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Lack of correlation between the responses to tilt testing and adenosine triphosphate test and the mechanism of spontaneous neurally mediated syncope

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Aims We prospectively correlated the results of tilt testing (TT) and adenosine triphosphate test (ATP) with the findings observed during a spontaneous syncopal relapse by means of an implantable loop recorder (ILR) in patients with a clinical diagnosis of neurally mediated syncope.
Methods and results We included patients with three or more clinically severe syncopal episodes in the last 2 years without significant electrocardiographic and cardiac abnormalities. Patients with orthostatic hypotension and carotid sinus syncope were excluded. After ILR implantation, patients were followed until the first documented syncope. Among 392 enrolled patients, 343 underwent TT, which was positive in 164 (48%), and 180 ATP test, which was positive in 53 (29%). Syncope was documented by ILR in 106 (26%) patients after a median of 3 months. Patients with positive and negative TT had similar baseline characteristics, syncopal recurrence rate, and mechanism of syncope, but those with positive TT had more frequently no or slight rhythm variations during spontaneous syncope (45 vs. 21%, $P = 0.02$). An asystolic pause was more frequently found during spontaneous syncope than during TT (45 vs. 21%, $P = 0.02$), but there was a trend for those with an asystolic response during TT also to have an asystolic response during spontaneous syncope (75 vs. 37%, $P = 0.1$). Patients with positive ATP test responses showed syncopal recurrence rates and mechanism of syncope similar to those with negative ATP tests.
Conclusion In patients with neurally mediated syncope, clinical characteristics, outcome, and mechanism of syncope are poorly correlated and not predicted by the results of TT and ATP test. Therefore, these tests are of little or no value in guiding specific therapy.

Introduction

The correlation of spontaneous syncopal episodes with an abnormal finding detected by an implantable loop recorder (ILR) can be regarded as a reference standard when an arrhythmia is suspected to have a role in the genesis of syncope. In previous ILR studies,[1–4] the observations at the time of syncope were heterogeneous, with asystole accounting for up to a half of the syncopal events. The International Study on Syncope of Uncertain Etiology 2 (ISSUE-2)[5] showed that a new strategy based on simple initial evaluation, early application of an ILR, and therapy delayed until ILR-documentation of the mechanism of syncope is safe and can guide effective therapy in patients with recurrent suspected neurally mediated syncope.

Tilt testing (TT) and adenosine triphosphate (ATP) test are generally regarded as useful tests for the diagnosis of suspected neurally mediated syncope.[6,7] The capability of these tests to predict the exact mechanism of spontaneous syncope should have practical, diagnostical, and therapeutical importance. However, it has been questioned in a few small studies. Moya *et al.*[1] found a correlation between TT and spontaneous findings in four out of eight patients and

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Deharo *et al*.[8] in seven of 11 patients. Donateo *et al*.[9] found a correlation between ATP test and spontaneous findings in eight out of 16 patients and Deharo *et al*.[8] in four out 11 patients.

In this study, we prospectively evaluated whether the responses to TT and ATP test were correlated and therefore could predict the clinical outcome and the mechanism of ILR-documented spontaneous syncope employing the much larger population of the ISSUE-2.[5]

Methods

The ISSUE-2[5] was a multicentre, prospective, observational study enrolling consecutive patients who underwent an ILR implantation for suspected neurally mediated syncope. Patients were enrolled at 63 European and American centres; enrolment began in June 2002 and ended in July 2004. The Steering Committee designed the trial. The Medtronic Corporation funded the trial and provided a study manager to supervise its conduct. Data were sent by investigators through the web to an independent clinical research organization (RDES SL, Barcelona, Spain) that maintained the database, issued data clarification forms and, assisted by Medtronic clinical monitors, verified source documents. The sponsor had no access to the database and did not participate in the analysis of the results or in the writing of the article. All the analyses were performed by the Endpoints Committee members with the assistance of a statistician. The study was approved by the institutional review boards, and patients provided informed consent.

Patients

Eligible patients were at least 30 years of age, had suffered, in the last 2 years, from three or more syncope episodes of suspected neurally mediated syncope with a severe clinical presentation (because of high number of episodes that affect patient's quality of life or high risk for physical injury due to unpredictable occurrence) requiring treatment initiation. Patients with carotid sinus syncope were excluded.

