



# The application of a standardized strategy of evaluation in patients with syncope referred to three syncope units

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**Background** The appropriate diagnostic work-up of patients with syncope is not well defined. We applied the guidelines of Italian ‘Associazione Nazionale Medici Cardiologi Ospedalieri’ to a group of consecutive patients with syncope referred to three Syncope Units. The aim of the study was to evaluate the applicability of those guidelines in the ‘real world’ and their impact on the use of the tests.

**Methods** We evaluated 308 consecutive patients with syncope (mean age  $61 \pm 20$  years; median of three syncopal episodes per patient). The hierarchy and appropriateness of diagnostic tests and the definitions of the final diagnosis followed standardized predefined criteria. In brief, all patients underwent initial evaluation consisting of history, physical examination, supine and upright blood pressure measurement and standard electrocardiogram (ECG) (only in patients >45 years or with history of heart disease). Any subsequent investigations were based on the findings of the initial evaluation. Priority was given to cardiological tests (prolonged ECG monitoring, exercise test, electrophysiological study), or to neurally mediated

tests (carotid sinus massage, tilt test, ATP test), or to neuro-psychiatric tests, as appropriate.

**Findings** The initial evaluation alone was diagnostic in 72 patients (23%). One further test was necessary for diagnosis in 65 patients (21%),  $\geq 2$  tests in 64 (21%) and  $\geq 3$  tests in 50 (16%). The diagnostic yield was 10% for ECG, 3% for echocardiogram, 16% for Holter, 5% for exercise test, 27% for electrophysiological study, 57% for carotid sinus massage, 52% for tilt testing and 15% for ATP test. At the end of the work-up the mechanism of syncope remained unexplained in 57 patients (18%).

**Conclusions** When standardized criteria based on the appropriateness of indications are used, few simple tests are usually needed for diagnosis of syncope.

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**Key Words:** syncope, diagnosis, ambulatory ECG exercise test, electrophysiological study carotid sinus massage, tilt test, ATP test.

## Introduction

In clinical practice, patients with syncope undergo several examinations, very often with negative results. A major issue about tests for evaluating the aetiology of syncope is that it is not possible to measure their diagnostic value because there is no reference or gold

standard for most of the tests employed in this condition. In order to try to overcome this problem, specific guidelines have been developed by scientific societies to provide generally accepted diagnostic standardized criteria. In this study we sought to apply to a group of patients with syncope referred to three syncope units the diagnostic flow chart proposed by the Italian ‘Associazione Nazionale Medici Cardiologi Ospedalieri’ (ANMCO) in 1995<sup>[1]</sup>. Furthermore, since that diagnostic strategy was largely accepted by the Guidelines on Syncope of the European Society of Cardiology in 2001<sup>[2]</sup> we sought to determine whether the result could also be extrapolated to those latter guidelines.

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## Methods

We analysed the records of 308 consecutive patients affected by syncope referred to three syncope units (those of the hospitals of Lavagna, Reggio Emilia and Cento, Italy) from August 1998 to July 1999. Patients were recruited if they had a syncopal episode in the previous 2 months and were >18 years. Syncope was defined as transient, self-limited loss of consciousness, usually leading to falling. Patients affected by non-syncopal events, namely other disorders with impairment or loss of consciousness resembling syncope (i.e. transient ischemic attacks, metabolic disorders, epilepsy, intoxication, cataplexy, drop attacks, somatization disorders) that could be identified during the initial evaluation were not considered for evaluation.

### *Diagnostic flow-chart*

The diagnostic protocol used (Fig. 1) was derived from that of the guidelines of the Italian 'Associazione Nazionale Medici Cardiologi Ospedalieri'<sup>[1]</sup> with few changes. It has been previously described<sup>[3]</sup>. In brief, it consist of two steps.

