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Stepwise evaluation of syncope: A prospective population-based controlled study

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Abstract

Background: Evaluation of syncope remains often unstructured. The aim of the study was to assess the effectiveness of a standardized protocol designed to improve the diagnosis of syncope.
Methods: Consecutive patients with syncope presenting to the emergency departments of two primary and tertiary care hospitals over a period of 18 months underwent a two-phase evaluation including: 1) noninvasive assessment (phase I); and 2) specialized tests (phase II), if syncope remained unexplained after phase I. During phase II, the evaluation strategy was alternately left to physicians in charge of patients (control), or guided by a standardized protocol relying on cardiac status and frequency of events (intervention). The primary outcomes were the diagnostic yield of each phase, and the impact of the intervention (phase II) measured by multivariable analysis.
Results: Among 1725 patients with syncope, 1579 (92%) entered phase I which permitted to establish a diagnosis in 1061 (67%) of them, including mainly reflex causes and orthostatic hypotension. Five-hundred-eighteen patients (33%) were considered as having unexplained syncope and 363 (70%) entered phase II. A cause for syncope was found in 67 (38%) of 174 patients during intervention periods, compared to 18 (9%) of 189 during control ($p<0.001$). Compared to control periods, intervention permitted diagnosing more cardiac (8%, vs 3%, $p=0.04$) and reflex syncope (25% vs 6%, $p<0.001$), and increased the odds of identifying a cause for syncope by a factor of 4.5 (95% CI: 2.6–8.7, $p<0.001$). Overall, adding the diagnostic yield obtained during phase I and phase II (intervention periods) permitted establishing the cause of syncope in 76% of patients.
Conclusion: Application of a standardized diagnostic protocol in patients with syncope improved the likelihood of identifying a cause for this symptom. Future trials should assess the efficacy of diagnosis-specific therapy.
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Keywords: Syncope; Diagnostic protocol; Controlled study

1. Introduction

Syncope is defined as a sudden and transient loss of consciousness and postural tone followed by spontaneous recovery due to transiently reduced cerebral blood flow. This

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symptom often prompts people to seek medical attention, has a large differential diagnosis and is difficult to investigate [1,2].

When syncope remains unexplained by clinical history, physical examination and baseline electrocardiography (ECG), physicians use a wide range of testing modalities to reach a diagnosis [3]. This work-up is often unstructured and results in an inappropriate use of medical resources and various diagnostic yields [4–6]. Consequently, guidelines have been developed to provide recommendations on the diagnostic evaluation of syncope [3,7,8]. In daily practice, different strategies have been tested with the aim of improving assessment of syncope. These studies, however, had limited generalizability, either because they included patients referred to cardiology clinics [9,10], and/or there was no control group allowing to measure the possible improvement in diagnostic yield [11,12].

We performed a prospective controlled interventional trial in two large primary and tertiary care hospitals to measure the diagnostic impact of a standardized stepwise diagnostic protocol for unselected patients presenting with syncope as a chief complaint.

2. Methods

2.1. Setting

The study was conducted from January 1st 2003 to June 30th 2004 in the emergency departments and the general internal medicine clinics of two primary and tertiary care public hospitals. The Hôpital Cantonal (1100 beds) is the main teaching hospital of the University of Geneva Medical School (Geneva, Switzerland) and the Centre Hospitalier Universitaire Vaudois (800 beds) is the main teaching hospital for the University of Lausanne Medical School (Vaud, Switzerland).

2.2. Patients

Patients ≥18 years of age admitted in the emergency department with a chief complaint of syncope were eligible. Syncope was defined as a sudden and transient loss of consciousness with an inability to maintain postural tone and followed by spontaneous recovery. Patients with vertigo, dizziness, trauma-associated loss of consciousness, alcohol-

