Pacing and vasovagal syncope: back to our physiologic roots

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Received: 29 June 2017 / Accepted: 1 July 2017 / Published online: 14 July 2017
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Enthusiasm for permanent cardiac pacing as a treatment for vasovagal syncope has ebbed and flowed for 30 years. Several case series conducted during the first decade of this period were strongly positive, culminating in randomized clinical trials conducted in Europe and North America. The first studies included patients randomized to receive a pacemaker versus those receiving conventional attempts at treatment. These studies all seemed to show a strong benefit [1]. A second series involved all patients receiving pacemakers, with some programmed to modes that were nearly off. These studies were single-blind, in that the treating physicians knew who received which programming and the patients did not; these results too were strongly positive [1]. In fact, they were so strongly positive that investigators were skeptical, and two formal double-blind randomized trials were subsequently conducted. Both of these latter studies featured all patients receiving pacemakers, with half the pacemakers essentially inactivated. Double blinding was maintained as much as possible, and the results of both studies were resoundingly negative. The earlier treatment effects all appeared to be due to a placebo effect, possibly including investigators unknowingly conveying more optimism to patients who received active pacing [1].

In light of the results of these double-blind studies, enthusiasm for pacing ebbed for nearly 10 years. During this time Brignole and colleagues reported an opus of work utilizing implantable cardiac monitors in patients with

syncope. Based on this work, these researchers conducted a double-blind randomized clinical trial of pacing focused on patients in the community setting who had a long asystolic pause either with or without syncope. The results were significantly although incompletely positive, but surprisingly only patients with negative tilt tests appeared to benefit [2]. Specifically, patients with asystole during positive tilt tests did not benefit. Over this same period a series of small open-label studies appeared to show benefit from pacing with devices with an algorithm called closed-loop stimulation (CLS), which have sensors activated by increased ventricular contractility [3]. This is thought to precede the terminal events preceding vasovagal syncope. In essence, they should activate rapid pacing and prevent syncope.

That brings us to today. Pacing either prevents vasovagal syncope, or it does not. If it does, it prevents syncope only in patients with asystole, but this may not be due to the vasovagal reflex. And the CLS sensor may be necessary for preventing syncope by pacing, or perhaps not. Finally, there is a powerful placebo effect lurking in the wings of all randomized trials with vasovagal syncope.

Brignole and colleagues are conducting a proof-of-two-principles double blind randomized clinical trial [4]. Patients with moderately frequent vasovagal syncope who are over 40 years of age will be eligible for inclusion only if they have had a positive tilt test with an asystolic response, and the CLS pacemaker will be used. This trial will have the benefit of targeting patients only most likely to respond, and who are selected without first implanting a cardiac monitor. If the study results are positive, clinicians might reflect on several points. First, how complete was the blinding? Patients might be asked at study exit to guess their therapy, and the results corrected post hoc for this effect [1]. Second, was this a test of permanent pacing or of

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permanent CLS pacing? To address this point, a future study would need to include two arms with active pacing, only one of which had the CLS sensor activated. Third, why might a study of patients selected for asystole be positive when the earlier substudy [2] of a very similar population was negative? Was this due to suboptimal blinding, or was it truly a CLS effect? Fourth, did the investigators report all syncopal spells during the observation period, or just the first one? There is enormous variability in the natural history of vasovagal syncope [5], and total syncope count needs to be assessed if possible. This is a chronic issue with randomized trials of vasovagal syncope. Finally, how many patients will truly benefit? Most patients improve, only a minority of patients have asystolic vasovagal syncope, and investigators are now quite reluctant to implant pacemakers in young people and people who have not yet exhausted other treatments.

These questions aside, this is a study that needs to be done, and Dr. Brignole and his colleagues are to be commended for developing and conducting it. If the study reaps positive results, it not only will provide more evidence for the efficacy of pacing in patients with vasovagal syncope, but also raise some interesting physiologic questions. For example, how exactly does CLS-triggered pacing work when other pacing seems to be ineffective? Does it intervene so early in the reflex cascade that it terminates it? Is this due to changes in AV synchrony, or to ventricular twist mechanics? Or does it, in some fashion, maintain venous

return just enough that the reflex cascade abates? Gratifyingly, clinical interventional research is now feeding back on its basic physiology roots.

Compliance with ethical standards

Conflict of interest The author reports no relationships with industry or any conflicts of interest.

Funding None.

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