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Département de Médecine

Service de Cardiologie

**Stepwise evaluation of unexplained syncope
in a large ambulatory population**

THÈSE

préparée sous la direction du Docteur Etienne Pruvot,

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RAPPORT DE SYNTHÈSE

Évaluation standardisée de la prise en charge de la syncope récidivante d'origine indéterminée

La syncope est un symptôme clinique fréquent mais son origine demeure indéterminée jusque dans 60% des cas de patients admis dans un centre d'urgences. Le développement de consultations spécialisées de la syncope a considérablement modifié l'évaluation des patients avec une syncope inexpliquée en les orientant vers des stratégies d'investigations non-invasives, tels que le tilt-test, le massage du sinus carotidien et le test d'hyperventilation. Cependant, il existe peu de données dans la littérature concernant dans la performance diagnostique réelle de ces tests fonctionnels.

Notre travail de recherche porte sur l'analyse des données des 939 premiers patients adressés à la consultation ambulatoire de la syncope du CHUV pour l'investigation d'une syncope d'origine indéterminée. L'objectif de notre travail de thèse est 1) d'évaluer la performance diagnostique de l'algorithme de prise en charge standardisé et de ses différents tests pratiqués dans le cadre de notre consultation et 2) de déterminer les caractéristiques cliniques communes des patients avec un diagnostic final de syncope d'origine rythmique ou vaso-vagale.

Notre travail de thèse démontre qu'un algorithme de prise en charge standardisé basé sur des tests non-invasifs permet de déterminer 2/3 des causes de syncope initialement d'origine indéterminée. Par ailleurs, notre travail montre que des étiologies bénignes, telles que la syncope d'origine vaso-vagale ou psychogène, représentent la moitié des causes syncopales alors que les arythmies cardiaques demeurent peu fréquentes. Finalement, notre travail démontre que l'absence de symptomatologie prodromique, en particulier chez les patients âgés avec une limitation fonctionnelle ou un allongement de la durée de l'onde P à l'électrocardiogramme, suggère une syncope d'origine rythmique. Ce travail de thèse contribuera à optimiser notre algorithme de prise en charge standardisée de la syncope d'origine indéterminée et ouvre de nouvelles perspectives de recherche dans le développement de modèles basés sur des facteurs cliniques permettant de prédire les principales causes syncopales.

Stepwise Evaluation of Unexplained Syncope in a Large Ambulatory Population

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Background: Up to 60% of syncopal episodes remain unexplained. We report the results of a standardized, stepwise evaluation of patients referred to an ambulatory clinic for unexplained syncope.

Methods and Results: We studied 939 consecutive patients referred for unexplained syncope, who underwent a standardized evaluation, including history, physical examination, electrocardiogram, head-up tilt testing (HUTT), carotid sinus massage (CSM) and hyperventilation testing (HYV). Echocardiogram and stress test were performed when underlying heart disease was initially suspected. Electrophysiological study (EPS) and implantable loop recorder (ILR) were used only in patients with underlying structural heart disease or major unexplained syncope. We identified a cause of syncope in 66% of patients, including 27% vasovagal, 14% psychogenic, 6% arrhythmias, and 6% hypotension. Noninvasive testing identified 92% and invasive testing an additional 8% of the causes. HUTT yielded 38%, CSM 28%, HYV 49%, EPS 22%, and ILR 56% of diagnoses. On average, patients with arrhythmic causes were older, had a lower functional capacity, longer P-wave duration, and presented with fewer prodromes than patients with vasovagal or psychogenic syncope.

Conclusions: A standardized stepwise evaluation emphasizing noninvasive tests yielded 2/3 of causes in patients referred to an ambulatory clinic for unexplained syncope. Neurally mediated and psychogenic mechanisms were behind >50% of episodes, while cardiac arrhythmias were uncommon. Sudden syncope, particularly in older patients with functional limitations or a prolonged P-wave, suggests an arrhythmic cause. (PACE 2009; 32:S202–S206)

unexplained syncope, standardized stepwise evaluation, diagnostic testing, psychogenic pseudo-syncope, P-wave duration

