

Treatment of Unexplained Syncope

A Multicenter, Randomized Trial of Cardiac Pacing Guided by Adenosine 5'-Triphosphate Testing

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Background—The origin of 40% of syncope cases remains unknown even after a complete diagnostic workup. Previous studies have suggested that ATP testing has value in selecting successful therapy. This patient-blinded, multicenter, randomized superiority trial tested whether, in patients with syncope of unknown origin, selecting cardiac pacing in those with a positive ATP test leads to fewer recurrences than those who do not receive pacing.

Methods and Results—From 2000 to 2005, 80 consenting patients (mean age, 75.9 ± 7.7 years; 81% women; 56% without diagnosed structural heart disease) with syncope of unknown origin and atrioventricular or sinoatrial block lasting > 10 seconds (average, 17.9 ± 6.8 seconds) under ATP administration (20-mg IV bolus) were recruited from 10 hospitals, implanted with programmable pacemakers, and randomized to either active pacing (dual-chamber pacing at 70 bpm) or backup pacing (atrial pacing at 30 bpm). Patients were followed up regularly for up to 5 years for any syncope recurrence, the primary outcome. Mean follow-up was 16 months. Syncope recurred in 8 of 39 patients (21%) randomized to active pacing and in 27 of 41 (66%) randomized to backup pacing (control), yielding a hazard ratio of 0.25 (95% confidence interval, 0.12–0.56). After recurrence, the 27 recurrent control patients were reprogrammed to active pacing, and only 1 reported subsequent syncope.

Conclusion—This study suggests that, in elderly patients with syncope of unknown origin and positive ATP tests, active dual-chamber pacing reduces syncope recurrence risk by 75% (95% confidence interval, 44–88).

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Key Words: adenosine triphosphate ■ pacemaker, artificial ■ randomized controlled trials ■ syncope ■ syncope, vasovagal

Syncope is defined as a transient, short-lasting, and self-limiting loss of consciousness caused by temporary cerebral hypoperfusion.¹ The incidence of syncope increases significantly with age.^{1,2} Syncope of unknown origin (SUO) is defined as a syncope for which no clear explanation has been found after a conventional workup; it heavily affects the cost of medical care.^{3,4} As the longevity of the Western population increases,⁵ the incidence of syncope and of secondary injuries will also increase with time. Despite an extensive workup, the origin of syncope remains unexplained in 20% to 40% of patients.^{1,6,7} SUO may be neurally mediated; its current treatment is based on the avoidance of triggering situations, orthostatic training, and drug therapy, all with uncertain long-term results.

Clinical Perspective on p 36

The ATP test was introduced in 1986 to identify those SUO patients with predominantly neurally mediated cardiac inhibition who may benefit from cardiac pacing therapy.⁸ The present clinical trial was carried out to test the hypothesis that, in patients with SUO, cardiac pacing instituted on the basis of a positive ATP test is an effective long-term therapy for significantly reducing syncope recurrences.

Methods

Study Overview and Objective

Patients with SUO recruited in 10 European centers were screened conventionally¹ and subjected to the ATP test, as previously de-

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scribed.⁹ SUO patients with a negative test were ineligible for the study and were followed up and treated conventionally. Those with a positive test who gave written consent were randomized to either an active pacing mode or a control mode (described below) and then implanted with a dual-chamber pacemaker. Patients were blinded to their pacing mode; investigators were not. After implantation, patients were systematically followed up every 6 months and were asked to report any syncope immediately on recurrence. The study objective was to test whether the groups differed in the rate of syncope recurrence as measured by syncope-free survival. The study was approved by the ethics committee of each hospital. A copy of the protocol can be found at https://www.healthstudies.umn.edu/trc/en/en_protocol-2002-02-21.pdf.

Patients

Patients >18 years of age who presented with isolated or recurrent episodes of syncope that remained unexplained by the usual screening tests (history, clinical examination, orthostatic hypotension investigation, echocardiogram, ECG, and Holter) were recruited after either a short stay in the emergency room or a visit to the outpatient clinic. Electrophysiological studies, exercise tests, EEGs, and brain scans were also performed when the site investigator deemed them necessary to complete a patient's evaluation. Patients who agreed to participate and signed the consent form were eligible for further evaluation. Patients were ineligible if they had at least one of the following: positive electrophysiological study, carotid sinus hypersensitivity,¹ sustained or episodic atrial or ventricular tachycardias, documented sinus or atrioventricular (AV) node conduction disorders (including first-degree AV block), presence of an implantable pacemaker or defibrillator, enrollment in a heart transplant waiting list, pregnancy, asthma or severe chronic bronchitis, systemic infection, or diabetes mellitus.