*Step 1: Initial evaluation.* The initial evaluation consisted of history, physical examination, supine and upright blood pressure measurement and standard electrocardiogram (ECG) (the latter only in patients >45 years or with history of heart disease). This initial evaluation was considered diagnostic of the cause of syncope, and no other investigation was deemed necessary, in the following situations: (1) Vasovagal syncope, diagnosed if precipitating events such as fear, severe pain, emotional distress, instrumentation or prolonged standing were associated with typical prodromal symptoms. (2) Situational syncope, diagnosed if syncope occurred during or immediately after micturition, defaecation, coughing or swallowing. (3) Orthostatic syncope, diagnosed when documented orthostatic hypotension was associated with syncope or pre-syncope. (4) Syncope due to cardiac ischaemia, diagnosed when symptoms were present with ECG evidence of acute myocardial ischaemia. (5) Syncope due to cardiac arrhythmia, diagnosed by ECG when there was: (a) sinus bradycardia <40 beats/min or repetitive sinoatrial blocks or sinus pauses >3 s, (b) 2nd degree Mobitz II or 3rd degree atrioventricular block, (c) alternating left and right bundle-branch block, (d) rapid paroxysmal supra-ventricular tachycardia or ventricular tachycardia, (e) pacemaker malfunction with cardiac pauses.

*Step 2: Laboratory investigations.* If the cause of syncope remained unexplained after the initial evaluation, subsequent tests were based on the presence or absence of structural heart disease or abnormal ECG. When heart disease was suspected or ascertained, or ECG was abnormal, priority was given to cardiovascular tests; otherwise priority was given to neurally mediated tests.