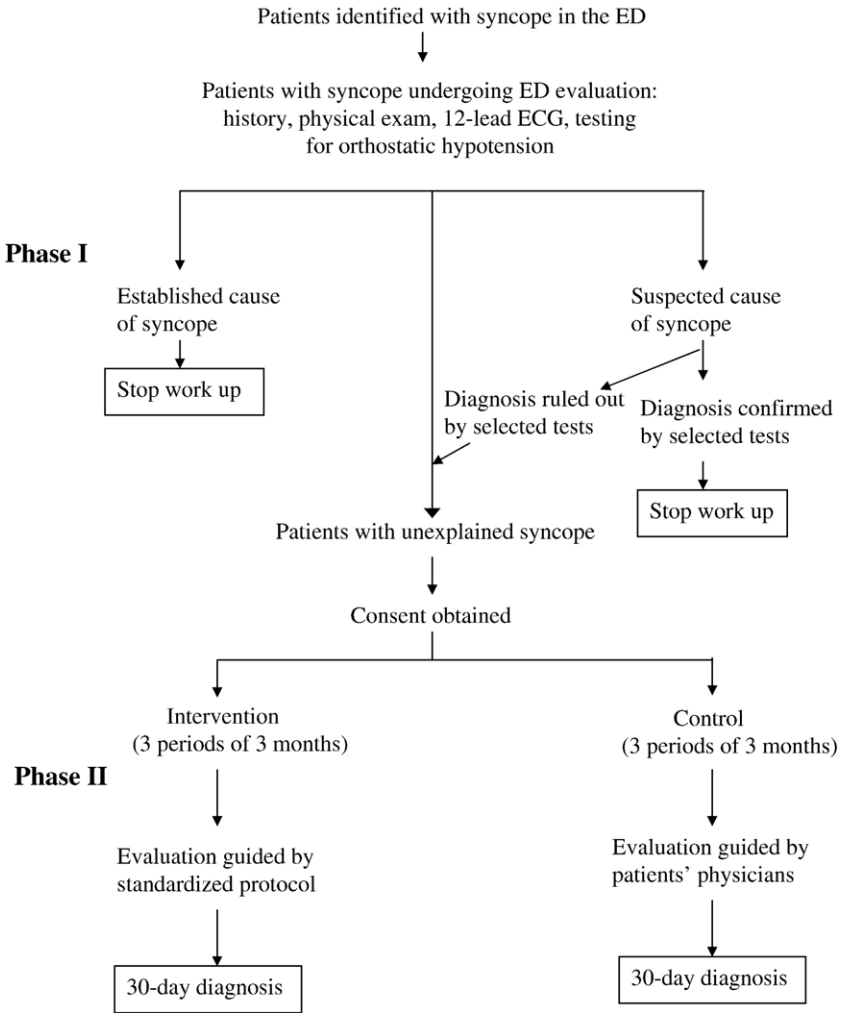

Fig. 1. Study design and inclusion scheme.

associated loss of consciousness, or symptoms suggesting seizure disorders (prolonged recovery, witnessed sustained tonic–clonic movement) were excluded.

2.3. Study design

This was a prospective study including two consecutive phases (Fig. 1). Phase I occurred from time of arrival to discharge from the emergency department. Eligible patients underwent a standardized evaluation including: history, physical and neurological examination; laboratory tests; and 12-lead ECG. This evaluation was performed by emergency department residents using a standardized structured chart. This data form contained variables related to the past and present clinical history (e.g. number of syncope episodes, occurrence and duration of associated symptoms, current medications), and physical examination (including measurements of systolic blood pressure in the supine and upright position). A dedicated research physician at each site supervised daily patients' inclusion and completion of data collection.

Based on explicit predefined criteria (see Appendix), and using data collected during the initial evaluation (chart review), study investigators classified patients as follows: 1) patients in whom a cause of syncope was established based on the initial evaluation; 2) patients in whom a cause of syncope was suspected by the presence of suggestive signs and symptoms during initial evaluation, but which required confirmation by targeted diagnostic procedures (e.g., computed tomography for suspicion of pulmonary embolism); and 3) patients with unexplained syncope. Patients in the second group with negative targeted tests and those in the third group were asked to participate in phase II.

During phase II, evaluation of patients with unexplained syncope was carried out in the general internal medicine inpatient services when patients were hospitalized or in outpatient clinics when patients were discharged from the emergency department. This phase included alternating intervention and control periods of 3-month duration. During the first, third and fifth control periods, the choice of whether and which tests to perform was left to physicians in charge of the patients with no intervention from study investigators. During the second, fourth and sixth intervention periods, evaluation of patients with unexplained syncope was standardized and dictated by a standardized evaluation protocol.

This study was approved by both institutional Ethics Committees. Patients' informed consent was deemed unnecessary for phase I, but written informed consents was mandatory before enrollment into phase II. Patients with dementia, poor health status (e.g. malignancy, severe stroke), or inability to undergo any diagnostic test were excluded from phase II.