Patient Enrollment

Eligible patients were evaluated with the following tests in this order: a sequential right and left carotid sinus massage in the supine and, if negative, upright positions; the ATP test; and finally an optional head-up tilt test at the discretion of the site investigator. Carotid sinus massage and head-up tilt test were performed according to guidelines.¹⁶

The ATP test is administered to a supine patient connected to an ECG recorder. The test consists of an intravenous bolus of 20 mg ATP (Striadyne, Genopharm Group) followed by a rapid flush of 20 mL dextrose (5%).⁹ ATP injection characteristically causes the following 5-phase sequence of ECG: (1) slowing of the sinus rhythm; (2) short episode of first- or second-degree AV block (sometimes phase I is followed by phase III without occurrence of phase II); (3) "cardiac pause," defined as a third-degree AV block or, more rarely, isolated or associated sinoatrial block of variable duration, determining the outcome of the test; (4) resumption of normal AV conduction preceded by a second- and a first-degree AV block; and (5) a reflex sinus tachycardia. Resumption of normal sinus rhythm and AV conduction marks the end of the response.

On the basis of the distribution of test results in a sample of asymptomatic healthy individuals, the test is considered positive when phase III cardiac pause exceeds 10 seconds, regardless of any specific time interval between consecutive ventricular contractions (R-R) (and ignoring junctional or ventricular escape beats) and regardless of secondary symptoms.⁹ The ECG tracings recorded during the ATP test were reviewed by 2 independent examiners, and the patient was eligible if both reviewers declared the test positive.

Randomization and Blinding

Patients with a positive ATP test were randomized with equal probability to 1 of the 2 pacing mode groups; the patient was not told which one. Randomization was performed by the use of sealed envelopes distributed by the data coordinating center and was stratified by center (and no other factors) in blocks of 10 to ensure balanced allocation. The research staff was not blinded to pacing mode. No attempt was made to evaluate the success of patient blinding.

Pacemaker Implantation and Programming

After randomization, the patient was implanted with a rate-responsive dual-chamber pacemaker of the investigator's choosing. The pacemaker was programmed either to dual-chamber pacing and sensing with both inhibition and triggering (DDD) at 70 bpm or to atrial pacing and sensing with inhibition (AAI) at 30 bpm. Active DDD pacing at 70 bpm was chosen as the paced mode because it can maintain an effective hemodynamic status, and thus may prevent syncope caused by cardiac pause. The AAI pacing at 30 bpm was chosen to provide only a minimal-rate atrial pacing in case of sinoatrial block without preventing syncopal symptoms (except in rare instances), and served as the placebo control mode.

Follow-Up

Patients were followed up every 6 months and were instructed, as were their relatives, to report each syncope recurrence similar to those occurring before enrollment in the study. After the first reported recurrence of syncope, pacemakers were reprogrammed as follows: For patients initially programmed in AAI mode, the pacemaker was switched into DDD mode at 70 bpm; for patients in DDD mode, the DDD mode was maintained, but at the physician's discretion, either rate-responsive pacing or a rate drop-sensing algorithm that immediately increases the pacing rate for a few minutes when a third-degree AV block is detected could be added. The patient case report had a section for reporting adverse effects, and the investigators were free to treat adverse effects according to their usual practice.

Statistical Analysis

Sample size was determined by the method of Wu et al.¹⁰ With the assumption of a 40% recurrence rate in the placebo group on the basis of an earlier study⁹ and a therapeutic effect of at least a 55% reduction in cumulative recurrence rate on the basis of the randomized pilot study,¹¹ inclusion of 198 subjects yields 80% power, with a 2-sided type I error rate of 5%. However, smaller sample sizes still yield sufficient power against larger effects. For example, 76 participants provide 75% power against an effect of 70%, with the same recurrence and type I error rates.

