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Highlights in clinical autonomic neurosciences: Novel Insights about Vasovagal Syncope and Postural Tachycardia Syndrome from Autonomic Testing

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The Benefit of Pacemaker Therapy in Patients with Presumed Neurally-Mediated Syncope and Documented Asystole is Greater when Tilt Test is Negative. An Analysis from the Third International Study on Syncope of Uncertain Etiology (ISSUE-3).

Brignole M, Donateo P, Tomaino M, Massa R, Iori M, Beiras X, Moya A, Kus T, Deharo JC, Giuli S, Gentili A, Sutton R. (Lavagna, Italy)

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Article Summary

In the Third International Study on Syncope of Uncertain Etiology (ISSUE-3) cardiac pacing was effective in reducing the relative risk of recurrence of syncope by 57% in patients with presumed vasovagal syncope (VVS) and documented asystole but syncope still recurred in 25% of them at 2 years. The authors investigated the role of tilt testing (TT) in predicting recurrences of syncope. In 136 patients enrolled in the ISSUE-3, TT was positive in 76 and negative in 60. An asystolic response predicted a similar asystolic form during implantable loop recorder monitoring, with a positive predictive value of 86%. The corresponding values were 48% in patients with non-asystolic TT and 58% in patients with negative TT ($p=0.001$ vs. asystolic TT). Fifty-two patients (26 TT+ and 26 TT-) with asystolic VVS received a pacemaker. Syncope recurred in 8 TT+ and in 1 TT- patients. At 21 months, the estimated product-limit syncope recurrence rates were 55% and 5%, respectively ($p=0.004$). The TT+ recurrence rate was similar to that seen in 45 untreated patients (control group), which was 64% ($p=0.75$). The recurrence rate was similar between 14 patients with asystolic and 12 with non-asystolic responses during tilt testing ($p=0.53$). Cardiac pacing was very effective in VVS patients with documented asystolic episodes in whom TT was negative; conversely, there was insufficient evidence of efficacy from this

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dataset in patients with a positive TT even when spontaneous asystole was documented. Present observations are unexpected and need to be confirmed by other studies.

Commentary

The appropriate use of permanent pacemaker implantation in patients with recurrent vasovagal syncope has long been controversial and unclear. Several studies from the 1990s suggested that dual-chamber pacemaker implantation was highly effective in reducing syncope burden by about 90%. When methodologically more stringent studies involving true double blinding were performed in the following years, none of 3 large studies were able to show a statistically significant benefit. The Second Vasovagal Pacemaker Study (one of the negative studies), found a point estimate of a 30% reduction in recurrent syncope with pacing, yet the study was negative because it was powered for a 50% risk reduction. These data would suggest that there are some patients with vasovagal syncope that might benefit from pacing, but that we did not have an optimal method to identify these patients.

The ISSUE-3 study was designed to assess whether vasovagal syncope patients with spontaneous asystole would benefit from permanent pacemaker implantation. The ISSUE-3 study design involved implanting a loop recorder in a large numbers of vasovagal syncope patients and then to await a recurrent faint to obtain a symptom-rhythm correlation. Those patients with recurrent faints had a pacemaker implanted and were then randomized to having it turned ON (could pace) or OFF (sense only). This relatively small study (in terms of randomized patients) showed a highly significant 57% relative risk reduction in recurrent fainting. Finally, there was a way forward to better select patients that would benefit from permanent pacemaker therapy. Despite the large steps forward with that study, it is noteworthy that 25% of patients who met the stringent inclusion criteria for pacemaker implantation and were randomized to have pacing ON still fainted during follow-up. Even though the appropriate patient selection improved, there is still much further to go.

The authors from the ISSUE-3 study now report on a post-hoc analysis in an effort to better refine the inclusion of patients who will benefit from permanent pacemaker implantation. Many patients had a tilt table test, even though it was not mandated. They sought to assess if a positive tilt table test could help to select patients who might benefit from pacemaker implantation. Instead, they found exactly the opposite. Of 52 patients who received a pacemaker and were randomized to pacing ON, 50% had a positive tilt table test and the other 50% had a negative tilt table test. There were 9 recurrent faints in this cohort, and 8 occurred in the positive tilt table test group and only 1 occurred in a patient with a negative tilt table test. That led to an estimated 21 month syncope recurrence rate of 55% the positive tilt table test group compared to only 5% in the negative tilt table test group.

What explanations could there be for this counter-intuitive finding? One possibility is that this finding was just due to random chance. This was not a pre-specified hypothesis and one must be cautious not to greatly alter clinical practice until this in treating finding can be reproduced in a different cohort. Assuming that this finding is real, it is possible that patients with a positive head up tilt test (regardless of the VASIS classification of the response) may have a vascular mechanism that is partially responsible for the syncope. If so, that vascular

mechanism may not be as responsive to cardiac pacing. Taken at face value, this suggests that tilt table testing may have an important role in the evaluation of patients with vasovagal syncope who are being considered for permanent pacemaker implantation. While 2 decades ago it was thought that patients with a positive tilt table test should get a pacemaker, now it may be the exact opposite.