2.4. Intervention

During phase II (intervention periods), the diagnostic strategy was standardized. Specifically, patients with a normal ECG and no history of heart disease were evaluated for reflex causes only if syncope was recurrent (≥2 episodes) or severe (car crash and/or major trauma). Those with a first

Table 1
Demographic and clinical characteristics of study patients

	All patients (phase I) (n=1579)	Patients with unexplained syncope (phase II, n=363)		
		Intervention group (n=174)	Control group (n=189)	p value
Age (years)				
Mean (±SD)	61 (±23)	0.5 (±21)	67.1 (±19)	0.002
No ≥75 years (%)	423 (27)	61 (35)	89 (46)	0.002
Male sex (%)	710 (45)	76 (44)	98 (52)	0.1
History of syncope (%)				
Single or rare episode	988 (63)	104 (60)	108 (57)	0.7
Recurrent (≥2) episodes	591 (37)	70 (40)	81 (42)	0.7
Major trauma	281 (18)	35 (20)	47 (24)	0.3
Comorbidities (%)				
Hypertension	518 (33)	61 (35)	72 (38)	0.6
Diabetes	143 (9)	20 (11)	25 (13)	0.7
Coronary artery disease	156 (10)	23 (13)	37 (19)	0.1
Previous myocardial infarction	89 (6)	14 (8)	19 (10)	0.6
Congestive heart failure	91 (6)	18 (10)	21 (11)	0.9
Normal electrocardiography (%)	1011 (64)	81 (47)	92 (49)	0.8
Classification groups				
Heart disease or abnormal ECG		93 (53)	97 (51)	0.7
No heart disease, normal ECG and ≥2 episodes of syncope		60 (34)	72 (41)	0.5
No heart disease, normal ECG and first episode of syncope		21 (12)	20 (11)	0.6
Electrocardiography abnormalities (%)				
Conduction disorder[a]		21 (12)	25 (13)	0.7
Old myocardial infarction		17 (10)	27 (14)	0.2
Rhythm abnormalities[b]		19 (11)	22 (14)	0.9

[a] Bundle branch block, bifascicular block, and types I and II atrioventricular block.
[b] Atrial fibrillation, sinus pause ≥2 and <3 s, sinus bradycardia >35 and ≤45 bpm, multiple premature ventricular beats, pacemaker-dependent rhythm.

uncomplicated episodes were not investigated. Tests for reflex syncope included tilt testing and bilateral supine and upright carotid sinus massage (CSM) [3,7,13]. If negative, patients were asked to undergo psychiatric assessment [14]. In the presence of heart disease and/or abnormal ECG, evaluation included transthoracic echocardiography and 24-hour ECG monitoring. Stress test was performed when coronary artery disease (CAD) was suspected. Patients with positive stress test or established CAD underwent coronary angiography and revascularization when indicated [15]. Electrophysiological studies (EPS) were performed in patients with: 1) previous myocardial infarction with a left ventricular ejection fraction (LVEF) $\leq$40% or regional wall motion abnormalities; 2) nonischemic dilated cardiomyopathy and LVEF $\leq$40%; or 3) ECG (Holter) findings suggestive of sinus node dysfunction or atrioventricular block. Patients with recurrent ($\geq$2 episodes) or severe syncope were also tested for reflex syncope if the cardiac evaluation was negative.

2.5. Procedures and data collection

The decision regarding hospital admission was left to emergency physicians. As a general rule in our institutions, patients with unexplained syncope were admitted to general internal medicine services with cardiologists working as consultants. In outpatient clinics, patients were evaluated by general internists, with attending cardiologists available on request.

During intervention periods (phase II) the evaluation was carried out by study investigators and followed strictly