Patient characteristics and test outcomes were summarized by means and SDs or tabulated by frequency, and were compared by *t* tests or χ^2 tests of homogeneity. The primary end point was the time to the first syncope recurrence, and groups were compared by intention-to-treat analysis. Kaplan-Meier estimates of cumulative recurrence-free survival probabilities were used to compare groups for the primary analysis. To control for the potential differential effect of a study center, center-stratified analyses of the main outcome were performed with Cox regression. Cox regression was also used to examine the effects of age, sex, underlying structural heart disease, and concomitant risk factors of ischemic heart disease. All analyses were performed with S-Plus version 7.0 (S-Plus 7 for Windows; Insightful Corp, Seattle, WA).

Independent Data Access and Analysis

The principal investigator (D.F.) had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The analysis itself was conducted by an independent academic statistician (T.R.C.) using his institution's computer equipment and receiving no funding from any outside interests for this work or for his authorship work. The principal investigator (D.F.) conceived the project and collaborated with the independent academic statistician (T.R.C.) to design the study, to critically review the analyses, and to draft the manuscript. The remaining authors collaborated on the conduct of the study, acquisition of the data, and critical review of the report. All authors read and approved the final version of the report before submission.

Results

The ATP test was positive in 88 SUO patients screened for potential inclusion during the planned accrual period between January 2000 and May 2005; 80 consented patients were

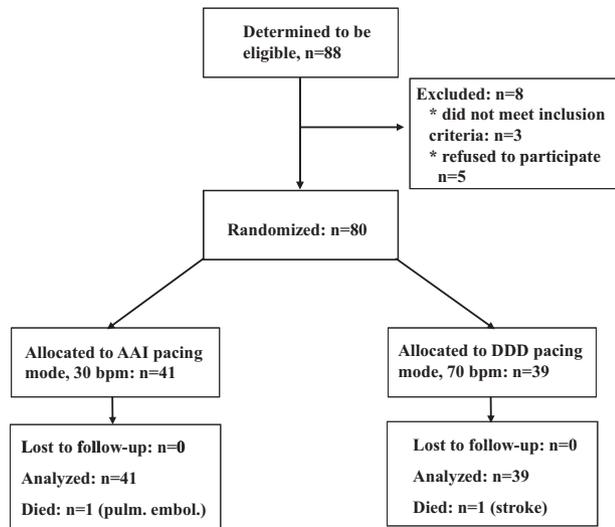


Figure 1. Consolidated Standards of Reporting Trials (CONSORT) diagram showing disposition of all subjects for recruitment, randomization, and follow-up. AAI indicates atrial pacing and sensing with inhibition; DDD, dual-chamber pacing and sensing with both inhibition and triggering.

randomized and implanted with a pacemaker (Figure 1). Their ages ranged from 48 to 91 years (mean±SD, 75.9±7.7 years); 65 (81%) were women; and 35 (44%) had controlled structural heart disease, 18 (23%) of ischemic origin (Tables 1 and 2). At least 1 risk factor for ischemic heart disease was reported for 74% of patients, hypertension being the most

Table 1. Comparing of Sex, Structural Heart Disease, and Risk Factors for Ischemic Heart Disease in the Paced and Nonpaced Groups

Variables	Study Group				Overall (N=80)	
	Paced (DDD) (n=39)		Nonpaced (AAI) (n=41)		Frequency, n	%
Sex						
Women	30	77	35	85	65	81
Men	9	23	6	15	15	19
Structural heart disease						
None	22	56	23	56	45	56
Ischemic	9	23	9	22	18	23
Hypertensive	7	18	9	22	16	20
Valvular	7	18	2	5	9	11
Other	1	3	1	2	2	3
Risk factors						
None	12	31	9	23	21	26
Hypertension	21	54	20	51	41	51
Diabetes mellitus	6	15	13	33	19	24
Smoking	2	5	3	8	5	6
Obesity	4	10	3	8	7	9

DDD indicates dual-chamber pacing and sensing with both inhibition and triggering; AAI, atrial pacing and sensing with inhibition.

Table 2. Comparison of Age, Heart Rate, Cardiothoracic Index, and Phase III Duration in the Paced and Nonpaced Groups

Variables	Study Group		
	Paced (DDD) (n=39)	Nonpaced (AAI) (n=41)	Combined (N=80)
Age, y	75.7±8.4	76.2±7.1	75.9±7.7
Resting heart rate, bpm	71.1±10.8	71.1±9.4	71.1±10.1
Cardiothoracic index, %*	49.9±7.6	50.9±6.0	50.4±6.8
Phase III duration, s†	17.3±6.1	18.3±7.5	17.8±6.8

DDD indicates dual-chamber pacing and sensing with both inhibition and triggering; AAI, atrial pacing and sensing with inhibition. Values are mean±SD.

