ESC European Society of Cardiology

European Heart Journal (2021) **42**, 4499–4500
doi:10.1093/eurheartj/ehab383

DISCUSSION FORUM

About syncopal recurrences in Biosync trial

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Online publish-ahead-of-print 21 June 2021

This commentary refers to the article 'Cardiac pacing in severe recurrent reflex syncope and tilt-induced asystole', by M. Brignole *et al.*, https://doi.org/10.1093/eurheartj/ehaa936; 'Effectiveness of Closed Loop Stimulation pacing in patients with cardioinhibitory vasovagal reflex syncope is questionable', by W. Wieling and D.L. Jardine, https://doi.org/10.1093/eurheartj/ehab157; and the discussion pieces 'Efficacy of the Biosync trial, or when facts prompt a reconsideration of theories', by J.G. van Dijk *et al.*, https://doi.org/10.1093/eurheartj/ehab376 and 'Efficacy of the Biosync trial: the information published from this trial to date is not sufficient to change theory', by W. Wieling and D.L. Jardine, https://doi.org/10.1093/eurheartj/ehab379.

Two possible reasons can explain syncopal recurrences that were observed in a minority of patients of the Biosync trial[1]: one is the late onset of asystole and the other is the suboptimal pacing.

In his letter,[2] van Dijk appropriately addressed the timing of asystole with respect to the onset of loss of consciousness, which is relevant. He correctly observed that we did not use the concept of 'late asystole' in the inclusion criteria of the BIOSync-CLS trial,[1] as it may be impractical or difficult to ascertain in many centres. Agreeably, the inclusion of patients with late asystole may have reduced the estimated benefit of pacing, thus reinforcing study results. Indeed, late asystole may represent one of the major causes of the few syncopal recurrences still observed in the active study group, despite pacing. In his pivotal study on the temporal relationship of asystole to the onset of transient loss of consciousness during tilt-induced reflex syncope, Saal and van Dijk *et al.*[3] observed that late asystole, defined as that occurring three seconds before the onset of loss of consciousness, or later, occurred in one-third of subjects. In these patients, the authors argued that pacing may have little benefit as it would probably start too late to prevent syncope. It is worth noting that the rate of late asystole observed by van Dijk is consistent with the 22% syncope recurrence rate at 2 years observed in the Biosync-CLS trial. This finding suggests some causal relationship.

In another pivotal study, van Dijk *et al.*[4] convincingly proved that the onset of cardioinhibition is a real turning point as it is the marker of activation of the vasovagal reflex, i.e. greater hypotension (sympathetic withdrawal) and bradycardia (vagal output). On average, cardioinhibition starts 1–2 min before syncope and 7–8 min after vasodepression. At syncope, both reduced stroke volume and low heart rate contribute to a drop in cardiac output and blood pressure. Therefore, in order to support blood pressure during vagal reaction, pacing at an adequately high rate, as suggested by Kurbaan *et al.*,[5] should cover all this interval. The analysis of some tilt-tests performed during the Biosync-CLS study showed that pacing with closed-loop stimulation (CLS) seems to be perfectly triggered at a sufficiently high rate (90–100 b.p.m.), around the maximum spontaneous heart rate (*Figure 1*). However, with the present CLS system, the basic pacing rate resumes in a short time, when the cardioinhibitory (vagal) reflex may be still present. Thus, suboptimal heart rate is often delivered at the time of maximum vagal reaction that is when adequately high heart rate could prevent syncope. It is advisable that

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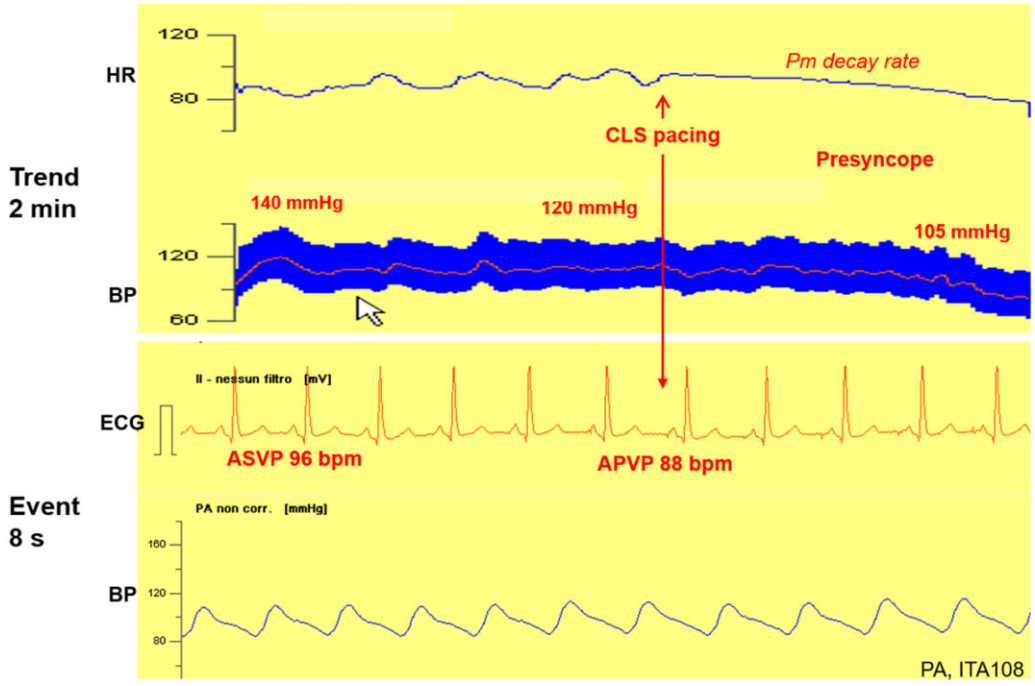

Figure 1 A case of pacing with closed-loop stimulation during the tilt test. The pacing starts at the very beginning of an impending syncope. Closed-loop stimulation pacing introduces atrial stimulation at a rate of 88 b.p.m. when spontaneous sinus rate falls from its maximum value of 96 b.p.m. (there is ventricular fusion throughout). The vasovagal reflex continues as shown by the progressive decrease of blood pressure. The closed-loop stimulation response may be suboptimal in this case. It is expected that the persistence of a pacing rate at 88 b.p.m. or even higher around 96 b.p.m. for the total duration of the vasovagal reflex would have been helpful in aborting or at least limiting the blood pressure fall. APVP, atrial pacing, ventricular pacing; ASVP, atrial sensing, ventricular pacing; CLS, closed-loop stimulation.

future devices will offer a programmable pacing decay, able to maintain an adequately high rate for all the duration of the vasovagal event.

In conclusion, the brilliant theories raised by the two pivotal pathophysiological studies are confirmed by facts (Biosync results). Thanks for the inspiration.

Conflict of interest: none declared.

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