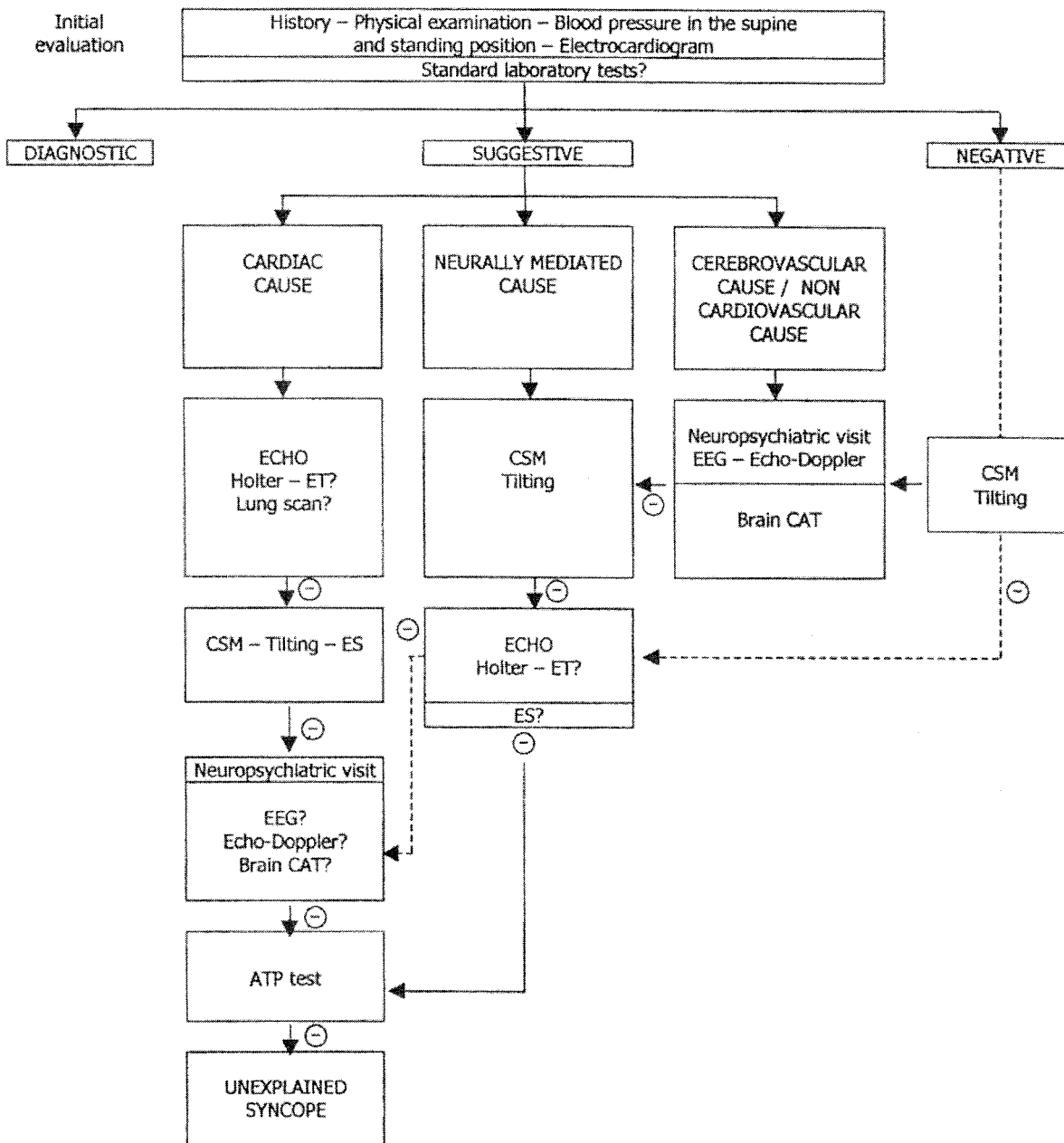
The appropriateness of the tests followed predefined criteria. Echocardiography was defined as appropriate when cardiac disease was suspected. Prolonged ECG monitoring was appropriate in the presence of palpitations closely related to syncope or in patients with suspected arrhythmia. Exercise testing was appropriate in patients with syncope during or shortly after exertion or when myocardial ischaemia was suspected. Electrophysiological study was appropriate when non invasive tests, though inconclusive, suggested a possible cardiac cause (i.e. bundle branch block or nonsustained ventricular tachycardia, etc.) or when severe heart disease (i.e. heart failure, systolic ventricular dysfunction, etc.) was present. When structural heart disease was absent, carotid sinus massage was appropriate as the first test in patients >40 years. Tilt testing was appropriate as the first test in patients <40 years and, after a negative carotid sinus massage, in patients >40 years. ATP (adenosine triphosphate) testing was appropriate when carotid sinus massage and tilt testing were negative. The investigation was considered diagnostic, and the diagnosis was of: (1) Mechanical cardiac syncope, in the presence of severe valvular stenosis or other flow obstructions; (2) Arrhythmic syncope (diagnosed by prolonged ECG monitoring) when there was: a correlation between syncope and an ECG abnormality (brady- or tachyarrhythmia); or, in the absence of a clear correlation, when ventricular pauses >3 s, 2nd degree Mobitz II or or 3rd degree atrioventricular block or rapid paroxysmal atrial or ventricular tachycardia were detected. (3) Arrhythmic syncope (diagnosed by electrophysiological study) when there was: sinus node recovery time >3 s, baseline HV interval  $\geq$  100 ms or appearance of infra-Hisian 2nd or 3rd degree atrioventricular block during atrial pacing or after ajmaline administration; induction of syncopal or hypotensive atrial or ventricular tachyarrhythmias. (4) Carotid sinus syncope, when carotid sinus massage, performed in both the supine and upright positions, induced syncope in the presence of bradycardia and/or hypotension. (5) Tilt-induced syncope, when the loss of consciousness was induced during tilt testing in the presence of bradycardia and/or hypotension. (6) Adenosine-sensitive syncope, when a bolus of 20 mg of ATP induced a cardiac pause >6 s.

On completion of the laboratory evaluation, if no cause of syncope could be determined, the work-up was re-appraised. If unexplored clues to possible neurological or psychiatric disease came to light, further neuropsychiatric assessment was made.

## Results

### *Patients' characteristics*

The 308 consecutive patients with syncope, 164 of whom were males, had a mean age of  $61 \pm 20$  years; they had had a median of three syncopal episodes (interquartile



**Figure 1** Algorithm for diagnostic approach to syncope proposed by the Italian 'Associazione Nazionale Medici Cardiologi Ospedalieri'<sup>[1]</sup>, modified with introduction of the adenosine triphosphate (ATP) test. Circled minus sign = not a diagnostic examination; ? = indication to be evaluated case by case; CAT = computed axial tomography; CSM = carotid sinus massage; ECHO = echocardiogram; EEG = electroencephalogram; ES = electrophysiologic study; ET = exercise test.

