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The Role of Pacing in Elderly Patients with Unexplained Syncope

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Abstract

Purpose of Review To discuss the role of pacing in elderly patients with unexplained syncope.

Recent Findings In patients with recurrent syncope with suspected reflex mechanism, the decision of pacemaker implantation can be guided by a standardized algorithm which includes carotid sinus massage, tilt-table testing, and implantable loop recorder. Cardiac pacing may reduce recurrent syncope in cardioinhibitory carotid sinus syndrome. In select elderly patients with recurrent cardioinhibitory vasovagal syncope, cardiac pacing may also reduce syncope recurrence. There is no role of cardiac pacing in patients with without a cardioinhibitory response. There is increasing evidence that closed loop stimulation reduces the recurrence of cardioinhibitory vasovagal syncope. In patients with syncope and a positive electrophysiology study consistent with sinoatrial or conduction system disease, cardiac pacing has been shown to reduce recurrent syncope. Cardiac pacing is also effective in reducing recurrent syncope when high-grade atrioventricular block is documented on electrocardiography monitoring. In elderly patients with unexplained syncope and bundle branch block on ECG, diagnostic algorithm should be followed according to guidelines; empirical pacing is generally not recommended.

Summary Permanent pacemaker implantation may be effective to reduce recurrent syncope in select groups of elderly patients. It is important to consider additional investigations to evaluate elderly patients with unexplained syncope. The results of these testing would guide the decision on permanent pacemaker implantation.

Keywords Syncope · Elderly · Pacemaker

Background

Unexplained syncope is defined as syncope for which a cause is undetermined after an initial evaluation that is deemed appropriate by the experienced healthcare provider [1••]. The initial evaluation includes, but is not limited to, a thorough history, physical examination, and ECG. The subsequent diagnostic evaluation and management of unexplained syncope in the elderly remains challenging as this is a high-risk population [2] with multiple potential causes of syncope not necessarily related to bradycardia [3]. In many countries, the chronological age of 65 years has been accepted as the definition of an "elderly" person [4]. Syncope becomes increasingly common with increasing age, from 5.7 per 1000 patients per year in the 7th decade to 19.5 per 1000 patients per year in the 9th decade [2]. Elderly patients commonly have polypharmacy, in both cardiovascular and psychotropic medications, which increases the risk of syncope and falls [5, 6]. The 2-year mortality in elderly patients with syncope was reported to be 20% [7]. Unexplained falls may also be a presentation of syncope in the elderly. Fall-related injuries are associated with significant subsequent morbidity including decline in functional status, fractures, and likelihood of nursing home placement [8, 9].

In general, pacing therapy can be effective in reducing recurrent syncope when the primary mechanism of syncope is related to a bradycardic mechanism, either from a neurally mediated cardiac inhibition, or a bradyarrhythmia from sinoatrial or conduction system disease. Transient bradycardia in some patients may render a timely diagnosis challenging. Mixed mechanisms of bradycardia and orthostatic hypotension may lead to incomplete response to pacemaker therapy.

This review will discuss the role of pacing in various subgroups of elderly patients with unexplained syncope. The

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subgroups are categorized based on findings of additional diagnostic testing that may be pursued when syncope remains unexplained after initial evaluation (Fig. 1). Tachycardia-mediated syncope will not be discussed in this review.

Carotid Sinus Massage and Carotid Sinus Syndrome

Mechanical manipulation of the carotid sinus may lead to neurally mediated bradycardic or vasodilatory response. Carotid sinus hypersensitivity (CSH) is diagnosed when carotid sinus massage leads to a ventricular pause lasting for > 3 s and/or fall in systolic blood pressure of > 50 mmHg [1••]. CSH is common in elderly patients. One study showed that among elderly patients without a prior history of syncope, 24% had cardioinhibitory CSH (ventricular pause for > 3 s) [10].

Carotid sinus syndrome is diagnosed when there is reproduction of spontaneous symptoms associated with CSH and a history of unexplained syncope compatible with reflex mechanism. Carotid sinus syndrome (CSS) is categorized as cardioinhibitory CSS if there is ventricular pause for > 3 s. In elderly patients with unexplained syncope, carotid sinus massage can be useful to assess the presence of CSS, especially if initial evaluation raises suspicion that syncope could be due to a reflex mechanism [11••]. Carotid sinus massage should not be performed if bruit is present on examination or a history of transient ischemic attack or stroke within the last 3 months [1].

