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

Michele Brignole1*, Richard Sutton2, Carlo Menozzi3, Roberto Garcia-Civera4, Angel Moya5, Wouter Wieling6, Dietrich Andresen7, David G. Benditt8, Nicoletta Grovale9, Tiziana De Santo9, and Panos Vardas10 for the International Study on Syncope of Uncertain Etiology 2 (ISSUE 2) Group

1Department of Cardiology, Arrhythmologic Centre, Ospedali del Tigullio, Via don Bobbio 24, 16033 Lavagna, Italy; 2Department of Cardiology, Royal Brompton and Harefield Hospitals, London, UK; 3Department of Cardiology, Ospedale S Maria Nuova, Reggio Emilia, Italy; 4Department of Cardiology, H. Clínicas, Valencia, Spain; 5Department of Cardiology, Hospital General Vall d’Hebron, Barcelona, Spain; 6Department of Internal Medicine, Academisch Medisch Centrum, Amsterdam, The Netherlands; 7Department of Cardiology, Krankenhaus Am Urban, Berlin, Germany; 8Department of Cardiology, University of Minnesota, Minneapolis, USA; 9Clinical and New Business Development Division, Medtronic Italia, Rome, Italy; and 10Department of Cardiology, University Hospital of Crete, Herakleion, Greece

Received 10 March 2006; revised 27 May 2006; accepted 6 July 2006; online publish-ahead-of-print 24 July 2006

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-documented 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, diagnostic, and therapeutic 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
Deharo et al. in seven of 11 patients. Donato et al. found a correlation between ATP test and spontaneous findings in eight out of 16 patients and Deharo et al. 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.

Methods

The ISSUE-2 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 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 ≤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 all 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. 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.

A positive response to ATP test was defined as the induction of complete AV block (or sinus pause) with a ventricular pause ≥6.0 s.

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. The study protocol has been previously published.

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 syncope event were collected. ECG-documented syncopal 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. 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 ± 6 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). 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.
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 syncope 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 \( \geq 3 \text{s} \) 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.
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 2** The mechanism of syncope documented by ILR in 106 patients and assigned according to the ISSUE classification

| 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 |
| Type 1B, Sinus bradycardia plus AV block | Progressive sinus bradycardia followed by AV block (and ventricular pause/s) with concomitant decrease in sinus rate | 9 |
| Type 1C, AV block | Sudden onset AV block (and ventricular pause/s) with concomitant decrease in sinus rate |
| 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 | 8 |
| Type 3B, Increase in heart rate >10% but <30% and <120 bpm; or, decrease >10% but <30% and >40 bpm |
| Type 4: Tachycardia—increase of heart rate >30% or >120 bpm |
| Type 4A, Progressive sinus tachycardia | 16 (15%) |
| Type 4B, Atrial fibrillation | 7 |
| Type 4C, Supraventricular tachycardia | 3 |
| Type 4D, Ventricular tachycardia | 1 |

---

**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. Log-rank test showed no difference between groups.
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).

### 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; 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 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. 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. 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: 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. 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. This is not surprising if we consider that, in this as well as in previous ILR studies, 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.

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. Therefore, the ATP test is definitely of no value in guiding ILR-based therapy. The observation in this study, as well in previous ones, 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 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. 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.

Acknowledgements

This study was officially endorsed by the European Heart Rhythm Association and was supported by a grant from Medtronic Europe.

Conflict of interest: R.S. reports having served as a consultant for Medtronic Inc., and D.G.B. for Medtronic 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. Eckens, V. Andersen, E. Sousani, C. Eppacher, J. St Ores; Statistical Analysis: T. De Santo.

Centres and investigators (in order of number of patients recruited)

