DDD Cardiac Pacing in Vaso-vagal Syncope

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Vaso-vagal syncope is the term used to describe a heterogenous group of neurally mediated disorders that manifest as collapse and transient loss of consciousness. For over twenty years there has been investigation into a potential role for cardiac pacing in the treatment of vaso-vagal syncope (VVS). This short review will give a brief overview of VVS and discuss research and current guidance.

Overview of VVS

VVS is exceptionally common and accounts for up to 50% of transient losses of consciousness attending the emergency department. It is mediated by an acute impairment of the homeostatic neurological and cardiovascular responses that maintain cerebral perfusion. Inappropriate activation of the Bezold-Jarisch reflex by mechanoreceptors within the left ventricle has been implicated as the stimulus for this impairment. This activation occurs due to a reduction in ventricular filling as a result of reduced venous return coupled with a reflex increase in myocardial contractility. This leads to the anomalous situation where the baroreceptor reflex causes a bradycardia at the same time that there is increasing inotropy. This increases vagal stimulation and reduces sympathetic tone causing further vasodilatation and reduction in heart rate resulting in VVS.

Both neural (vasodepression) and cardiovascular (cardioinhibitory) responses play a role in VVS. However, their relative contribution to VVS can vary and differentiation requires either non-invasive haemodynamic monitoring (such as Implantable Loop Recorder (ILR)) or Head Up Tilt Testing (HUTT).

The VASIS classification of positive responses to tilt testing provides a simple tool to help clinicians describe a patient's VVS and to potentially target therapy.

Table 1. VASIS classification of positive responses to HUTT

| Type 1: Mixed. HR decreases by >10% but does not decrease to < 40bpm for >10s. BP falls before HR. |
| Type 2A: Cardioinhibition without asystole. Min HR >40 bpm for >10s, or asystole occurs for <3s. BP falls before HR. |
| Type 2B: Cardioinhibition with asystole. Min HR <40bpm for >10s or asystole occurs for >3s. BP falls before or coincident with HR. |
| Type 3: Vasodepressor. HR does not fall >10% from maximum rate during tilt |

Dual Chamber Pacing and VVS

Pacemaker insertion has been a treatment strategy proposed for both type 1 and 2 responses of the VASIS classification. Studies initially compared the implantation of a dual chamber pacemaker to standard, conservative treatment. In the Vasovagal Pacemaker Study (VPS), dual chamber pacing with a rate drop response algorithm (DDD-RDR) was compared with standard therapy in patients with
confirmed bradycardia during a positive HUTT. At a year’s follow up, 6 of 27 patients who had been paced had had further VVS compared with 19 of 27 treated with standard therapy- a significant difference resulting in early termination of the study. Similar findings were reported in the VASIS and the SYDIT studies. These two studies investigated patients with reasonably frequent syncope (>3 syncope in the last 2 years) and cardioinhibition with asystole on HUTT (VASIS) or relative bradycardia on HUTT (SYDIT).

It should be noted that none of the trials were blinded. There is thus a risk of potential bias. The early termination of both VPS and SYDIT by the Data Monitoring Committees on safety grounds also raises the possibility that any treatment effect may be overestimated.

Nonetheless with the observed beneficial effect of DDD-RDR compared with standard therapy from these trials, the next logical step was to compare pacing with placebo (i.e with a control group with a pacemaker implanted but programmed to ODO as opposed to DDD)

There have been three important studies looking at this.

Vasovagal Pacemaker Study 2 (VPS 2) took patients with frequent syncope (> 6 episodes in total or > 3 in years and a positive HUTT) and randomised them to either DDD-RDR or ODO (i.e pacemaker turned “on” vs “off”)6. At just after an average of 2 years follow up, 33% of those paced DDD had had recurrent syncope compared with 42% of those paced ODO (p=0.14, ns). At two year follow up in the Vasovagal Syncope and Pacing Trial (SYNPACE) 50% of those paced DDD had recurrent syncope compared with 38% of those paced ODO- again a non-significant but far from encouraging result.7

These disappointing results have forced a more rigorous and critical assessment of the data which is excellently laid out in a recent review article8. In short, there is marked difference in syncope rates between the control groups is VPS 1 (80%) and VPS 2 (42%). Two possible explanations exist for this and it is likely that both play some part. First, there may well a very strong placebo effect applied as a result of undergoing pacemaker implantation. The second explanation relates to the inclusion criteria of both VPS2 and SYNPACE. VPS 2 did not require a cardioinhibitory response for inclusion and the response was only present in 52% of patients in SYNPACE (the other 48% had a mixed response to HUTT). This begs the question as to whether the inclusion criteria cast too wide a net rather than focussing on those with a pure cardio-inhibitory response where there is the most biological plausibility for pacemaker insertion.

