Canadian Trial of Physiological Pacing
Effects of Physiological Pacing During Long-Term Follow-Up

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Background—The Canadian Trial of Physiological Pacing (CTOPP) reported that the risk of stroke or cardiovascular death was similar between patients receiving ventricular versus physiological pacemakers at the end of the original follow-up period of 3 years. However, the occurrence of atrial fibrillation was significantly less frequent with physiological pacemakers. To assess a potential delayed benefit of physiological pacing, follow-up of patients in this study was extended to 6 years.

Methods and Results—A total of 1474 patients requiring a pacemaker for symptomatic bradycardia were randomized to receive ventricular and 1094 to physiological pacemakers. The primary outcome was stroke or cardiovascular death. The study was completed in July 1998, and follow-up was extended to July 2001. At a mean follow-up of 6.4 years, there was no difference between treatment groups in the primary outcome of cardiovascular death or stroke. There was no significant difference in total mortality or stroke between groups. There was a significantly lower rate of development of atrial fibrillation in the physiological group, with a relative risk reduction of 20.1% (CI, 5.4 to 32.5; P=0.009).

Conclusions—The CTOPP extended study does not show a difference in cardiovascular death or stroke, or in total mortality, or in stroke between patients implanted with ventricular or physiological pacemakers over a mean follow-up of >6 years. However, there is a persistent significant reduction in the development of atrial fibrillation with physiological pacing. (Circulation. 2004;109:357-362.)

Key Words: pacemakers ■ mortality ■ stroke ■ fibrillation

The Canadian Trial of Physiological Pacing (CTOPP) was the first large randomized clinical trial to examine the benefits of physiological pacing that maintained atrioventricular synchrony (dual-chamber or atrial pacing) compared with ventricular pacing with regard to the composite outcome of cardiovascular death and stroke. After a mean of 3.0 years of follow-up, CTOPP reported that there was no significant benefit of physiological pacing over ventricular pacing in reducing cardiovascular death or stroke. There was no reduction in overall mortality or in hospitalization for congestive heart failure. There was a moderate, statistically significant reduction in the development of atrial fibrillation. Another large trial, the Mode Selection Trial in Sinus Node Dysfunction (MOST), subsequently reported similar results. A post hoc analysis of CTOPP evaluated the relationship between unpaced heart rate and the effect of pacemaker selection. A low unpaced heart rate was used as a marker of those who might pace more frequently. This study reported that those with an unpaced heart rate <60 bpm benefited from physiological pacing, with a significant reduction in the incidence of cardiovascular death or stroke.

A small, randomized study of atrial versus ventricular pacing in patients with sinus node dysfunction, the Danish Study, initially reported no benefit of physiological (AAI) pacing at a mean follow-up of 3 years. However, after a more extended follow-up of 5.5 years, significant reductions in death and in atrial fibrillation were reported. Other small studies have shown variable results with regard to outcomes of death and stroke. In light of the apparent delayed benefit seen in the Danish Study, we extended the follow-up of CTOPP by another 3 years to assess whether a significant difference in the primary study outcome would develop over time.

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Methods
Details of the protocol of the principal CTOPP study have been published.1 Patients receiving their first pacemaker for symptomatic bradycardia (sinus node dysfunction, atrioventricular block, or both) were eligible for CTOPP. Patients <18 years of age, those in chronic atrial fibrillation, and those with life expectancy <1 year were excluded. CTOPP randomized 2568 patients (1474 to ventricular pacing and 1094 to physiological pacing) at 32 centers in Canada. Pacemakers were implanted within 48 hours of randomization.

The likelihood of more frequent pacing was estimated by observation of the unpaced heart rate at the first follow-up visit between 2 and 8 months after pacemaker implantation. The pacemaker was temporarily programmed to a rate of 40 bpm (VVI or AAI), and the underlying ventricular rate was recorded as the unpaced heart rate. Unpaced heart rate data were not available in 12% of patients.

After completion of the principal CTOPP study, a simplified follow-up was undertaken for the subsequent 3 years. Patients were followed up annually, either in the Pacemaker Clinic or by telephone contact (with the patients or physicians). Study outcomes in the extended phase were the composite outcome of cardiovascular death or stroke (primary outcome), total mortality, stroke, and new development of atrial fibrillation. The initial CTOPP analysis did not demonstrate any difference in hospitalization for congestive heart failure, and because of the need to simplify follow-up in the extended study, this outcome was not collected.

Data analysis was performed on an intention-to-treat basis. The risk of outcome events between physiological and ventricular pacing was estimated by the Kaplan-Meier method, and the results were compared by log-rank tests.7,8 Cox proportional-hazards modeling was used to evaluate the effects of baseline variables and unpaced heart rate on potential benefits of physiological pacing.9 All analyses were stratified according to study center.