range 1–5). Suspected or certain structural heart disease or abnormal ECG was present in 158 patients. The final diagnosis at the end of the diagnostic work-up was: neurally mediated syncope or orthostatic hypotension in 192 patients (62%), cardiac syncope in 56 (18%), and neuropsychiatric syncope after the reappraisal process in 3 patients (1%); syncope remained unexplained in 57 patients (18%)

### Findings

The initial evaluation allowed us to establish the cause of syncope in 72 patients (23%). Laboratory investigations (second step of evaluation) were performed in 236 patients (77%) and were diagnostic in 176 (57%) (Fig. 2). One single laboratory test was sufficient for diagnosis in 65 patients (21%), 2 tests in 64 (21%) and

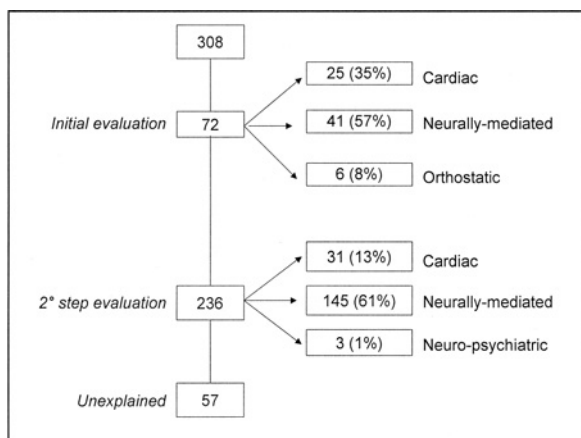


Figure 2 Diagnostic flow results.

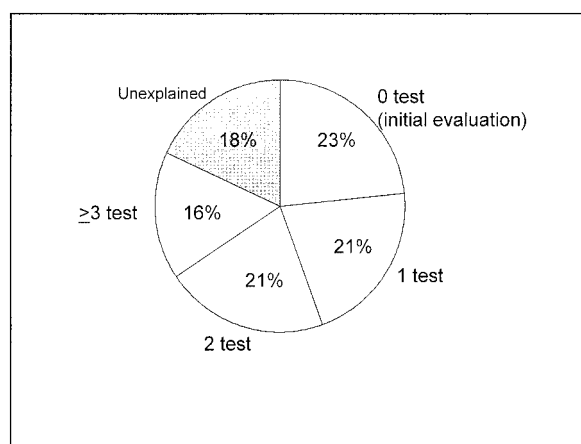


Figure 3 Number of appropriate tests necessary for diagnosis.

≥3 tests in 50 patients (16%); finally the diagnosis remained unexplained in 57 patients (18%) despite more than 3 tests (Fig. 3). Only 13% of patients who underwent the second-step evaluation had a final diagnosis of cardiac syncope: echocardiography was diagnostic in 3 cases, prolonged ECG monitoring in 13 cases, exercise test in 1 case and electrophysiological study in 14 cases.

The appropriateness of indications for the diagnostic tests and the diagnostic yield of tests, as defined in 'Methods', are shown in the Table 1. Apart from the initial evaluation, the most frequently used tests were carotid sinus massage and tilt testing, which were appropriately indicated in more than half of the patients; cardiological investigations were used in a minority of patients.

## Discussion

A major issue in the use of diagnostic tests is that syncope is a transient symptom and not a disease.

Table 1 Appropriateness and diagnostic yield of the tests in 308 patients who had a final diagnosis assigned according to the Guidelines on Management of Syncope

| Test                                 | Appropriate | Diagnostic yield |
|--------------------------------------|-------------|------------------|
| History/physical exam/blood pressure | 308 (100%)  | 47 (15%)         |
| ECG                                  | 241 (78%)   | 25 (10%)         |
| Echocardiogram                       | 103 (33%)   | 3 (3%)           |
| Holter                               | 82 (27%)    | 13 (16%)         |
| Exercise test                        | 22 (7%)     | 1 (5%)           |
| Carotid sinus massage                | 177 (57%)   | 44 (24%)         |
| Tilt testing                         | 161 (52%)   | 94 (58%)         |
| ATP test                             | 47 (15%)    | 7 (15%)          |
| Electrophysiological study           | 51 (17%)    | 14 (27%)         |

Note. The table does not include three further patients with a final diagnosis of neuro-psychiatric syncope after the reappraisal process.

