ORIGINAL ARTICLE

Diagnosis of neurally mediated syncope at initial evaluation and with tilt table testing compared with that revealed by prolonged ECG monitoring. An analysis from the Third International Study on Syncope of Uncertain Etiology (ISSUE-3)

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▶ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/heartjnl-2013-304399).

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Received 3 June 2013
Revised 2 October 2013
Accepted 3 October 2013
Published Online First 24 October 2013

ABSTRACT

Objective According to the guidelines of the European Society of Cardiology, a presumed diagnosis of neurally mediated syncope (NMS) can be made when patients have a consistent history and competing diagnoses are excluded. In the present study, we compared the initial diagnosis of NMS by means of implantable loop recorder (ILR) documentation.

Methods In this prospective multicentre observational study which involved 51 hospitals in nine countries in Europe and Canada, 504 NMS patients ≥40 years, who had suffered ≥3 syncopal episodes in the previous 2 years received an ILR and were followed up for a mean of 15±11 months.

Results ILR recorded a spontaneous syncope in 187 cases, with an estimated diagnostic yield of 47% at 3 years. ILR findings were consistent with the initial diagnosis of presumed NMS in 162 (87%) patients whereas did not confirm NMS in another 25 (13%), who had an intrinsic cardiac arrhythmic cause (atrial tachyarrhythmias (#6), long pause on termination of tachyarrhythmia (#8), persistent bradycardia (#3), ventricular tachycardia (#4)) or a non-arrhythmic loss of consciousness (non-syncopal (#3), orthostatic hypotension (#1)). No clinical baseline feature was able to predict an intrinsic cardiac cause with the exception of more frequent non-syncopal atrial tachyarrhythmias on clinical history, which were present in 38% of cardiac versus 5% of NMS patients (p=0.001). Tilt table testing (TT) was positive in 76/136 (56%) presumed NMS and in 9/21 (43%) non-NMS patients (p=0.35); an asystolic response was present in 28/136 (21%) NMS and in 0/21 (0%) non-NMS patients (p=0.03).

Conclusions ILR findings showed results other than NMS in a small, although non-negligible, number of patients older than 40 years. TT was unable to discriminate between presumed NMS and non-NMS with the exception of an asystolic response which was highly specific.

To cite: Ungar A, Sgobino P, Russo V, *et al*. *Heart* 2013;**99**:1825–1831.

According to the guidelines of the European Society of Cardiology,[1 2] a presumed diagnosis of neurally mediated syncope (NMS) can be made when patients have a history consistent with this diagnosis and competing diagnoses are excluded. Guideline recommendations are based on a strong pathophysiological background, clinical experience from observational studies and the consensus of experts. Nevertheless, patients are typically asymptomatic at the time of evaluation and the diagnosis of NMS often remains presumptive. A widely accepted standard of reference for confirmation of the diagnosis does not yet exist.

When a NMS is suspected, tilt (table) testing (TT) is frequently performed after the initial evaluation in order to confirm the diagnosis. The diagnostic value of TT has been questioned.[3] In particular, the accuracy of TT has not been fully validated against populations with defined causes of syncope. The main reason has been the lack of a reliable gold standard of reference.

In the present study, we aimed to compare the diagnosis of NMS made at initial evaluation and with TT with that obtained with the documentation of a spontaneous event made by implantable loop recorder (ILR).

METHODS

Patient selection

The multicentre, prospective Third International Study on Syncope of Uncertain Etiology (ISSUE-3) included patients ≥40 years old who had suffered ≥3 syncopal episodes of likely NMS aetiology in the previous 2 years. NMS was defined as any form of reflex syncope, with the exception of carotid sinus syndrome, and a sufficiently severe clinical presentation to warrant specific treatment. These individuals received an ILR and were followed up. In accordance with the guidelines of the European Society of Cardiology,[1 2] NMS was considered likely when the clinical history was consistent with NMS and competing diagnoses were excluded. Patients were excluded if they had one or more of the following features: (1) cardiac abnormalities which suggested cardiac syncope (overt heart

failure; EF <40%; old or recent myocardial infarction; hypertrophic or dilated cardiomyopathy; clinically significant valvular disease; sinus bradycardia <50 bpm or sinoatrial block; Mobitz I second-degree atrioventricular block; bundle branch block; rapid paroxysmal supraventricular tachycardia or ventricular tachycardia; pre-excited QRS complexes; prolonged QT interval; Brugada syndrome and arrhythmogenic right ventricular cardiomyopathy); (2) symptomatic orthostatic hypotension diagnosed by standing blood pressure measurement and (3) non-syncopal loss of consciousness (eg, epilepsy, psychiatric, metabolic, drop attack, cerebral transient ischaemic attack, intoxication and cataplexy).