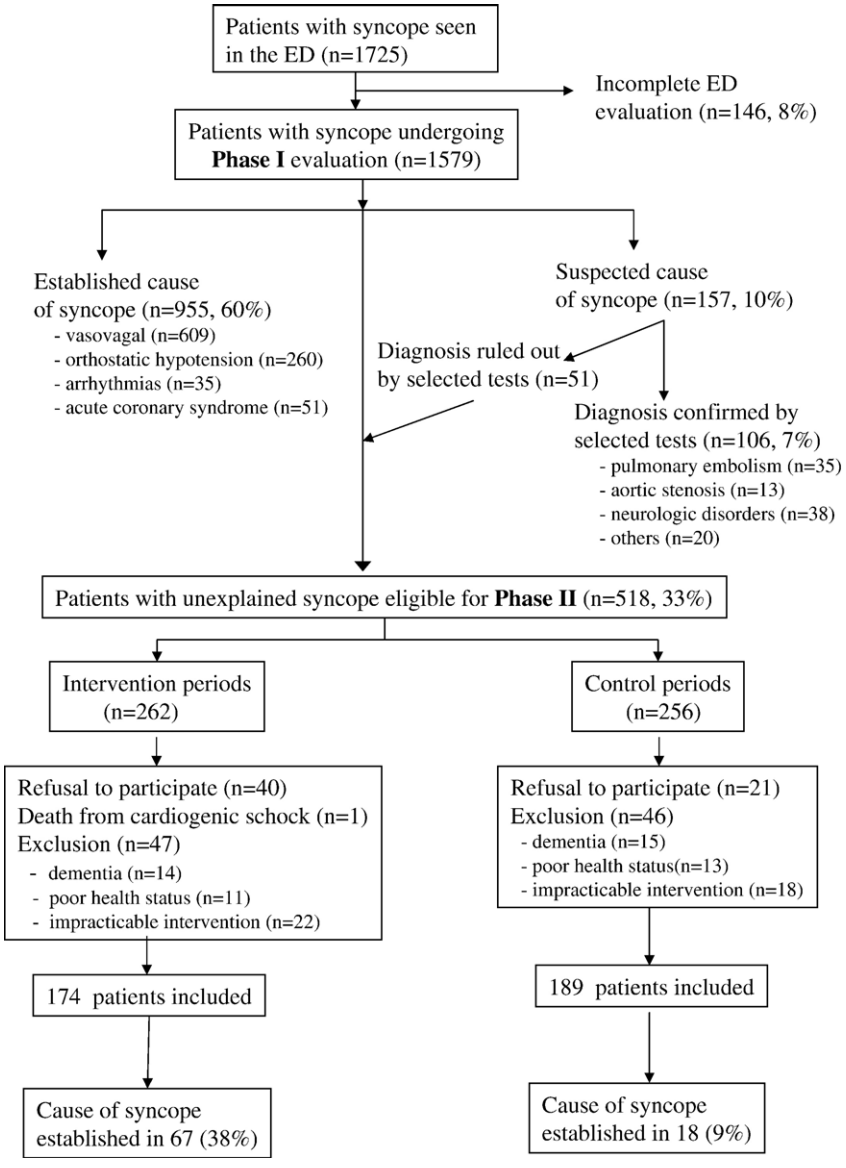

Fig. 2. Results of the stepwise evaluation of patients with syncope.

the sequence of tests dictated by study protocol. Prior consent was obtained from physicians in charge of patient. Selected tests were performed either by one of the investigators or by cardiologists involved in the protocol. During control periods, the choice of whether and which tests to perform was left to physicians in charge of patients. The selected tests were performed by consultant cardiologists unaware of the study protocol. The research physicians collected the results of any tests ordered during both study periods.

In our institution, the duration of physician's rotation in the in- and out-patient clinics is 3 months. Thus, in the majority of study periods patients were assessed by different physicians. As it matched our alternating intervention and control periods (3 months), it minimized physicians' maturation and contamination of intervention over control periods.

2.6. Diagnostic criteria

Presumed diagnoses established by physicians in charge of patients were not accepted. The cause for syncope was attributed at 30 days according to explicit predefined criteria (see Appendix) [3,7]. If a cause was uncertain, the diagnosis was reached by consensus of a committee composed of three internists and two cardiologists. The choice of a diagnosis-specific treatment if the cause of syncope was identified was left to physicians in charge of patients.

2.7. End points and statistical analysis

Primary endpoints of the study included: 1) the diagnostic yield of the evaluation protocol and of individual diagnostic tests; and 2) the number of tests performed. The diagnostic yield was calculated as the number of patients with positive diagnostic tests divided by the number of patients tested.

Variables were compared using Student t test for continuous variables, and χ^2 or Fisher exact test for dichotomous variables. A 2-tailed p value ≤ 0.05 indicated statistical significance. We used multivariable logistic regression analyses to measure the impact of the intervention (phase II), while controlling for covariates such as age, hospital, and time elapsed from beginning of the study. Age and hospital were entered in the model in order to adjust for differences in populations or local medical practices, while the study periods were taken into account to adjust for a possible learning effect.

Kappa statistics were used to measure inter-observer agreement between investigators for classifying syncope as explained or unexplained after phase I. A random sample of 72 cases including 36 in each category was chosen. The analysis was performed by independent investigators blinded to patients' classification and using clinical data collected during phase I.

Statistical testing was performed using SPSS version 9.0 (SPSS Inc., Chicago Ill).

Table 2
Spectrum of diseases causing syncope

	Initial Evaluation (phase I) (n=1579)	Patients with unexplained syncope (phase II)		
		Intervention group (n=174)	Control group (n=189)	p value
Reflex syncope (%)				
Classical vasovagal	476 (30)	0	0	
Situational	133 (8)	0	0	
Tilt-induced	0	37 (21)	7 (4)	
Carotid sinus hypersensitivity	0	11 (6)	4 (2)	
Total	609 (39)	43 [a] (25)	11 (6)	<0.001
Orthostatic hypotension (%)	260 (16)	0	0	
Cardiac arrhythmias (%)				
Conduction disorder	20 (1.3)	6 (3.5)	2 (1)	
Supraventricular tachycardia	6 (0.3)	2 (1)	1 (0.5)	
Ventricular tachycardia	9 (0.6)	6 (3.5)	2 (1)	
Total	35 (2)	14 (8)	5 (3)	0.04
Organic heart disease (%)				
Acute coronary syndrome	51 (3)	0	0	
Pulmonary embolism	35 (2)	0	0	
Aortic stenosis	13 (0.8)	1 (0.5)	1 (0.5)	
Others	0	2 (1)	1 (0.5)	
Total	99 (6)	3 (2)	2 (1)	0.9
Neurologic [b] (%)	38 (2)		0	0
Miscellaneous [c] (%)	20 (1.2)	0	0	
Psychogenic pseudo-syncope (%)	0	7 (4)	0	<0.001
Total explained syncope (%)	1061 (67)	67 (38)	18 (9)	<0.001

