

## Permanent Pacemaker Therapy for Neurally Mediated Syncope Stuart J. Connolly

*Circulation*. 2012;125:2552-2553; originally published online May 7, 2012;  
doi: 10.1161/CIRCULATIONAHA.112.109280

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231  
Copyright © 2012 American Heart Association, Inc. All rights reserved.  
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the  
World Wide Web at:

<http://circ.ahajournals.org/content/125/21/2552>

**Permissions:** Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the [Permissions and Rights Question and Answer](#) document.

**Reprints:** Information about reprints can be found online at:  
<http://www.lww.com/reprints>

**Subscriptions:** Information about subscribing to *Circulation* is online at:  
<http://circ.ahajournals.org/subscriptions/>

## Permanent Pacemaker Therapy for Neurally Mediated Syncope

Stuart J. Connolly, MD

Neurally mediated syncope (also known as fainting and vasovagal syncope) is by far the most common cause of transient loss of consciousness. Fainting is almost always benign, and most people who faint have nontraumatic syncope episodes occasionally throughout their lives with minimal adverse consequences. Most episodes of fainting occur in the erect posture and have typical warning symptoms such as light-headedness or nausea that allow the individual to avoid serious injury if he or she loses consciousness. In a small number of people, however, fainting is a serious medical problem; typically, these are patients with episodes that occur with little or no warning or occur very frequently. Recurrent neurally mediated syncope can mean the inability to drive or to work, and syncope episodes can cause serious injury, albeit rarely. In such patients, neurally mediated syncope is a significant medical problem for which there are no easy solutions.

---

### Article see p 2566

---

Reflex vasodilation and bradycardia are the 2 main pathophysiological mechanisms underlying neurally mediated syncope, often acting together. Most pharmacological therapies are directed at limiting the vasodilation component; however, there is little evidence that medical therapies (fluid loading,  $\beta$ -blockers, fludrocortisone, or midodrine) are effective; a recent meta-analysis concluded that there are no proven effective pharmacological therapies for the prevention of neurally mediated syncope.<sup>1</sup> There is modest evidence that countermeasures such as leg crossing can help some patients.<sup>2</sup> Because transient bradycardia or asystole is often observed during neurally mediated syncope, cardiac pacing has been evaluated to treat severely symptomatic patients with frequent events. The challenge of pacemaker therapy for this condition, however, is that vasodilatation may still cause fainting, even after bradycardia is prevented by pacing.

Two small, randomized, unblinded studies of pacemaker implantation compared with no pacemaker reported large treatment benefits with pacemaker therapy,<sup>3,4</sup> but it soon became clear that these results were affected by a substantial placebo effect of receiving a pacemaker. In subsequent trials of pacing that were blinded by means of implanting a

pacemaker in all subjects and then randomizing patients to have the pacemaker programmed on or programmed off, the reduction in syncope was modest and not statistically significant.<sup>5,6</sup> The apparent placebo effect of pacing is consistent with the clinical observation that neurally mediated syncope often has emotional triggers (eg, smell, pain, disgust), and the emotional reaction to actually receiving a pacemaker appears to have influenced outcomes importantly.<sup>7</sup> In the larger of the 2 blinded trials evaluating pacing programmed on versus programmed off, the relative reduction in syncope recurrence was 30% with a wide confidence interval that included an increase in syncope of 33% or a decrease of 63%.<sup>5</sup> Pacemaker complications were not rare in that study, with lead dislodgement or repositioning in 7 of 48 pacemaker patients and other complications, including vein thrombosis, pericardial tamponade, and generator pocket infection. From these studies, we learned that treating the bradycardia component of neurally mediated syncope does not work very well, presumably because reflex vasodilation continues to cause syncope. The lack of hard evidence for benefit from pacing, together with the risk of adverse events, indicated to most physicians that permanent pacing had little or no role in the management of neurally mediated syncope. The possibility remained, however, that one could select patients with a greater chance of responding to pacing by identifying those in whom bradycardia was the only (or at least dominant) mechanism of fainting.

The importance of the Third International Study on Syncope of Uncertain Etiology (ISSUE-3) is the new approach used to identify patients in whom bradycardia is likely to be the principal mechanism of neurally mediated syncope and the subsequent use of a blinded randomized trial to evaluate whether identified patients would benefit from pacing.<sup>8</sup> The ISSUE-3 investigators used a chronically implanted loop recorder (ILR) to document whether asystole occurred at the time of spontaneously occurring syncope in highly symptomatic patients. During a mean follow-up of 1 year after ILR implantation in 511 patients with recurrent neurally mediated syncope, syncope recurred in 185 (36%). The lack of recurrence of syncope in a majority of these previously highly symptomatic patients reminds us that this disease has a variable course and that regression to the mean is a very important principle affecting all systems in which there is inherent variability (Patients are systematically more likely to present for medical care when they are at their worst, and many inevitably fluctuate back to a less severe state over time). Among the 185 patients with recurrent syncope identified by the ISSUE-3 investigators, asystole  $\geq 3$  seconds was seen in 72. These 72 patients and 17 others in whom asystole of  $\geq 6$  seconds detected by the ILR in the absence of recurrent syncope were eligible for the trial of pacing programmed on

---

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

From Hamilton Health Sciences, Hamilton, ON, Canada.

Correspondence to Stuart J. Connolly, MD, Population Health Research Institute, Hamilton Health Sciences, 237 Barton St E, Hamilton, ON L8L 2X2, Canada. E-mail [connostu@phri.ca](mailto:connostu@phri.ca)

(*Circulation*. 2012;125:2552-2553.)

© 2012 American Heart Association, Inc.

