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Tilt test in paced patients: Is it worth the effort?



Introduction

Syncope is an important symptom that though most commonly benign, deserves extensive evaluation since it can also be caused at times by life threatening causes that are potentially treatable. An important cause of syncope is symptomatic bradycardia either due to sick sinus syndrome or atrioventricular block that is treated easily by pacemaker therapy. However, the most common cause of syncope in patients with normal heart is vasovagal or neurocardiogenic syncope where pacemaker therapy has a very limited role. When syncope recurs in a patient who received the pacing therapy for the same symptom, it not only becomes very difficult to explain to the patient but also poses significant diagnostic challenges.

Head-up tilt test (HUTT) has been in use for evaluation of patients with suspected recurrent vasovagal syncope for many decades. However, data regarding its use in patients with pacing devices is scanty. Hence, the study by Haarmark et al. in this issue of the journal [1], reporting the results of HUTT in patients with pacemakers and recurrent syncope is a welcome addition to the literature. Though, the authors suggest that a positive HUTT even in a patient with pacemaker indicates a diagnosis of vasovagal syncope implying a benign condition, syncope in paced patients and role of HUTT in its evaluation has to be interpreted in the right perspective. The following discussion points may help in this regard.

Is syncope seen in patients with pacemakers despite normal pacing system function?

Syncope or similar symptoms after implantation of pacemakers (or other cardiac implantable devices) is not as uncommon as is thought despite a clear cause and standard indication of pacing. The incidence may depend on the indication of implant - lowest when the indication was symptomatic atrioventricular block in structurally normal heart,

highest when the indication was primarily vasovagal syncope and in between in patients with sick sinus syndrome where it may be seen in up to 17.5% of patients [2–5].

The etiology of syncope in paced patients is variable and may include vasovagal syncope, postural hypotension, drug induced hypotension, ventricular arrhythmias, acute myocardial ischemia and last but not the least pacing system malfunction [6].

When syncope occurs in a patient with pacemaker, one is tempted to believe that a malfunction in the pacemaker or the lead/s is responsible for the recurrence of symptoms. It may actually be true when the syncope occurs early after implant and the abnormality and likely cause of it is usually obvious on pacemaker interrogation. However, when the time to recurrent syncope is long after implant, contrary to the popular belief, pacing malfunction is seen only in a small percentage (less than 10%) of patients [4,6]. Hence, these patients need extensive evaluation as in patients without pacemaker and diagnosis remains quite challenging. A definite cause remains elusive in a large percentage (up to 30%) of patients with syncope occurring after pacemaker implantation [3,6].

Are there identifiable predictors of syncope in paced patients?

The predictors of syncope in paced patients includes extremes of age (<40 years and >80 years) [2], previous history of syncope [2,3], past history of myocardial infarction or heart failure and presence of co-morbidities [2]. Among non-paced patients, vasovagal syncope is the most common cause of syncope in young patients whereas in elderly patients cardiac causes, drug induced and postural hypotension are the predominating causes [7]. All these age-related causes may not be or only partially helped with pacing and hence similar etiologies may exist even in paced patients at the extremes of age.

History of syncope prior to pacing is a strong predictor of syncope in paced patient and suggests that co-existing etiology, for example vasovagal, may be responsible for syncope although pacing was performed for an already established indication like sick sinus syndrome [3].

Does the indication of pacing or mode of pacing predict the occurrence of syncope?

Single chamber AAI/R pacing in patients with sick sinus syndrome with intact atrioventricular conduction has been the preferred choice in most recommendations and guidelines [8] of pacing despite the fact that most implanters across the globe prefer to implant dual-chamber pacemakers in such situations. The presence of known risk, though small, of development of atrioventricular block over time in these patients and the development of pacing algorithms that prevent unnecessary right ventricular pacing has been used as the justification for dual-chamber pacing by these implanters. The recent European guidelines [9] of pacing, in fact have now recommended dual-chamber pacing with AV delay management as the first choice in patients with sick sinus syndrome (with AAI/R pacing as second choice) based on the results of the DANPACE trial [10].

Still based on old recommendations, many patients still have AAI/R pacemakers and may develop syncope due to development of AV block. In the sub-study of DANPACE trial [2], 21 of the 54 patients who required upgradation to a dual-chamber system experienced syncope. However, the repeat data analysis after excluding these 54 patients revealed similar incidence and predictors of syncope post pacemaker implant. Similar to this fact, one should remember that as in the report by Haarmark et al. [1], syncope in patients with AAI/R may be due to coexisting vasovagal syndrome rather than development of AV block. It may be worthwhile explaining these issues to the patient before upgrading the device in the absence of documented AV block.

Whether syncope is more likely to occur in patients paced for sick sinus syndrome than for AV block has not been evaluated. Although unexplained syncope in patients when the indication of pacing is AV block is quite rare [5], co-existing vasovagal syncope may be responsible for occurrence of syncope in these patients. Interestingly, in the current report by Haarmark et al. [1], pacing indication was not statistically different between HUTT positive and negative patients with syncope after pacing.

Why is the incidence of positive HUTT higher in pacemaker patients with syncope?

The current study by Haarmark et al. [1] showed that 54% of patients with pacing devices and syncope or presyncope had a positive response to HUTT that is much higher than the response seen in non-paced patients. Does it suggest that the paced patients have a higher chance of having vasovagal syncope or is due to other reasons? The patients with pacemaker and syncope are a highly selected population in which bradyarrhythmia as a cause of syncope is automatically excluded provided the pacing system function is normal. Also, since most pacemakers record high atrial and ventricular rate episodes, tachyarrhythmia as a cause of syncope will be evident on pacemaker interrogation. Moreover, it is very likely that these patients underwent complete evaluation for syncope prior to pacemaker implant and hence any significant

structural heart disease likely to result in syncope would have already been excluded. Hence, in this patient population only few remaining causes of syncope are plausible, of which vasovagal syncope is the most likely cause. It is not surprising therefore, that these patients have a higher positivity rate during HUTT.