[a] Findings are not mutually exclusive (see text).
[b] Includes atypical seizures (n=25), transient ischemic attack (n=8) and intracranial hemorrhage (n=5).
[c] Includes: gastrointestinal hemorrhage (n=13, aortic dissection (n=7).

3. Results

3.1. Phase I

Over the 18-month study period, 1725 (1.2%) of the 144 869 patients seen in the emergency departments of both hospitals had a chief complaint of syncope. Of these, 1579 (92%) had standardized initial evaluation. Patients ($n=146$, 8%) in whom features from emergency evaluation were lacking (e.g. testing for hypotension) were excluded. Table 1 depicts the characteristics of study patients and Fig. 2 the diagnostic yield of each phase of the evaluation.

Initial evaluation (phase I) permitted to establish a diagnosis in 955 patients (60%) and, based on suggestive clinical findings, prompted selected tests in 157 additional patients (10%). Suspected diagnoses were confirmed by targeted tests in 106 of them. Overall, phase I lead to a diagnosis in 1061 patients (67%). Table 2 summarizes the spectrum of diseases causing syncope identified in phase I. These included mainly reflex causes (39%) and hypotension (16%). Life-threatening causes of syncope such as arrhythmias (2%), acute coronary syndrome (3%) or pulmonary embolism (2%) remained rare. After phase I, 518 patients (33%), including 51 with unconfirmed suspected diagnoses, were considered as having unexplained syncope.

Agreement in classification of syncope etiology (explained vs unexplained) performed on a random sample of patients yielded a global kappa of 0.83 ($p<0.001$), representing good inter-physician's agreement.

3.2. Phase II

Among patients ($n=518$) eligible for phase II, 363 (70%) were included: 174 during intervention, and 189 during control periods (Fig. 2). Patients who refused to participate were significantly older (mean age, 72±18 years, $p=0.001$) than those who did (mean age, 64±20 years). The rate of hospitalization for patients with unexplained syncope was 38% during intervention periods and 40% during control.

During intervention (phase II), application of the protocol allowed to establish a cause for syncope in 67 of 174 patients (38%), compared with 18 of the 189 patients (9%, $p<0.001$) during control. Application of the protocol allowed to establish a cause for syncope in respectively 34%, 40% and 39% of patients during the three intervention periods, compared to 7%, 12% and 11% during control ($p<0.01$). Table 2 details the spectrum of diseases causing syncope identified during phase II. Compared with control periods, intervention allowed to diagnose significantly more arrhythmias (8%, vs 3%, $p=0.04$) and reflex syncope (25% vs 6%, $p<0.001$). Fig. 3 depicts each step of the intervention. Overall, 93 patients underwent cardiac evaluation which resulted in a diagnostic yield of 18%. Holter was diagnostic in 6 of 93 patients (6%) and electrophysiological testing in 8 of 21 patients (38%). Hundred and three patients were evaluated for reflex syncope and, if negative, for psychiatric disorders. The diagnostic yield of this sequence was 49%. CSM was diagnostic in 11 patients (11%), seven in the supine and four in the upright position, while tilt testing