While thinking about how to interpret these findings, another issue that needs to be resolved is the minimum definition of “success.” Is the minimum goal the elimination of syncope in patients in whom a permanent pacemaker is implanted? However, it may also be useful if a permanent pacemaker could prolong the presyncopal prodrome and delay the onset of syncope, or reduce the burden of frequent syncope? It is possible that these outcomes, all of which would have qualified as “pacemaker failure” in the ISSUE-3 study, may lead to less injury for our patients and could perhaps improve the quality of life. Of course, these secondary benefits would need to be demonstrated in future clinical trials of pacing for vasovagal syncope.

In the meantime, these authors have certainly shared with us some very interesting data that will need to be considered carefully as we move forward.

Structural and functional small fiber abnormalities in the neuropathic postural tachycardia syndrome.

Gibbons CH, Bonyhay I, Benson A, Wang N, Freeman R. (Boston, USA)

PLoS One. 2013 Dec 27;8(12):e84716.

Article Summary

This article sought to define the neuropathology, clinical phenotype, autonomic physiology and differentiating features in individuals with neuropathic and non-neuropathic postural tachycardia syndrome (POTS). Subjects with POTS (n=24) and healthy control subjects (n=10) had skin biopsy analysis of intra-epidermal nerve fiber density (IENFD), quantitative sensory testing (QST), cholinergic sudomotor testing and cardiovascular autonomic testing. Subjects completed quality of life, fatigue and disability questionnaires. Subjects were divided into neuropathic and non-neuropathic POTS, defined by abnormal IENFD and abnormal small fiber and sudomotor function. Neuropathic POTS patients (9 of 24) had significantly lower resting and tilted heart rates; reduced parasympathetic function; and lower phase 4 Valsalva maneuver overshoot compared with those with non-neuropathic POTS ($P<0.05$). Neuropathic POTS subjects also had less anxiety and depression and greater overall self-perceived health-related quality of life scores than non-neuropathic POTS subjects. A sub-group of POTS patients (cholinergic POTS) had abnormal proximal sudomotor function and symptoms that suggest gastrointestinal and genitourinary parasympathetic nervous system dysfunction. The authors concluded that POTS subtypes may be distinguished using small fiber and autonomic structural and functional criteria. Patients with non-neuropathic POTS have greater anxiety, greater depression and lower health-related quality of life scores compared to those with neuropathic POTS. These

findings suggest different pathophysiological processes underlie the postural tachycardia in neuropathic and non-neuropathic POTS patients.

Clinical Summary

Most clinicians that care for patients with Postural Tachycardia Syndrome (POTS) agree that it is not a single pathophysiological entity, but rather a collection of varied underlying pathophysiologies with a similar resultant phenotype of excessive orthostatic tachycardia. While numerous pathophysiological concepts have been identified, including “neuropathic POTS” and “hyperadrenergic POTS”, these categorizations are not discrete and mutually exclusive. This precludes their use to categorize and endophenotype individual patients.

Neuropathic POTS was first defined by Jacob et al. in 2000 (Jacob et al., 2000). Investigators performed painstaking studies and showed that some POTS patients had reduced norepinephrine spillover in their legs, suggesting the presence of a partial sympathetic neuropathy. Norepinephrine spillover studies are much too complicated and laborious to ever be useful for the clinical care of patients, and so clinicians sought out alternative tests. The most commonly used test is the Quantitative sudomotor axonal reflex test (QSART), which segmentally tests the sympathetic cholinergic (and not noradrenergic) nerve integrity. Others have defined “neuropathic POTS” based on reduced intraepidermal nerve fiber density (IENFD) from skin biopsy. The challenge in looking at these groups in isolation is that they might also qualify as being “hyperadrenergic” based on separate criteria involving plasma norepinephrine levels.

It is in this context that Gibbons et al. have published this paper. They offer another definition of “neuropathic POTS”. They required a “neuropathic POTS” patient to have an abnormal IENFD and either an abnormal cholinergic sweat test or an abnormal temperature based quantitative sensory test. Everyone else was classified as “non-neuropathic POTS”. The non-neuropathic POTS group had higher heart rates (both supine and with tilt), larger amplitude phase 4 blood pressure overshoots with Valsalva, more anxiety and depression, and lower health-related quality of life. I suspect that many, but not all, of these “non-neuropathic POTS” patients are those that we might otherwise classify as “hyperadrenergic”. These subgroup differences may explain some of the differences in the prevalence of anxiety and depression reported in studies from different POTS research centers.

Perhaps even more interesting is the secondary analysis in which they broke the patient cohort into groups based on normal or abnormal sweat testing. The patients with abnormal sweat testing reported more gastrointestinal and genitourinary symptoms, which could relate to problems with the parasympathetic and/or cholinergic nervous system. These data suggest that the importance of sweat testing might be to find patients with cholinergic problems (primarily affecting the parasympathetic nervous system), and not the sympathetic nervous system.

There is currently no simple way to classify POTS or delineate the underlying pathophysiology. The present study adds to the complexity. It would be helpful to know the relationship between these subgroups and standing norepinephrine levels (a marker of

sympathetic nervous system tone). It would also be of interest to know about the autonomic innervation of the skin. 'These studies could be pivotal in endophenotyping POTS patients to come up with an individualized approach to the treatment of POTS.

This proposed classification scheme must be confirmed in other studies. For the moment, however, it suggests a subgroup more likely to have autonomic test abnormalities (neuropathic POTS); a subgroup more likely to have anxiety, depression and impaired quality of life (non-neuropathic POTS); and a subgroup more likely to have parasympathetic nervous system abnormalities (cholinergic POTS).

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