Patients with positive and negative TT responses were included. The Italian protocol[4] was recommended, which consists of 60°–70° passive tilting for 20 min or until syncope occurs. If the passive tilt phase did not induce syncope, 0.4 mg sublingual nitroglycerine spray was administered to the patient while the table was maintained in the same position; the test was continued for 15 min after pharmacological challenge. Positive TT responses were considered induction of syncope; positive responses were classified according to the New Vasovagal Syncope International Study (VASIS) classification[5] as an asystolic or VASIS 2B form (those with an asystole ≥3 s) or mixed or vasodepressor forms (all the other forms without asystole). TT was considered negative if syncope did not occur.

Study protocol

After ILR implantation, all patients were followed up quarterly until the first documented syncopal recurrence, occurrence of a diagnostic arrhythmic event or the end of the study. Events were classified according to the ISSUE classification[6] as type 1 (asystole >3 s), type 2 (bradycardia), type 3 (slight or no rhythm variations) and type 4 (tachycardia).

The following ILR findings were considered consistent with a likely or possible NMS, irrespective of the clinical presentation of the event, and adjudicated by the End-point Committee:

- Asystolic syncope >3 s (likely NMS)
- Non-syncopal asystole >6 s (likely NMS)
- Syncope and progressive intermittent bradycardia (likely mixed NMS)
- Syncope and no or slight rhythm variations (possible hypotensive NMS or orthostatic hypotension).

Conversely, the following findings did not confirm NMS and established an arrhythmic intrinsic syncope:

- Symptomatic paroxysmal atrial fibrillation, including brady-tachy forms, that is, sinus arrest at the end of a paroxysmal supraventricular tachycardia
- Symptomatic paroxysmal supraventricular tachycardia, including brady-tachy forms, that is, sinus arrest at the end of a paroxysmal supraventricular tachycardia
- Paroxysmal ventricular tachycardia.

The protocol was approved by a research ethics board at each centre and each patient provided signed informed consent. The full study protocol has been previously published,[7] as have the results of the randomised trial.[8]

Statistical analysis

Continuous data are shown as averages±SDs or medians (25th–75th centile), as appropriate, while absolute and relative frequencies were used to describe categorical data. The Shapiro–Wilk test was performed to check the skewness of distributions. The unpaired Student t test or the non-parametric Mann–Whitney tests was used to compare continuous variables depending on data distribution. Fisher's exact test was used to compare proportions. The time to the first recurrence of syncope was analysed by means of Kaplan–Meier survival curves. Analyses were carried out by means of SAS V.9.3 (Chicago, Illinois, USA).

RESULTS

Study participants were enrolled from July 2006 to November 2010 and follow-up concluded in November 2012. Among 509 eligible, five patients dropped out before ILR implantation and were excluded. Over a mean observation period of 15 ±11 months, ILR recorded an event in 187 (37%) out of 504 patients, with an estimated probability of 31% (95% CI 27 to 36) at 1 year, 40% (95% CI 36 to 45) at 2 years and 47% (95% CI 40 to 53) at 3 years (figure 1). The baseline clinical characteristics of the patients with a diagnosis were similar to those without, with few marginal exceptions (table 1). During the ILR observation period, six patients died, five developed an acute coronary syndrome, two developed heart failure and one had a cerebral transient ischaemic attack. The ILR was explanted in

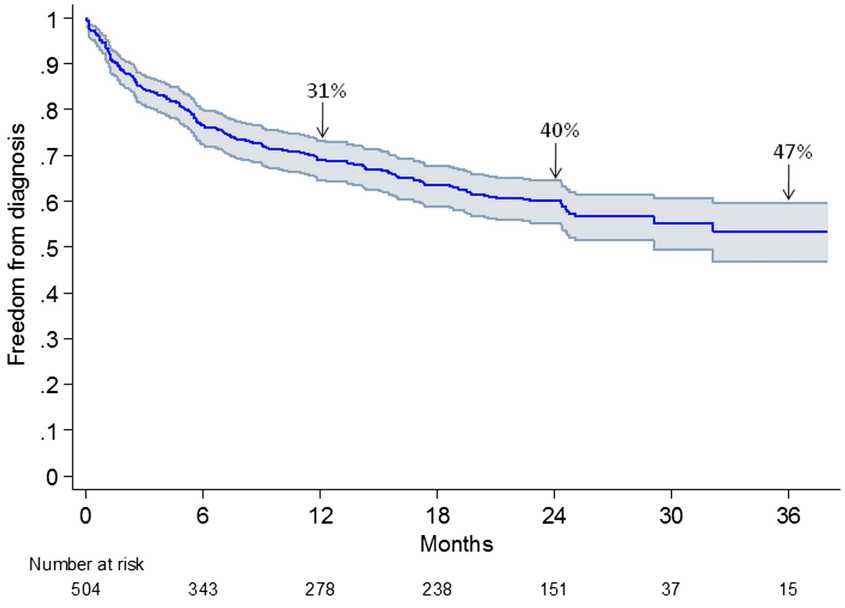

Figure 1 Estimated total diagnostic yield of syncope and CI (grey zone). Access the article online to view this figure in colour.

