EDITORIAL

UKPACE: to die, or not to die . . . Is that the question?

Joseph C. Lin, MaryAnn Goldstein, and David G. Benditt*

Department of Medicine, Cardiovascular Division, Cardiac Arrhythmia Center, University of Minnesota Medical School, Mail Code 508, 420 Delaware Street SE, Minneapolis, MN 55455, USA

Publication of the United Kingdom Pacing and Cardiovascular Events (UKPACE) trial in 2005 brings to three the number of important randomized clinical trials that call into question what formerly had seemed to be a bullet-proof principle of modern cardiac pacemaker therapy, namely the apparent desirability of maintaining a normal atrioventricular (AV) timing relationship. Indeed, as a group, UKPACE and two earlier North American trials [the Canadian Trial of Physiological Pacing (CTOPP) and the Mode Selection Trial (MOST) in sinus node dysfunction (SND)] may influence physicians and health insurers to advocate, based on a mortality cost-effectiveness basis, for a return to the predominance of single-chamber ventricular pacing. However, before turning back the clock, the messages delivered by these studies warrant careful examination.

CTOPP and MOST compared outcomes during dual-chamber and single-chamber ventricular pacing in over 4500 patients with AV block and/or SND and reported no overall difference in mortality or stroke. However, more than two-thirds of the patients enrolled in these two trials were paced for treatment of SND, a condition in which the frequency of pacing may vary widely from patient to patient, and death is a less relevant endpoint than is preventing syncpe, reducing thromboembolic risk or improving exercise tolerance.

UKPACE, the most recently published of the three major clinical trials noted earlier, randomized cardiac pacemaker treatment candidates ≥70 years of age with AV block between dual- (n = 1012) and single-chamber devices (n = 1009), and further subdivided the single-chamber population into two groups: fixed-rate ventricular pacing (n = 504), and rate-modulated single-chamber pacing (n = 505). The resulting three subgroups proved to be reasonably comparable in terms of age, gender, New York Heart Association (NYHA) functional class, AV conduction disease, symptoms, co-morbidities, and medications. Further, a high pacing ‘burden’ was anticipated in all patients by virtue of the fact that the study compared outcomes in older patients who required pacing for high-grade AV block (approximately 74% complete AV block, 26% second-degree AV block). Unlike in CTOPP, an attempt was made in UKPACE to quantify the actual pacing burden prospectively (at the first month follow-up). Findings indicated that pacing was required approximately 94% of the time in the single-chamber group versus 99% in the dual-chamber group (P < 0.001). Thus, it appears that UKPACE offers insight into the effects of pacing mode in a broad range of older patients in whom frequent pacing of any form is occurring on a daily basis. On the other hand, UKPACE findings should be interpreted in the context of limitations imposed by the selection process that occurred during study enrollment. Among 16 375 screened patients, UKPACE investigators identified 5308 patients (32.4%) with AV block. However, 945 of these were excluded on the basis of pre-determined exclusion criteria and approximately 2400 additional patients were eliminated by virtue of declining to participate, physician reluctance to include patients, or other reasons. Thus, in the end, the study population comprised approximately 37% (1972 of 5308) of screened patients with AV block, and 45% (1972 of 4363) of eligible patients. The authors are commended for so clearly laying out the basis for this important attrition of study candidates.

Although a 45% enrolment rate is not atypical for such randomized clinical trials, we are nevertheless curious about the 2400 un-enrolled patients. Although no data are available to substantiate this speculation, one wonders whether these un-enrolled patients were deemed by their physicians to be susceptible to pacemaker syndrome, or for some other reason not thought to be best served by risking placement of a single-chamber device and were therefore steered away from the study. The findings of UKPACE, therefore, must be considered with the possibility of selection bias in mind.

The primary endpoint of UKPACE was the assessment of the impact of pacemaker mode on mortality outcome; essentially, UKPACE tested the hypothesis that dual-chamber pacing improves total mortality among elderly patients with AV block, compared with ventricular pacing alone. However, it is well recognized that in patients with AV block (as is also true in patients with SND) mortality is primarily a reflection
of the severity of the underlying disease state, and is less dependent on the conduction system status.\textsuperscript{4,5} Thus, it is not surprising to find that after a median follow-up period of 4.6 years, the UKPACE Intention-to-treat analysis demonstrated no significant difference in total mortality between the dual- and single-chamber pacing arms. As an aside, it should be noted that ‘on-treatment’ outcomes (accounting for the failed dual-chamber implants that continued to be assessed in the ‘dual-chamber paced group’) were not reported.

