M, Yang EH, Estes NA III, et al. Diagnosing syncope, Part 1, value of history, physical examination and electrocardiography: Clinical efficacy assessment project of the American College of Physicians. *Ann Intern Med* 1997;126:989–996.
- Linzer M, Yang EH, Mark Estes III NA, et al. Diagnosing syncope, part 2, unexplained syncope. Clinical efficacy assessment project of the American College of Physicians. *Ann Intern Med* 1997;127:76–86.
- Brignole M, Alboni P, Benditt DG, et al. Guidelines on management (diagnosis and treatment) of syncope- update 2004. The task force on syncope, European society of cardiology. *Europace* 2004;6:467–537.
- Krahn AD, Klein GJ, Yee R, et al. Use of an extended monitoring strategy in patients with problematic syncope. *Reveal Investigators. Circulation* 1999;99:406–410.
- Krahn AD, Klein GJ, Fitzpatrick A, et al. Predicting the outcome of patients with unexplained syncope undergoing prolonged monitoring. *Pacing Clin Electrophysiol* 2002;25:37–41.

24. Josephson ME. Clinical Cardiac Electrophysiology: Techniques and Interpretations, 2nd Edition. Philadelphia, Lea and Febinger, 1993.
25. Gatzoulis KA, Mamarelis II, Theopistou AM, et al. Tilt table testing in syncopal patients with sick sinus syndrome. A guide to pathophysiology and management? *Ann Noninvasive Electrocardiol* 1999;4:115-120.
26. 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;104:1261-1267.
27. Brignole M, Menozzi C, Moya A, et al. Mechanism of syncope in patients with bundle branch block and negative electrophysiological test. *Circulation* 2001;104:2045-2050.
28. McAnulty JH, Kaufman S, Murphy E, et al. Survival in patients with intraventricular conduction defects. *Arch Intern Med* 1978;138:30-35.
29. Scheinman MM, Peters RW, Suave MJ, et al. Value of the H-Q interval in patients with bundle branch block and the role of prophylactic permanent pacing. *Am J Cardiol* 1982;50:1316-1322.
30. Dhingra RC, Palileo E, Strasbeg B, et al. Significance of HV interval in 517 patients with chronic bifascicular block. *Circulation* 1981;64:1265-1272.
31. Morady F, Higgins J, Peters RW, et al. Electrophysiologic testing in bundle branch block and unexplained syncope. *Am J Cardiol* 1984;54:587-591.
32. Kaul L, Dev V, Narula J, et al. Evaluation of patients with bundle branch block and "unexplained" syncope: A study based on comprehensive electrophysiologic testing and ajmaline stress. *Pacing Clin Electrophysiol* 1988;11:289-297.
33. Fujimura O, Yee R, Klein GJ, et al. The diagnostic sensitivity of electrophysiologic resting in patients with syncope caused by transient bradycardia. *N Engl J Med* 1989;321:1703-1707.
34. Brunner M, Olschewski M, Geibel A, et al. Long term survival after pacemaker implantation. Prognostic importance of gender and baseline patient characteristics. *Eur Heart J* 2004;25:88-95.
35. Mittal S, Hao SG, Iwai S, et al. Significance of inducible ventricular fibrillation in patients with coronary artery disease and unexplained syncope. *J Am Coll Cardiol* 2001;38:371-376.
36. Buxton AE, Lee KL, Fisher JB, et al. For the Multicenter Unsustained Tachycardia Investigators. A randomized study of the prevention of sudden death in patients with coronary artery disease. *N Engl J Med* 1999;341:1882-1890.