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Electrophysiology

Progression to Chronic Atrial Fibrillation After Pacing: The Canadian Trial of Physiologic Pacing

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OBJECTIVES This study examined the effect of physiologic pacing on the development of chronic atrial fibrillation (CAF) in the Canadian Trial Of Physiologic Pacing (CTOPP).

BACKGROUND The role of physiologic pacing to prevent CAF remains unclear. Small randomized studies have suggested a benefit for patients with sick sinus syndrome. No data from a large randomized trial are available.

METHODS The CTOPP randomized patients undergoing first pacemaker implant to ventricular-based or physiologic pacing (AAI or DDD). Patients who were prospectively found to have persistent atrial fibrillation (AF) lasting greater than or equal to one week were defined as having CAF. Kaplan-Meier plots for the development of CAF were compared by log-rank test. The effect of baseline variables on the benefit of physiologic pacing was evaluated by Cox proportional hazards modeling.

RESULTS Physiologic pacing reduced the development of CAF by 27.1%, from 3.84% per year to 2.8% per year ($p = 0.016$). Three clinical factors predicted the development of CAF: age ≥74 years ($p = 0.057$), sinoatrial (SA) node disease ($p < 0.001$) and prior AF ($p < 0.001$). Subgroup analysis demonstrated a trend for patients with no history of myocardial infarction or coronary disease ($p = 0.09$) as well as apparently normal left ventricular function ($p = 0.11$) to derive greatest benefit.

CONCLUSIONS Physiologic pacing reduces the annual rate of development of chronic AF in patients undergoing first pacemaker implant. Age ≥74 years, SA node disease and prior AF predicted the development of CAF. Patients with structurally normal hearts appear to derive greatest benefits. (J Am Coll Cardiol 2001;38:167–72) © 2001 by the American College of Cardiology

Atrial fibrillation (AF) is the most common sustained arrhythmia and is associated with significant morbidity, mortality and substantial costs to the health care system (1-5). In fact, in the Framingham Heart study, AF was found to be a risk factor for death independent of other cardiovascular conditions (4). The role of pacing for the prevention of AF remains unclear. Specifically, the benefit of physiologic (atrial pacing or dual chamber pacing) over ventricular-based pacing on the development of and progression to chronic AF (CAF) in patients undergoing pacemaker implant remains unknown. Retrospective trials have suggested that physiologic pacing is associated with a reduction in CAF in patients undergoing pacemaker insertion (6–10). Due to the retrospective nature of these trials, it remains likely that selection bias contributed significantly to the outcomes measured. Two small, randomized trials comparing physiologic pacing with ventricular-based pacing have suggested a reduction in the rate of development of CAF (11–13). This benefit appeared to be seen predominantly in patients undergoing pacing for sick sinus syndrome.

The Canadian Trial Of Physiologic Pacing (CTOPP) (14) randomized 2,568 patients undergoing first pacemaker implant regardless of indication to physiologic versus ventricular-based pacing. It was hypothesized that physiologic pacing would reduce the incidence of AF in these patients and, consequently, statistically reduce the incidence of stroke or cardiovascular death. In CTOPP, physiologic pacing was found to reduce the annual rate of AF by 18%. However, this modest reduction in the rate of AF did not translate into a reduction in the composite primary end point of stroke or cardiovascular death. The short follow-up of three years may have reduced the ability to demonstrate an effect on stroke and cardiovascular death as the reduction in AF was seen only after two years. Alternatively, the treatment effect of physiologic pacing on total AF (paroxysmal AF and CAF) was of insufficient magnitude to reduce the incidence of stroke or cardiovascular death. Therefore, to further delineate the treatment effect of physiologic pacing on total AF burden, analysis of the prospectively determined end point of CAF was performed.

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Abbreviations and Acronyms

AF = atrial fibrillation
AV = atrioventricular
CAD = coronary artery disease
CAF = chronic atrial fibrillation
CI = confidence interval
CTOPP = Canadian Trial Of Physiologic Pacing
ECG = electrocardiogram
LV = left ventricle or left ventricular
MI = myocardial infarction
QOL = quality of life
SA = sinoatrial
VVIR = ventricular-based rate-responsive pacing

We hypothesized that the treatment effect of physiologic pacing would be greater using an end point of CAF. This would provide further evidence for a significant treatment effect of physiologic pacing. We also sought to determine clinical risk factors that predict greatest benefit from physiologic pacing for the prevention of CAF.