In accordance with current guidelines,[6,7] a neurally mediated mechanism was considered likely when, on the initial evaluation, there were suggestive data and the following competitive diagnoses could be ruled out: (i) suspected or definite heart disease and high likelihood of cardiac syncope, i.e. syncope during exercise; overt heart failure; ejection fraction $\leq$40%; old or recent myocardial infarction; hypertrophic cardiomyopathy; dilated cardiomyopathy; significant valvular disease; sinus bradycardia $<$50 bpm or sino-atrial block; Mobitz I second-degree atrioventricular block; Mobitz II second- or third-degree atrioventricular block; bundle branch block; rapid paroxysmal supraventricular tachycardia or ventricular tachycardia; pre-excited QRS complexes; prolonged QT interval; right bundle branch block pattern with ST-elevation in leads V1–V3 (Brugada syndrome); negative T waves in right precordial leads, epsilon waves, and ventricular late potentials suggestive of arrhythmogenic right ventricular dysplasia; (ii) symptomatic orthostatic hypotension diagnosed by standing blood pressure measurement; (iii) non-syncopal loss of consciousness (e.g. epilepsy, psychiatric, metabolic, drop-attack, cerebral transient ischaemic attack, intoxication, cataplexy); (iv) subclavian steal syndrome. All patients received carotid sinus massage of 10 s duration, supine and upright, and those with carotid sinus syncope were excluded.

TT and ATP test were recommended during the screening phase but they were not mandatory for the inclusion of the patients in the study group. The methodology of execution was that recommended in the recent guidelines.[6,7] A positive response to TT was defined as the induction of syncope in the presence of bradycardia, hypotension, or both, and positive responses were classified according to the New VASIS classification.[10] A positive response to ATP test was defined as the induction of complete AV block (or sinus pause) with a ventricular pause $\geq$6.0 s.[11]

Study protocol

Eligible patients were enrolled in the study if they had undergone ILR implantation (Reveal Plus, Medtronic). The recommended programmed mode was one manual event and 13 automatically recorded events for a total duration of 42 min of storage. Patients were instructed to activate the device after every episode of syncope. A screening log of eligible not-implanted patients was also collected. After ILR implantation, patients were followed quarterly until the first electrographically (ECG) documented syncope or for a maximum of 24 months. Neither any therapy nor specific counselling was prescribed during the follow-up. The mechanism of syncope was assigned according to the ISSUE classification by the Endpoints Committee members who analysed the records of all episodes.[12] The study protocol has been previously published.[13]

Objectives

Objectives of the study were to define the mechanism of syncope in patients with clinical diagnosis of neurally mediated syncope and to evaluate prospectively whether the responses to TT and ATP test were correlated and therefore could predict the clinical outcome and the mechanism of spontaneous syncope.

Outcome measures

The time of the first ECG-documented syncopal recurrence after ILR implantation and the time of the first documented or undocumented syncopal event were collected. ECG-documented presyncopal and asymptomatic episodes were not considered as endpoints.

Statistical methods

A sample size of 350 patients was calculated to be sufficiently large in order to derive an accurate assessment of positive and negative predictive accuracy of TT and ATP test to predict bradycardic/asystolic syncope.[13] Comparison between groups was performed with Student's *t*-test or the non-parametric Mann–Whitney *U* test for continuous variables and with Fisher's exact or McNemar test for proportions, as appropriate. All reported *P*-values were two-tailed and the value less than 0.05 was considered significant. The time to the first recurrence of syncope was analysed by means of Kaplan–Meier survival curves, which were compared using the log-rank test.

Results

The clinical characteristics of 392 analysed patients are listed in *Table 1*. Of these, 343 underwent TT, which was positive in 164 (48%), and 182 the ATP test, which was positive in 54 (30%) (*Figure 1*).

During a mean of 12$\pm$8 months of follow-up, 143 patients (36%) had a syncopal recurrence. Syncope was documented by ILR in 106 (26%) patients after a median of 3 months (interquartile range, 1–7), and the mechanism of syncope was classified according to the ISSUE classification (*Table 2*).[12] The most frequent finding, which was observed in 57/106 patients (54%), was one or more prolonged asystolic pauses ranging from 3 to 51 s, the maximum pause being a median of 11.5 s (interquartile range 6.3–18.5 s). Of the patients with an ILR documentation of spontaneous syncope, the correlation with TT response could be evaluated in 94 patients; in 52 of these also the correlation with ATP response could be evaluated.