The role of pacing in patients with CSS has been studied in multiple randomized controlled trials (Table 1). Claesson et al. studied 60 patients with cardioinhibitory CSS and found that rate of syncope in patients who received a pacemaker was 10% compared to 40% in the group that did not receive a pacemaker [14]. In a review of 601 paced and 305 unpaced patients with CSS, patients who received a pacemaker had approximately 75% relative reduction (relative risk 0.24, 95% confidence interval [CI] 0.12–0.48) in recurrence of

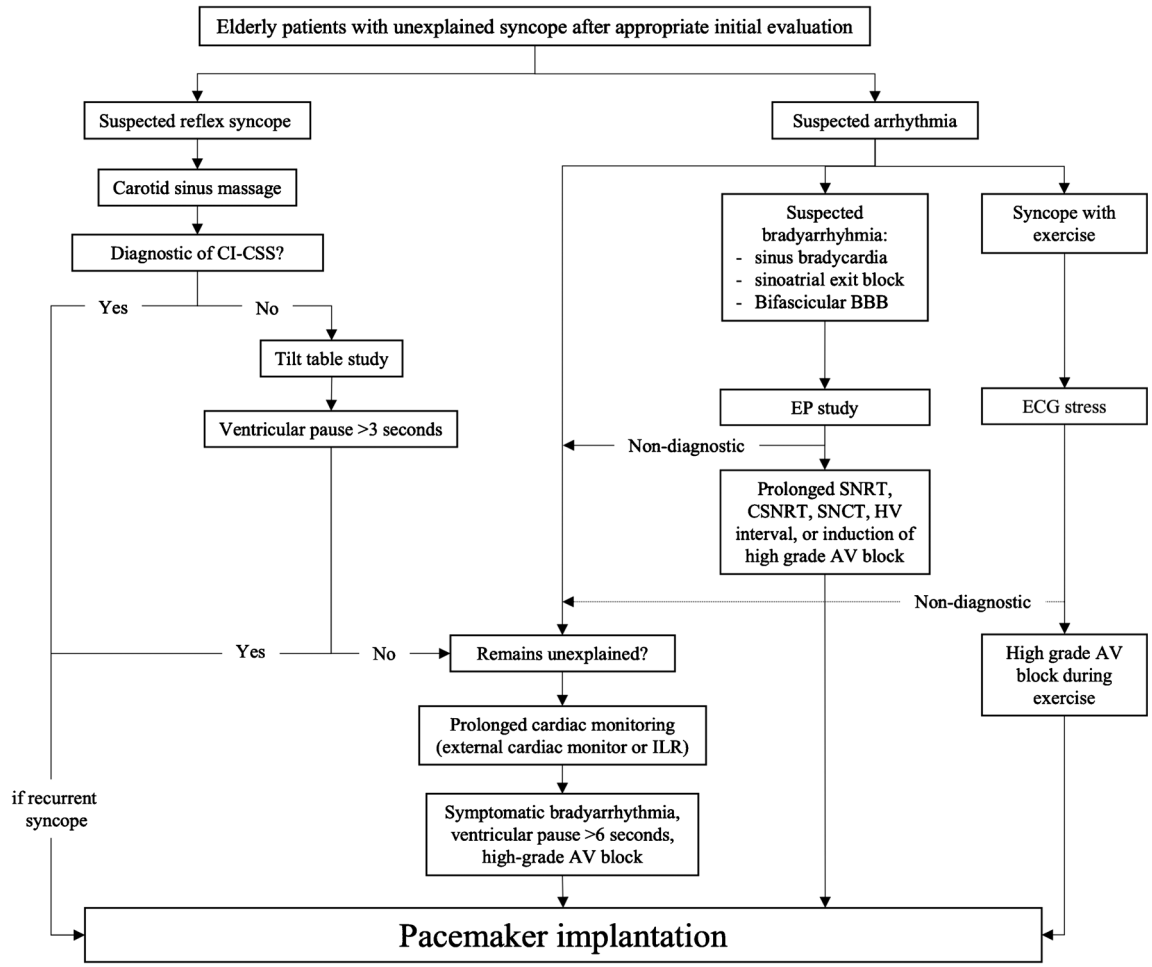

Fig. 1 Overview of decision pathway to pacemaker implantation in elderly patients with unexplained syncope. AV atrioventricular, BBB bundle branch block, CI cardioinhibitory, CSS carotid sinus syndrome, ECG electrocardiography, EP electrophysiology, ILR implantable loop recorder, MI myocardial infarction

