AAIR or DDDR pacing for sick sinus syndrome: the physiologic conundrum

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The results of the DANPACE multicentre trial were recently published.¹ There were 1415 patients with symptomatic sick sinus syndrome (SSS) and normal QRS width, randomly assigned to single-chamber AAIR pacing (707 patients) or dual-chamber DDDR pacing with a tailored atrio-ventricular (AV) delay, designed to prevent ventricular pacing (708 patients). During a mean follow-up period of 5.4 ± 2.6 years, paroxysmal atrial fibrillation (AF) was observed in 28.4% in the AAIR group vs. 23% in the DDDR group (P < 0.024). There were significantly more deaths (P = 0.024) and pacemaker reoperations (P < 0.001) in the single-chamber group, whereas there was no difference with chronic AF, stroke, and hospitalization for heart failure. Despite AV-delay tailoring, ventricular pacing in the DDDR group was 65% with a mean AV delay of 225 ± 39 ms.

These data are in contrast to the original Danish trial published in 2003 with the lead author being involved with both trials.² This smaller study of 177 patients had three groups randomized to AAIR, DDDR with short AV delay (DDDR-s), and DDDR with fixed long AV delay (DDDR-l). During a mean follow-up period of 2.9 ± 1.1 years, AF, both paroxysmal and chronic, was significantly less common in the AAIR group. Long-term DDDR pacing also induced left atrial dilatation, and in the DDDR-s group (90% ventricular pacing) there was also reduced left ventricular function.

Seeing the results are so different how does this compare with other studies? In 2003, Sweeney et al.³ reported a subgroup of 1339 patients with SSS enrolled in the MOST trial and randomized to DDDR (707 patients) or VVIR (632 patients) pacing. During a median follow-up time of 33.1 months in the DDDR arm, cumulative per cent ventricular pacing (Cum%VP) > 40% of the time was associated with a 2.6-fold increased risk of heart failure hospitalization compared with Cum%VP < 40%. Similarly, with DDDR pacing, the risk of AF increased 1% for each 1% increase in Cum%VP up to 85%.

As a follow-up to the MOST trial,³ the SAVE PACe⁴ trial with two authors from the MOST was a randomized controlled study of 1063 patients comparing dual-chamber minimal ventricular pacing with conventional dual-chamber pacing in patients with SSS. Minimal ventricular pacing was achieved using a number of proprietary search AV algorithms. The primary endpoint was the time to persistent AF. During a mean follow-up period of only 1.7 ± 1.0 years, there were 99.0% ventricular pacing with conventional DDDR and 9.1% in the minimal ventricular-paced group (P < 0.001). Persistent AF developed in 12.7% of conventional DDDR and 7.9% in the minimal ventricular-paced group (P = 0.004). Mortality and the rate of hospitalization for heart failure were similar in both arms of the study.

The presented all four trials had similar objectives, but different results and conclusions and hence present a conundrum on how to manage patients with SSS. The original Danish study² was small, but clear in its conclusions that AAIR pacing was preferred to DDDR. Although left ventricular dysfunction from right ventricular apical pacing was demonstrated in this study, it was the publication of the DAVID trial in 2002⁵ that stimulated physician interest, particularly when a series of confirmatory reports followed.⁶,⁷ The large MOST³ and SAVE PACe⁴ trials also confirmed the value of avoiding ventricular pacing in SSS, but fell short of recommending single-chamber AAI pacing. Now with the publication of the DANPACE¹ trial with its recommendations contrary to accepted dogma, once again questions are being asked about the need to minimize ventricular pacing in SSS, particularly with respect to the prevention of AF and heart failure.

There are many difficulties comparing the four trials because of differences in follow-up times, the subtle differences in the definition of AAIR pacing (single or dual chamber) with its varying ventricular-pacing contribution, the differences in pacemaker programming, the accuracy of data collection, the technology available at the time of the study, and the definition of AF as to whether it was paroxysmal or persistent.

In the DANPACE,¹ AF was diagnosed with a 12-lead electrocardiograph and pacemaker telemetry, but not memory retrieval as the AAIR arm did not have a mode-switching algorithm. The diagnosis of paroxysmal AF was made at one of the planned follow-up visits and chronic AF required the rhythm to be present at two consecutive and subsequent follow-up visits. The early Danish² trial in keeping with the technology at the time used only a 12-lead electrocardiograph at planned follow-up visits to confirm...
AF. Similarly, the MOST\textsuperscript{3} used a 12-lead electrocardiograph and categorized patients as having chronic AF if documented without intervening sinus rhythm on more than one visit. In comparison, the SAVE PACe\textsuperscript{4} used both electrocardiographic confirmation and device retrieved memory data to determine the time to persistent AF.

Over the years, we have come to expect with respect to AF that AAIR pacing is superior to all forms of ventricular pacing including DDDR.\textsuperscript{2–4} Both AAIR and DDDR pacing preserve AV synchrony. DANPACE\textsuperscript{1} now tells us that DDDR pacing with a tailored AV delay is superior in preventing AF compared with single-chamber AAIR. The reasoning given is that a prolonged AV delay with AAIR pacing actually encourages AF, particularly if the low rate is set at 60 ppm. This is despite the DDDR arm of the same trial having a mean programmed AV delay of 225 ms and 65% ventricular pacing.

Another factor to consider is the role of AF documented before inclusion in the study. It is not surprising that a prior history of AF\textsuperscript{8} resulted in a higher incidence of AF post-pacing in the DDDR group.\textsuperscript{1} Do other co-morbidities that encourage AF such as previous myocardial infarct, heart failure, hypertension, and diabetes play a role as well and explain the unexpected superiority of DDDR pacing?\textsuperscript{9}

DANPACE also provides confusing data on the incidence of heart failure with DDDR pacing.\textsuperscript{1} The trial involved a mean follow-up period over 5 years with no difference in the incidence of heart failure in either group. Atrio-ventricular synchrony was maintained in both groups and thus right ventricular apical pacing did not have a statistical detrimental effect on left ventricular function. This is possibly explained by the fact that an attempt was made to avoid ventricular pacing, but was still present in 65% of patients. Consequently, the DDDR cohort was a mixed group of patients with the potential liability of right ventricular apical pacing negated by the benefits of minimized ventricular pacing. In contrast, the original Danish\textsuperscript{5} and MOST studies\textsuperscript{3} demonstrated an increased incidence of heart failure from DDDR pacing. The SAVE PACe,\textsuperscript{4} however, was a short trial lasting 1.7 years and it was not surprising that the rate of hospitalization for heart failure was not significant.

In conclusion, the large, recently published DANPACE study has provided unexpected and largely unexplained results.\textsuperscript{1} However, many questions remain as to how dual-chamber systems should be programmed. To date, all the studies have involved right ventricular apical pacing. We now need to consider whether left ventricular dysfunction can be prevented by right ventricular pacing from sites outside the apex.

Conflict of interest: L.P. is a consultant for Medronic, St Jude Medical, Boston Scientific, and Sorin Group. H.G.M. is a consultant for St Jude Medical and Medtronic. The remaining authors report no conflicts of interest.

References