Clinical Trials for Cardiac Pacing in Bradycardia
The End or the Beginning?

Hung-Fat Tse, MD; Chu-Pak Lau, MD

Since the first report of clinical application of cardiac pacing more than 50 years ago, it remains the only effective long-term treatment of symptomatic bradycardia. Although the indications for the use of implantable cardiac pacemakers have expanded significantly over the past several years, sick sinus syndrome (SSS) and atrioventricular (AV) conduction disorders continue to be the major indications for permanent cardiac pacing in the United States and other parts of the world. Technological developments in modern pacemakers have significantly reduced the size of the devices to allow easy implantation and have provided a myriad of programming options to customize therapy. These advances have led to increased patient and physician acceptance of pacemaker therapy. Furthermore, because of the aging of populations worldwide, the number of patients with cardiac rhythm disturbances requiring pacemaker implantation is increasing. Recent studies in the United States have demonstrated that the annual number of pacemakers implanted has increased by almost 3-fold during the past decade.

In the early 1980s, the concept of “physiological pacing” was proposed to pursue normal cardiovascular physiology and to maintain AV synchronization and heart rate response to exercise. As a result, sophisticated pacemakers with dual-chamber sensing and pacing and rate-response algorithms have been developed. Pacing has evolved beyond a simple life-saving technology into a therapy that aims to improve patient quality of life and clinical outcomes. These perceived beneficial effects of physiological pacing were supported by early observations from short-term hemodynamic studies and retrospective analysis. Indeed, the practice of physiological pacing has been widely adopted by implanting physicians. Recent surveys have demonstrated that dual-chamber devices with rate-adaptive capabilities (DDDR) account for the majority (70%) of implanted pacemakers in Western countries and increasingly have been used in other parts of the world.

However, recent data from randomized, controlled trials have challenged this practice. In the first randomized trial comparing atrial (AAI) versus ventricular (VVI) pacing in 225 patients with SSS, Andersen et al reported a significant reduction of atrial fibrillation (AF) and thromboembolic events in the atrial pacing group compared with the ventricular pacing group. During longer follow-up of the same cohort of patients, Andersen et al observed additional beneficial effects of atrial pacing over ventricular pacing in terms of cardiovascular mortality, progression to chronic AF, and development of heart failure. However, 5 subsequent randomized, controlled trials in a larger population cohort have failed to confirm these benefits of atrial-based pacing over single-chamber ventricular pacing in patients with AV block or SSS. It is important to note that dual-chamber pacing (DDD) rather than atrial pacing alone was used as atrial-based pacing in these studies and might account for the differences in their results as compared with the Andersen study. In the Pacemaker Selection in the Elderly (PASE) study, the Canadian Trial of Physiological Pacing (CTOPP), the Mode Selection Trial in Sinus Node Dysfunction (MOST), and the United Kingdom Pacing and Cardiovascular Events (UKPACE) trial, there was no clear mortality benefit of dual-chamber pacing over ventricular pacing. Although both CTOPP and MOST showed a significant reduction in AF with dual-chamber pacing, no reduction of stroke was observed. However, all these studies were designed to detect 25% to 30% reduction in major clinical outcomes, and each individual trial did not have sufficient power to detect a smaller (5% to 10%) reduction in stroke and mortality by dual-chamber pacing.

The meta-analysis of the randomized trials on cardiovascular outcomes with atrial-based pacing compared with ventricular pacing in the present issue of Circulation is welcomed. Healey et al collected individual data from 7231 patients enrolled in these randomized, controlled trials to compare the effects of atrial-based versus ventricular-based pacing on mortality, composite outcome of stroke or cardiovascular mortality, stroke, heart failure, hospitalization, and AF. This analysis confirms that no significant differences in all-cause mortality or combined outcome of cardiovascular mortality and stroke can be observed between atrial-based or ventricular-based pacing. However, atrial pacing significantly reduces the incidence of AF by 20% and stroke by 19% as compared with ventricular pacing. These beneficial effects appear to be confined to those patients with SSS. In addition, no specific patient characteristics, including age, gender, history of hypertension, AF and heart failure, left ventricular ejection fraction, and low unpaced heart rate can predict a benefit from atrial-based pacing. Although these data appear
to provide an evidence base for cardiac pacing, there is limited information from these trials on how to optimize a pacemaker prescription in each individual patient. Except for elderly patients with AV block and limited exercise capacity, such as those enrolled into UKPACE,15 most patients will probably still receive atrial-based pacing. Most physicians believe that the modest benefits in the areas of AF and stroke, as shown in this meta-analysis, as well as the potential and perceived advantages of atrial-based pacing, including improvement of exercise capacity and quality of life, prevention of pacemaker syndrome, better device diagnostic function, and more flexible device programming, should outweigh the higher initial implant cost and complications rate of atrial-based pacing. For these reasons, these findings will have limited impact on existing clinical practice. Indeed, a recent survey after the publication of CTOPP has shown an increase rather than a decrease in the use of dual-chamber pacing in patients with bradycardia.17

With the modest beneficial findings of atrial-based pacing over ventricular pacing, it is unlikely that future trials will target pacing mode differences, especially with respect to major clinical end points such as mortality. However, these trials open up a few key issues to be addressed.