*A measure of the size of the heart relative to the size of the thorax.

†Length of the period of complete block used to determine the ATP test outcome.

frequent (51%). During the ATP test, the complete AV (78 patients) or sinoatrial (2 patients) block lasted 17.8±6.8 seconds. The duration and characteristics of the different phases of the ATP test were comparable to those previously published,^{9,11,12} including a low incidence of vagal atrial fibrillation (5 patients) and a large (average, 35%) increase in heart rate resulting from reflex sinus tachycardia commensurate with the degree of phase III vagal effect. No side effects after ATP injection were observed, except the expected short-lasting vasodilative flush (<3 minutes).

All patients received a rate-responsive dual-chamber pacemaker; 39 patients were assigned to the active pacing group (DDD mode at 70 bpm) and 41 to the control group (AAI mode at 30 bpm). The time to first syncope recurrence ranged from 7 days to 26 months.

Syncope recurred in 27 of the 41 patients (66%) programmed in the AAI pacing mode but in only 8 of the 39 patients (21%) programmed in the DDD pacing mode. The Kaplan-Meier estimates of 2-year recurrence-free survival were 31% (95% confidence interval, 19–53) for the AAI group and 77% (95% confidence interval, 65–93) for the DDD group (Figure 2). This

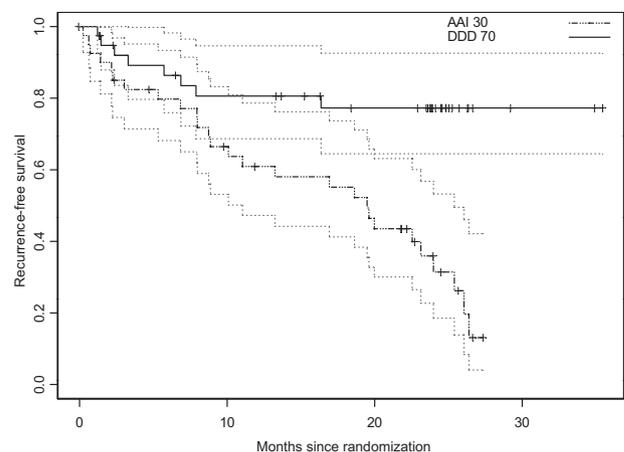


Figure 2. Kaplan-Meier estimates of recurrence-free survival by study treatment arm. Solid line represents the paced group experience; broken line (---), the nonpaced group; dotted line (---), 95% confidence intervals for the estimates; and +, censoring. AAI indicates atrial pacing and sensing with inhibition; DDD, dual-chamber pacing and sensing with both inhibition and triggering.

Table 3. Results of Cox Regression of Recurrence-Free Survival on Randomization Group Unadjusted and Adjusted for Sex, Age, and Clinical Factors

Variables	Hazard Ratio*	95% Confidence Limits	
		Lower	Upper
Randomization group (unadjusted)	0.25	0.12	0.56
Randomization group (adjusted)	0.23	0.08	0.60
Sex (men vs women)	0.49	0.18	1.30
Age at randomization†	0.99	0.94	1.04
Structural heart disease	0.94	0.43	2.09
Risk factors‡	2.06	0.61	6.97
Cardiothoracic index§	1.00	0.94	1.06

*The proportionate difference in risk of recurrence between the paced and nonpaced groups.

†Per year of age.

‡Presence of at least 1 of the risk factors in Table 1.

§A measure of the size of the heart relative to the size of the thorax.

is an estimated 60% reduction in the cumulative risk of recurrence in the 2 years after implantation for the DDD-paced group. The estimated proportional hazard ratio was 0.25 (95% confidence interval, 0.12–0.56; Table 3). Proportional hazards regression stratified by a study center did not change the results (data not shown). Adjusting for age, sex, underlying heart disease, and the presence of risk factors did not change the risk of recurrence substantially (Table 3).

When the pacemakers of the 27 control patients who experienced recurrences were reprogrammed to the DDD mode at 70 bpm, further symptoms occurred in only 1 patient. In the 8 DDD-mode patients with recurrence, the addition of supplementary algorithms was followed by decreased symptom severity (3 patients) or a lack of recurrence of symptoms (5 patients). Moreover, no pacemaker-related complications occurred during the study follow-up period.