Introduction

Syncope is a common disorder, which remains unexplained in up to 60% of patients referred to an emergency department.^{1,2} The investigation of unexplained syncope remains challenging. Some investigators have recently shown the superior performance of simple investigations in patients with syncope evaluated in emergency departments.^{1–3} However, little is known of the diagnostic performance of dedicated functional tests. We have shown, in a recent study of the first 317 patients referred to our ambulatory syncope clinic, that the investigation of unexplained syncope, using a standardized stepwise patient evaluation, yielded a diagnosis in 81% of patients, and that compared with patients whose syncope was neurally mediated (reflex). Those whose cause of syncope was an arrhythmia were older, had fewer prodromes, and had a longer P-wave duration.⁴ This study, which includes the first 900 ambulatory patients referred to our syncope clinic, (1) ex-

amined the diagnostic performance of a standardized stepwise investigation of unexplained syncope, and (2) compared the clinical characteristics of patients with arrhythmic versus reflex causes of syncope.

Patient Population and Methods

This prospective single center study was conducted in the ambulatory syncope clinic of Lausanne University Hospital, in Switzerland. Patients were referred for investigation of unexplained syncope or presyncope. The former was defined as a transient and self-limited loss of consciousness with inability to maintain postural tone and the latter as a near syncopal event.⁵ Patients with disease manifestations consistent with other disorders, such as seizure, vertigo, or coma, were excluded. The final population comprised 939 consecutive ambulatory patients referred to our syncope clinic for evaluation and management of unexplained syncope between December 1999 and October 2007.

Figure 1 illustrates our standardized stepwise patient evaluation. They underwent a baseline head-up tilt test (HUTT), followed by carotid sinus massage (CSM) in the supine and upright positions, and HUTT with intravenous adenosine and

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STEPWISE EVALUATION OF UNEXPLAINED SYNCOPE

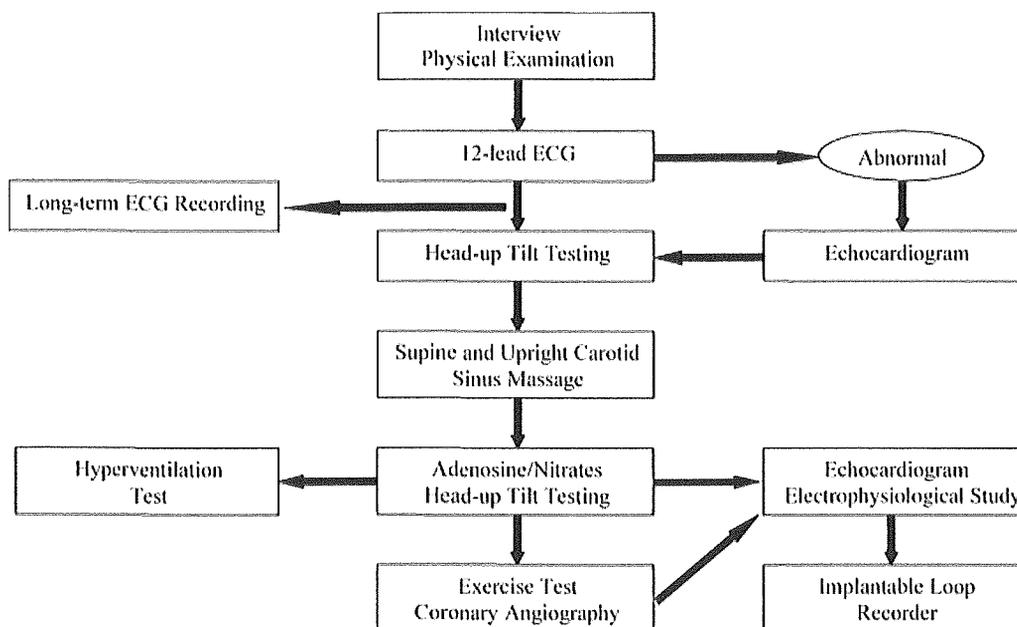


Figure 1. Standardized stepwise patient evaluation.

sublingual nitrates challenges. A hyperventilation test (HYV) was performed only in patients presenting with phobic, anxious, or depressive manifestations. Structural heart disease was ruled out on the basis of patient's history, physical examination and 12-lead electrocardiogram (ECG). Exercise testing and echocardiogram were performed when an underlying cardiac disorder was suspected. An electrophysiological study (EPS) was performed in patients presenting with an underlying cardiac disease or in patients whose initial noninvasive evaluation was negative, and who required further investigations. An implantable loop recorder (ILR; Reveal® Medtronic Inc., Minneapolis, MN, USA) was proposed to patients who had undergone a negative evaluation and suffered syncope-related complications. Importantly, a positive test was classified as diagnostic when the test-induced symptoms reproduced the clinical presentation; otherwise, the test was considered abnormal, though nondiagnostic.