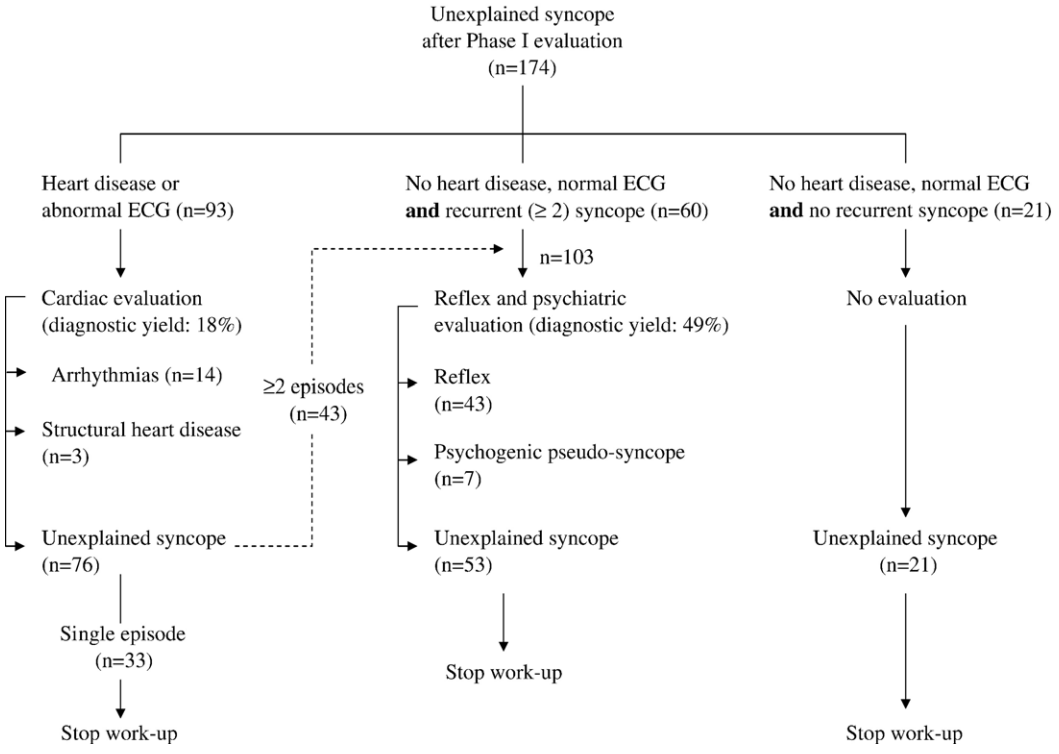

Fig. 3. Phase II. Detailed diagnostic yield of each step of the intervention protocol in patients with negative initial (phase I) evaluation.

was diagnostic in 37 (36%), including 5 with positive CSM. Psychiatric evaluation was completed in 47 among the 60 remaining patients, as 13 refused the questionnaire. It suggested psychiatric disorders in 27 patients (57%), including panic disorder ($n=13$), generalized anxiety ($n=7$), and depressive disorder ($n=7$). Among these, 7 patients were considered as having psychogenic pseudo-syncope because they had spontaneous event (i.e., panic attack, somatization) mimicking the index syncope during tilt testing. Finally, 21 patients with a first episode of syncope and no cardiac disease were not further investigated.

When evaluation was left to physicians in charge of patients (control periods), cardiac syncope was found in 7 patients (4%), including arrhythmias ($n=5$) and structural heart disease ($n=2$). Reflex syncope was diagnosed in 4 of the 48 patients (8%) undergoing CSM, and 7 of the 27 patients (26%) undergoing tilt testing (Table 2). Psychogenic pseudo-syncope was never diagnosed.

3.3. Diagnostic yield

In multivariable analyses, application of the protocol (phase II) increased the odds of identifying a cause for syncope by a factor of 4.5 (95% CI: 2.6–8.7, $p<0.001$) compared to control periods, while age (OR: 0.95, 95% CI: 0.9 to 1.1, $p=0.8$), center (OR: 0.7, 95% CI: 0.4 to 1.2, $p=0.2$), and time (OR: 1.2, 95% CI: 0.9 to 1.3, $p=0.1$) had no significant impact.

Adding the diagnostic yield obtained during phase II intervention periods (38%) to that obtained during phase I (67%) would allow to establish a cause for syncope in 76% of cases.

Table 3
Tests performed during phase II

	Intervention group ($n=174$)	Control group ($n=189$)
Tests indicated by the protocol		
Electrophysiological studies (EPS)	21	8
Tilt test	103	27
Carotid sinus massage (CSM)	90	48
24-hour Holter	93	68
Echocardiography	93	64
Total	400	215
Tests not indicated by the protocol		
Electrophysiological studies (EPS)	0	3
Tilt test	0	13
24-hour Holter	7	30
Echocardiography	7	29
Carotid echo-Doppler	9	26
Head CT or MRI	3	17
Electroencephalography	4	13
Miscellaneous [a]	2	16
Total	32	147
All tests	432	362

[a] Includes cardiac stress test, 24-hour blood pressure monitoring and signal-averaged ECG.

3.4. Number of tests performed

Table 3 details the number of tests performed. During intervention, application of the protocol-based sequence of tests resulted in 400 procedures (2.3 per patient), with 153 patients (88%) having at ≥ 2 procedures, and 66 (38%) at ≥ 3 procedures. Thirty-two tests in addition to the protocol were ordered. During control periods, 215 procedures were performed (1.2 per patient), despite same proportions of patients requiring evaluation for cardiac and/or reflex syncope compared with intervention (Table 1). Hundred and forty-two tests not indicated by the protocol were ordered.