Table 1 Randomized trials of pacemaker in carotid sinus syndrome and vasovagal syncope

Author, year	Patients	Study aim	Mean age	Endpoint	Intervention	Event	Comparator	Event	*P* value
Carotid sinus hypersensitivity and carotid sinus syndrome									
Brignole M, 1992 [12]	60	Pacing therapy in CI-CSS	70 ± 10	Recurrent syncope at 36 months	Pacemaker	9%	No pacemaker	57%	0.0002
Kenny R, 2001 (SAFE PACE) [13]	175	Pacing therapy in reduction of falls in older patients with CI-CSH	73 ± 10	Recurrent syncope at 12 months	Pacemaker	11%	No pacemaker	22%	0.063
Claesson J, 2007 [14]	60	Pacing therapy in CI-CSS	76 ± 10	Recurrent syncope at 12 months	Pacemaker	10%	No pacemaker	40%	0.008
Parry S, 2009 [15]	25	Pacing therapy in patients with CI-CSH and recurrent falls	77 ± 9	Number of falls	Pacemaker in DDD/RDR	4.04	Pacemaker in ODO	3.48	NS
Ryan D, 2010 (SAFE PACE 2) [16]	141	Pacing therapy in older patients with CI-CSH and unexplained falls	78 ± 7	Syncope recurrent events at 24 months	Pacemaker	0.42 mean events	No pacemaker	0.66 mean events	–
Vasovagal syncope									
Flammang D, 1999 [17]	20	Pacing therapy in patients with VVS and abnormal cardioinhibitory response during ATP test	72 ± 11	Syncope recurrence at 52 months	Pacemaker	0%	No pacemaker	60%	< 0.02
Connolly S, 1999 (VPS) [18]	54	Pacing in VVS with tilt test that induced syncope or presyncope, as well as relative bradycardia	43 ± 18	Syncope recurrence	Pacemaker	22%	No pacemaker	70%	< 0.0001
Sutton R, 2000 (VASIS) [19]	42	Pacing therapy in cardioinhibitory tilt positive VVS	60 ± 13	Syncope recurrence at 80 months	Pacemaker	5%	No pacemaker	61%	0.0006
Ammirati F, 2001 (SYDIT) [20]	93	Pacing in VVS positive tilt-table testing with syncope occurring in association with relative bradycardia (< 60 bpm)	58 ± 14	Syncope recurrence at 135 to 390 days	Pacemaker	4.3%	Beta-blockers	25.5%	0.004
Connolly S, 2003 (VPS II) [21]	100	Pacing therapy in VVS	50 ± 18	Syncope recurrence at 6 months	Pacing DDD	33%	PACING ODO	42%	NS
Raviele A, 2004 (SYNPACE) [22]	29	Pacing therapy in VVS with positive tilt test with asystolic or mixed response	53 ± 16	Syncope recurrence at 24 months	Pacemaker ON	50%	Pacemaker OFF	38%	0.58
Brignole M, 2012 (ISSUE-3) [23]	77	Pacing therapy in asystolic neurally mediated syncope	63 ± 13	Syncope recurrence at 24 months	Pacemaker ON	21.1%	Pacemaker OFF	48.7%	0.039
Closed loop stimulation for cardioinhibitory vasovagal syncope									
Occhetta E, 2004 (INVASY) [24]	26	Effect of dual-chamber CLS in patients with CI-VVS	59 ± 18	Syncope recurrence at 12 months	DDD-CLS	0%	DDI	78%	–
Russo V, 2013 [25]	50	Effect of dual-chamber CLS in syncope recurrence in patients with cardioinhibitory VVS	53 ± 5	Syncope recurrence at 18 months	CLS on	2%	CLS off	16%	0.007
Baron-Esquivias G, 2017 (SPAIN) [26•]	46	Pacing with DDD-CLS in patients with CI-VVS	56 ± 11	Syncope recurrence at 12 months	DDD-CLS	8.7%	Sham DDI	45.7%	–
Palmisano P, 2018 (TIRECS) [27•]	30	Effect of CLS pacing in syncope induced by tilt test in patients with CI-VVS	62 ± 14	Syncope during tilt test	DDD-CLS	30%	DDD	76.7%	< 0.001

