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EDITORIAL

Pacing for repeated vagal reflex-mediated syncope: an old problem with a solution

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This editorial refers to 'Cardiac pacing in severe reflex syncope and tilt-induced asystole', by M. Brignole *et al.*, on page 508.

Syncope is one of the most disturbing symptoms for any individual and is one of the more frequent reasons for visiting the emergency department, constituting 1–2% of all visits. Most commonly, syncope is explained by the vasovagal reflex triggered by, for example, pain or standing, causing prodromes of unease followed by pre-syncope or self-terminating loss of consciousness (LOC). Roughly 50% of all syncope is vasovagal reflex syncope but 30% is not benign and is induced by arrhythmia and structural heart disease. To rule out the latter, cardiac syncope is a cornerstone in cardiology specialist training.

Vasovagal reflex syncope can often be averted or modified by raising the legs or muscle activity counter pressure action in response to prodromal symptoms. However, a small proportion of patients experience recurrent syncope and yet experience few or no prodromes. Although LOC itself is also self-terminating in such patients, recurrent syncope may result in falls and sometimes fractures, especially if prodromes are mild or absent.

Vasovagal reflex syncope typically has a vasodepressor and a cardioinhibitory component. For this reason, prompt atrioventricular pacing preferably before bradycardia/asystole arises has been shown to demonstrate benefit in syncope reduction for more than two decades, with mixed results. Pacing with rate drop response, in which a rate drop >40 b.p.m. induces pacing at 80 b.p.m., showed promising results in asystolic tilt-induced syncope. A recent addition is closed loop system (CLS) dual chamber pacing (DDD-CLS) which has raised hopes for patients with recurrent syncope.[1,2]

In this issue of the *European Heart Journal*, the BIOSync CLS study by Brignole *et al.* reported an impressive 77% reduction in syncope attacks in patients with severe recurrent reflex syncope randomized to DDD-CLS pacing.[3] This was a relatively small but well conducted controlled double-blind study, meaning that neither patients nor the independent outcome assessors were aware of the assigned treatment. Included patients had to be at least 40 years of age and to have had at least two episodes of unpredictable severe reflex syncope during the last year. In addition, syncope with an asystole >3 s induced by tilt testing was required to be included in the study since an asystolic tilt response previously has been shown to predict asystolic events during prolonged ECG monitoring.[4]

All patients received a pacemaker and were randomized to receive a dual chamber pacemaker with CLS capability programmed to either this active mode or to mere ventricular sensing, meaning no pacing. The study patients reported their own outcome on syncope and pre-syncope attacks through a 12-item self-reported questionnaire developed and validated for this trial. The study included 128 patients, of which 127 fulfilled the study protocol. There were four crossovers to the active pacing mode prior to the primary endpoint due to problematic recurrent pre-syncope. The study was analysed in terms of intention to treat, meaning that these crossovers were analysed as assigned to the inactive pacing mode. The BIOSync CLS study included mostly males in their early 60s and with, on average, three syncopal attacks in the last year. During tilt testing, the average pause was 8.6 s (5–18 s) with 89% sinus arrest and 11% atrioventricular block.

After a median follow-up time of 11.2 months, the Data and Safety Monitoring Board (DSMB) recommended termination on account of superiority of the DDD-CLS study arm. The relative risk reduction of the primary outcome syncope was 77% and the absolute risk reduction was 48% at 2 years in the DDD-CLS arm compared with the control arm, corresponding to a number needed to treat of only 2.2. The secondary endpoint of syncope or pre-syncope was reduced by 66%. The study was not constructed to determine whether this therapeutic benefit was induced by DDD pacing alone or the CLS algorithm, but this question is subject to ongoing studies. It is, however, tempting to assume that the CLS algorithm was instrumental since it may sense premonitory contractility changes as long as 8 min before

