EDITORIAL COMMENT

Stroke and Pacing Mode: Is Pacing Mode Important?*

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Sinus node disease, atrioventricular conduction disease, atrial fibrillation, and stroke all have markedly increased incidence in the elderly. Thus, there is frequently an overlap of these conditions. Many patients with pacemakers develop atrial fibrillation (1–3), and many patients with atrial fibrillation have concomitant sinus node dysfunction and receive pacemakers. This is not surprising in that the sinus node is within the right atrium and is prone to the same pathologic processes as the atria. Pathologic changes of the atria are the same in settings of advanced aging, sinus node dysfunction, and atrial fibrillation, demonstrating an increase in fibrosis and fat deposition, particularly in the approaches to the sinus and atroventricular nodes (4). Because of the high incidence of atrial fibrillation and other comorbid conditions of the elderly, such as diabetes, hypertension, and great vessel atherosclerosis, patients with pacemakers would be expected to have a high incidence of stroke.

“Physiologic” pacing has been considered to be a mode of pacing that preserves the normal atrioventricular activation sequence, that is, atrial-based pacing. Dual-chamber (DDD) pacing is most commonly used in North America and is required for patients with atroventricular conduction disease. Atrial pacing alone (AAI) can be used only in those with normal atroventricular conduction, that is, sinus node disease. In North America, AAI mode is uncommonly used but is favored in several European Countries, such as Denmark. Recent studies have suggested that DDD pacing may not be physiologic in that it alters ventricular activation sequence and hemodynamics (5,6).

Several small and large studies have evaluated the role of pacing mode on outcomes (1–3,7,8). All have included stroke as part of a combined primary outcome and, alone, as a secondary outcome. A small Danish study (1,7) compared AAI with ventricular pacing (VVI) pacing in patients with sinus node disease and showed a reduction in atrial fibrillation and stroke and a delayed reduction in mortality. The Canadian Trial Of Physiologic Pacing (CTOPP) examined patients with sinus or atrioventricular nodal disease and found no reduction in a combined outcome of cardiovascular mortality or stroke or stroke alone but a high incidence of atrial fibrillation (5.7%/year) and a significant reduction in atrial fibrillation by physiologic pacing (relative risk reduction [RRR] 18% at 3 years and 20% at 6 years) (2,8). The Mode Selection Trial (MOST) examined patients with sinus node dysfunction only and showed similar results with no difference in the primary combined outcome of mortality or stroke (3). Again, there was a high incidence of atrial fibrillation, both before pacing (50%) and in follow-up (8.8%/year) with a significant reduction in incidence by DDD pacing mode (RRR 21%).

The current study by Greenspon et al. (9) in this issue of the Journal examined the population of patients who incurred a stroke in the MOST study cohort. Compared with historical data from patients with sinus node disease, they showed a very low rate of stroke (90 of 2,010 total patients), 2.2% at 1 year and 4.9% at 3 years. Over the mean follow-up of 33.1 months, there was no significant difference in the rate of stroke between the group with VVI pacing mode (4.9%) compared with the group with DDD mode (4%). The RRR of 18% was not statistically significant.

This study provides a valuable contribution in its ability to evaluate the factors at implant that were associated with subsequent stroke. After multivariable analysis, previous stroke and systemic embolism, hypertension, Caucasian race, and New York Heart Association functional class III/IV heart failure were associated with an increased risk of stroke. Pacing mode was not associated with risk of stroke. Atrial fibrillation after randomization also was associated with a significantly increased stroke risk.

Antithrombotic therapy was monitored. At baseline, 46% of the patients in the study were on aspirin, and 23% were on warfarin. In follow-up, new development of atrial fibrillation was “closely associated” with introduction of warfarin (p = 0.001). Evaluation of the 1,204 patients who never received warfarin showed that previous stroke or transient ischemic attack and age were the only significant variables that were associated with increased risk of stroke.