ATP=Adenosine triphosphate.

Typically, patients are asymptomatic at the time of evaluation and the opportunity to capture a spontaneous event during diagnostic testing is rare. Furthermore, it is not possible to measure test sensitivity and specificity, as there is no reference or gold standard for most of the tests used in this condition. In other words, the casual relationship between a diagnostic abnormality and syncope in a given patient is often presumptive; therefore no set of criteria and no algorithm for diagnosing syncope may be considered ideal and certain. Only a large consensus among experts can avert the lack of scientific evidence. Consequently, there is a need for specific and generally accepted criteria to maximize the diagnostic yield as are those developed by ad-hoc task forces of the major scientific societies. In this study we applied the guidelines on syncope of the Italian 'Associazione Nazionale Medici Cardiologi Ospedalieri'<sup>[1]</sup> that were largely accepted by the more recent guidelines of the European Society of Cardiology<sup>[2]</sup>. For this reason, the present study was not aimed to validate the recommendations of the guidelines, but rather, to evaluate their applicability in the 'real world' of syncope units and their impact on the use of tests. The main results of this study are that, when standardized criteria are used, few simple tests are usually needed for the diagnosis of syncope and that the pre-test appropriateness of indications increases the diagnostic yield of the tests. For example, only ≤2 tests were necessary for diagnosis in 66% of the patients (Fig. 3). The most useful tests, other than the initial evaluation, were neurally mediated tests, i.e. tilt testing and carotid sinus massage. This is easy to explain, as reflex syncope was the most frequent aetiology we found. These results justify wide use of these tests in the evaluation of syncope. Tilt testing and carotid sinus massage are probably underused in clinical practice. Indeed, they were not very frequently used in previous population-based studies<sup>[4-9]</sup> and in the real world<sup>[10-11]</sup>.



By contrast, the present results are in agreement with the prevalence of positive responses found in those studies that specifically assessed their diagnostic value<sup>[12-16]</sup>.

Cardiac syncope accounted for a minority of patients (56 out of 308). Some of these could be identified by the standard ECG during the initial evaluation. Only 13% of patients undergoing the 2° step evaluation received a final diagnosis of cardiac syncope (Fig. 2). If cardiac tests had been performed in all (or most) of these cases, the diagnostic yield would have been unacceptably low and several sophisticated and expensive tests would have been useless. This also has practical implications in reducing the costs of the syncope work-up. For example, the diagnostic yield of ECG monitoring was 16%, far higher than the 4% average reported in the literature<sup>[17]</sup>; the electrophysiological study was appropriately performed in a small number of patients, giving a good diagnostic yield, even though the positivity criteria were more restrictive than those used in the literature<sup>[18]</sup>. Although echocardiography is only seldom diagnostic per se, its use is justified in order to confirm or exclude the presence of heart disease and, therefore, to guide subsequent cardiac evaluation.

Compared with previous studies<sup>[4-9,18]</sup>, we had a lower positivity rate of diagnosis based on the initial evaluation. This was due to the more restrictive criteria we used and to some selection of the patients referred to the syncope units. Similarly, the number of patients with neuropsychiatric syncope was lower than in the literature<sup>[4-9,18]</sup>. This result might not reflect the true prevalence of this type of loss of consciousness, since the patients with seizure disorders, neurological symptoms or psychiatric disorders were easily identified on initial evaluation and thus not included (see 'Methods'). However, the percentage we found expresses the real prevalence of such disorders that are initially misdiagnosed and that need an accurate work-up to be correctly identified.

## Limitations

The patients were those referred to the syncope units, therefore they represent a preselected population that is likely to be different from the general population of patients with syncope. For example, it is likely that the true prevalence of typical vasovagal syncope may be underestimated. Moreover, no follow up data are provided. Therefore, we could not determine if any potentially life threatening causes of syncope were missed. Finally, it is possible that dual pathology may have been missed by only performing limited tests.

## Conclusions

When standardized criteria are used, few simple tests are usually needed for the diagnosis of syncope. The appropriateness of indications increases the diagnostic yield of the tests.

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