Table 1 Characteristics of the patients at enrolment

	Total ($n = 392$)	Tilt positive ($n = 164$)	Tilt negative ($n = 179$)	*P*-value	ATP positive ($n = 54$)	ATP negative ($n = 128$)	*P*-value
Mean age (year)	66 ± 14	64 ± 14	65 ± 14	0.521	69 ± 13	62 ± 13	0.002
Male gender, *n* (%)	177 (45)	61 (37)	89 (50)	0.019	13 (24)	58 (45)	0.007
Syncope events							
Syncope: median (interquartile range)	6 (4–10)	6 (4–11)	6 (4–10)	0.469	5 (4–10)	6 (4–15)	0.529
Syncope (last 2 years): median (interquartile range)	4 (3–5)	4 (3–5)	4 (3–5)	0.628	4 (3–5)	4 (3–5)	0.230
Interval between first and last episode: median year (interquartile range)	7 (4–14)	8 (4–19)	6 (4–13)	0.179	7 (5–22)	7 (5–18)	0.701
Age at first syncope	54 ± 20	51 ± 20	53 ± 20	0.289	55 ± 22	50 ± 19	0.146
History of presyncope, *n* (%)	212 (54)	90 (55)	98 (55)	0.977	30 (56)	69 (54)	0.838
Presyncope: median (interquartile range)	5 (3–10)	6 (4–10)	5 (3–10)	0.411	5 (3–9)	6 (3–10)	0.250
Hospitalization for syncope, *n* (%)	219 (56)	84 (52)	106 (60)	0.137	30 (56)	68 (53)	0.764
Injuries related to fainting, *n* (%)	230 (59)	105 (64)	101 (57)	0.148	39 (72)	74 (58)	0.067
Major injuries (fractures, brain concussion)	82 (21)	36 (22)	37 (21)	0.791	11 (20)	24 (19)	0.818
Minor injuries (bruises, etc.)	185 (47)	85 (52)	81 (46)	0.239	32 (59)	61 (48)	0.167
No warning at the onset of the attack (last and/or previous episode), *n* (%)	194 (50)	82 (50)	96 (54)	0.468	25 (46)	63 (50)	0.684
Typical vasovagal/situational presentation (last and/or previous episode), *n* (%)	161 (41)	76 (47)	72 (40)	0.250	27 (50)	55 (43)	0.384
Atypical presentation (uncertain), *n* (%)	230 (59)	87 (53)	106 (60)	0.250	27 (50)	73 (57)	0.384
Normal electrocardiogram, *n* (%)	338 (87)	145 (89)	154 (87)	0.581	50 (93)	116 (91)	0.781
No structural heart disease, *n* (%)	336 (86)	140 (86)	152 (86)	0.885	48 (89)	109 (86)	0.578
Medical history, *n* (%)							
Cardiac disease	53 (14)	22 (14)	25 (14)	0.885	6 (11)	18 (14)	0.578
Hypertension	178 (45)	69 (42)	81 (46)	0.555	32 (59)	50 (39)	0.012
Any neurological disease	35 (9)	13 (8)	16 (9)	0.752	8 (15)	11 (9)	0.217
Diabetes	30 (8)	14 (9)	12 (7)	0.521	7 (13)	9 (7)	0.251
Any therapy at the time of enrolment, *n* (%)	152 (39)	59 (36)	70 (39)	0.552	26 (48)	49 (38)	0.217
Antihypertensive	111 (28)	41 (25)	51 (29)	0.467	21 (39)	34 (27)	0.098
Psychiatric	34 (9)	16 (10)	13 (7)	0.406	6 (11)	15 (12)	0.907
Antiarrhythmic	19 (5)	5 (3)	11 (6)	0.175	1 (2)	4 (3)	1.000
Others	28 (7)	13 (8)	12 (7)	0.662	1 (2)	11 (9)	0.113

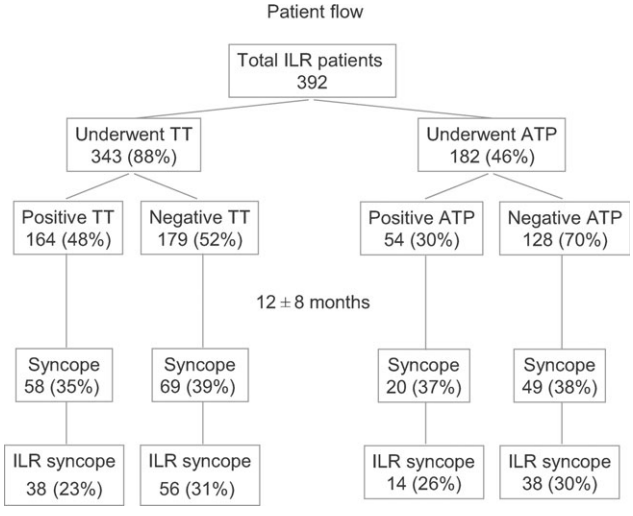

Figure 1 Patient flow.