Does a positive HUTT indicate a diagnosis of vasovagal syncope in these patients and does it have a clinical utility?

HUTT is in clinical use for evaluation of patients with syncope for almost three decades with the belief that a positive result indicates a diagnosis of vasovagal syncope. However, recently there has been skepticism in its clinical utility due to variable sensitivity and specificity and inability to help in the diagnosis in situations where other modalities have failed to make a diagnosis. That is, it helps in the diagnosis of vasovagal syncope with good sensitivity and specificity in individuals where the diagnosis is already apparent on workup but in patients with initially unexplained syncope it shows many false positive (proven to be arrhythmic later) [11] or false negative (undiagnosed after full workup and likely vasovagal) results [12]. The scenario is not likely to be different in paced patients with syncope.

This has led to a new different interpretation of HUTT wherein a positive result on HUTT is believed to indicate a hypotensive susceptibility to the passive postural stress rather than a diagnosis of vasovagal syncope [13]. This hypothesis also explains why some patients (who have the hypotensive susceptibility and hence a positive HUTT) with a particular arrhythmia (or any other possible etiology of syncope) have syncope whereas others do not. Thus, according to this interpretation of HUTT, a positive result with HUTT suggests the presence of hypotensive susceptibility that plays a role in causing syncope irrespective of the etiology and mechanism of syncope [13].

Extrapolating the same thinking to patients with syncope who already have a pacemaker, and in whom cardiac arrhythmia as a cause of syncope is unlikely (bradycardia unlikely with normal pacemaker functioning and tachyarrhythmia excluded by pacemaker diagnostics), a positive HUTT will suggest the presence of hypotensive susceptibility that is not corrected by pacing. In this patient population, it may be suggestive but not diagnostic of vasovagal syncope with a strong vasodepressor component and also explains high positivity rate of HUTT. On the other hand, a negative HUTT will not rule out a diagnosis of vasovagal syncope and will not help in diagnosis. Hence, the clinical utility of HUTT for diagnosing the cause of syncope will be limited in pacemaker patients presenting with syncope.

Does HUTT help in guiding pacemaker therapy in patients with vasovagal syncope?

Though the initial studies suggested that pacemaker therapy may be beneficial in some patients with vasovagal syncope, the randomized studies have shown inconsistent results with

most suggesting absence of benefit. It is very clear that younger (<40 years) patients with vasovagal syncope almost never benefit from pacing. Some elderly patients who have documented prolonged asystole or pauses during spontaneous syncope do show benefit with pacing as was seen in the ISSUE-3 trial [14]. A substudy of ISSUE-3 trial showed that the patients who were HUTT positive and treated with pacemaker therapy had a very high recurrence of syncope similar to patients that were not treated. In contrast, the patients with asystole (on prolonged ECG monitoring) during spontaneous syncope who were HUTT negative had very low recurrence of syncope and were the most likely to benefit from pacing [15].

Thus, this substudy again suggested that a positive HUTT results indicates hypotensive susceptibility and may predict lack of benefit with pacing whereas a negative HUTT in a patient with documented asystole during spontaneous syncope may guide towards pacemaker therapy.

A positive HUTT in patients with syncope who already have a pacemaker may again suggest hypotensive susceptibility and also confirms the finding of ISSUE-3 substudy regarding the lack of benefit of pacing if the primary reason for the implant was vasovagal syncope. A positive HUTT may also guide withdrawal or dose reduction of antihypertensive or vasodilator medications in these patients as a part of treatment. Though, few studies have suggested that these medications may enhance the hypotensive susceptibility during HUTT, whether their withdrawal can help in improving clinical outcomes in HUTT positive patients with syncope remains to be studied.

Can HUTT help in assessing the prognosis of pacemaker patients with syncope?

The patients with pacemaker or other devices who have syncope have a worse prognosis and higher mortality as has been seen in the DANPACE study [2]. Even in the SCDHEFT trial comparing implantable defibrillator, amiodarone and placebo among patients with left ventricular dysfunction, occurrence of syncope was associated with increased mortality in all the three groups [16]. Though, conditions like vasovagal syncope and pacemaker treated sick sinus syndrome are considered benign, syncope due cardiac causes or arrhythmias have a worse prognosis. But interestingly, syncope in patients treated for these conditions with device therapy is still associated with increased mortality indicating that syncope is just a surrogate marker of mortality risk that is primarily determined by the underlying heart disease and associated comorbid conditions. The study by Haarmark et al. in this issue of the journal [1] has not looked in to the prognosis of patients with syncope but it will be interesting to see whether the result of HUTT is a predictor of mortality in patients with pacemaker who have syncope.

Conclusions

The present study along with the scanty existing literature indicates that syncope is not uncommon in patients with pacemakers. The etiology of syncope in these patients is

variable and diagnosis often challenging. Though, pacing system malfunction is logically the most obvious cause, it is rare and easily identifiable. HUTT may show a positive response more commonly in paced patients, as also seen in the study published in this issue, suggesting a diagnosis of vasovagal syncope as a coexisting etiology. However, it should be interpreted in the right perspective and with the understanding that a positive test may merely suggest hypotensive susceptibility rather than the diagnosis. Whether HUTT can help in guiding treatment by withdrawing antihypertensive medications needs to be studied in large scale trials.

Conflict of interest

None.

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