The initial interview focused systematically on the presence and duration of prodromes and recovery manifestations, including nausea, diaphoresis, blurred vision, paresthesia, vertigo, palpitation, anxiety, tongue biting, and confusion. Syncope-related trauma was classified as major, when associated with a bone fracture, head or internal organ injury, or a car accident; otherwise, it was classified as minor. The P-wave duration was measured before any investigation to avoid a methodological bias, by averaging three consecutive cycles from leads II and AV_L.

The causes of syncope were classified according to the guidelines of the European Society of Cardiology.⁵ The ultimate cause of syncope was assigned by one of the investigators (E.P.) at the end of the stepwise evaluation. For statistical analyses, the ultimate cause of syncope was classified as (1) arrhythmic, including bradyarrhythmias due to atrioventricular block or sick sinus syndrome, supra- or ventricular tachyarrhythmias, and cardioinhibitory carotid sinus syndrome (CSS); (2) Vasovagal or psychogenic, including tilt-induced syncope and psychogenic pseudo-syncope; (3) Hypotensive, including orthostatic hypotension and vasodepressive CSS; (4) Miscellaneous, including situational syncope and neurological disorders; and (5) unexplained, when none of the above was applicable.

Statistical Analysis

Continuous variables were compared using Student's *t*-test. Categorical variables were compared using the χ^2 test. A P value <0.01 was considered statistically significant.

Results

Clinical Characteristics and Causes of Syncope

During the study period, 939 consecutive outpatients were enrolled. Table I shows the baseline clinical characteristics of the study population. Their mean age was 52 years, and mean number of syncopal episodes was 10, with 13% of patients referred for presyncope only. Syncope was the cause

Table I.

Baseline Characteristics of the Study Population

Age (y)	52 ± 21
Women	461 (49)
Hypertension	261 (28)
Hypercholesterolemia	257 (27)
Diabetes mellitus	71 (8)
Active smoker	216 (23)
Ischemic heart disease	77 (8)
Syncope frequency	10 ± 35
Presyncope only	120 (13)
Years elapsed since first episode	5 ± 8
Minor trauma	251 (27)
Major trauma	105 (11)
Hospitalization	497 (53)
Car accident	60 (6)
Driving license withdrawal	33 (3.5)

Values are means ± standard deviation or numbers (%) of observations.

of hospitalization in 53%, car accident in 6%, and driving license withdrawal in 3.5% of the patients. Table II shows the final causes of syncope, diagnosed after the standardized stepwise evaluation. Overall, a final diagnosis was established in 66%, while syncope remained unexplained in 34%. Importantly, arrhythmic causes were uncommon (6%), while neurally mediated syncope was diagnosed in 42%, including tilt-induced syncope in

Table II.

Final Causes of Syncope

	n (%)
Neurally mediated	396 (42)
Vasovagal (tilt-induced)	258 (27)
Situational	15 (2)
Vasodilatative carotid sinus syndrome	27 (3)
Cardio-inhibitory carotid sinus syndrome	96 (10)
Psychogenic pseudosyncope	129 (14)
Orthostatic hypotension	31 (3)
Cardiac arrhythmias	52 (6)
Tachyarrhythmias	35 (4)
Supraventricular tachycardia	19 (2)
Ventricular tachycardia	16 (2)
Bradyarrhythmias	17 (2)
Sick sinus syndrome	9 (1)
AV block	8 (1)
Miscellaneous	12 (1)
Unexplained	319 (34)

27%. Cardioinhibitory CSS was diagnosed in 96 patients (10%) and psychogenic pseudo-syncope in 131 (14%), with spontaneous hysterical conversion or panic attacks in 22% and triggered by HYV in 78% of these 131 patients. The distribution of final diagnoses according to age <70 years (n = 241) versus ≥70 years (n = 78) and men (n = 168) versus women (n = 151) was analyzed. Syncope remained unexplained in 1/3 of all cases, independent of age (34% vs 33%, respectively) and gender (35% vs 33%, respectively). In patients <70 years of age, vasovagal and psychogenic causes combined were significantly more prevalent (49%) and arrhythmic and hypotensive causes less prevalent (10% and 4%, respectively) than in patients ≥70 years of age (17%, 34%, and 13%, respectively, P < 0.01).