First, atrial-based pacing significantly reduces the relative risk of AF by 24% and the composite outcome of stroke and cardiovascular death by 17% in patients with SSS. However, there is a lack of relation between the reduction of AF and the reduction of stroke. Many episodes of AF are asymptomatic, and it is possible that suppression of unrecognized episodes of AF by atrial pacing may contribute to stroke reduction or that early detection of such episodes by modern pacemaker memory might have prompted early initiation of anticoagulation. Therefore, future studies should focus on defining the role of pacemaker diagnostics and monitor function to guide the appropriate use of therapy to reduce the risk of AF and stroke in high-risk populations.

Second, the current approach of physiological pacing does not provide incremental benefit over ventricular pacing in reducing mortality rates and heart failure in patients with bradycardia. This is not an unexpected finding given the older age of the pacemaker patients who have multiple comorbid conditions. As shown in the meta-analysis,16 the mean of the study population was 76 years, and on average, 45% of these patients had hypertension.16 In UKPACE,15 the annual mortality rate of the study population was as high as 7.4%. Furthermore, up to 40% to 50% of deaths in MOST14 and UKPACE15 were not due to cardiovascular causes. Therefore, it is difficult to translate the benefit of maintaining AV synchrony by physiological pacing into an improvement in survival. Moreover, as discussed by Healey et al,16 the favorable hemodynamic effect of preserved AV synchrony may also be attenuated by “nonphysiological” ventricular dyssynchrony induced by right ventricular apical pacing.7,18 The relative importance of AV versus ventricular synchrony on the long-term clinical outcome in patients with SSS should be addressed by the ongoing Danish Multicenter Randomized study on AAI or DDD Pacing in Sick Sinus Syndrome trial.7

Third, an alternative approach of physiological pacing is needed in different populations of patients requiring pacemakers. In patients with SSS and preserved AV conduction, unnecessary ventricular pacing should be avoided. This can be achieved by using AAI pacing, as demonstrated in the Andersen study. Furthermore, several new modes of dual-chamber pacing have been developed to minimize ventricular pacing by using either different AV hysteresis algorithms or “mode switch” between AAI and DDD. These methods to reduce unnecessary ventricular pacing may be preferable to AAI pacing mode alone because a significant proportion of SSS patients must be protected from or treated for intermittent AV block.19 In addition, an alternative right atrial pacing site at a septum location is associated with a short intrinsic AV conduction time and may further avoid unnecessary ventricular pacing. This alternative site may provide an additional mechanism for atrial pacing to prevent AF in patients with SSS. Future trials are needed to determine the optimal atrial-based pacing mode in patients with SSS.

Fourth, in patients with AV block who need ventricular pacing most of the time, the optimal approach to achieve physiological pacing remains unclear. Although emerging data have indicated potentially deleterious effects from the ventricular dyssynchrony that is induced by right ventricular apical pacing,7,18 data supporting the use of other alternative ventricular pacing sites are limited. In UKPACE,15 the annual incidence of heart failure was only 3.2%. In patients with normal left ventricular function, the adverse ventricular remodeling induced by right ventricular apical pacing may take some time to manifest.18 In contrast, right ventricular apical pacing may be more deleterious in patients with preexisting left ventricular dysfunction. Therefore, future prospective, randomized clinical trials are warranted to compare the long-term clinical outcome of conventional right ventricular apical pacing with other alternative ventricular pacing sites, such as the right ventricular septum, left ventricle, or even in both ventricles for patients with AV block.

Last but not least, even in the absence of a clear survival benefit, it remains unclear whether the modest improvement in clinical outcome and quality of life warrants the increased cost and complication rate associated with the dual-chamber pacemaker. In PASE and MOST but not in CTOPP, modest improvements in quality of life are observed in patients with SSS during dual-chamber pacing,11-14 and no quality-of-life data were available in UKPACE.15 Recent data from the MOST trial have suggested that dual-chamber pacing indeed increases quality-adjusted life expectancy at an acceptable cost.20 Cost-effectiveness of the device should always be considered when a new pacing modality is evaluated in future pacing trials.

In conclusion, despite all the effort in recent randomized, controlled trials to identify the best pacing mode in patients with bradycardia, there is limited information on the optimal pacemaker prescription for each individual patient. Atrial-based pacing will continue to be the “favored pacing model” despite the somewhat modest observed benefit over ventricular-based pacing, barring economic considerations. However, the results from these trials do help to set the agenda for future research on cardiac pacing, which will focus on pacing sites, pacing diagnostics, and cost-effectiveness.
Disclosures

None.

References


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