Correlation between TT and spontaneous syncope

The patients with positive TT showed similar baseline characteristics, with the exception of higher prevalence of males in TT negative patients (*Table 1*), and syncopal recurrence rate (*Figure 2*) than those with negative test. The mechanism of syncope was also similar in both groups, but those with positive TT had more frequently no or slight rhythm variations during spontaneous syncope [45 vs. 21%, odds ratio 3.0 (95% CI 1.2–7.3), $P = 0.02$] (*Table 3*).

Among positive TTs (five passive and 33 nitroglycerine), the electrocardiographic patterns observed during TT were also poorly correlated with those observed during spontaneous syncope. An asystolic pause ≥ 3 s was more frequently found during spontaneous syncope than during TT [45 vs. 21%, $P = 0.02$; odds ratio 5.5 (95% CI 1.0–72)] (*Figure 3*), but there was a trend for those with an asystolic response during TT also to have an asystolic response during spontaneous syncope (75 vs. 37%, $P = 0.1$) (*Table 4* and *Figure 3*). Although with ILR an asystolic syncope was equally frequent

Table 2 The mechanism of syncope documented by ILR in 106 patients and assigned according to the ISSUE classification[10]

Type 1: Asystole—RR pause ≥3 s		57 (54%)
Type 1A, Sinus arrest		
Progressive sinus bradycardia or initial sinus tachycardia followed by progressive sinus bradycardia until sinus arrest	32	
Type 1B, Sinus bradycardia plus AV block	9	
Progressive sinus bradycardia followed by AV block (and ventricular pause/s) with concomitant decrease in sinus rate		
Sudden onset AV block (and ventricular pause/s) with concomitant decrease in sinus rate		
Type 1C, AV block		
Sudden onset AV block (and ventricular pause/s) with concomitant increase in sinus rate	16	
Type 2: Bradycardia—decrease of heart rate >30% or <40 bpm for >10 s		4 (4%)
Type 3: No or slight rhythm variations—variations of heart rate <30% and heart rate >40 bpm		29 (27%)
Type 3A, No variation or <10% variation in heart rate	21	
Type 3B, Increase in heart rate >10% but <30% and <120 bpm; or, decrease >10% but <30% and >40 bpm	8	
Type 4: Tachycardia—increase of heart rate >30% or >120 bpm		16 (15%)
Type 4A, Progressive sinus tachycardia	7	
Type 4B, Atrial fibrillation	3	
Type 4C, Supraventricular tachycardia (except sinus)	5	
Type 4D, Ventricular tachycardia	1	

in patients <70 years than in those ≥70 years [27/53 (51%) vs. 29/53 patients (49%)], during TT, an asystolic response was more frequent in patients <70 years than in those ≥70 years [7/50 (14%) vs. 1/44 (2%), $P = 0.05$]. Also, the correlation between mixed and vasodepressor responses and spontaneous syncope was weak (*Figure 3*). Indeed, only 15/30 patients (50%) with mixed or vasodepressor response had a spontaneous mechanism during ILR, consistent with those responses (i.e. slight rhythm variations), whereas a total of 11/30 patients (36%) had asystole and four (14%) had tachycardia during ILR observations.

Correlation between ATP and spontaneous syncope

This could be evaluated in 52 patients who had undergone ATP tests at enrolment and subsequently had an ILR documentation of a spontaneous syncope. The 14 patients who had a positive response had AV block of 12.8 ± 7.9 s duration with a median maximum pause of 8.1 ± 2.5 s. The patients with positive and negative ATP had similar syncopal recurrence rate (*Figure 4*) and mechanism of syncope (*Table 5* and *Figure 5*). Responses consistent with spontaneously documented syncope were found in only 26

Table 3 Correlation between TT response and the mechanism of syncope, as documented by ILR in 94 patients

ILR response	Tilt positive ($n = 38$)	Tilt negative ($n = 56$)	*P*-value
Type 1, asystole	17 (45%)	30 (54%)	0.53
Type 2, bradycardia	0 (0%)	4 (7%)	0.14
Type 3, no or slight rhythm variations	17 (45%)	12 (21%)	0.02
Type 4, tachycardia	4 (10%)	10 (18%)	0.39