This study shows some predictable and some unexplained results. First, the rate of stroke was low. The incidence of stroke in CTOPP was even lower at 1.1%/year. Both of these studies are in stark contrast to previous studies of the sinus node population, both in observational studies (10,11), where risks of stroke were up to 10%/year and in Andersen’s prospective study, where stroke rate was 3.5%/year (1,7). The low rate of stroke is likely explained by increased use of antithrombotic therapy in CTOPP and MOST that were conducted after trials convincingly showed the benefits of antithrombotic therapy in atrial fibrillation. The current study documents the appropriate increased use of warfarin in those patients who developed atrial fibrillation.

The stroke risk in this study and CTOPP is close to that expected in a general population of this age. The Framingham cohort demonstrates an incidence of stroke of 8.4 per 1,000 in men and 6.1 per 1,000 in women age 65 to 74 years and 16.2 per 1,000 in men and 13.5 per 1,000 in women age 75 to 84.
years (12). One might expect a higher stroke rate in a paced population because of the high prevalence of risk factors such as hypertension, atrial fibrillation, diabetes, and underlying heart disease. The increased treatment of risk factors and use of antithrombotic therapy, particularly in a trial setting, may reduce the risk back to that of the general population.

There are some surprising findings from this study that may be the result of the relatively small number of patients who developed stroke and others that are simply mystifying. The failure to demonstrate significance of known risk factors for stroke, namely diabetes, smoking history, and male gender may be explained by the small numbers (13,14). The authors did not attempt to explain the paradoxical finding of increased risk in the Caucasian population. Other cohorts have shown that non-Caucasian populations have a higher incidence of stroke. Again, the small numbers in any subgroup may explain this finding, but it does bring into question the statistical strength of the other associations.

As demonstrated by the randomized trials of pacing mode, there is an unequivocal and sustained reduction in the development of atrial fibrillation using atrial based pacing modes. The failure of this to translate into a significant reduction in stroke in CTOPP and MOST may be the result of the appropriate use of antithrombotic therapy. However, the result may also be the result of inadequate sample size. The Mode Selection Trial and CTOPP showed nonsignificant 18% and 12% RRRs of stroke. Neither was powered to detect a difference in stroke alone. Meta-analysis of these studies and the impending United Kingdom Pacing and Cardiovascular Events study (15) will be important. The ongoing Danish Multicenter Randomized Study on AAI versus DDD Pacing in Sick Sinus Syndrome study (16) will evaluate the role of ventricular pacing in the DDD mode by comparing it with AAI pacing. However, even if the combined results of these studies show a significant reduction in stroke with physiologic pacing modes, the clinical significance of any reduction is likely to be small compared with identification of those at risk. Although the final verdict on the association of pacing mode and stroke is important, identification of patient characteristics that may be associated with stroke is likely more so. The present study is important in focusing health professionals on the ongoing risk of stroke in the paced population, particularly those with baseline risk factors.

There are several other factors that should be considered in a discussion of pacemakers and stroke. Detailed diagnostic capabilities of newer pacemakers are able to log episodes of atrial fibrillation. This may increase the ability to predict those at risk of stroke and/or death (17) and use of these data to institute antithrombotic therapy should be encouraged. Pacing may result in rate smoothing and decrease the ability of patients to identify symptoms associated with atrial fibrillation. Patients who undergo atrioventricular nodal ablation are largely unable to tell when they are in atrial fibrillation. Therefore, paced patients who have had atrial fibrillation and risk factors for stroke likely should be on permanent anticoagulant therapy.

The present study focuses us on the importance of identification of those at risk of stroke in a population of patients receiving pacemakers. Baseline characteristics are largely those that predispose to stroke in the general population and development of atrial fibrillation after pacemaker implantation increases the risk. We can extrapolate from this study that it is important to treat modifiable risk factors and to be vigilant for the development of atrial fibrillation, including use of diagnostic data, and to prescribe antithrombotic therapy aggressively as indicated.

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