ATP adenosine triphosphate, *CI* cardioinhibitory, *CLS* closed loop stimulation, *CSH* carotid sinus hypersensitivity, *CSS* carotid sinus syndrome, *NS* not significant, *VVS* vasovagal syncope

syncopal episodes compared to patients who did not receive cardiac pacing [28].

Therefore, guidelines have recommended that permanent cardiac pacing is reasonable in elderly patients with cardioinhibitory or mixed CSS with recurrent syncope [1••, 11••]. Dual-chamber pacing is preferred rather than single-chamber ventricular pacing although comparative effective clinical studies in assessing the method of pacing are scarce [29]. In the absence of a cardioinhibitory reflex, cardiac pacing is not indicated. Conversely, studies in patients with unexplained falls and findings of cardioinhibitory CSH showed that cardiac pacing did reduce subsequent falls [13, 16].

Tilt-Table Study and Vasovagal Syncope

It is generally thought that tilt-table study provokes a vasovagal response by venous pooling and orthostatic stress, and therefore, is used to assess the susceptibility of a vasovagal response with a postural change. In the assessment of syncope in the elderly with suspected reflex mechanism, tilt-table study can be useful [1••, 11••]. The hemodynamic response to orthostatic stress determines whether there is a vasodepressor, cardioinhibitory, or mixed response.

The rationale of cardiac pacing in patients with tilt-induced vasovagal syncope (VVS) is that pacing may overcome the bradycardia and asystole response from the cardioinhibitory reflex [20]. As cardiac pacing does not prevent the vasodepressor response of vasodilation and hypotension, there is less benefit of pacing in patients with tilt-table induced vasodepressor response [23]. There have been multiple randomized trials that assessed the role of pacing in patients with VVS (Table 1). The Vasovagal Pacemaker Study (VPS) and the Vasovagal Syncope International Study (VASIS) showed benefit in favor of pacing [18, 19]. However, the second Vasovagal Pacemaker Study (VPS-II) and the Vasovagal Syncope and Pacing (SYNPACE) trial which were double-blinded trials did not find benefit of pacing, suggesting that the benefit of pacing in VVS was driven by placebo [21, 22]. However, VPS-II and SYNPACE enrolled patients without an asystolic tilt response. The International Study on Syncope of Uncertain Etiology 2 (ISSUE-2) registry suggested that there may be a role for pacing in patients with VVS with documented cardio-inhibition on implantable loop recorder (ILR) [30]. This finding was confirmed in the International Study on Syncope of Uncertain Etiology 3 (ISSUE-3) study [23]. Subsequent substudy of ISSUE-3 found that patients with negative tilt study and subsequent spontaneous pauses of document by ILR had the most benefit from cardiac pacing, suggesting that tilt study reveals a vasodepressor component, even when cardio-inhibition is dominant [31]. It is worth noting that an asystolic response during tilt testing did predict a similar asystolic finding during ILR documented syncope with a positive predictive value of 86% [31].

The Syncope Unit Project 2 (SUP-2) study incorporated a positive tilt-table study as an indication for cardiac pacing in a standardized algorithm and found reduced syncope recurrence with cardiac pacing [32•]. The study assessed a standardized algorithm for patients aged > 40 years (mean age of 70 years) with severe (impaired quality of life), unpredictable (without or with very short prodromes), and recurrent (at least two episodes) reflex syncope [33]. With the standardized algorithm, recurrence rate of syncope was reduced to 9% (95% CI, 6–12) at the first year, 15% (95% CI, 10–20) at the second year, and 20% (95% CI, 29–57) in the third year [32, 33]. These were lower than in unpaced controls who had recurrence rate of syncope of 22% (95% CI, 18–26) in the first year, 37% (95% CI, 30–43) in the second year, and 43% (95% CI, 29–57) in the third year.