**Italy** (214 patients): Arcispedale S. Maria Nuova, Reggio Emilia: C. Menozzi, N. Bottoni; Ospedale S. Filippo Neri, Roma: F. Ammirati, M. Santini; Ospedali del Tigullio, Lavagna: M. Brignole, P. Donatoe; Ospedale Umberto I, Mestre: A. Vareire, F. Giaia; Ospedale S. Camillo De Lellis, Rieti: S. Orazi; Ospedale Civile, Cento: P. Alboni, M. Dinelli; Ospedale San Luca, Milano: G. Perego; R. Brambilla; Ospedale San Pietro Ignace, Fucecchio: A. Del Rosso; Ospedale S. Gerardo dei Tintori, Monza: A. Vincenti, S. De Cecilia; Ospedale Civile, Bentivoglio: B. Sassone; Ospedale di Versilia, Lido di Camaiore: M.T. Baratto; Ospedale Pontenuovo, Firenze: A. Ungar; Ospedale S. Luigi, S. Curro; Catania: M. Guzilia, M. Francese; Ospedale S. Spirito in Sassia, Roma: L. Pandolfo, M. Burattini; Ospedale per gli Infermi, Faenza: D. Cornachia; Policlinico di Modena, Modena: E. Casali; Ospedale Bolognini, Seriate: P. Giani; Policlinico Seconda Università degli studi, Napoli: L. Santangelo, S. Panicco; Ospedale San Antonio e Biagio, Alessandria: G. De Marchi; Ospedale S. Orsola Fatebenefratelli, Brescia: A. Marchetti; Clinica Cardiologica dell’Università di Padova, Padova: G. Buja, F. Polino; Clinica Villa Tiberia, Roma: A. Spampinato, G. Bruni; Ospedale Riguardo, Milano: M. Lunati; Clinica Noto Pasqualino, Palermo: G. Buttera.

**Spain** (109 patients): Hospital Clínico, Valencia: R. Garcia-Civera, S. Morell, R. Ruiz, R. Sanjuan; Hospital General de Albacete, Albacete: J.F. García-Sacristán; Hospital Xeral de Vigo, Vigo: X. Beiras, E. García; Hospital Vall d’Hebrón, Barcelona: A. Moya, C. Alonso; Hospital Virgen de la Arrixaca, Murcia: A. García-Alberola, J. Lacunza; Hospital Clínico San Carlos, Madrid: J. Villacastín, N. Pérez-Castellano; Hospital General de Valencia, Valencia: J. Roda, V. Palianca; Hospital del Mar, Barcelona: J. Martí, J. Delclós; Hospital Virgen de las Nieves, Granada: M. Alvarez, L. Tercedor; Hospital Virgen de la Salud, Toledo: E. Castellanos; Hospital de Santa María, Lleida: J. Tomás-Mauri; Hospital Puerta de Hierro, Madrid: I. Fernández-Lozano, J. Toquero; Hospital de Alarcos, Ciudad Real: J. Bénezet; Hospital Complejo Hospitalario, León: M.L. Fidalgo; Hospital General de Alicante, Alicante: J.G. Martínez; Hospital Rio Hortega, Valladolid: B. Herreros, F. Muñoz.

**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. Schroder-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. Meiners, 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, Herakleon: P. Vardas; AHEPA, Thessaloniki: G.E. Louridas, V. Vasilikos.

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

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

**References**

1. Moya A, Brignole M, Menozzi C, Garcia-Civera R, Tognarini S, Mont L, Botto G, Giada F, Cornachia D. Mechanism of syncope in patients with isolated syncope and in patients with tilt-positive syncope. *Circulation* 2001;104:1261–1267.

2. Krahn AD, Klein GJ, Yee R, Takle-Newhouse T, Norris C. Use of an extended monitoring strategy in patients with problematic syncope. *Reveli Investigators. Circulation* 1999;96:406–410.

3. Krahn A, Klein G, Yee R, Skanes AC. Randomized assessment of syncope trial. Conventional diagnostic testing vs a prolonged monitoring strategy. *Circulation* 2001;104:46–51.

4. Farwell D, Freemantle N, Sulke N. Use of implantable loop recorders in the diagnosis and management of syncope. *Eur Heart J* 2004;25:1257–1263.

5. Brignole M, Sutton R, Menozzi C, Garcia-Civera R, Moya A, Wieling W, Andresen D, Benditt DG, Vardas P. Early application of an implantable loop recorder allows a mechanism-based effective therapy in patients with recurrent suspected neurally mediated syncope. *Eur Heart J* 2006;27:1085–1092.