4. Discussion

Our study showed that a standardized evaluation of syncope including noninvasive assessment followed by a protocol-based sequence of tests guided by cardiac status and frequency of events allowed to establish a cause for syncope in 76% of cases. Noninvasive assessment revealed the cause of syncope in two-third of patients, while specialized tests permitted to establish a diagnosis in 38% compared to 9% when the choice of the evaluation strategy was left to physicians in charge of the patients. The protocol-based sequence of tests increased the likelihood of identifying a cause for syncope by a factor of four compared to usual practice, diagnosing significantly more cardiac and reflex syncope.

Our results confirmed that current evaluation strategies for unexplained syncope were often haphazard and resulted in poor diagnostic yield [4–6]. Whereas diagnostic tests usually recommended to diagnose cardiac or reflex syncope were greatly underused, investigations of unproven diagnostic utility (e.g. brain imaging) were frequently overused. In this regard, implementation of standardized diagnostic strategy and/or the development of multidisciplinary syncope unit appear critical to improve patients' management [16]. Our study also evaluated important issues such as the applicability of a diagnostic protocol in a large population of unselected patients. Our protocol was not applicable in 30% of eligible patients, either because of patients' refusal, poor health status, or severe cognitive impairment. These patients were significantly older, suggesting that age could be a limiting factor in our protocol application.

After initial evaluation, a high diagnostic yield was achievable when testing was restricted to selected patients. The diagnostic yield of cardiac evaluation reached 18%, whereas evaluation for reflex causes or pseudo-syncope provided a diagnosis in 49% (Fig. 3). Psychiatric disorders were detected in 57% of patients in whom other causes of syncope were excluded. This prevalence may appear high. However, a relation between psychiatric disorders and syncope was found to be common [17–19]. Although a causal relationship between these entities can be questioned, studies suggest that appropriate care of patients with psychiatric disorders significantly reduced syncope recurrence [20].

Four studies reported the performance of evaluation strategies in patients with syncope [9–12]. Two included patients referred to cardiology clinics and gave priority to cardiovascular tests for patients with suspected or confirmed heart disease and to neurally-mediated tests for the others; a diagnosis was achieved in respectively 70% and 81%. [9,10]. Others assessed the efficacy of a protocol in unselected patients; a diagnosis was established in respectively 78% and 98% of cases [11,12]. Both studies, however, did not include a control group, a limitation addressed by our study design. In addition, the present study, presents a complete pathway to investigate syncope, starting from a noninvasive work-up and ending with specialized tests in targeted patients. We also addressed intentionally pragmatic issues: patients without heart disease and a single episode of syncope (12% of eligible patients) and those with severe comorbid conditions were not investigated.

Our study has limitations. First, because syncope is a nonspecific episodic symptom, the diagnostic gold standard remains documentation of an abnormality occurring during a spontaneous event. Unfortunately, this is rarely possible. Although we used explicit and diagnostic criteria that most experts in the field would accept, none are indisputable [3,7]. Second, we choose the diagnostic yield as main outcome measure. However, establishing the cause of syncope is only a prerequisite before starting therapy aiming at reducing mortality, syncope recurrence or increasing quality of life. Our study, however, was not designed to assess the efficacy of therapy. This should be formally evaluated by randomized controlled trials with patients assigned to standardized diagnosis-specific therapy, and including a long follow-up. Third, our protocol-based sequence of tests might be challenged. For example, diagnostic tests such as implantable loop recorders were not part of the study, although this tool proved to be useful in patients with a high recurrence rate of syncope [21]. Similarly, electrophysiological testing was performed in patients with nonischemic dilated cardiomyopathy, despite its controversial usefulness in this setting [22]. Fourth, our study design raises the danger that the investigations offered to control patients were contaminated by physicians' knowledge of the protocol, with the results of underestimating the true effect of the intervention (contamination bias). Finally, the balance between the costs of diagnostic tests and its benefits on clinical outcome needs to be addressed in a formal cost-utility analysis.

In conclusions, our study showed that a stepwise diagnostic evaluation of syncope including noninvasive clinical assessment followed by sequence of tests considering cardiac status and frequency of events allowed to establish a cause for syncope in 76% of cases. In patients with syncope remaining unexplained after initial assessment, evaluation was suboptimal and use of the protocol increased the likelihood of identifying a cause for this symptom by a factor of four. These results should prompt trials assessing the efficacy of diagnosis-specific therapy.

Appendix A. Procedures and diagnostic criteria

A.1. Phase I [3,7]

The diagnosis of classical vasovagal syncope was accepted when triggering events (fear, pain, instrumentation or prolonged standing) were associated with typical prodromal symptoms. Situational syncope was accepted if symptom occurred during swallowing, defecation, or cough.