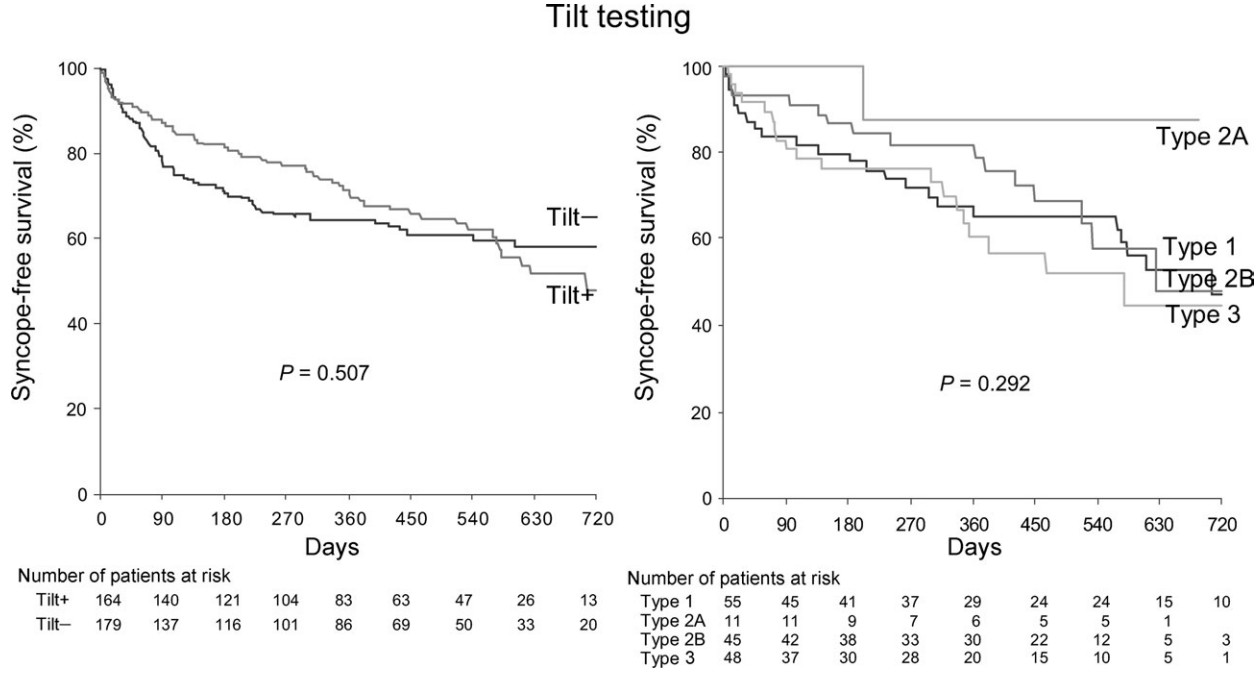

Figure 2 (Left) Kaplan–Meier estimates of syncopal recurrence in patients with positive and negative responses to TT. (Right) Kaplan–Meier estimates of syncopal recurrence in patients with cardioinhibitory (Type 2A and 2B), mixed (type 1), and vasodepressor (type 3) responses according to the New VASIS classification.[10] Log-rank test showed no difference between groups.

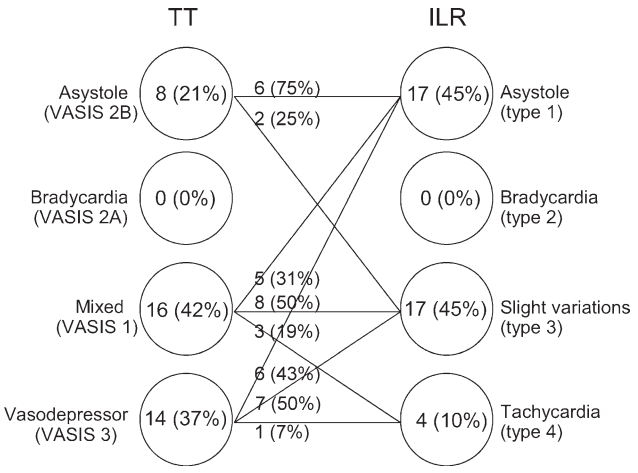

Figure 3 Correlation between the TT response and the mechanism of syncope, as documented by ILR in 38 patients.