Overall, the results of randomized trials on cardiac pacing in cardioinhibitory tilt-positive patients have been contrasting, resulting in divergence of opinions in this topic. Cardiac pacing may be reasonable in elderly patients with recurrent frequent unpredictable VVS and prolonged spontaneous pauses (≥ 3 s with syncope, or asymptomatic pause ≥ 6 s). Opinions diverge on pacemaker implantation in tilt-positive patients with cardioinhibitory response, but it may be reasonable, especially since an asystolic tilt response also predicts asystolic finding with ILR. It is clear that pacing should not be offered to patients where tilt-table testing only shows vasodepressor response.

There is also increasing evidence that dual-chamber pacing with closed loop stimulation leads to fewer syncope recurrences compared to conventional dual-chamber pacing (Table 1) [24, 25, 26•, 27•]. Closed loop stimulation is a rate-responsive mode that increases pacing rate prior to VVS. It uses intracardiac impedance as a surrogate of cardiac contractility and detects when there is an increase in cardiac contractility which comes before VVS. In the Closed Loop Stimulation for Neuromediated Syncope (SPAIN) study, patients with recurrent cardioinhibitory VVS who received cardiac pacing with closed loop stimulation had a lower syncope recurrence rate compared to patients who did not receive cardiac pacing (8.7% vs. 45.7%; hazard ratio 6.7; 95% CI 2.3 to 19.8) [26•]. In the Tilt test-Induced REsponse in Closed-loop Stimulation (TIRECS) study, an addition of closed loop stimulation was shown to reduce the occurrence of syncope induced by tilt-table test compared to standard dual-chamber pacing and sensing, with both triggered and inhibited mode (DDD) (30% vs. 77%) [27•].

Algorithm for Cardiac Pacing in Reflex Syncope

One proposed algorithm is to evaluate patients with recurrent reflex syncope with a comprehensive diagnostic algorithm, starting with a carotid sinus massage (CSM) and tilt-table

study [32•]. Findings of a positive diagnostic test consistent with a cardioinhibitory response would prompt implantation of a dual-chamber pacemaker. If the initial testing is negative, ILR would be recommended to detect any pauses correlated to recurrent syncope. This algorithm was assessed in the SUP-2 study, as discussed earlier [33].

Adenosine Triphosphate Testing and Adenosine-Sensitive Syncope

Prior studies have suggested that adenosine triphosphate (ATP) test can be a useful tool to identify patients with high risk of severe reflex-mediated cardioinhibitory response [17, 34]. The clinical entity known as adenosine-sensitive syncope typically describes patients with unexplained syncope, a normal heart with no features of conduction disease on ECG, low plasma adenosine levels, and a high induction rate of transient prolonged sinoatrial or atrioventricular block [35].

In the ATP multicenter study of elderly patients with unexplained syncope and positive ATP tests, dual-chamber pacing reduced syncope recurrence by 75% (95% CI 44–88) [34]. Positive ATP test was defined as sinoatrial block lasting for more than 10 s under a 20-mg intravenous bolus of ATP. Nonetheless, there is still limited data on the role of ATP testing and cardiac pacing in patients with clinical features of adenosine-sensitive syncope [17, 34, 36, 37].

Electrophysiology Study and Bradyarrhythmias

Electrophysiology study can be useful in selected patients with syncope suspected of an arrhythmic nature. In general, electrophysiology study (EPS) is not useful in patients with no palpitations, normal ECG, and no underlying heart disease [1••, 11••].

An EPS can be considered in patients with suspected sinus node dysfunction-mediated intermittent pause-causing syncope. At baseline, patients may have sinus bradycardia or sinoatrial exit block on ECG or ambulatory rhythm monitoring but not associated with any symptoms. Overdrive suppression is a protocol to assess the sinoatrial recovery time (SNRT) (Fig. 2). It is generally considered to be abnormal when SNRT is ≥ 1500 ms, or corrected SNRT of ≥ 525 ms. Sinoatrial conduction time (SACT) is determined by programmed atrial premature depolarizations. It is considered to be abnormal when SACT is ≥ 125 ms. Although abnormal SNRT or SACT is fairly specific for sinus node dysfunction, sensitivity is moderate at best.