Apart from the lesser importance of conduction system disease versus severity of underlying heart condition as a key determinant of mortality risk, the choice of mortality as the primary outcome measured in UKPACE was less than ideal for more practical reasons. It is our observation that physicians and patients today tend to consider pacing primarily as a means of improving quality of daily life, i.e. reducing susceptibility to pacemaker syndrome, preventing or treating symptoms of atrial fibrillation, and reducing the economic and life-style burden of heart failure. Consequently, even in the absence of a demonstrable mortality benefit attributable to dual-chamber pacing, UKPACE may not convincingly prove that patients will not derive any additional benefits from dual-chamber compared with ventricular pacing alone. The Pacemaker Selection in the Elderly (PASE) trial\textsuperscript{6} attempted to address this issue.

PASE, unlike the three larger trials previously mentioned, was conducted specifically to assess the effect of pacing mode on health-related quality-of-life. PASE randomized 407 patients who required permanent pacing (49% AV block, 43% SND, 8% other indications) to dual-chamber pacing or single-chamber ventricular pacing and was specifically powered to detect differences in quality of life, as assessed by serial comprehensive surveys (SF-36). During 30 months of follow-up, quality of life significantly improved after pacemaker implantation in both treatment arms, but no significant differences were observed between the two pacing modes. Subgroup analysis, however, indicated that patients with SND had significantly better quality of life and cardiovascular functional status with dual-chamber pacing than with ventricular pacing, but these benefits were not demonstrated for patients with AV block. These observations should be considered, however, in the context of a 26% crossover to dual-chamber pacing among patients assigned to ventricular pacing; the basis for this substantial crossover rate was primarily pacemaker syndrome. The high rate of crossover in PASE may have effectively decreased the power of the study to detect meaningful differences between the two treatment arms, as all endpoints were analysed on an intention-to-treat basis. Thus, despite the substantial number of ‘single-chamber’ patients having dual-chamber devices, the outcome continued to be registered in the ‘single-chamber’ camp. An on-treatment analysis of PASE was not published, but would be interesting to see.

A similarly high crossover rate (31%) from ventricular pacing to dual-chamber pacing, (due to intolerance of pacing mode) was observed in MOST.\textsuperscript{6} Pacing tolerance and quality of life, as assessed by serial comprehensive surveys (SF-36), were formally assessed as secondary endpoints. After extended follow-up, significant improvements were demonstrated for six of eight indices measuring quality of life and functional status in patients assigned to dual-chamber pacing compared with those having ventricular pacing.

In contrast to findings from MOST and PASE, only 3% of patients assigned to ventricular pacing in UKPACE and 4% of patients assigned to ventricular pacing in CTOPP crossed over to dual-chamber pacing. One potential explanation may be selection bias. In UKPACE, the selection of patients (see earlier comment), especially by referring physicians, may have biased the study against individuals likely to exhibit pacemaker syndrome symptoms (i.e. more active individuals), in effect selecting for those who are less active. Other reasons for differences in crossover rates among these studies may be explained in part by differences in the detail with which the studies assessed quality of life and pacing tolerance. MOST and PASE, the two studies with high crossover rates from single-chamber to dual-chamber pacing, assessed quality of life as a formal endpoint, using a comprehensive and validated tool to evaluate the endpoint. These two studies systematically assessed patient’s symptoms and quality of life at frequent pre-defined intervals for all patients for the full duration of the study, and for this reason, would be more likely to detect patients who experience intolerance of pacing mode than would UKPACE or CTOPP. CTOPP only assessed quality of life in an abbreviated fashion at 6 months post-implant (and not at baseline) for 67% of patients. A small but more comprehensive CTOPP sub-study, which found no difference in quality of life between the two pacing arms, was probably inadequately powered to detect meaningful differences in patient symptoms, as complete data were gathered for a mere 8% of trial participants. Quality of life was not indicated as a pre-specified endpoint in UKPACE, and the rigorousness of any quality-of-life observations, which are as yet unpublished, remains to be seen.

