Permanent Pacemaker Therapy for Neurally-Mediated Syncope

Running title: Connolly; Pacemakers for recurrent fainting

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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 non-traumatic 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 which allow the individual to avoid serious injury if they lose consciousness. In a small number of people however, fainting is a serious medical problem; typically these are patients with episodes that may occur with little or no warning, or occur very frequently. Recurrent neurally-mediated syncope can mean inability to drive or to work, and syncope episodes can rarely cause serious injury. In such patients, neurally-mediated syncope is a significant medical problem for which there are no easy solutions.

Reflex vasodilation and bradycardia are the two 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 effective pharmacologic therapies for the prevention of neurally-mediated syncope\(^1\). There is modest evidence that counter-maneuvers such as leg crossing can help some patients\(^2\). Because transient bradycardia or asystole are 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 that vasodilatation may still cause fainting, even after bradycardia is prevented by pacing.

Two small randomized unblinded studies of pacemaker implantation, versus no pacemaker, reported large treatments benefits with pacemaker therapy\(^3,4\), but it soon became
clear 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\(^5\,6\). The apparent ‘placebo-effect’ of pacing is consistent with the clinical observation that neurally-mediated syncope often has emotional triggers (e.g. smell, pain, disgust), and the emotional reaction to actually receiving a pacemaker appears to have influenced outcomes importantly\(^7\). In the larger of the two 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\(^5\). Pacemaker complications were not rare in that study, with lead dislodgement or repositioning in 7 out 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 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 if identified patients would benefit from pacing\(^8\). They used a
chronically implanted Loop recorder (ILR) to document whether asystole occurred at the time of spontaneously occurring syncope in highly symptomatic patients. During mean follow up of one year after implanting the loop recorder in 511 patients with recurrent neurally-mediated syncope, recurrent syncope occurred 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).

Amongst the 185 patients with recurrent syncope identified by the ISSUE investigators, asystole \( \geq 3 \) seconds was seen in 72. These 72, along with 17 others in whom asystole of \( \geq 6 \) seconds detected by the ILR in absence of recurrent syncope, were eligible for the trial of pacing programmed ON 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% that 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 to benefit from pacing and that this will reduce symptoms in carefully selected patients. The use of the ILR to select patients whom could benefit from a pacemaker is however 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 only seen in 89/511 (17%) patients with previously documented highly symptomatic neurally-mediated syncope. In these patients, the treatment effect of pacing is

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estimated to be a 57% reduction in syncope. This means that 10% of all patients receiving the ILR would be estimated to subsequently derive a benefit from pacing. Balancing this, one must also consider the complications of a permanent dual chamber pacemaker. Lead dislodgments 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. Use of the ILR to evaluate the highly symptomatic patient with neutrally-mediated appears useful. This is intervention, although invasive, has few serious complications and it provides the opportunity to identify patients potentially responsive to pacing, and also 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 implementing interventions.

Some patients will have neurally-mediated syncope recurrence at a time when there is ECG monitoring in place, either in hospital or during provocative testing such as with head up tilting and pharmacologically induced vasodilation. Do the results of ISSUE-3 apply only to patients in whom asystole is documented by 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 ≥6 seconds in absence of recurrent syncope. Asystole associated 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 as 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 long-standing, symptomatic, recurrent neurally-mediated syncope in 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.

**Conflict of Interest Disclosures:** None

**References:**


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