Table 4 Correlation between asystolic responses to TT (VASIS type 2B) and the mechanism of syncope, as documented by ILR in 38 patients

ILR response	TT positive		*P*-value
	Asystole ≥3 s ($n = 8$)	No asystole ($n = 30$)	
Asystole ≥3 s ($n = 17$)	6 (75%)	11 (37%)	0.10
No asystole ($n = 21$)	2 (25%)	19 (63%)	

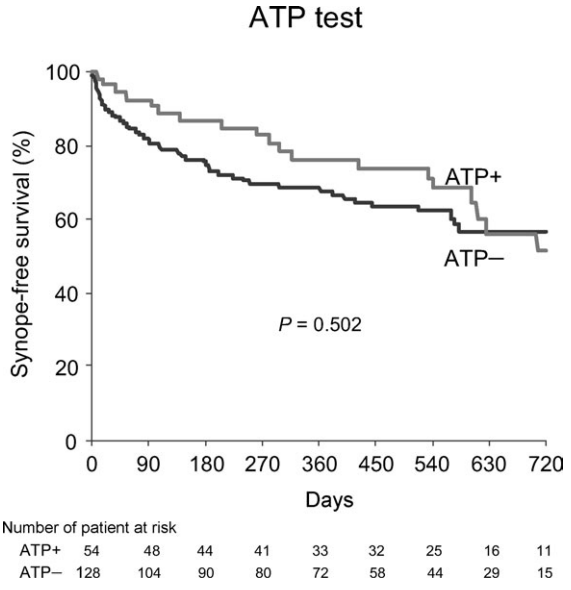

Figure 4 Kaplan–Meier estimates of syncopal recurrence in patients with positive and negative responses to the ATP test. Log-rank test showed no difference between groups.

(54%) patients (*Figure 5*). Thus, ATP test results were unrelated to the mechanism of the spontaneously documented syncope. ATP results were also independent from TT results.

Compared with the patients with negative test, those with positive ATP test were older, and there were more females and more patients with hypertension (*Table 1*).

Table 5 Correlation between ATP response and the mechanism of syncope, as documented by ILR in 52 patients

ILR response	ATP positive ($n = 14$)	ATP negative ($n = 38$)	*P*-value
Type 1, asystole	8 (57%)	18 (47%)	0.76
Type 2, bradycardia	0 (0%)	2 (5%)	1.0
Type 3, no or slight rhythm variations	5 (36%)	13 (34%)	1.0
Type 4, tachycardia	1 (7%)	5 (13%)	1.0

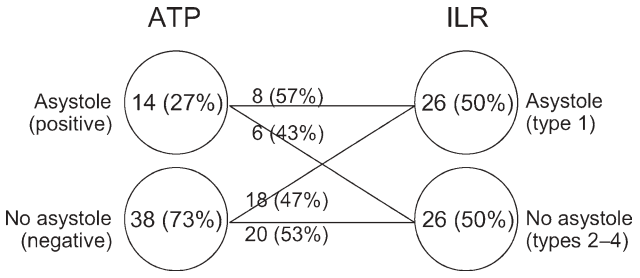

Figure 5 Correlation between the ATP test response and the mechanism of syncope, as documented by ILR in 52 patients.

Discussion

Electrocardiographic findings in patients with suspected neurally mediated syncope

This study shows that a long asystole is the most frequent finding at the time of spontaneous syncope in patients with suspected neurally mediated syncope and that asystolic responses are more frequent during spontaneous syncope than during induced syncope. These findings are consistent with those of two previous smaller studies.[1,8] This study also shows that the heterogeneous findings at the time of syncope can easily be classified according to major categories such as those of the ISSUE classification.[12]

Despite the enhancement of diagnostic capabilities by the ILR in providing a correlation between electrocardiographic findings and syncope, the device is still unable to provide any information about arterial blood pressure and cerebral blood flow, which are involved in causing syncope. Moreover, the exact nature of a documented arrhythmia, i.e. intrinsic cardiac vs. extrinsic reflex, may remain uncertain. For all these reasons, the underlying mechanism of syncope is still largely uncertain and aetiology can only be inferred.[12] For example, on the one hand, the findings of progressive sinus bradycardia, most often followed by ventricular asystole due to sinus arrest, or progressive tachycardia followed by progressive bradycardia and, eventually, ventricular asystole due to sinus arrest (type 1A, 1B, and 2 of ISSUE classification[12]) suggest that the aetiology of syncope is neurally mediated[1]; on the other hand, the observation that a minority of patients had documentation of an atrial or ventricular tachyarrhythmia at the time of recurrence of syncope, a mechanism that is probably inconsistent with the initial neurally mediated diagnosis, suggests that a primary cardiac aetiology was the major determinant of syncope (type 4B, 4C, and 4D).[12] Nevertheless, the study population was of patients who, in accordance with

current guidelines,[6,7] are usually diagnosed as affected by a likely neurally mediated syncope and, in absence of an ILR observation, are managed with conventional treatments of neurally mediated syncope.