6. Brignole M, Alboni P, Benditt D, Bergfeldt L, Blanc JJ, Thomsen PE, van Dijk G, Fitzpatrick A, Hohnloser S, Janousek J, Kapoor W, Kenny RA, Kulakowski P, Moya A, Raviele A, Sutton R, Theodorakis G, Wieling W. Guidelines on management (diagnosis and treatment) of syncope. *Eur Heart J* 2001;22:1256–1306.
7. Brignole M, Alboni P, Benditt D, Bergfeldt L, Blanc JJ, Thomsen PE, van Dijk G, Fitzpatrick A, Hohnloser S, Janousek J, Kapoor W, Kenny RA, Kulakowski P, Masotti G, Moya A, Raviele A, Sutton R, Theodorakis G, Ungar A, Wieling W. Guidelines on management (diagnosis and treatment) of syncope—Update 2004. Europace 2004;6:467–537.

8. Deharo JC, Jego C, Lanteaume A, Dijane P. An implantable loop recorder study of highly symptomatic vasovagal patients: the heart rhythm observed during a spontaneous syncope is identical to the recurrent syncope but not correlated with the head-up tilt test or ATP test. J Am Coll Cardiol 2006;47:587–593.

9. Donateo P, Brignole M, Menozzi C, Bottoni N, Alboni P, Dinelli M, Del Rosso A, Croci F, Oddone D, Solano A, Puggioni E. Mechanism of syncope in patients with positive adenosine triphosphate tests. J Am Coll Cardiol 2003;41:93–98.

10. Brignole M, Menozzi C, Del Rosso A, Costa S, Gaggioli G, Bottoni N, Bartoli P, Sutton R. 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.

11. Brignole M, Gaggioli G, Menozzi C, Gianfranchi L, Bartoletti A, Bottoni N, Lolli G, Oddone D, Del Rosso A, Pellinghelli G. Adenosine-induced atrio-ventricular block in patients with unexplained syncope. The diagnostic value of ATP test. Circulation 1997;96:3921–3927.

12. Brignole M, Moya A, Menozzi C, Garcia-Civera R, Sutton R. Proposed electrocardiographic classification of spontaneous syncope documented by an implantable loop recorder. Europace 2005;7:14–18.

13. The Steering Committee of the ISSUE 2 study. International Study on Syncope of Uncertain Etiology 2 (ISSUE 2): the management of patients with suspected or certain neurally mediated syncope after the initial evaluation. Rationale and study design. Europace 2003;5:317–321.

14. Sheldon R, Rose S, Koshman M. Comparison of patients with syncope of unknown cause having negative or positive tilt-table tests. Am J Cardiol 1997;80:581–585.

15. Grimm W, Degenhardt M, Hoffman J, Menz V, Wirths A, Maisch B. 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;18:1465–1469.

16. Connolly SJ, Sheldon R, Thorpe KE, Roberts RS, Ellenbogen KA, Wilkoff BL, Morillo C, Gent M for the VPS II Investigators. Pacemaker therapy for prevention of syncope in patients with recurrent severe vasovagal syncope: Second Vasovagal Pacemaker Study (VPS II). JAMA 2003;289:2224–2229.

17. Giada F, Raviele A, Menozzi C, Speca G, Orazi S, Gasparini G, Sutton R, Brignole M. The vasovagal syncope and pacing trial (Synpace). A randomized placebo-controlled study of permanent pacing for treatment of recurrent vasovagal syncope. Eur Heart J 2004;25:1741–1748.

18. Sutton R, Brignole M, Menozzi C, Raviele A, Alboni P, Giani P, Moya A. Dual-chamber pacing in treatment of neurally mediated tilt-positive cardioinhibitory syncope. Pacemaker vs no therapy: a multicentre randomized study. Circulation 2000;102:294–299.

19. Ammirati F, Colivicchi F, Santini M. Permanent cardiac pacing vs medical treatment for the prevention of recurrent vasovagal syncope. A multicenter, randomized, controlled trial. Circulation 2001;104:52–57.

20. Perennes A, Borel ML, Lebras Y, L’Her C, Fatemi M, Blanc JJ. Epidemiology, clinical features and follow-up of patients with syncope and positive adenosine triphosphate test. J Am Coll Cardiol 2006;47:594–597.

21. Molgard H, Sorensen E, Bjerregard P. Minimal heart rates and longest pauses in healthy adult subjects on two occasions eight years apart. Eur Heart J 1989;10:758–764.

22. Kantelip JP, Sage E, Duchene-Marullaz P. Findings on ambulatory electrocardiographic monitoring in subjects older than 80 years. J Electrocardiol 1990;23:171–176.