Table 1 Baseline patient characteristics

Characteristics	All patients n=504	ILR diagnosis n=187	No ILR diagnosis n=317
Length of follow-up (SD), months	15±11	8±8	20±11
Age, mean (SD), years	65 (13)	64 (13)	66 (12)
Men, No. (%)	228 (45)	88 (47)	140 (44)
Syncope events			
Total events, median (IQR)	7 (4–10)	7 (5–10)	6 (4–10)
≥7 episodes, No. (%)	251 (50)	98 (52)	153 (48)
Events in the last 2 years, median (IQR)	4 (3–6)	4 (3–6)	4 (3–6)
≥4 episodes, No. (%)	311 (61)	123 (66)	188 (34)
Events in the last 2 years without prodromes, median (IQR)	2 (0–4)	2 (0–4)	3 (0–4)
Age at first syncope, mean (SD), years	51 (22)	48 (22)	53 (21)
Interval between first and last episodes, median (IQR), years	5.5 (2–22)	8 (3–23)*	5 (2–19)*
History of presyncope, n (%)	237 (47)	101 (54)**	136 (43)**
Hospitalisation for syncope, n (%)	308 (61)	116 (62)	192 (61)
Injuries related to fainting, n (%)			
Major injuries (fractures, brain concussion)	83 (16)	19 (10)	64 (20)
Minor injuries (bruises, contusion, haematoma)	230 (46)	86 (46)	144 (45)
Typical vasovagal presentation, n (%)	205 (41)	87 (46)	118 (37)
Typical situational presentation, n (%)	81 (16)	30 (16)	51 (16)
Without prodromes	287 (57)	102 (54)	185 (58)
Medical history, n (%)			
Structural cardiac abnormalities	60 (12)	22 (12)	38 (12)
Atrial tachyarrhythmias	40 (8)	18 (10)	22 (7)
Hypertension	246 (49)	91 (49)	155 (49)
Diabetes	56 (11)	19 (10)	37 (12)
Neurological/psychiatric disorders	30 (6)	6 (3)	24 (8)
Concomitant medications, No. (%)			
Antihypertensive	257 (51)	94 (50)	163 (51)
Psychiatric	64 (13)	24 (13)	40 (13)
Any other drugs	167 (33)	55 (29)	112 (35)
Mean number of drugs per patient	1.4 (1.4)	1.3 (1.4)	1.4 (1.5)
Baseline mean heart rate, bpm	70 (11)	69 (10)	70 (11)
Supine arterial blood pressure (SD), mm Hg	131 (17)	131 (17)	131 (17)
Standing arterial blood pressure	120 (21)	121 (19)	120 (22)
Echocardiogram:			
LV EF (SD), %	61 (6)	62 (6)	60 (6)
LV diastolic diameter (SD), mm Hg	49 (6)	49 (7)	49 (6)
LV systolic diameter (SD), mm Hg	32 (6)	32 (7)	32 (6)
Any abnormality, %	47 (9)	15 (8)	32 (10)
Tilt testing: performed, No. (%)	439 (87)	157 (84)	282 (89)
Positive of those performed, No. (%)	204 (46)	85 (54)	119 (42)
Asystolic response, No. (%)	52 (12)	28 (18)***	24 (9)***
Non-asystolic response	152 (35)	57 (36)	95 (34)

p Values: *0.04; **0.02; ***0.002; ILR, implantable loop recorder; n, number.

the absence of an end point in 16 patients owing to pocket infection or patient's request (intolerance).

Comparison with clinical evaluation

Of those patients with a diagnosis, 162 (87%) had ILR findings which were consistent with the initial diagnosis of NMS: 79 had syncope with asystole >3 s (median 10 s (IQR 5–17)), 20 non-syncopal asystole >6 s (median 8 s (IQR 6–11)), 20 syncope with bradycardia and 43 syncope with no or slight rhythm variations. The clinical presentation of 109 available syncopal episodes, which reproduced the previous events in the opinion of the patients, was typical vasovagal in 34%, typical situational in 13% and atypical or no prodromes in 53% of cases. In another 25 (13%) patients, the initial diagnosis of NMS was not confirmed by ILR findings (figure 2). In 21 of these, an intrinsic cardiac arrhythmia cause was diagnosed: symptomatic paroxysmal atrial tachyarrhythmia (atrial fibrillation #3 or atrio-ventricular (AV) nodal re-entrant tachycardia #3), long pause on termination of supraventricular tachyarrhythmia (#8) and ventricular tachycardia (#4)—which were all diagnosed by ILR documentation—and persistent bradycardia (#3), which was documented during outpatient visits. No single or combinations of clinical baseline features were able to predict an intrinsic cardiac cause, with the exception of more frequent non-syncopal atrial tachyarrhythmias on clinical history, which were present in 38% of cardiac vs 5% of NMS patients (p=0.001); conversely, a history of typical vasovagal presentation was more frequent in NMS patients than in cardiac patients (49% vs 24%, p=0.04) (table 2). Finally, four