Results
Patient Enrollment/Treatment Assignment
The details of the patient screening and the treatment assignment have been reported.1 There were 2568 patients randomized in CTOPP, 1094 to physiological pacemakers, and 1474 to ventricular pacemakers. Of those assigned to physiological pacing, 93.5% received a physiological device, and of those assigned to ventricular pacing, 99.1% received a ventricular device. As previously reported, there was no difference between treatment groups in baseline characteristics or indications for pacing.3

Completeness of Follow-Up
At the end of the main study on July 1, 1998, 2002 patients remained eligible for the extended follow-up. Of these, 7 (0.3%) were never seen during the extended follow-up. The percentage follow-up at years 1, 2, and 3 of the extended follow-up were 98.4%, 95.2%, and 94.9%, respectively. The majority of patients lost to follow-up were unable to be contacted. The mean follow-up of patients randomized to the 2 study groups was the same at 6.4 years.

Pacing Mode Compliance Over Time
For patients randomized to ventricular pacing, 93% were still in VVI(R) pacing mode with a ventricular pacemaker at 8 years (Figure 1). For patients randomized to physiological pacing, 75% were receiving physiological pacing at 8 years.

Outcome Events
As shown in Figure 2, the primary composite outcome of cardiovascular death or stroke occurred at a rate of 6.1% per year in patients assigned to ventricular pacing and at a rate of 5.5% per year in patients assigned to physiological pacing.

Subgroup Analyses
The relationship between baseline clinical features and treatment effect was explored with regard to the primary outcome. As shown in Figure 4, no subgroup of patients experienced any benefit with physiological pacing compared with ventricular pacing. Of particular note, there is no interaction between treatment and age, even though in the initial report of the CTOPP results, there was a trend toward more benefit of physiological pacing against atrial fibrillation was unchanged from the initial report.1 There were no differences in total mortality or in stroke between the pacing groups.
Discussion

Main Findings
In patients with symptomatic bradycardia receiving a pacemaker, no significant reduction in cardiovascular death or stroke from physiological pacing occurred during a mean follow-up period of 6.4 years. The definition of physiological pacing in this study was atrial-based pacing, thus maintenance of atrioventricular synchrony. The reduction in development of atrial fibrillation at the end of the initial 3-year follow-up persisted during the extended follow-up. Physiological pacing reduced the number of patients who developed atrial fibrillation from 5.7% per year with ventricular pacing to 4.5% per year with physiological pacing. This 20.1% risk reduction was highly significant at 6.4 years of mean follow-up. The absolute risk reduction was 6.9% over the mean follow-up of 6.4 years. For every 100 patients treated over this period, physiological pacing would be expected to prevent atrial fibrillation in 7 patients. Extrapolated over a 10-year life expectancy of a typical pacemaker generator, physiological pacing might be expected to prevent atrial fibrillation in 11 of 100 patients treated. The number needed to treat with a physiological pacemaker to prevent atrial fibrillation is 9. Previous studies suggest that it may not be physiological pacing that prevents atrial fibrillation but rather ventricular pacing that may promote its development by permitting atrial bradycardia, stretch of the atria by atrial contraction against closed atrioventricular valves, and retrograde atrial electrical activation.

Compliance to ventricular pacing mode was high. In CTOPP, change of pacing mode for those assigned to ventricular pacing implied pacemaker generator change. The rate of upgrade to physiological pacing was <1% per year. Approximately 20% of patients assigned to physiological pacing had been converted to ventricular pacing since the initial implantation.

Importance of Atrial Fibrillation
Although a reduction in development of atrial fibrillation by physiological pacing is of potential patient benefit, the recent results of the AFFIRM Trial indicate that the clinical impact of this effect may be less important than previously thought. AFFIRM has shown that maintenance of sinus rhythm by antiarrhythmic drugs does not reduce stroke and mortality. Similarly, in the extended CTOPP, the reduction in atrial fibrillation does not translate into a statistically significant effect on the composite of cardiovascular death or stroke.

Subgroup Effects
The trend in the initial CTOPP report for younger patients to benefit more from physiological pacing has disappeared in this extended study. This may be related only to a random difference. However, there is some suggestion that this may be related to a small trend toward benefit of physiological pacing in the older group. Nonetheless, the CTOPP extended study clearly demonstrates that there is no difference in the benefit of physiological pacing with regard to the primary outcome related to age.

The subgroup analysis evaluating the relationship between unpaced heart rate and pacemaker selection previously reported...
was provocative and suggested that a benefit of physiological pacing was more pronounced in patients with low unpaced heart rate, who might be expected to use their pacemakers more frequently. One would expect that if this effect were true, with extended follow-up and a much greater number of events, this effect would become very striking. However, the interaction between unpaced heart rate and treatment effect in the extended follow-up was not statistically significant either for the primary outcome or for atrial fibrillation. A randomized clinical trial of physiological pacing versus ventricular pacing in pacemaker-dependent patients is required to test the hypothesis that patients who are pacemaker dependent have a lower rate of death and stroke with physiological pacing. A limitation of the present analysis was the inability to accurately track the percentage of time paced in either group. The unpaced heart rate was used as an indicator of those who might pace more frequently. However, this cannot be expected to accurately reflect the true percentage of pacing. Current technology would permit an accurate assessment of pacing frequency.