The ISSUE 3 study dealt with the issue of inclusion criteria. The first stage of the study investigated the cause of recurrent syncope (3 episodes in the last 2 years) in 511 patients over the age of 40 by implanting an ILR. ILR investigation yielded 89 patients who had documented asystole (pause >6s) at the time of collapse.9 The mean age of these patients was 63. 77 of these patients went on to pacemaker insertion and were randomised to DDD-RDR or ODO. At two years 25% of those paced DDD-RDR had had one documented syncopal episode compared with 57% of those set to ODO.
Closed Loop Stimulation

As has been discussed above, VVS and the associated symptoms are heralded by an increase in myocardial contractility. Closed loop stimulation (CLS) is a pacing algorithm designed to assess beat to beat changes in systolic cardiac impedance. By constantly monitoring cardiac impedance the algorithm allows the surrogate identification of changes in contractility. When a sudden increase in contractility is noted, as occurs in the VVS prodrome, then the pacemaker will attempt to prevent a vaso-vagal episode with rapid sequential AV pacing. Theoretically the CLS algorithm will allow earlier identification of possible VVS than DDD-RDR that reacts to drops in heart rate - a physiological response further along the VVS mechanistic pathway.

The landmark trial investigating a role for this algorithm was the INVASY trial. 50 patients with severe and recurrent vasovagal syncope and a positive HUTT with cardioinhibition were included. They all received a DDD-CLS pacemaker and were randomised to DDD-CLS or DDI mode for one year. 9/26 patients were randomized to DDI mode and 17/26 to DDD-CLS mode. Of those randomised to DDI, 7 out of 9 patients had syncope recurrence within 1 year where 0/26 randomised to DDD-CLS had further syncope. These results prompted intervention by the steering committee who decided to halt further randomisation. The 9 patients were reprogrammed to DDD-CLS and had no further syncopal episodes in the subsequent year. A further 24 patients recruited in the second stage of the study were programmed in DDD-CLS mode With a mean follow-up of 19 ± 4 months, none of the 41 patient programmed DDD-CLS reported VVS and only 4 reported occasional presyncope. The authors noted a potential 22% placebo effect purely as a result of pacemaker insertion.

Similarly positive results have been reported comparing DDD-CLS and DDD more recently. DDD-CLS has been shown to perform favourably in a small retrospective analysis comparing it with DDD-RDR. The benefits of CLS pacing seem to continue into the long term with a reduction in syncopal episodes at 61 (+/- 35) months. These studies suggest that there is a potentially exciting role for DDD-CLS in the management of patients with recurrent syncope and evidence of cardioinhibition.

Other Considerations and Difficulties with Study Interpretation

It is well recognised that there is a bi-modal age distribution in VVS with peaks in teenage years and the over 65 years. The younger cohort often “grow out” of their tendency towards VVS and the condition typically follows a benign course. This is an important consideration with regard to the use of devices in this group as the de novo implantation risks of permanent pacemaker insertion (leads displacement, pneumothorax and infection) and later generator upgrades (infection) may well accrue over the course of a lifetime to an intolerable overall level. Thus guidelines do not advocate the use of permanent pacemakers in this young cohort and significant discussion with both the patient and the multi-disciplinary team should be held before embarking on pacemaker implantation in a young patient for VVS.

Given the frequency of VVS, it is surprising how few studies have investigated the role of pacing in its treatment. What is more, the overall number of patients involved in these studies is small. The widely accepted appreciable placebo effect of inserting a pacemaker and the early termination of many of these studies further undermines the restricted amount of evidence in this field. Inclusion criteria for each trial varies making comparisons between findings difficult. Criticism can be also be made that inclusion criteria have been insufficiently rigorous (VPS2). There is also the possibility that studies have included patients with primary sinus node disease where
no HUTT monitoring was performed, particularly given the mean age of patients found to have “cardio-inhibitory” response (ISSUE 3).

ISSUE 3 also demonstrated the small proportion of patients with recurrent syncope who may benefit from pacing therapy (89 out 511 screened by ILR fitted ISSUE 3 inclusion criteria).

Many of these problems stem from the difficulty in accurate differentiation of VVS from primary conduction disease and thereafter further classification of VVS. Ideally, patients should undergo both HUTT and ILR implantation to fully characterise their syncope prior to inclusion in future studies.

Nonetheless, there does seem to be a trend towards a reduction in VVS in patients suffering from recurrent syncope and cardio-inhibition on HUTT i.e in a high risk group. Algorithms such as CLS may well provide further benefit when compared with DDD pacing and have a biologically plausible mode of action. There is a need for larger, randomised studies comparing DDD-CLS with DDD-RDR and ODO.

In the mean time the poor evidence base for pacing in VVS is reflected in the international guidelines which promote conservative management wherever possible.15 16 Pacing for VVS is given a class IIb recommendation for patients aged over 40 with refractory, recurrent syncope and cardio-inhibition on HUTT in both ESC and ACC/AHA guidelines. The ACC/AHA guidelines also give a IIa recommendation for syncope without clear, provocative events and with a documented hypersensitive cardioinhibitory response of 3 seconds or longer. There is no reference to specific algorithms in international guidelines perhaps reflecting the lack of attention the guidelines give to the subject as a whole.

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