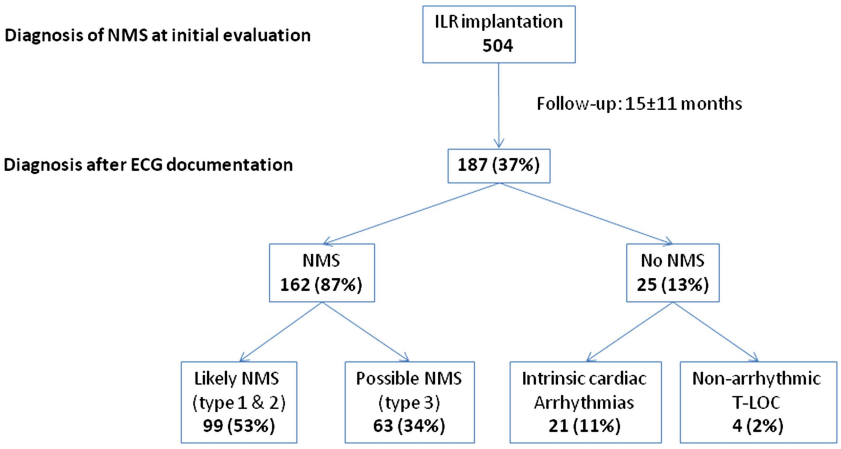

Figure 2 Diagnostic flow. T-LOC, transient loss of consciousness; ILR, implantable loop recorder; NMS, neurally mediated syncope. Access the article online to view this figure in colour.

patients had an episode of loss of consciousness in the absence of rhythm variations at ILR, which was re-evaluated and attributed to orthostatic hypotension (#1) and non-syncopal loss of consciousness (#3).

Comparison with tilt TT

Among the 187 patients with a recorded event, TT was positive in 85 (during the passive phase in 24 and during drug challenge in 61) and negative in 72 (not performed in 30). TT was positive in 76 NMS and in 9 non-NMS patients (p=0.35) (table 3); sensitivity and specificity of a positive test were 56% (95% CI 53% to 59%) and 57% (95% CI 36% to 77%), respectively. The sensitivity of TT was not different in the 93 patients with ILR documentation of asystole or bradycardia (likely NMS) and in the 43 patients with ILR documentation of syncope with no or slight rhythm variations (possible NMS): 59% (95% CI 54% to 63%) vs 49% (95% CI 39% to 58%). The specificity of TT was 53% (95% CI 29% to 75%) in the 17 patients with an intrinsic arrhythmia.

An asystolic response was present in 28 NMS (10 during passive and 18 during drug challenge) and in 0 non-NMS patients (p=0.03); sensitivity and specificity of an asystolic test were 21% (95% CI 18% to 21%) and 100% (95% CI 82% to 100%), respectively.

Passive only TT was positive in 22 NMS and in two non-NMS patients (p=0.74); sensitivity and specificity of the passive phase were 16% (95% CI 13% to 17%) and 90% (95% CI 71% to 98%), respectively.

Similar TT results were observed in patients without a recorded event (table 3).

DISCUSSION

The study suggests a diagnosis different from the original one of NMS in a small, although non-negligible, number of older patients when the initial diagnosis—based on clinical history and exclusion of competing causes according to guidelines—was validated by ECG documentation of a spontaneously occurring event. Most of the changes in diagnosis were due to intrinsic cardiac arrhythmias, which were largely unpredictable by baseline characteristics. This aspect, which has not yet been clarified in the literature, may be relevant in clinical practice. TT was unable to discriminate between cardiac (non-NMS) and presumed NMS with the exception of an asystolic response which was highly specific. Therefore, the additional diagnostic value of TT to clinical evaluation is of little help in establishing the diagnosis of NMS.