Comparison With Other Studies

The CTOPP Extended Study does not reproduce the delayed benefit with regard to mortality seen in the extended Danish Study. This may be because the Danish Study was small and the number of patients reaching a mean follow-up of 5.5 years was very small. Furthermore, the reduction of mortality in the Danish trial achieved only a borderline significance ($P=0.04$) and may have been a result of chance. There was a major difference in patient population in the 2 studies, because the Danish Study enrolled only patients with sinus node disease, and therefore, physiological pacing was achieved by atrial pacing. In CTOPP, almost all patients in the physiological group received dual-chamber pacing, and even patients with sinus node dysfunction probably paced a proportion of the time in the ventricle.

The term "physiological" was used in CTOPP to reflect the terminology at the time of development of the trial. Previous nonrandomized trials claiming marked benefits of dual-chamber pacing used the same term. Clearly, there is a strong indication that pacing from the right ventricle (usually at the apex) is not really physiological. Pacing the atrium and ventricle sequentially may solve the problem of unsynchronized contraction and prevention of atrial bradycardia, but the ventricular activation sequence is clearly not physiological. Recent studies using biventricular pacing have suggested improvement in patients with left bundle-branch block, and an extension of the theory behind this improvement suggests that right ventricular pacing might be deleterious.

The recently published Dual-chamber And VVI Implantable Defibrillator (DAVID) study randomized patients receiving implantable defibrillators (ICDs) either to backup pacing at 40 bpm or to DDD-R pacing at a rate of 70 bpm. The composite end point of death or hospitalization with heart failure was greater in the group receiving
DDD-R pacing than in the backup pacing group. This increased mortality and morbidity may be related to the increased heart rate or the right ventricular pacing or a combination of the two.

**Interactions of Unpaced Heart Rate With the Primary Outcome and Atrial Fibrillation**

<table>
<thead>
<tr>
<th>Outcome Event</th>
<th>Ventricular, %/y</th>
<th>Physiological, %/year</th>
<th>RRR, %</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke or CV death</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UHR ≤60</td>
<td>6.8</td>
<td>5.2</td>
<td>24.4</td>
<td>6.3–39.0</td>
<td>0.011*</td>
</tr>
<tr>
<td>UHR &gt;60</td>
<td>5.1</td>
<td>4.9</td>
<td>0</td>
<td>-31.0–23.8</td>
<td>1.0</td>
</tr>
<tr>
<td>AF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UHR ≤60</td>
<td>6.5</td>
<td>4.1</td>
<td>35.6</td>
<td>17.0–50.0</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>UHR &gt;60</td>
<td>4.1</td>
<td>3.5</td>
<td>18.6</td>
<td>-13.0–41.4</td>
<td>0.22</td>
</tr>
</tbody>
</table>

CV indicates cardiovascular; UHR, unpaced heart rate (bpm); AF, atrial fibrillation; and RRR, relative risk reduction. *P = 0.11 for interaction of UHR and treatment effect. †P = 0.21 for interaction.

The Mode Selection Trial in Sinus Node Dysfunction (MOST) implanted dual-chamber pacemakers in patients with sinus node disease. The patients were then randomized to ventricular pacing versus dual-chamber pacing and followed up for a mean of 33.1 months. Congruent with the results of the CTOPP Extension, there was no difference in mortality, cardiovascular mortality, or stroke. There was a very similar benefit with regard to reduction of atrial fibrillation and a significant but weak benefit with regard to hospitalization for heart failure.

Two further important studies are pending. The UK Pace Study is evaluating elderly patients, >70 years of age, with atrioventricular block. This study will be important for evaluating the effect of pacing mode in a group in which many will have continuous ventricular pacing. Another Danish study is evaluating the benefits of atrial pacing alone (ensuring spontaneous ventricular depolarization) versus dual-chamber pacing in patients with sinus node disease (the Danish Multicenter Randomized Study on Atrial Inhibited versus Dau-Chamber Pacing in Sick Sinus Syndrome [DAN-
PACE [Study]. This study will be important in identifying the potential deleterious effect of right ventricular pacing as discussed above.

Clinical Implications
Although there is a strong preference for atrial-based atroventricular sequential pacing in most developed countries, current evidence from randomized clinical trials provides only modest support for this approach. Dual-chamber pacemakers are more expensive, have more complications, and may require earlier replacement because of reduced generator longevity. Clinical trials have so far failed to show clear benefit for dual-chamber pacing in terms of reduction of death or stroke. Conversely, CTOPP and each of the other randomized trials have shown modest nonsignificant mortality reductions or a marginally significant reduction in mortality with physiological pacing. A rigorous meta-analysis is required after reporting of the United Kingdom Pacing and Cardiovascular Events (UKPACE) Trial to evaluate whether the choice of a physiological pacemaker results in a small but real reduction in mortality and stroke. At present, the hard evidence in favor of physiological pacing remains sketchy. Results of ongoing and future studies may show enhanced benefits of more physiological pacing techniques.

Appendix
The following persons and institutions (listed in descending order according to the number of patients followed up) participated in the extended phase of the Canadian Trial of Physiological Pacing.


Acknowledgments
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