Predictive value of TT

This study shows that the mechanism of spontaneous syncope as documented by an ILR is poorly correlated with the results of TT. Owing to the high rate of discordance between test and reference standard, the clinical utility of TT in predicting the spontaneous event is modest.

The syncopal recurrence rate was not predicted by the results of TT (*Figure 1*), as shown previously by others.[1,14,15] However, the patients with positive TT more frequently had no or slight rhythm variations during spontaneous syncope than those with negative TT (*Table 3*). The reason for this small difference is unclear, and its clinical utility is useless because of the unacceptably low positive predictive value (58%) and sensitivity (45%) (*Figure 2*).

Asystolic responses are more frequent during spontaneous syncope than during induced syncope. In the present study, an asystolic response (i.e. type 2B of the New VASIS classification) is present in 21% of positive tests, the same percentage observed in the original New VASIS description.[10] Although with ILR an asystolic syncope was equally frequent in the younger as in the older patients, during TT, an asystolic response was more frequent in the younger patients.

As a consequence, TT has a low sensitivity in detecting asystolic responses during spontaneous syncope. However, there was a trend for patients with asystolic responses during TT to have an asystolic event during spontaneous syncope (*Table 4* and *Figure 2*). This correlation gives a 75% probability of an asystolic response during TT to predict an asystolic event during spontaneous syncope with a low sensitivity of 35% This latter observation is reinforced by pooling the data of this study with those of the first ISSUE study[1]: eight out of 10 patients with an asystolic response during TT also showed an asystolic event during spontaneous syncope compared with 14/36 with mixed or vasodepressor response [$P = 0.02$, odds ratio 6.3 (95% CI 1.2–34), positive predictive value 80%]. In other words, it seems that an asystolic response during TT is able to predict an asystolic response during spontaneous syncope with a 20% risk of misdiagnosis, but a mixed or vasodepressor response during TT cannot exclude an asystolic spontaneous syncope.

This study was not aimed to evaluate the effect of TT to guide therapy. However, on the basis of these findings, it has been found that a mechanism-specific therapy guided by TT results has potential limitations and seems less likely to be effective than ILR-based therapy. These findings might give an explanation of the controversial results of controlled trials of tilt-guided therapy, specifically those evaluating the effect of pacing therapy. The efficacy of pacemaker therapy was questioned after two recent controlled blind trials failed to prove superiority of cardiac pacing over placebo of unselected patients with positive TT.[16,17] Conversely, other controlled unblind pacemaker trials in which patient inclusion was largely made by the presence of an asystolic TT response showed efficacy of cardiac pacing.[18,19] This is not surprising if we consider that, in this as well as in previous ILR studies,[1–4] the mechanism of syncope was heterogeneous, with bradycardia or asystole accounting for up to a half of the syncopal events.

Predictive value of ATP

In the present study, ATP test was positive in 30% of the patients. This figure is similar to the 28% rate reported in the literature in a study using the same methodology.[11]

The syncopal recurrence rate bore no relationship with the ATP results (*Figure 3*), and the mechanism of spontaneous syncope as documented by ILR was not predicted at all by the results of the ATP test (*Table 5* and *Figure 4*). These results are consistent with those of previous studies.[8,9] Therefore, the ATP test is definitely of no value in guiding ILR-based therapy. The observation in this study, as well in previous ones,[11,20] that ATP-positive patients had a few peculiar clinical characteristics that differentiated them from the others (*Table 1*) remains largely unexplained and seems to have no practical value.

Limitations

The ISSUE classification[12] is based on observations during syncope. We do not know whether similar findings are also present in the general population. For example, what is the prevalence of pauses >3 s among subjects without history of syncope? This question is of practical importance because the absence of pauses in patients without syncope would increase the value of the same findings in patients with syncope. We know from previous studies on 24 h Holter monitoring that pauses >3 s are very rare in subjects without syncope and these were never observed among 259 healthy older adults pooled from three studies.[21–23] Admittedly, this finding cannot be automatically translated to ILR, which has much more powerful capabilities of detecting abnormalities, if any. An analysis from ISSUE 2 study (data not yet published) showed that an asymptomatic asystolic pause >3 s was detected in only 1/158 (0.6%) documented events among patients with diagnosis of non-asystolic syncope compared with 13/25 (52%) documented events among patients with a diagnosis of asystolic syncope ($P < 0.001$). However, even if these findings seem to suggest a good specificity of asystolic pauses <3 s, uncertainty still persist on their value.