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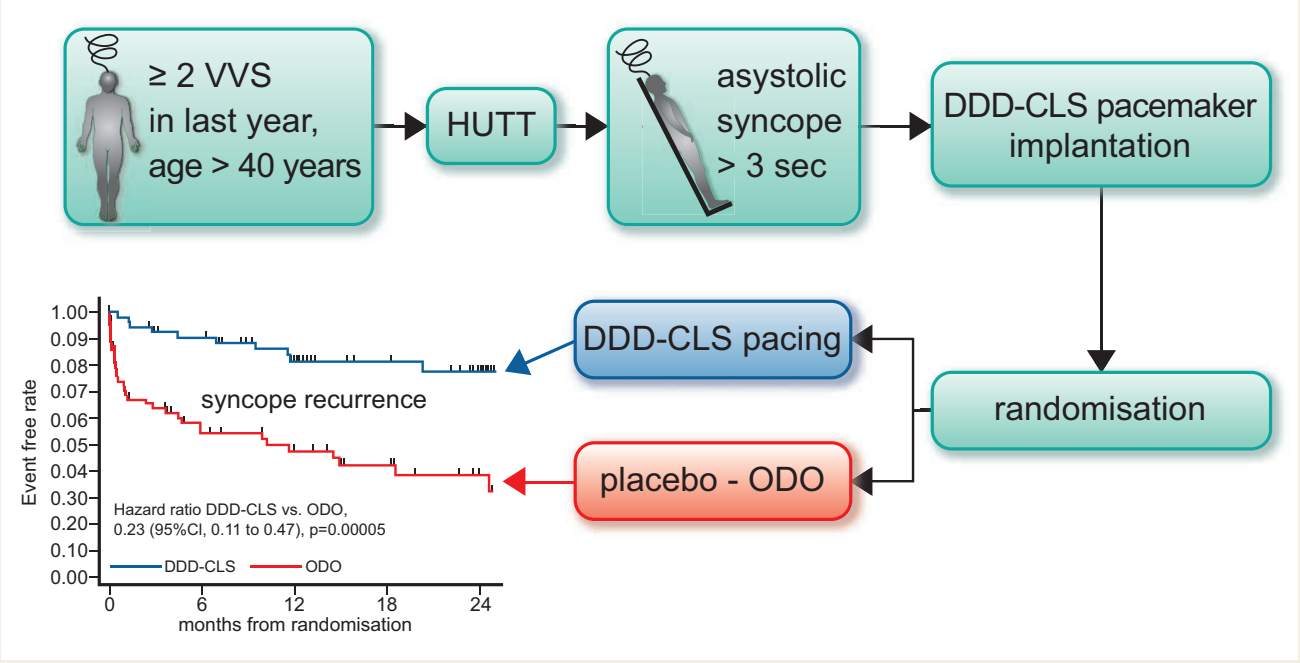

Figure 1 Syncope recurrence in the BIOSync CLS study: a randomized controlled study comparing cardiac pacing to inactive pacing in severe reflex syncope confirmed by Tilt-induced asystole. HUTT = head-up tilt test, ODO = inactive pacing, VVS = vasovagal reflex syncope, DDD-CLS = atrioventricular pacing with closed loop stimulation.

syncope occurs, i.e. well before a pathological rate drop to which conventional DDD pacing responds. As a result, DDD-CLS may induce beneficial pacing in a more timely way compared with DDD pacing.

The DDD-CLS pacing algorithm monitors cardiac contractility, adapting the pacing rate correspondingly, meaning a higher paced rate at higher contractility. The system is based on the principle that the detection of an increase in contractility in an earlier stage of a vasovagal syncope induces atrioventricular pacing which can counterbalance vagal reaction. The CLS algorithm was tested previously to demonstrate that prompt pacing during head-up tilt testing prevents syncope.[2]

The authors should be complimented for the results of their study and also for the strong methodology with blinding, sham control, and the use of a robust tool of patient-reported syncope recurrence. An intriguing finding was that active pacing seems to prevent mostly early recurrences within the first few months (figure 2A of their paper). Patients with early recurrence may differ from those with later recurrence, e.g. by a (temporary) higher activity of their disease around the time of inclusion. Alternatively, patients being implanted with a sham pacemaker may have stopped their preventive syncope measures, believing they are protected by the pacemaker.

The present impressive results agree with those of a much smaller randomized crossover study.[2] In BIOSync CLS, syncope recurrence was seen in 16% vs. 53% of patients at 1 year, and in 22% vs. 68% at 2 years, respectively. Thus two studies, albeit with somewhat different design, reported impressive reductions in recurrent syncope during DDD-CLS compared with control pacing in highly symptomatic patients.

Why does the vasovagal reflex induce recurrent syncope and how can cardiac pacing with a CLS help? Vasovagal syncope has been described to have three main components.[5] First there is a sympathetic nerve activity-mediated increase in cardiac contractility followed by vagal nerve activity-induced bradycardia or asystole, and thirdly vasodepression and a fall in blood pressure. If the vasodepressor component is dominant, pacing does not work, as evidenced by the BIOSync CLS and SPAIN[3] studies in which some patients experienced syncope in spite of pacing. Yet the most common response during head-up tilt testing is a mixture of cardioinhibition and vasodepression, making it challenging to determine suitable candidates for pacing. Saal *et al.*[5] studied the utility of tilt testing in demonstrating the temporal relationship of asystole to onset of transient loss of consciousness in tilt-induced syncope. In about two-thirds, asystole came before a blood pressure fall by >3 s, a time believed to be enough to prevent syncope. In the remaining third, vasodepression was the dominant and initial mechanism and often resulted in a more pronounced blood pressure drop than in those with predominantly a cardioinhibitory mechanism.

It thus remains a challenge to identify suitable patients for DDD-CLS pacing and avoid futile implantations or needless complications. In fact, 4% of patients in the BIOSync CLS study suffered lead-related complications. This is also the reason why patients below the age of 40 should not be treated with pacemakers.[6] An effective algorithm to select patients with recurrent vasovagal reflex syncope for pacing is needed. In the meantime, considering the available studies, tilt testing appears useful and, if applied judiciously and expertly, it may enhance appropriate application of pacing for vasovagal syncope.

The SPAIN study led to a Class IIb recommendation for DDD pacing in the 2018 ESC syncope guidelines.[6] The convincing results of the BIOSync CLS study published in this issue may contribute to broaden the recommendations for patients with recurrent vasovagal reflex syncope. There may indeed be a solution to an old problem.

Conflict of interest: none declared.

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