METHODS

Thirty-two Canadian centers participated in the CTOPP trial, which has been reported elsewhere (14). Patients were eligible if the following inclusion criteria were met: 1) first pacemaker implantation, 2) absence of CAF, 3) age >18 years old. Patients were excluded if the pacemaker indication was related to atrioventricular (AV) node ablation or if the patients were not expected to survive two years. Implanting centers were allowed to choose one of a number of randomization ratios resulting in an uneven randomization (57:43 ventricular:physiologic).

After giving informed consent, patients were randomized no more than 48 h before the scheduled pacemaker implant. Patients randomized to physiologic pacing could receive a dual-chamber device or an atrial pacemaker if an intraoperative atrial pacing test demonstrated 1:1 AV conduction up to an atrial rate of 130 beats/min. Patients in both treatment arms were required to receive a rate responsive pacemaker if chronotropic incompetence was demonstrated or if permanent third-degree AV block was the indication and patients were randomized to the ventricular arm.

Baseline clinical characteristics have been published and were well balanced between the groups (14). Briefly, the indication for pacing was AV nodal disease alone in 52% of patients and sinoatrial (SA) disease alone in 35% of patients. Demographics for the entire study population are tabulated in Table 1.

The primary outcome for the trial was the composite end point of stroke or cardiovascular death. The development of AF after randomization was also considered an important outcome. An occurrence of AF was defined as any documented episode of AF lasting greater than 15 min. Documentation of AF required electrocardiogram (ECG) or rhythm strip evidence. All patients who were found to have had an episode of AF were required to return for subsequent rhythm recording (ECG or rhythm strip) at one week. Patients who were found to have persistent AF lasting greater or equal to one week were defined as having CAF.

Table 1. Baseline Patient Characteristics

	All Patients (n = 2,568)
Mean age	72.7 ± 10.3
Male gender	58.8%
NYHA class ≥2	39.0%
Pacing indication	
SA node disease	33.7%
AV node disease	51.6%
Both	8.3%
Other	4.2%
Unknown	2.3%
Medical history	
Myocardial infarction	25.1%
Documented CAD	17.5%
Stroke or TIA	9.5%
Prior atrial fibrillation	21.1%
Diabetes mellitus	14.8%
Systemic hypertension	35.2%
Left ventricular function	
Clinical assessment—normal*	51.3%
Clinical assessment—abnormal*	11.9%
Objective assessment—normal†	18.6%
Objective assessment—abnormal†	16.1%

*Physician clinical impression of left ventricular systolic function; †left ventricular systolic function assessed by echocardiography or angiography.
AV = atrioventricular; CAD = coronary artery disease; NYHA = New York Heart Association; SA = sinoatrial; TIA = transient ischemic attack.

The cumulative risk of developing CAF over time from randomization was estimated using the Kaplan-Meier (15) approach and compared between treatments with a Mantel-Haenszel test (16) stratified by center. The stratification was prespecified and based on the fact that the fraction of patients randomized to conventional pacing was allowed to vary from center to center. Cox's proportional hazard model (17) was used in the analysis. Although we have quoted the annualized event rates (number of events/patient years at risk) as useful summary statistics, treatment effects have been expressed as hazard ratios and relative risk reductions (i.e., 1-hazard ratio) with their associated confidence intervals (CI) and p values. The Cox model was also used both to explore the way patient factors influenced the subsequent risk of CAF and to look for potential "subgroup effects."