Age is the first consideration. Almost all young patients who have a syncopal loss of consciousness have NMS, and this can be teased out and confirmed in most cases through careful analysis of the patient's history. In older patients (age >40 is a reasonable definition of older according to ISSUE-3 inclusion criteria), the situation is quite different for several reasons; history is less clearly indicative of vasovagal syncope in older patients,[9 10] the risk of potentially fatal causes and comorbidities rises[11] and at least two types of more recently understood bradycardia (NMS and adenosine-sensitive heart block) exist. These bradycardias can be treated with permanent pacing.[8 12 13] A primary tachyarrhythmia was a not infrequent cause of syncope which was caused either directly at the onset of the tachyarrhythmia itself or by a long pause (range 3.5–9 s) which occurred at the termination of the tachyarrhythmia as a consequence of a delayed recovery of sinus node automaticity. An example is shown in figure 3. While in most cases the ILR documentation was the first documentation of tachyarrhythmia, eight patients had already a history of asymptomatic atrial tachyarrhythmia which was considered insufficient for the diagnosis lacking the evidence of a causal relationship. This means that syncope can be an epiphenomenon of an atrial tachyarrhythmia, which is not always present in a given patient. On the other hand, the role of autonomic reflexes in favouring syncope in patients with atrial tachyarrhythmia is well known. Some studies[14 15] showed that in predisposed TT+ patients, a NMS can be triggered by the sudden onset of an atrial arrhythmia, albeit the intrinsic cardiac trigger and the specificity of therapy justify classification of these forms as cardiac syncope. In other words, multiple mechanisms—intrinsic arrhythmia and reflex susceptibility—might operate together to cause syncope in the same patient. Even if the history of a spurious tachyarrhythmia should suggest a causal role in the genesis of syncope, however the causal effect could be confirmed only in eight and was excluded in other eight patients (table 2) among a total of 40 patients with a history of asymptomatic atrial tachyarrhythmia (table 1). Therefore, in older patients, ILR monitoring is a reasonable means of investigation and may now be regarded as an additional useful tool for confirming the diagnosis and starting specific therapy.

As yet, a standard of reference for confirming the diagnosis does not exist. The central problem is that there is no good evidence-based clinical definition of the syndrome of NMS. Most studies[16–18] have used strict diagnostic criteria without incorporating follow-up information. Some authors have refined history-taking criteria by using a quantitative history score

Table 2 Factors predicting intrinsic cardiac syncope

Characteristics	NMS n=162	Cardiac arrhythmia n=21
Length of follow-up (SD), months	8±8	6±8
Age, mean (SD), years	64 (13)	68 (11)
Men, No. (%)	74 (46)	13 (62)
Syncope events:		
Total events, median (IQR)	8 (5–12)	5 (4–8)
≥8 episodes, No. (%)	83 (51)	6 (29)
Events in the last 2 years, median (IQR)	4 (3–7)	4 (3–4)
≥4 episodes, No. (%)	107 (66)	14 (67)
Events in the last 2 years without prodromes, median (IQR)	2 (0–4)	3 (1–4)
Age at first syncope, mean (SD), years	48 (22)	53 (11)
Interval between first and last episodes, median (IQR), years	9 (3–23)	5 (2–23)
History of presyncope, n (%)	89 (55)	10 (48)
Hospitalisation for syncope, n (%)	101 (62)	14 (67)
Injuries related to fainting, n (%)		
Major injuries (fractures, brain concussion)	18 (11)	1 (5)
Minor injuries (bruises, contusion, haematoma)	75 (46)	9 (43)
Typical vasovagal presentation, n (%)	80 (49)*	5 (24)*
Typical situational presentation, n (%)	28 (17)	2 (10)
Without prodromes	87 (54)	14 (67)
Medical history, n (%)		
Structural cardiac abnormalities	19 (12)	2 (10)
Atrial tachyarrhythmias	8 (5)**	8 (38)**
Hypertension	76 (47)	14 (67)
Diabetes	16 (10)	3 (14)
Neurological/psychiatric disorders	7 (4)	1 (0)
Concomitant medications, No. (%)		
Antihypertensive	78 (48)	15 (71)
Psychiatric	23 (12)	0 (0)
Any other drugs	44 (27)	7 (33)
Mean number of drugs per patient	1.3 (1.3)	1.5 (1.3)
Baseline mean heart rate, bpm	69 (9)	71 (14)
Supine arterial blood pressure (SD), mm Hg	131 (17)	131 (18)
Standing arterial blood pressure	121 (19)	120 (23)
Echocardiogram:		
LV EF (SD), %	62 (6)	61 (7)
LV diastolic diameter (SD), mm Hg	49 (6)	47 (9)
LV systolic diameter (SD), mm Hg	32 (7)	32 (6)
Any abnormality, %	13 (8)	2 (10)
Tilt testing: performed, No (%)	136 (84)	17 (81)
Positive of those performed, No. (%)	76 (56)	8 (47)
Asystolic response, No. (%)	28 (17)	0 (0)
Non-asystolic response	48 (30)	8 (47)

p Values: *0.04; **0.001.
n, number; NMS, neurally mediated syncope.