*Circulation* is available at <http://circ.ahajournals.org>  
DOI: 10.1161/CIRCULATIONAHA.112.109280

versus pacing programmed off; 77 consented to study enrollment. The results of this randomized trial are reported in this issue. Syncope recurred in 8 of 38 with pacing programmed on and in 19 of 39 with it programmed off, a relative risk reduction of 57%, which was statistically significant.

What have we learned from this study? Although the trial is small and the *P* value is marginal, it is reasonable to conclude that the ILR can be used to identify patients who have a good chance of benefiting from pacing and that this will reduce symptoms in carefully selected patients. However, the use of the ILR to select patients who could benefit from a pacemaker is limited by the large number of patients in whom the ILR must be implanted to identify a small number of patients who will then potentially benefit from implantation of a pacemaker. In ISSUE-3, asystole was seen in only 89 of 511 patients (17%) with previously documented, highly symptomatic, neurally mediated syncope. In these patients, the treatment effect of pacing is estimated to be a 57% reduction in syncope. This means that 10% of all patients receiving the ILR would be estimated to subsequently derive benefit from pacing. Balancing this, we must also consider the complications of a permanent dual-chamber pacemaker. Lead dislodgements were seen in 4 of 38 patients in ISSUE-3. Vein thrombosis, pocket infection, myocardial perforation, and premature lead or generator system failure are less common but real problems that may occur. These considerations make it clear that pacemaker therapy is suitable for a very select group of patients. Using the ILR to evaluate the highly symptomatic patient with neurally mediated appears to be helpful. This intervention, although invasive, has few serious complications, provides the opportunity to identify patients potentially responsive to pacing, and can detect other causes of syncope such as tachycardia. Furthermore, it provides a useful period of objective documentation of the frequency and severity of symptoms before interventions are implemented.

Some patients will have neurally mediated syncope recurrence at a time when ECG monitoring is in place, either in the hospital or during provocative testing such as testing with head-up tilting and pharmacologically induced vasodilation. Do the results of ISSUE-3 apply only to patients in whom asystole is documented without an ILR during spontaneous syncope recurrence? Spontaneous syncope with asystole appears to be the defining characteristic of the ISSUE-3 patients, although some patients were enrolled with asystole of  $\geq 6$  seconds in the absence of recurrent syncope. Asystole associated with tilt testing and other provocation may well be different from that occurring spontaneously and should generally not be interpreted as an indication for pacing without

documentation of a spontaneous asystole episode. In addition, asystole during spontaneous neurally mediated syncope is only a reason to consider pacing if the patient is symptomatic from recurrent syncope episodes. We need to interpret the results of ISSUE-3 cautiously because this is a single small trial with a *P* value that is just at the margin of conventional statistical significance.

In conclusion, the results of ISSUE-3 offer hope to a small group of highly symptomatic patients with longstanding, symptomatic, recurrent, neurally mediated syncope among whom, there is now reason to believe, we can identify those who will have a reasonable response to permanent pacemaker therapy. However, given the limitations of our evidence, clinicians should proceed cautiously in putting these findings into practice.

## Disclosures

None.

## References

1. Romme JJ, Reitsma JB, Black CN, Colman N, Scholten RJ, Wieling W, Van Dijk N. Drugs and pacemakers for vasovagal, carotid sinus and situational syncope. *Cochrane Database Syst Rev*. 2011;CD004194.
2. van Dijk N, Quartieri F, Blanc JJ, Garcia-Civera R, Brignole M, Moya A, Wieling W; PC-Trial investigators. Effectiveness of physical counterpressure maneuvers in preventing vasovagal syncope: the Physical Counterpressure Manoeuvres Trial (PC-Trial). *J Am Coll Cardiol*. 2006;48:1652–1657.
3. Sutton R, Brignole M, Menozzi C, Raviele A, Alboni P, Giani P, Moya A. Dual-chamber pacing in the treatment of neurally mediated tilt-positive cardioinhibitory syncope: pacemaker versus no therapy: a multicenter randomized study: the Vasovagal Syncope International Study (VASIS) Investigators. *Circulation*. 2000;102:294–299.
4. Connolly SJ, Sheldon RS, Roberts RS, Gent M. The North American Vasovagal Pacemaker Study (VPS): a randomized trial of permanent cardiac pacing for the prevention of vasovagal syncope. *J Am Coll Cardiol*. 1999;33:16–20.
5. Connolly SJ, Sheldon R, Thorpe KE, Roberts RS, Ellenbogen KA, Wilkoff BL, Morillo C, Gent M; VPS II Investigators. Pacemaker therapy for prevention of syncope in patients with recurrent severe vasovagal syncope: Second Vasovagal Pacemaker Study (VPS II): a randomized trial. *JAMA*. 2003;289:2224–2229.
6. Raviele A, Giada F, Menozzi C, Specia G, Orazi S, Gasparini G, Sutton R, Brignole M; Vasovagal Syncope and Pacing Trial Investigators. A randomized, double-blind, placebo-controlled study of permanent cardiac pacing for the treatment of recurrent tilt-induced vasovagal syncope: the Vasovagal Syncope and Pacing Trial (SYNPACE). *Eur Heart J*. 2004;25:1741–1748.
7. Sud S, Massel D, Klein GJ, Leong-Sit P, Yee R, Skanes AC, Gula LJ, Krahn AD. The expectation effect and cardiac pacing for refractory vasovagal syncope. *Am J Med*. 2007;120:54–62.
8. Brignole M, Menozzi C, Moya A, Andresen D, Blanc JJ, Krahn AD, Wieling W, Beiras X, Deharo JC, Russo V, Tomaino M, Sutton R. Pacemaker therapy in patients with neurally mediated syncope and documented asystole: Third International Study on Syncope of Uncertain Etiology (ISSUE-3): a randomized trial. *Circulation*. 2012;125:2566–2571.

KEY WORDS: Editorials ■ syncope