Several clinical factors were included in the model: age ≥74 years, (the median for the group), history of documented myocardial infarction (MI) or documented coronary artery disease (CAD) without prior MI, documented prior AF (duration > 30 s) in the prior six months, history of hypertension, history of diabetes mellitus, evidence of documented sinus node disease or left ventricular (LV) function assessed as either normal or abnormal. Patients with documented assessment of LV function (LV angiogram of echocardiography) within the prior two years had LV function determined by this assessment. Left ventricular

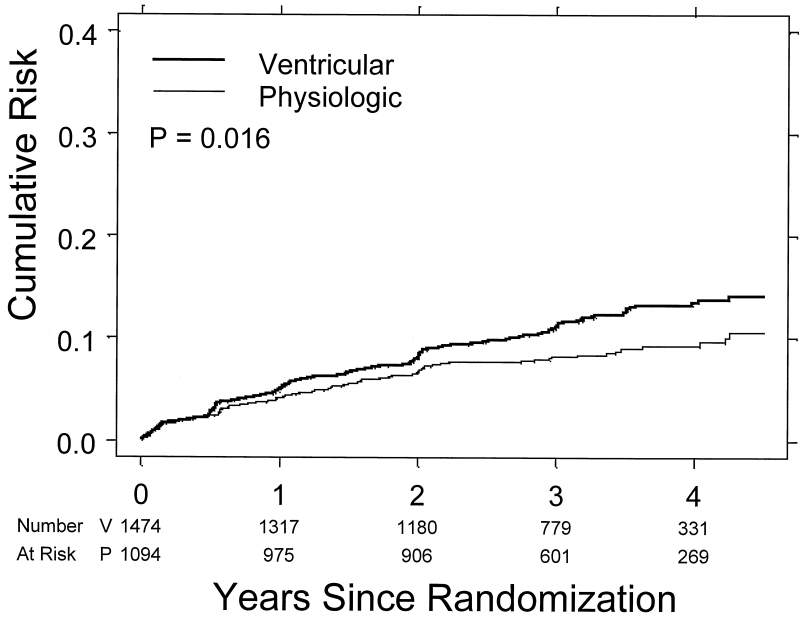

Figure 1. Cumulative risk of the development of chronic atrial fibrillation over time for the groups receiving ventricular (V) and physiologic (P) pacing. The curves diverge between 6 and 12 months and continue to diverge over time.

function was determined to be abnormal if a wall motion abnormality or hypertrophy was seen. If LV function had not been assessed in the prior two years, a presumptive assessment was made as apparently normal or abnormal based on clinical assessment.

RESULTS

Two thousand five hundred sixty-eight patients were randomized with a ratio of 57:43 (ventricular:physiologic), resulting in 1,474 ventricular-based implants and 1,094 physiologic pacing implants. Physiologic pacing reduced the rate of development of CAF from 3.84% per year to 2.80% per year, a relative risk reduction of 27.1%, (95% CI: 5.5 to 43.6, $p = 0.016$). Figure 1 shows the cumulative risk of development of CAF over time. The curves separate at approximately six months and continue to diverge thereafter.

Of the clinical factors investigated in this study, three predicted the development of CAF after controlling for treatment. Age ≥74 years was associated with an annual risk of 3.83% versus 2.95% for those <74 years ($p = 0.057$). The presence of SA node disease was associated with an annual risk of 5.66% versus 1.86% for those without ($p < 0.001$). Prior AF was associated with an annual risk of 9.64% versus 2.04% for those without ($p < 0.001$) (Table 2). Other clinical factors were not statistically predictive for the development of CAF.

To determine whether specific subgroups might derive more or less benefit from physiologic pacing, Cox proportional hazard modeling was performed. For each subgroup, hazard ratios with 95% CIs are reported in Table 3. Figure 2 illustrates these results graphically, including the associated CIs and p values. The treatment effect of physiologic pacing was evenly distributed among all subgroups except those with a history of MI or coronary disease and those patients with abnormal LV function who appeared to derive no benefit. There was a statistical trend for patients free of previous MI or CAD and patients with apparently normal LV function to derive greatest benefit from physiologic pacing. The hazard ratios of treatment effect for those patients with and without prior MI or CAD are 0.62 (95% CI: 0.45 to 0.86) and 1.0 (95% CI: 0.64 to 1.55, $p = 0.09$). The hazard ratios of treatment effect for those patients with normal and abnormal LV function are 0.64 (95% CI: 0.47 to 0.87) and 1.01 (95% CI: 0.63 to 1.62, $p = 0.11$). Patients