questionnaire.[19] Others have used long-term clinical follow-up to assess the accuracy of the initial diagnosis, with recurrent episodes, clinical findings or death during follow-up being deemed incompatible with the initial diagnosis.[20] These methods have limitations. TT has proved unable to reliably distinguish between NMS and other forms, owing to the low sensitivity and specificity of the test.[3] Moreover, the accuracy of TT has not been fully validated against populations with defined causes of syncope. In this study, TT was positive in 43% of non-NMS patients, thus suggesting very poor specificity. Patients with negative and positive responses to TT have similar symptoms, similar symptom burdens and similar recurrence rates of syncope.[19 21–24] Finally, there is a lack of correlation between responses to tilt testing and the mechanism of spontaneous NMS detected by ILR.[24]

Limitations

We acknowledge that the ILR strategy also has two important pitfalls when used as a standard of reference for the diagnosis of NMS.

First, the diagnosis of NMS cannot be considered certain in several cases even after ILR documentation of an event. Indeed, while the documentation of progressive sinus bradycardia or progressive tachycardia followed by progressive bradycardia and, perhaps, ventricular asystole due to sinus arrest virtually confirm a neurally mediated mechanism,[6 23 25] the finding of

Table 3 Responses to tilt TT in patients with presumed NMS (ILR-documented and ILR-undocumented) and in patients in whom NMS was not confirmed by ILR findings

TT protocol/response	No ILR diagnosis n=282	NMS n=136	Non-NMS n=21	p Value (NMS likely vs non-NMS)
Passive+drug challenge (%):				
Any positive response	119 (42)	76 (56)	9 (43)	0.35
Negative response	163 (58)	60 (44)	12 (57)	
Passive+drug challenge (%):				
Asystolic response (VASIS 2B)	24 (9)	28 (21)	0 (0)	0.03
Any non-asystolic response	258 (91)	108 (79)	21 (100)	
Passive only (%):				
Any positive response	27 (10)	22 (16)	2 (10)	0.74
Negative response	255 (90)	114 (84)	19 (90)	

ILR, implantable loop recorder; NMS, neurally mediated syncope; TT, table testing.

sudden-onset paroxysmal atrio-ventricular block with concomitant increase in sinus rate cannot exclude an adenosine-mediated block.[12 13] Moreover, the documentation of syncope in the absence of rhythm variations by making the assumption of hypotensive NMS cannot exclude orthostatic hypotension or another unknown cause of syncope. In these cases, the ILR-based diagnosis of NMS can only be considered assumed. Thus, the diagnostic accuracy of clinical evaluation could be even lower than the 87% reported here.

Second, more than half of our patients had no ILR-documented events over 3 years of follow-up; thus, the initial diagnosis could not be confirmed. Although the clinical characteristics of these patients were fairly similar to those with a diagnosis (table 1), we cannot exclude the possibility that diagnostic accuracy might have been different if they had had ILR documentation. ILR studies[23 26 27] in general have reported a relatively high rate of non-recurrence of syncope or another diagnostic finding although Furukawa *et al*[28] followed patients for a longer period and they were able to demonstrate that in as much as 80% of patients a diagnosis of the cause of syncope could be made.

Finally, the presumptive diagnosis was made in tertiary centres specialising in syncope evaluation. It is likely that this overestimates the value of clinical diagnosis if made by primary care providers.

CONCLUSIONS AND PRACTICAL PERSPECTIVES

In conclusion, a non-negligible risk of misdiagnosis exists when NMS is diagnosed in patients >40 years according to clinical history, physical examination and exclusion of other competing causes even if strict standardised guideline-based diagnostic criteria are applied when comparison with ILR findings is made. These patients are indistinguishable from true NMS patients on standard clinical evaluation and were potentially at risk of life-threatening arrhythmias, which could be identified and treated only by means of an ILR strategy.

The use of TT in order to confirm the diagnosis is hampered by low sensitivity and specificity. In this regard, an interesting original finding of this study is that an asystolic positive response (VASIS 2B) seems to have an excellent specificity even if to the detriment of sensitivity; in other words, the finding of an asystolic response allows confirmation of the initial diagnosis of NMS. Specificity is also improved when passive phase only of TT is used, but its low positivity rate limits its usefulness. These data are anticipated to move use of the ILR more towards being the 'gold standard' in diagnosis of presumed NMS from clinical assessment.