This study shows that syncope is difficult to predict and most patients did not have recurrence during the 12-month follow-up period. Therefore, a longer follow-up would have been probably helpful in order to determine the mechanism of syncope in other patients. Theoretically, these late-recurrent patients could have mechanisms different from the early-recurrent patients. Longer follow-up was limited by the battery longevity of the present ILR generation. By extrapolating the recurrence curve shown in *Figure 2*, we can expect that 4 years of follow-up would be necessary to detect syncope in about 80% of the patients.

The study correlated one test with the first ILR-documented episode. Reproducibility of spontaneous episodes was not systematically evaluated; a weak reproducibility of spontaneous responses would impair the importance of the results. An analysis of those patients who had multiple syncopal episodes in the ISSUE 2 study (data not yet published) showed that an asystolic syncope was present in three of the four (75%) patients who had a first asystolic syncope vs. none of the nine (0%) patients who

had a first non-asystolic syncope ($P = 0.01$); moreover, ISSUE 2 study therapy,[5] a proven effective-specific therapy, was administered on the basis of the first ILR finding, thus indirectly supporting a good reproducibility of spontaneous mechanisms of syncope.

Conclusions and practical implications

In patients with neurally mediated syncope, clinical characteristics, outcome, and mechanism of syncope are poorly correlated with and not predicted by the results of TT and ATP test. ISSUE 2 therapy study[5] showed that pacing is effective when asystole is documented at the time of syncope and that a strategy based on therapy delayed until ILR documentation is useful. The capability of TT and ATP to predict ILR spontaneous syncope would allow to anticipate therapy and avoid ILR implant. Unfortunately, this correlation being weak or absent, these tests are probably of little or no value for guiding specific therapy with the exception, perhaps, of asystolic responses during TT.

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Conflict of interest: R.S. reports having served as a consultant for Medtronic Inc., and D.G.B. for Medtronic Inc., St Jude Medical Inc., and Cardionet Inc., during the period of this investigation. N.G. and T.D.S. are employees of Medtronic Italy.

Appendix

The following persons participated in the ISSUE-2 study. Steering Committee: M. Brignole (Chair), R. Sutton, C. Menozzi, A. Moya, R. Garcia-Civera, D.G. Benditt, P. Vardas, W. Wieling, D. Andresen, R. Migliorini, D. Hollinworth; Endpoints Committee: M. Brignole, C. Menozzi, R. Sutton, A. Moya; Database Electronic Management: RDES SL, Barcelona, Spain; Study Management: M. Brignole, N. Grovale, F. Zanna; Clinical Monitors: N. Grovale (Chair), F. Zanna, M.P. Lopez, S. Mohammad, A. Guthmann, M. Manders, D. Van Aggel, D. Erckens, V. Andersen, E. Sousani, C. Eppacher, J. St Ores; Statistical Analysis: T. De Santo.

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The Netherlands (31 patients): Atrium Medisch Centrum, Heerlen: A.J.J. Aerts; St Antonius Ziekenhuis, Nieuwegein: L.V.A. Boersma; Academisch Medisch Centrum, Amsterdam: W. Wieling; Lucas/Andreas Ziekenhuis, Amsterdam: J.M. Schroeder-Tanka; St Franciscus Gasthuis, Rotterdam: R. Van Mechelen; Medisch Centrum Alkmaar, Alkmaar: J.H. Ruiter.

Germany (30 patients): Krankenhaus Am Urban, Berlin: D. Andresen, C. Ehlers; University Klinikum Hamburg-Eppendorf, Hamburg: T. Meinerts, A. Schuchert; Klinikum Chemnitz, Chemnitz: T. Vieth; Klinikum Großhadern der L-M Universität, München: C. Reithmann; Evangelisches Krankenhaus, Holzminden: P. Von Lowis of Menar.

UK (26 patients): Bristol Royal Infirmary, Bristol: T. Cripps; Eastbourne DGH, Eastbourne: N. Sulke; Royal Brompton Hospital, London: R. Sutton; Newcastle General Hospital, University of Newcastle, Newcastle: R.A. Kenny; Glenfield Hospital, Glenfield: J.D. Skehan; St Peter's Hospital, Chertsey: V. Paul, M. Wrigley.

USA (14 patients): University of Minnesota, Minneapolis: D.G. Benditt.

Greece (13 patients): University Hospital of Crete, Herakleion: P. Vardas; AHEPA, Thesaloniki: G.E. Louridas, V. Vasilikos.

Denmark (three patients): HS Bispebjerg Hospital, København: T.N. Jakobsen; University Hospital, Odense: E.H. Simonsen, J.B. Johansen.

Austria (two patients): Bezirkskrankenhaus Hall, Tirol: W. Grander.

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