Discussion

This study shows that the ATP test is an effective diagnostic tool to identify SUO patients who may benefit from cardiac pacing. Effective pacing reduced the risk of recurrent syncope in this group of patients by $\approx 75\%$ during a 2-year follow-up. ATP has been used for >60 years to terminate reentrant supraventricular tachycardias involving the AV node.^{13,14} The hypersensitivity to ATP of a specific cohort of SUO patients could suggest a vagal involvement in their syncope origin, which constitutes the rationale for its use as a diagnostic tool in this setting.

Two prior studies evaluated the ATP test for assessing the cardio-inhibitory response in SUO.^{9,11} In the first, an observational study, the duration of this response did not exceed 10 seconds in 95% of a population of 51 asymptomatic healthy individuals; thus, a positive test was defined as a cardiac pause caused by AV or sinoatrial block exceeding 10 seconds.⁹ In the same study, this criterion was subsequently applied to 316 SUO patients; among those patients with a positive ATP test, 83% elected implantation with a dual-chamber pacemaker and had fewer and milder symptom

recurrences than those without a pacemaker (14% versus 48%; $P < 0.0001$).⁹ Patients with a negative ATP test showed no benefit from pacemaker therapy. The second study, a single-center pilot trial, randomly assigned pacemaker implantation to half of the 20 patients with a positive ATP test; those with pacemakers showed no syncope recurrence.¹¹ However, these studies had several limitations. In the former, patients were not randomized to pacemaker therapy; in the latter, the sample size was small (10 subjects per arm), the study involved only 1 center, and the potential for a placebo effect was uncontrolled (Patients in the control group were not implanted). Thus, this patient-blinded, multicenter, randomized trial was initiated to definitively evaluate the potential of the ATP test in selecting permanent cardiac pacing for SUO patients.¹⁵

Patients randomly assigned to pacing had, on average, a nearly 75% lower hazard of symptom recurrence (1–0.25; Table 3), and their chances of surviving at least 2 years without recurrence (Kaplan-Meier estimates; Figure 2) were ≈ 2.5 higher than for control patients, a highly statistically significant result. These results clearly support the usefulness of the ATP test in indicating cardiac pacing as an effective therapy in SUO patients.

Because ATP is not a universally approved drug, some investigators have been using adenosine under the assumption that the cardiovascular effects of ATP and adenosine are identical. The effects of ATP differ substantially from those of adenosine. Extracellular ATP is rapidly degraded to adenosine; therefore, it can exert the same effects as adenosine. However, before its degradation, it triggers a central vagal effect (cardio-cardiac reflex) by activating P2X receptors located on the vagal nerve sensory terminals in the inferoposterior wall of the left ventricle.^{16–19} Adenosine does not activate P2 receptors and therefore does not trigger this reflex. Thus, ATP can mimic all actions of adenosine but not vice versa.

Not only do some of the effects of ATP and adenosine differ, but they also have different molecular weights (507 versus 267 g/mol). Thus, the interpretation of the available research must take into account not only the different receptors that mediate their respective actions but also the relative dose. Because of the differential molecular weights of the 2 compounds, the effective dose of ATP is approximately half that of adenosine; the known efficacy of 18 mg adenosine and 20 mg ATP in terminating AV node reentry strongly suggests that different mechanisms of actions mediate the AV node conduction block induced by the 2 drugs. This is not a trivial issue; for example, in a recent study with a subcohort of 18 younger SUO patients (average age, 55 years), 18 mg adenosine or 20 mg ATP was used as a biologically equivalent agent to provoke cardiac pause.²⁰ In another study, pacemaker therapy was instituted in a small group of 10 younger vasovagal syncope patients (average age, 57 years) on the basis of a positive adenosine test (20-mg intravenous bolus); no syncope recurrence was observed during a limited follow-up period.²¹ In view of the above, it is difficult to compare the results of these studies with the present results.

The 2009 European guidelines on SUO¹ deem acceptable both the 10-second cardiac-pause criterion used in this study

and the 6-second R-R interval criterion suggested elsewhere^{22,23} as determinants of the outcome of the ATP test in the evaluation of SUO patients, but the guidelines suggest that the use of the ATP or adenosine test should remain under investigation. The present findings suggest that these guidelines may be too restrictive and should be revisited. Indeed, this study provides strong evidence that the ATP test and the 10-second cardiac pause criterion can be used effectively to identify SUO patients who may benefit from pacemaker therapy. It should be emphasized that several previous studies have attempted to evaluate the ATP or the adenosine test using the 6-second R-R interval criterion in SUO patients. Remarkably, none have determined the efficacy of pacing in patients with a positive test based on that criterion.^{22–25} Further studies are needed to shed light on any clinical significance of the 6-second R-R interval criterion.