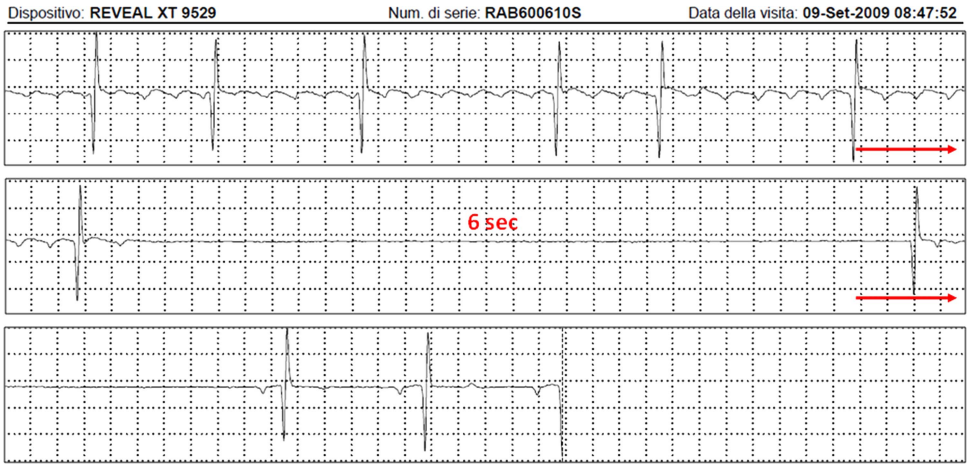

Figure 3 The figure shows the implantable loop recorder (ILR) recorded ECG of a patient who had a known asymptomatic paroxysmal atrial flutter. ILR finally documented an episode of syncope, which was due to a 6 s pause at the termination of the atrial flutter before the recovery of sinus node automaticity. Access the article online to view this figure in colour.

Key messages

What is already known about this subject?
A presumed diagnosis of neurally mediated syncope (NMS) can be made when patients have a history consistent with this diagnosis and competing diagnoses are excluded. A widely accepted standard of reference for confirmation of the diagnosis does not yet exist. In particular, the accuracy of tilt (table) testing (TT) has not been fully validated against populations with defined causes of syncope.

What does this study adds?
The study suggests a diagnosis different from the original one of NMS in a small, although non-negligible, number of older patients when the initial diagnosis—based on clinical history and exclusion of competing causes according to guidelines—was validated by ECG documentation of a spontaneously occurring event by means of implantable loop recorder. TT was unable to discriminate between cardiac (non-NMS) and presumed NMS with the exception of an asystolic response which was highly specific.

How might this impact on clinical practice?
Most of the changes in diagnosis were due to intrinsic cardiac arrhythmias, which were largely unpredictable by baseline characteristics. This aspect, which has not yet been clarified in the literature, may be relevant in clinical practice. The additional diagnostic value of TT to clinical evaluation is of little help in establishing the diagnosis of NMS.

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Collaborators The investigators in the ISSUE-3 study are listed in the online supplementary appendix.

Contributors Each author contributed significantly to the submitted work. In particular, they contributed to (1) conception and design or analysis and interpretation of data or both; (2) drafting of the manuscript or revising it critically for important intellectual content; and (3) final approval of the manuscript submitted. MB, PI of the ISSUE-3 study, are responsible for the overall content as guarantor.

Funding The study was funded by Medtronic Bakken Research Center.

Competing interests MB reports receiving modest consultancy fees from Medtronic and being a direct shareholder of F2 solution; RS is a consultant to Medtronic, receiving modest fees, and is a paid lecturer for St Jude Medical; AM reports receiving modest consultancy fees from Medtronic; XB reports receiving limited consultancy fees from Medtronic and St Jude Medical; HHE reports being a limited paid lecturer or tutor for Medtronic, St. Jude, Boston, Sorin and conducting advisory board activity for MSD; NG is an employee of Medtronic.

Patient consent Obtained.

