Physiological pacing: a moving target?

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This editorial refers to ‘Long-term clinical effects of ventricular pacing reduction with a changeover mode to minimize ventricular pacing in a general pacemaker population’†, by M. Stockburger et al., on page 151

During the 1990s and the early years of the 2000s, there was considerable debate on the advantages of ‘physiological’ pacing, which at that time denoted dual-chamber vs. single-chamber pacing. A series of landmark studies, including the MOST, PASE, CTOPP, and UKPACE trials, randomized patients with various indications for pacing into DDD vs. VVI pacing modes. Despite high hopes and great belief in the advantages of ‘physiological’ pacing, these studies demonstrated only a modest advantage of the ‘physiological’ approach, expressed by a reduction of atrial fibrillation (AF), mostly limited to patients with sinus node disease (SND) indication for pacing.1

While DDD pacing modes demonstrated only modest effect, the atrial-only (AAI) mode performed much better than VVI in patients with SND in a Danish trial.2 With increased understanding of the deleterious effect of ventricular pacing (mainly apical), the results of the Danish trial as well as those of the later DAVID and DAVID II trials3 were interpreted as demonstrating that the physiological advantage of atrial-based pacing is partially offset by unnecessary RV pacing, an implicit part of standard DDD mode. Given the potential progression of atrioventricular (AV) nodal disease in patients with AAI pacing and the perceived better safety and reliability of back-up ventricular pacing, the stage was set for the development of algorithms to minimize ventricular pacing.

The SAVE PACE trial was the first landmark study of a right ventricular (RV) pacing minimization algorithm. This randomized study has clearly shown the advantage of avoiding ventricular pacing in patients with SND, who demonstrated a lower rate of development of persistent AF.4 However, subsequent studies in both SND and AV block patients, including the DANPACE,5 the PreFER MVP,6 and the MINERVA7 trials, did not support the results of the SAVE PACE trial. It is conceivable that the inclusion of different patient populations, especially patients with AV block, and the use of different endpoints were responsible for this difference. Nevertheless, the approach of DDD with RV pacing minimization was quickly adopted, and current European Society of Cardiology (ESC) guidelines support the use of DDD pacemakers with algorithms promoting intrinsic AV conduction.

The results of the ANSWER randomized trial have now been published.8 This trial suggests that the use of an aggressive strategy for ventricular pacing reduction in a general dual-chamber pacemaker population (equally distributed between SND and AV block populations) is both effective and safe, but yields only marginal benefits in terms of clinical outcome for reducing cardiac mortality and heart failure (HF) hospitalization rates, regardless of the pacing indication.

The ANSWER trial enrolled patients with recent dual-chamber pacemaker implantation for bradycardia indication (SND, 52% second- or third-degree, intermittent or permanent AV block, 48%), without history of AF. The devices used were SafeR capable, which is an AAI pacing with permanent RV monitoring, allowing for automatic DDD mode switch in case of acute high degree AV block.

At 1 month after implantation, patients were assigned either to the SafeR mode or to a conventional DDD pacing mode, and had subsequent 6 monthly follow ups, with the final visit scheduled for 3 years after implantation.

As expected, ventricular pacing was significantly reduced in the SafeR group both at 1 year (4.8% vs. 95%;  P < 0.001) and at 3 years (11% vs. 93%;  P < 0.001), without any difference in adverse outcomes of syncope (1.6% vs. 2.8%;  P = 0.42) and all-cause mortality (8.3% vs. 9.4%;  P = 0.61). Also, in the study group, the syncpe events were not considered device related and there was no documentation of any mode-switch-induced ventricular arrhythmia, suggesting that the SafeR algorithm is not arrhythmogenic.

The primary clinical composite endpoint (hospitalization for HF or AF or cardioversion) did not differ significantly between the two groups. This is in keeping with the findings of previous studies that analysed similar endpoints in patients with dual-chamber pacemakers for SND.5–7 However, a secondary endpoint analysis showed promising results, demonstrating the SafeR mode to be associated with reduced cardiac mortality or HF hospitalization [hazard ratio (HR) 0.49;  P = 0.02]. This apparent contradiction mandates further investigations.

While the SafeR algorithm was able to decrease the percentage of ventricular pacing in patients with AV block in the ANSWER trial, the authors do not provide us with subgroup analysis of the results in the...
two main groups of patients—SND vs. AV block. It is possible that the SafeR algorithm improved the results in SND patients while AV block patients did not benefit from it, or even got worse by excessive non-physiological PR prolongation, which may affect left ventricular (LV) filling and atrial emptying, and promote AF.7 The conclusion regarding these two groups will have to be postponed until after subgroup analysis.

Despite the physiological rationale of the DDD with minimized pacing algorithm, the results of the ANSWER trial as well as other previously mentioned trials fail to demonstrate an overwhelming advantage of pacing minimization approaches over conventional pacing. This lack of effect is counterintuitive, as was the lack of effect of ‘physiological’ dual-chamber pacing in the studies of the previous decade. Are we missing something?

There are several potential explanations for this apparent paradox.

(i) Several studies including the ANSWER trial combined patients with SND and AV block, whereas the effect may be limited to or more apparent in SND patients.

(ii) The use of these algorithms together with atrial pacing and some slowing of the conduction system may create very long AV intervals that may affect ventricular filling and atrial emptying in a manner that counterbalances the beneficial effects of ventricular synchronization. The exact balance and the turning point between gain of intraventricular synchronization (by extending AV delay allowing conduction to the ventricles) and the loss of AV synchronization (by an excessive AV delay) remains to be explored.

(iii) The pacemaker memorizes events that are listed as paced beats but are in fact fusion beats, which may decrease the difference between paced and non-paced groups.

Finally, other techniques for prevention of pacing-induced LV dysfunction should be explored along with pacing prevention algorithms. Alternate pacing sites such as septal and outflow tract pacing have been looked at without a clear conclusion so far,9 as were the use of cardiac resynchronization therapy (CRT) instead of DDD pacing in the majority of pacemaker recipients with AV nodal disease.10

The ANSWER trial demonstrated that the SafeR mode safely reduces ventricular pacing in a mixed population of patients in need of new pacemakers. While demonstrating mixed results regarding clinical benefit, it remains to be seen whether subgroups of the population tend to benefit more from this approach.

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References