Table 2. Clinical Predictors of Chronic AF

Factor	Status	Chronic AF		p Value for HR
		Events	Rate/yr	
Treatment	Ventricular	167	3.84	
	Physiologic	92	2.8	0.016
Age	<74	112	2.95	
	≥74	147	3.83	0.057
SA node disease	No	82	1.86	
	Yes	171	5.66	< 0.001
Prior AF	No	128	2.04	
	Yes	131	9.64	< 0.001
MI/CAD	No	175	3.23	
	Yes	84	3.79	0.425
Hypertension	No	158	3.16	
	Yes	101	3.85	0.261
Diabetes	No	223	3.37	
	Yes	36	3.50	0.715
LV function	Normal	188	3.30	
	Abnormal	71	3.65	0.473

AF = atrial fibrillation; HR = hazard ratio; LV = left ventricular; MI/CAD = myocardial infarction/coronary artery disease; SA = sinoatrial.

Table 3. Hazard Ratios and 95% Confidence Intervals for Subgroup Analysis

Factor		Hazard Ratio*	Lower Limit	Upper Limit	p Value†
Age	<74	0.65	0.43	0.97	
	≥74	0.78	0.56	1.09	0.47
MI/CAD	No	0.62	0.45	0.86	
	Yes	1.0	0.64	1.55	0.09
LV function	Normal	0.64	0.47	0.87	
	Abnormal	1.01	0.63	1.62	0.11
SA node disease	No	0.66	0.41	1.04	
	Yes	0.75	0.54	1.03	0.65
Atrial fibrillation	No	0.65	0.45	0.95	
	Yes	0.8	0.56	1.15	0.45
Hypertension	No	0.71	0.51	0.99	
	Yes	0.76	0.50	1.15	0.8
Diabetes	No	0.76	0.57	1.0	0.47
	Yes	0.57	0.27	1.19	

*The hazard ratio gives the treatment effect of physiologic pacing relative to ventricular pacing in the given subgroup; †the p value is for the test of interaction between treatment and the risk factor.

LV = left ventricular; MI/CAD = myocardial infarction/coronary artery disease; SA = sinoatrial.

with SA node disease did not appear to derive greater benefit from physiologic pacing (p = 0.65).

DISCUSSION

The major finding of this study was that physiologic pacing is associated with a reduction in the rate of development of CAF in patients undergoing first pacemaker implant. The current analysis demonstrated a 27% relative risk reduction, from 3.84% per year to 2.80% per year, in the annual rate of development of CAF over a mean follow-up period of three years. This supports the primary analysis of the CTOPP, which found a reduction in the annual incidence of any episode of AF from 6.6% per year with ventricular-based pacing to 5.3% per year with physiologic pacing, a 18% relative risk reduction over the same period (14). Taken together, these analyses provide strong evidence that physiologic pacing reduces the burden of AF in a large cohort of patients undergoing pacemaker implantation. It remains to be seen whether this will translate into a reduction in stroke or cardiovascular death with longer follow-up. Given the magnitude of reduction of CAF with physiologic pacing, this remains an entirely plausible hypothesis.

Few studies have prospectively studied the effect of physiologic pacing on the development of paroxysmal or CAF. Andersen et al. (11) randomized 225 patients exclusively with sick sinus syndrome to receive atrial physiologic rate-responsive pacing (AAIR) or ventricular-based rate-responsive pacing (VVIR). The initial analysis at a follow-up of 3.3 years failed to demonstrate a reduction in the incidence of AF. However, after a mean of 5.5 years, a reduction in the incidence of total AF and CAF was demonstrated (12). A second trial randomized 210 patients, 110 with sick sinus syndrome and 100 with AV block to physiologic pacing or VVIR (13). Physiologic pacing was associated with a significant reduction in the incidence of CAF over a maximum follow-up of five years; however, the magnitude of the benefit was not reported. The Pacemaker Selection in the Elderly (PASE) study compared quality of life (QOL) measurements as well as the rate of development