In our study, the ATP test identified a group of patients who benefited from cardiac pacing, but the therapy did not completely eliminate recurrent episodes, leaving $\approx 23\%$ of the population still at risk before pacemaker reprogramming. A potential explanation for this finding is that an individual patient may have >1 mechanism for syncope and that the ATP test reveals only one of those causes, ie, the potential conduction block of excessive duration. Because of the polymorphic aspect of SUO attacks, the ATP test does not exclude the coexistence of other potential mechanisms responsible for syncope; further diagnostic tests or devices capable of uncovering other mechanisms may be necessary, even in elderly patients who have a positive ATP test. In addition, only a subset of patients yield a positive ATP test, and this study does not address how to diagnose and treat the remaining patients. For example, some of the elderly patients with SUO whose ATP test was negative may also benefit from the use of pacemaker. This remains an unanswered question.

On that matter, recent research has focused on using an implantable loop recorder (ILR) to determine an arrhythmic cause for SUO.^{25–28} These studies show a lack of correlation between positive ATP test, tilt test, and ILR results. The discrepancy between the adenosine test results and those of the ILR can be explained, at least in part, by the following: (1) a small number of younger patients were tested in these studies; (2) adenosine rather than ATP was used; and (3) the 6-second R-R interval criterion instead of the 10-second cardiac-pause criterion was used. Randomized, blinded trials evaluating the efficacy of the ILR in identifying patients who may benefit from pacing therapy are ongoing.²⁹ If successful, these trials might illuminate the role of ILR in determining the appropriate therapy for SUO patients. They might, for example, suggest a strategy wherein ATP testing is done initially followed by longer-term ILR observation for those with negative ATP test results to identify other arrhythmic causes.

Study Limitations

The study was of adequate size to show the rather large overall effect but was underpowered to look for differences in effect by subgroups of age, sex, indications, comorbidities, or other factors. Thus, the negative results from analyses com-

paring these subgroups are not definitive. The patients enrolled in the study tended to be older and thus more likely to have cardio-inhibitory causes for syncope, so it may be that the test is more appropriate in these older patients. Identifying other subgroups more likely to benefit from ATP testing must await larger or more targeted studies.^{15,23,28,29}

In addition to their negative chronotropic and dromotropic actions on sinus and AV nodes, ATP and adenosine suppress sinus, junctional, and, mainly, ventricular activity, which may affect the R-R interval in a variable way. The mechanism responsible for this differential effect is likely the differential pacemaker currents measured in these different cardiac areas (ie, the role of the hyperpolarization-activated inward current) and the indirect antiadrenergic action of adenosine.³⁰

Although it is plausible that the above-mentioned effects contributed to the cardiac pauses seen in this study, the study was not designed to test this hypothesis in vasovagal patients or to differentiate the effects of exogenous and endogenous adenosine in a given patient.

Finally, this study was not designed to examine the question of the role of head-up tilt testing, either alone or in combination with ATP testing, in determining pacing therapy for SUO. The answer to this question awaits a study focused on that issue.

Conclusions

This single-blind, multicenter, randomized trial strongly suggests that the ATP test, exhibiting at least a 10-second cardiac pause, is a useful diagnostic tool for identifying a subset of SUO patients who may benefit from dual-chamber pacemaker therapy. Thus, the ATP test may be an additional practical tool for decision making by the clinician in the management of SUO patients.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Syncope commonly occurs in the general population, especially in the elderly; its origin remains unexplained in up to 40% of patients. Permanent cardiac pacing represents an effective therapy in patients with syncope of unknown origin that results from neurally mediated cardio-inhibition. The ATP test was introduced in 1986 as a convenient and safe tool to identify patients with syncope of unknown origin with neurally mediated cardiac inhibition. This patient-blinded, multicenter, randomized trial demonstrated that, in patients with syncope of unknown origin and a positive ATP test with no other precluding possible indications, cardiac pacing is an effective therapy, leading to a significant reduction of syncope recurrences. Although only some patients with syncope of unknown origin have a positive ATP test, this quick and safe procedure should be considered part of the armamentarium of syncope diagnosis.