In bifascicular bundle branch block, the concern is high-degree atrioventricular (AV) block may be present intermittently. In elderly patients, it is reasonable to pursue EP study with the goal to detect prolonged HV interval of ≥ 70 ms, infra-Hisian block, or induction of Mobitz II or third-degree AV block by incremental pacing identify groups with high risk of developing AV block. His-Purkinje conduction reserve may be assessed by pharmacological agents that are known to impair His-Purkinje conduction. During an invasive EPS, findings of His-Purkinje disease such as prolonged HV interval at rest or induction of His-Purkinje block with incremental pacing may be absent. In these cases, a pharmacological stress test (ajmaline, procainamide, or disopyramide) of the His-Purkinje system should be considered to unmask poor His-Purkinje system reserve [38, 39]. Findings that would suggest propensity for spontaneous infra-His block are doubling of the H-V interval, resultant H-V interval exceeding 100 msec, or precipitation of second- or third-degree infra-His block [40].

Cardiac pacing should be considered in patients with a history of unexplained syncope if EPS reveals prolonged corrected SNRT or SNCT. In patients with bifascicular bundle branch block, cardiac pacing is indicated if EPS reveals prolonged HV interval, infra-Hisian block (Fig. 3), or Mobitz II or third-degree AV block by incremental atrial pacing or pharmacological challenge [32•, 41]. Studies have shown reduced syncope recurrence in patients with a positive EPS who underwent pacemaker implantation [42•, 43••, 44•]. It is also worth noting that in patients with infra-nodal conduction disease, His-bundle pacing can be performed [45]. Vijayaraman et al. reported a success rate of 76% of patients with infra-nodal block [46]. Possible reasons for recruitment of the distal His and bundle branches with His pacing include longitudinal dissociation in the His bundle with pacing adjacent to or distal to the block, different source-sink relationship during pacing, and virtual electrode polarization effect [46].

Empirical pacing in elderly patients with unexplained syncope and bifascicular block is generally not recommended. Some exceptions may be reasonable in selected elderly patients after initial diagnostic testing, including patients with concerning history, such as syncope with very minimal

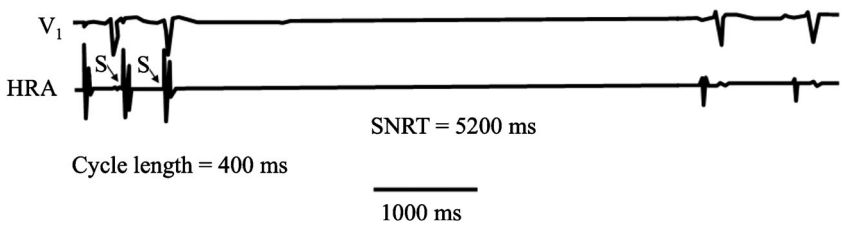

Fig. 2 Sinus node recovery time (SNRT). Normal sinus node response following a paced atrial cycle length of 400 ms (S)