Diagnostic Yield of Individual Tests

Table III shows the diagnostic yield of individual tests. Since the standardized evaluation was applied sequentially, not all tests were systematically performed. Among noninvasive tests, HYV yielded the best diagnostic performance (49%) followed by HUTT (38%), CSM (28%), and long-term ECG recordings (28%). HYV and long-term ECG recordings were used selectively, in patients with psychiatric manifestations and ≥1 episode of syncope/week. Among invasive tests, the diagnostic performance of EPS was poor (22%) despite a strict patient selection. In contrast, ILR yielded a diagnosis in 30 of 54 patients (56%), who presented with syncope-related complications and a negative noninvasive diagnostic evaluation. An arrhythmic cause was confirmed in 20% of patients, including sick sinus syndrome in 11%, and supraventricular tachyarrhythmias in 9%. A hypotensive cause was suspected in 17% on the basis of the ILR recorded heart rate

Table III.

Diagnostic Yield of Individual Tests

Electrocardiogram	10/939 (1)
Orthostatic blood pressure test	37/870 (4)
Head-up tilt test	317/844 (38)
Carotid sinus massage	200/714 (28)
Hyperventilation test	140/284 (49)
Long-term electrocardiogram	16/58 (28)
Echocardiogram	10/143 (7)
Exercise test	8/70 (12)
Electrophysiological study	35/156 (22)
Implantable loop-recorder	30/54 (56)

Values are numbers of diagnostic tests/number of tests performed (% yield).

STEPWISE EVALUATION OF UNEXPLAINED SYNCOPE

Table IV.

Baseline Clinical Characteristics and Distribution of Statistically* Significant Prodromes According to Causes of Syncope

	Arrhythmia n = 148	VV/Psy n = 387	Hypotension n = 58	Miscellaneous n = 27	Unexplained n = 319	Total n = 939
Age (year)	67 ± 11	43 ± 16	64 ± 15	55 ± 14	53 ± 21	52 ± 21
Women	58 (39)	224 (58)	20 (34)	8 (30)	151 (47)	461 (49)
Hypertension	65 (44)	56 (15)	26 (44)	9 (33)	105 (33)	261 (28)
Ischemic heart disease	29 (20)	13 (3)	10 (17)	1 (4)	24 (8)	77 (8)
NYHA class ≥ II	44 (30)	14 (4)	19 (32)	6 (22)	31 (10)	114 (12)
P-wave duration (ms)	112 ± 16	98 ± 12	113 ± 16	108 ± 12	103 ± 16	103 ± 15
QRS duration (ms)	97 ± 15	88 ± 11	95 ± 16	92 ± 11	92 ± 15	91 ± 14
No prodrome	69 (47)	25 (6)	15 (25)	5 (19)	135 (42)	249 (27)
Nausea/vomiting	19 (13)	129 (33)	6 (10)	3 (11)	36 (11)	193 (21)
Diaphoresis	42 (28)	316 (82)	19 (33)	11 (41)	104 (33)	492 (52)
Blurred vision	26 (18)	191 (49)	27 (46)	8 (30)	82 (25)	334 (36)
Paresthesia	2 (1)	85 (22)	2 (3)	1 (4)	15 (5)	105 (11)
Vertigo/dizziness	54 (36)	235 (61)	28 (47)	17 (63)	92 (29)	426 (45)
Palpitations	9 (6)	82 (21)	4 (7)	4 (15)	29 (9)	128 (14)

Mean ± standard deviation, unmarked data are n (%).

*P < 0.01 in the comparison of Rhythm, VV/Psy and other three categories pooled.

VV/Psy = pooled vasovagal syncope and psychogenic pseudo-syncope; NYHA = New York Heart Association.

during clinical events and confirmed by selected tests. The remaining causes of syncope included vasovagal (9%), epilepsy (6%), situational (2%), and psychogenic (2%). It is noteworthy that the three patients diagnosed with epilepsy had a negative neurological evaluation, including electroencephalogram before ILR implantation. Importantly, 92% of the final causes of syncope were identified using noninvasive tests, while invasive test yielded diagnoses in an additional 8% of patients.