Orthostatic hypotension was defined as a symptomatic decrease in systolic blood pressure (SBP) $\geq$20 mm Hg, or a decrease of 10 to 20 mm Hg leading to a SBP < 90 mm Hg. SBP was measured after patients had rested in a supine position for 5 min. Patients were then asked to stand for 5 min with pressure measurements performed immediately and after 1, 3 and 5 min.

Initial ECG findings were considered diagnostic: 1) 3rd degree atrioventricular block; 2) sinus pause >3 s; 3) bradycardia $\leq$35 bpm; 4) sustained ventricular tachycardia (VT); and 5) S-T elevation myocardial infarction.

Pulmonary embolism was diagnosed with a strategy that included D-dimer measurement, lower limb venous ultrasound and helical computed tomography. Severe aortic stenosis was considered as a cause when echocardiography showed a mean aortic gradient =50 mm Hg and a valvular area =0.9 cm^2. Evaluation by staff neurologist and brain imaging was required to accept neurologic disorders (e.g. seizures, transient ischemic attack) as the cause of syncope.

A.2. Phase II [3,7,13,14]

Patients were classified according to cardiac history and ECG status. A cardiac history was considered positive in the presence of angina pectoris or remote myocardial infarction, documented valvular disease or other types of cardiomyopathy. The ECG was classified as abnormal in the presence of at least one of the following abnormalities: 1) atrial fibrillation; 2) sinus pause $\geq$2 and <3 s; 3) sinus bradycardia >35 and $\leq$45 bpm; 4) conduction disorders (e.g., bundle branch block, 2nd degree Mobitz I atrioventricular block, bifascicular block); 5) Q waves suggestive of remote myocardial infarction; and 6) multiple premature ventricular beats. This definition notably excluded first degree atrioventricular block, nonspecific ST-T segments abnormalities, sinus tachycardia and premature atrial contractions. For risk stratification purposes, phase I patients classified as having vasovagal or orthostatic syncope and presenting with an ECG showing a bundle branch block or Q waves suggestive of remote myocardial infarction were considered as having unexplained syncope.

Relevant findings on transthoracic Doppler echocardiography included: left ventricular ejection fraction $\leq$40%, regional wall motion abnormalities, and other cardiomyopathies, such as nonischemic dilated cardiomyopathy, arrhythmogenic right ventricular dysplasia, or hypertrophic obstructive cardiomyopathy.

We considered 24-hour ECG (Holter) monitoring to be diagnostic of syncope in the presence of serious arrhythmias with simultaneous syncope or near-syncope. Serious arrhythmias included: 1) sinus pause ≥ 3 s; 2) sinus bradycardia ≤ 35 bpm; 3) atrial fibrillation with slow ventricular response (RR interval ≥ 3 s); 4) supraventricular tachycardia (SVT) ≥ 30 s at ≥ 180 beats/min or associated with hypotension; 5) 2nd (Mobitz II) and 3rd degree atrioventricular block; and 6) sustained (≥ 30 s) ventricular tachycardia (VT).

EPS were considered diagnostic in the following cases: 1) prolonged corrected sinus node recovery time (≥ 1000 ms) as indicative of sinus node disease; 2) prolonged baseline H–V interval (≥ 100 ms), or second- or third-degree His–Purkinje block, as observed during incremental atrial pacing or elicited by intravenous administration of ajmaline or procainamide; 4) rapid supraventricular tachycardia associated with hypotension; and 5) sustained monomorphic VT.

Right and left CSM for up to 5 s was performed in the supine and upright position. Carotid sinus hypersensitivity was considered to be the cause of syncope when symptoms were associated with cardiac asystole lasting ≥ 3 s and/or a decrease in systolic blood pressure ≥ 50 mm Hg. Contraindications to CSM included: transient ischemic attack or stroke within the past 3 months or the presence of carotid murmur.

Upright tilt testing was performed on a foot-plate electrically motorized table with continuous ECG and noninvasive beat-to-beat finger arterial blood pressure measurements. Patients were tilted at 70° for 30 min, followed by a sublingual nitroglycerin challenge for 10 min if passive phase was negative. A diagnostic test was defined as syncope or near syncope in association with hypotension and/or bradycardia matching the clinical event that caused the test to be stopped.

Evaluation for psychiatric disorders was performed using the Primary Evaluation of Mental Disorders, a validated screening questionnaire diagnosing specific psychiatric disorders using criteria from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). The diagnosis of psychogenic pseudo-syncope was accepted if, during tilt testing, patients diagnosed with psychiatric disorders had symptoms reproducing the index syncope but no hypotension and/or bradycardia.

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