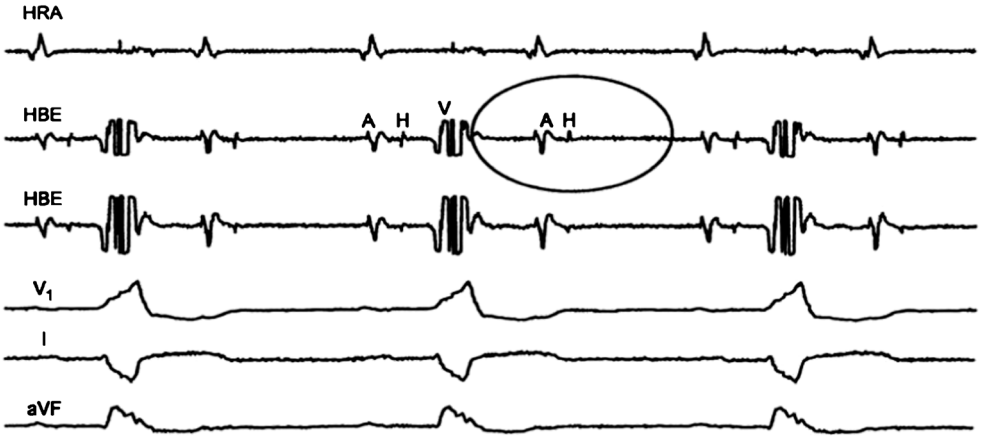

Fig. 3 Spontaneous infra-Hisian 2:1 atrioventricular block. Seventy-eight-year-old man with underlying right bundle branch block and baseline H-V interval of 80 ms with spontaneous infra-Hisian 2:1 atrioventricular block during electrophysiology study. Every other A-H complex is not followed by a ventricular depolarization

prodrome and associated with significant trauma, or if syncope occurred in a supine position or during exertion [11••, 41]. However, it is important to know that studies have shown that this empirical pacing strategy does not completely eliminate recurrent syncope. Kalscheur et al. showed that the syncope recurrence rate with empirical pacing in patients with unexplained syncope was 11% (95% standard error [SE] ± 7%) at 1 year, and 27% (95% SE ± 10%) at 5 years [43••]. In the Prevention of Syncope by Cardiac Pacing in Patients With Bifascicular Block (PRESS) study, 13.5% of patients who received empirical pacing for unexplained syncope had recurrent syncopal event at 2 years, not significantly different from 14.3% in the comparative group [47]. There was a significant reduction in presyncopal events from 32.6 to 11.5% with empirical pacing.

Exercise Testing and Exercise-Induced Conduction Disease

Syncope occurring during exercise is likely due to a cardiac etiology. Intermittent heart block may be elicited especially in patients with intraventricular conduction abnormalities on resting ECG. Exercise testing is indicated in patients who experience syncope during or shortly after exertion [1••, 11••].

Prior studies have shown that exercise-induced second- and third- AV block is typically associated with conduction block located distal to the AV node suggestive of significant conduction disease [48–50]. Pacemaker therapy is indicated in patients with a prior history of unexplained syncope and exercise-induced heart block.

Prolonged Electrocardiographic Monitoring

Prolonged electrocardiographic monitoring with ILR is reasonable in elderly patients with unexplained syncope in whom a comprehensive evaluation did not demonstrate a cause of syncope or lead to a specific treatment, and who do not have any other conventional indications for a pacemaker or implantable cardiac defibrillator (ICD) [11••].

ILR may also be considered in elderly patients with unexplained falls, as falls in the elderly may be due to syncopal events [11••]. Recent studies have shown that an arrhythmic cause could be identified in up to 24% of patients with unexplained falls [51, 52]. Maggi et al. who studied 29 patients with unexplained falls implanted with ILR showed that 24% of patients had arrhythmias documented by ILR [51]. Bhangu et al. who performed a prospective study of recurrent fallers over age of 50 showed that 20% of falls were attributable to a modifiable cardiac arrhythmia [52].

Cardiac pacing is recommended when there is a correlation between bradyarrhythmia and syncope based on recordings from the ILR. In the absence of symptoms, pacemaker should also be considered if there are periods of ventricular pause ≥ 6 s or Mobitz II second- or third-degree atrioventricular block [1••, 11••]. In the ISSUE-3 trial, patients with asystolic neutrally mediated syncope (ILR detecting ≥ 3 s asystolic pause with syncope, or ≥ 6 s asystolic pause without syncope) who received pacemaker had reduction in syncope recurrence [23].

Conclusion

Pacemaker therapy is effective in preventing recurrent syncope in elderly patients with documented pauses correlated with symptoms. Although effective in preventing intermittent bradycardia, recurrent symptoms of syncope are not uncommon in the elderly patients after pacemaker implantation because intermittent orthostatic hypotension and reduction of orthostatic reserve are likely present in some patients. Additional diagnostic testing such as carotid sinus massage, tilt-table testing, prolonged rhythm monitoring, treadmill exercise stress test, or EPS could be considered in selected patients. The results of these additional investigations would provide evidence for a shared decision based on most recent guidelines

for permanent pacemaker implantation in the elderly patients with unexplained syncope.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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and prolonged time to first recurrence in patients age ≥40 years with head-up tilt test-induced vasovagal syncope compared with sham pacing.

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