Clinical Characteristics and Distribution of Prodromes According to the Final Diagnosis

Table IV shows the baseline clinical characteristics and distribution of statistically significant prodromes according to causes of syncope. Compared with vasovagal syncope and psychogenic pseudo-syncope, patients with arrhythmic causes were older, had a lower functional capacity, a higher prevalence of hypertension and ischemic heart disease, a longer P-wave but similar QRS duration, and suffered more often from sudden syncope. Prodromes, such as nausea, diaphoresis, paresthesia, palpitations, and anxiety, were significantly more common in patients with vasovagal syncope and psychogenic pseudo-syncope than in patients with arrhythmic causes or other categories.

Discussion

Distribution of Causes of Syncope

The application of a standardized stepwise diagnostic evaluation identified a cause of syncope in 66% of patients. The distribution of final diagnoses is concordant with previous reports.⁶ Vasovagal (HUTT-induced) syncope was the most prevalent cause, while cardiac arrhythmias were uncommon. The higher prevalence of vasovagal syncope in younger and arrhythmic causes in older patients is concordant with previous studies.^{4,7,8} On the other hand, the 14% prevalence of psychogenic pseudo-syncope in our study is at variance with other studies, which reported <6% psychogenic origins of syncope.^{2,6} Others, however, have underestimated its true prevalence, which might be as high as 24% in a population presenting with unexplained syncope.^{9,10} Patients with psychogenic pseudo-syncope were rather young, women, and frequently suffered from presyncope, suggesting that psychiatric manifestations should be routinely sought in patients with unexplained syncope, and that psychogenic pseudo-syncope is not only a diagnosis of exclusion but can be firmly established. Following the standardized diagnostic evaluation, 1/3 of our patients remained without an explained cause. They shared some common characteristics with arrhythmic causes, such as a high prevalence of abrupt onset (43%) compared with other categories. In

54 of these patients an IRL was implanted and, surprisingly, multiple etiologies were finally established.

Diagnostic Yield of a Standardized Stepwise Evaluation

The diagnostic approach of patients with unexplained syncope is a clinical challenge. Despite multiple investigations, syncope remains unexplained in up to approximately 50% of cases.^{1,2} The superiority of standardized investigation strategies of unexplained syncope over usual practice has been recently shown in patients with syncope admitted to emergency departments.¹⁻³ The present study suggests that a standardized stepwise diagnostic evaluation establishes an etiology in 2/3 of patients referred for unexplained syncope to an outpatient clinic, a proportion concordant with other studies,^{2,4} and highlights the use of noninvasive tests for the investigation of unexplained recurrent syncope. In selected patients, however, ILR established a diagnosis in over 50% of recipients, confirming its incremental benefit in patients with unexplained syncope after a negative standardized diagnostic evaluation.

Clinical Characteristics and Distribution of Prodromes According to Causes of Syncope

Alboni et al. and Sheldon et al. recently observed an older age and fewer prodromes in patients with carotid sinus hypersensitivity or cardiac syncope compared with patients who present with other forms of neurally mediated syncope.^{7,8} Our study extends these observations to other causes of cardiac syncope. Patients with arrhythmic events were older, had a higher prevalence of hypertension and ischemic heart disease, and re-

ported fewer prodromes. Their functional capacity was lower and P-wave duration longer than in patients with reflex syncope. This study of >900 patients confirms our previous observations⁴ that clinical characteristics, syncope presentation, and P-wave duration may be used to identify a subgroup of patients more likely to suffer from arrhythmic syncope.

Limitations of the Study

The first limitation of our study was the absence of objective criteria for the diagnosis of psychogenic pseudo-syncope, which may have overestimated the true prevalence of this disorder. Final diagnoses, however, were established when the test-induced symptoms strictly matched the clinical event. Second, Krahn et al. recently reported a higher cost-effectiveness of the ILR over conventional testing in a similar design.¹¹ The diagnostic yield of conventional testing was surprisingly low (20%) compared with the present study (66%). The effectiveness of our stepwise evaluation needs to be addressed and compared with other investigation strategies in terms of recurrence and cost.

Conclusions

A standardized stepwise diagnostic evaluation focusing on noninvasive tests identified two-thirds of causes in patients referred to an ambulatory clinic for unexplained syncope. Vasovagal syncope and psychogenic pseudo-syncope accounted for >50% of all causes, while cardiac arrhythmias were uncommon. Sudden syncope, especially in older patients with functional limitations or a prolonged P-wave duration, suggested an arrhythmic cause.

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