We believe that the increased sensitivity with which PASE and MOST were able to detect intolerance of pacing mode may explain in part the higher rates of crossover seen in these two studies. Furthermore, all patients in PASE and MOST, regardless of pacing mode assigned, had both atrial and ventricular leads implanted prior to randomization and required only reprogramming to cross over from ventricular pacing to dual-chamber pacing. Patients in UKPACE and CTOPP required re-operation for mode reassignments. One could argue that the study design in PASE and MOST created a low threshold for crossover. However, this trial design in effect allowed these latter two studies to assess and validate intolerance of pacing mode. Indeed, in patients who crossed over from single-chamber pacing to dual-chamber pacing, significant increases in functional status and quality of life were identified.\textsuperscript{6,7} Thus, among individuals who do not tolerate single-chamber pacing, the dual-chamber alternative seems to provide important quality-of-life benefit that, absent an easy crossover option, would not be recognized and therefore would be under-reported.

Another possible explanation for the different crossover rates reported in these studies may be related to differences in culture, medico-legal considerations, and expectations in healthcare. MOST and PASE were conducted primarily in the United States where private healthcare and patient demands tend to drive clinical decision-making, whereas CTOPP and UKPACE were conducted in Canada and the United Kingdom, both of which have single-payer
nationalized healthcare systems. The former system may tend to be overly responsive to patient complaints that are suggestive of adverse pacing effects, whereas the latter environments may be biased against costly interventions. Presumably, the ‘real need’ for crossover lies somewhere between the values observed in PASE and MOST and those observed in CTOPP and UKPACE.

In conclusion, UKPACE demonstrated that dual-chamber pacing does not improve overall survival compared with ventricular pacing alone in older patients. This finding is not surprising, and reaffirms the data from the other major studies. However, the mortality endpoint is probably not the crucial determinant for mode selection in the majority of pacemaker patients. Day-to-day quality of life, susceptibility to atrial tachyarrhythmias, and concerns regarding excessive ventricular pacing are the keys to device decision at the present time. In the first case, quality-of-life benefits in large populations remain a source of controversy. However, the ‘within-patient’ experience provided by individuals not tolerating single-chamber pacing indicates that dual-chamber pacing offers important symptom benefits. Without means of determining exactly who will tolerate and who will not tolerate single-chamber pacing prior to implantation of a device, physicians can reasonably argue that the ‘dual-chamber choice’ is very defensible.

With regard to atrial tachyarrhythmias, UKPACE further contributes to the ambiguity created by conflicting results from the various pacing trials. Data from UKPACE are congruent with PASE, which found no difference in incidence of atrial fibrillation between the two pacing arms. These results, however, conflict with MOST, CTOPP, and the Danish pacing trial of elderly patients with SND, which did demonstrate significantly lower rates of atrial fibrillation in patients assigned to dual-chamber or atrial-based pacing.

Finally, the concern regarding the need to minimize ventricular pacing has substantially altered the landscape for future pacing trials, producing greater current interest in demonstrating the impact of pacing mode on left ventricular performance, susceptibility to heart failure, and the potential cost savings associated with the reduction of heart failure hospital admissions. UKPACE did not formally assess the impact of pacing mode on these increasingly relevant endpoints.

For the reasons discussed earlier, the value of dual-chamber pacing, though seemingly diminished at first glance, may be greater than UKPACE and earlier clinical trials would suggest. Consequently, in the end, we believe that concerns about pacing intolerance and quality of life will continue to be paramount in physicians’ minds when they come to choose a pacing system for their patients. These clinical considerations will drive increasing adoption of dual-chamber pacemakers (possibly with a growing proportion of these implanted as biventricular pacing systems), especially for the most ‘pacemaker-dependent’ patients. This development has already been presaged in Canada where, despite ‘negative press’ from the initial CTOPP publication, subsequent data have shown an increased interest in the use of dual-chamber pacing systems.12

References