Ethics approval Research ethics board at each centre.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Brignole M, Alboni P, Benditt DG, *et al*. Guidelines on management (diagnosis and treatment) of syncope—update 2004. *Europace* 2004;6:467–537.
2 Moya A, Sutton R, Ammirati F, *et al*. Guidelines for the diagnosis and management of syncope (version 2009). *Eur Heart J* 2009;30:2631–71.
3 Sheldon R. Tilt table testing and implantable loop recorders for syncope. *Cardiol Clin* 2013;31:67–74.
4 Bartoletti A, Alboni P, Ammirati F, *et al*. The Italian protocol: a simplified head-up tilt testing potentiated with oral nitroglycerin to assess patients with unexplained syncope. *Europace* 2000;2:339–42.
5 Brignole M, Menozzi C, Del Rosso A, *et al*. New classification of haemodynamics of vasovagal syncope: beyond the VASIS classification. Analysis of the pre-syncopal phase of the tilt test without and with nitroglycerin challenge. *Europace* 2000;2:66–76.
6 Brignole M, Moya A, Menozzi C, *et al*. Proposed electrocardiographic classification of spontaneous syncope documented by an implantable loop recorder. *Europace* 2005;7:14–18.
7 The Steering Committee of the ISSUE 3 Study. International study on syncope of uncertain aetiology 3 (ISSUE 3): pacemaker therapy for patients with asystolic neurally-mediated syncope: rationale and study design. *Europace* 2007;9:25–30.
8 Brignole M, Menozzi C, Moya A, *et al*. Pacemaker therapy in patients with neurally mediated syncope and documented asystole: Third International Study on Syncope of Uncertain Etiology (ISSUE-3): a randomized trial. *Circulation* 2012;125:2566–71.
9 Galizia G, Abete P, Mussi C, *et al*. Role of early symptoms in assessment of syncope in elderly people: results from the Italian group for the study of syncope in the elderly. *J Am Geriatr Soc* 2009;57:18–23.
10 Del Rosso A, Alboni P, Brignole M, *et al*. Relation of clinical presentation of syncope to the age of patients. *Am J Cardiol* 2005;96:1431–5.
11 Sun BC, Hoffman JR, Mangione CM, *et al*. Older age predicts short-term, serious events after syncope. *J Am Geriatr Soc* 2007;55:907–12.
12 Brignole M, Deharo JC, De Roy L, *et al*. Syncope due to idiopathic paroxysmal atrioventricular block: long-term follow-up of a distinct form of atrioventricular block. *J Am Coll Cardiol* 2011;58:167–73.
13 Flammang D, Church TR, De Roy L, *et al*. Treatment of unexplained syncope: a multicenter, randomized trial of cardiac pacing guided by adenosine 5′-triphosphate testing. *Circulation* 2012;125:31–6.
14 Leitch JW, Klein GJ, Yee R, *et al*. Syncope associated with supraventricular tachycardia: an expression of tachycardia or vasomotor response? *Circulation* 1992;85:1064–71.
15 Brignole M, Gianfranchi L, Menozzi C, *et al*. Role of autonomic reflexes in syncope associated with paroxysmal atrial fibrillation. *J Am Coll Cardiol* 1993;22:1123–9.
16 Kapoor WN, Karpf M, Wleand S, *et al*. A prospective evaluation and follow-up of patients with syncope. *N Engl J Med* 1983;309:197–204.
17 Sarasin FP, Louis-Simonet M, Carballo D, *et al*. Prospective evaluation of patients with syncope: a population-based study. *Am J Med* 2001;111:177–84.
18 Alboni P, Brignole M, Menozzi C, *et al*. Diagnostic value of history in patients with syncope with or without heart disease. *J Am Coll Cardiol* 2001;37:1921–8.
19 Sheldon R, Rose S, Connolly S, *et al*. Diagnostic criteria for vasovagal syncope based on a quantitative history. *Eur Heart J* 2006;27:344–50.
20 van Dijk N, Boer KR, Colman N, *et al*. High diagnostic yield and accuracy of history, physical examination, and ECG in patients with transient loss of consciousness in FAST: the fainting assessment study. *J Cardiovasc Electrophysiol* 2008;19:48–55.
21 Sheldon R, Rose S, Koshman ML. Comparison of patients with syncope of unknown cause having negative or positive tilt-table tests. *Am J Cardiol* 1997;80:581–5.
22 Grimm W, Degenhardt M, Hoffman J, *et al*. Syncope recurrence can better be predicted by history than by head-up tilt testing in untreated patients with suspected neurally mediated syncope. *Eur Heart J* 1997;18:1465–9.
23 Moya A, Brignole M, Menozzi C, *et al*. Mechanism of syncope in patients with isolated syncope and in patients with tilt-positive syncope. *Circulation* 2001;104:1261–7.
24 Brignole M, Sutton R, Menozzi C, *et al*. Lack of correlation between the responses to tilt testing and adenosine triphosphate test and the mechanism of spontaneous neurally mediated syncope. *Eur Heart J* 2006;27:2232–9.
25 Sud S, Klein G, Skanes A, *et al*. Implications of mechanism of bradycardia on response to pacing in patients with unexplained syncope. *Europace* 2007;9:312–18.
26 Brignole M, Sutton R, Menozzi C, *et al*. Early application of an implantable loop recorder allows effective specific therapy in patients with recurrent suspected neurally mediated syncope. *Eur Heart J* 2006;27:1085–92.
27 Edvardsson N, Frykman V, van Mechelen R, *et al*. PICTURE study investigators. Use of an implantable loop recorder to increase the diagnostic yield in unexplained syncope: results from the PICTURE registry. *Europace* 2011;13:262–9.
28 Furukawa T, Maggi R, Bertolone C, *et al*. Additional diagnostic value of very prolonged observation by implantable loop recorder in patients with unexplained syncope. *J Cardiovasc Electrophysiol* 2012;23:67–71.

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Heart 2013 99: 1825-1831 originally published online October 23, 2013
doi: 10.1136/heartjnl-2013-304399