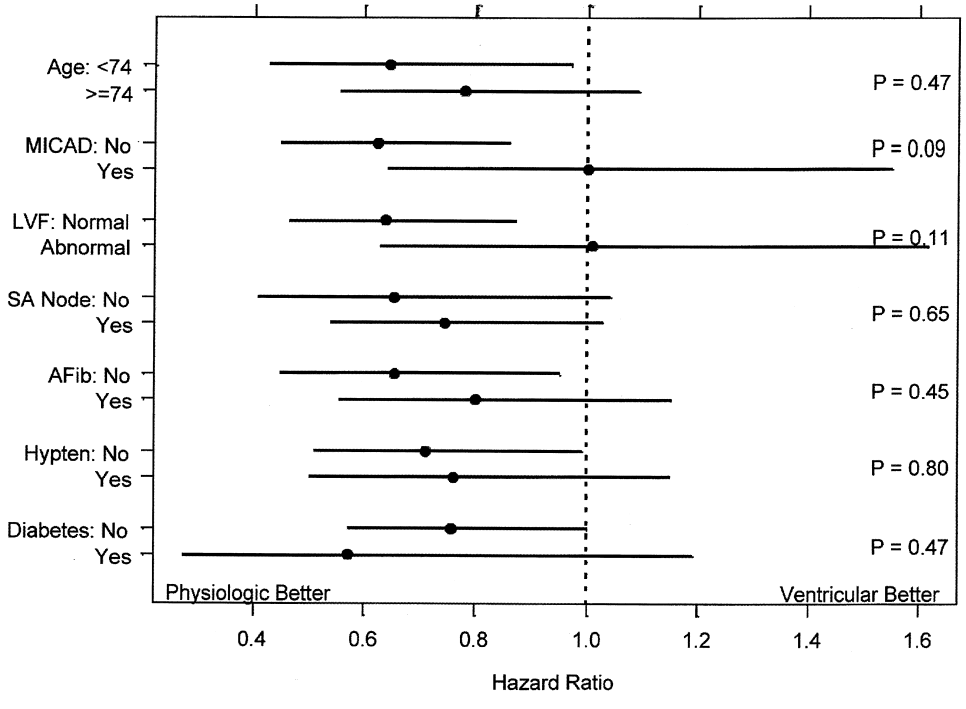

Figure 2. Distribution of treatment effect of physiologic pacing by subgroup. The hazard ratios **(solid circle)** and the 95% confidence intervals are plotted for the treatment effect of physiologic pacing. Associated p values are shown. See text for details. Afib = atrial fibrillation; Hypten = hypertension; LVF = left ventricular function; MICAD = myocardial infarction or coronary artery disease; SA = sinoatrial.

of AF in 407 patients. All received a dual chamber pacemaker but were randomized to dual chamber physiologic or ventricular pacing modes (18). Physiologic pacing was not associated with substantial improvement in QOL measurements or a reduction in the incidence of AF. Subgroup analysis of 175 patients with SSS was performed and demonstrated trends toward reductions in the secondary outcomes of death (20% to 12%, $p = 0.09$) and AF (28% to 19%, $p = 0.06$). As such, prior to CTOPP, the evidence that physiologic pacing prevents CAF comes exclusively from three small prospective trials representing approximately 500 patients with sick sinus syndrome.

The current analysis of 2,568 patients is the largest and most comprehensive prospective study to investigate the effect of physiologic pacing on the development of CAF. The benefit of physiologic pacing did not appear to be affected by the indication for pacing. Specifically, the group with sick sinus syndrome did not appear to derive greater benefit in this analysis or in the parent CTOPP analysis (14). It is important to note that the study by Andersen et al. (11,12) utilized exclusively atrial-based pacing, whereas the majority of physiologic pacing in CTOPP was dual chamber. The preserved synchronization of right ventricular or LV contraction with atrial pacing may be an important factor in the development of AF and subsequent stroke. Clearly, this hypothesis remains untested but warrants further study.

The current study also found clinical predictors for the development of CAF in this group. Not surprisingly, age ≥74 years, history of documented sinus node disease and a history of documented prior AF predicted the development of AF during follow-up. Previous retrospective (6–10) and small prospective studies have demonstrated similar findings in patients undergoing pacemaker implantation (11–13,15).

Subgroup analysis was performed to determine clinical factors that might predict the most benefit from physiologic pacing. It appeared that patients with preserved LV function and patients with no history of MI or CAD derive the most benefit from physiologic pacing. While the difference in hazard ratio in these subgroups did not reach statistical significance, a clear trend was seen. The 95% CIs are very wide, suggesting a small number of events within these groups. As these patients continue to be followed and further events are documented, the significance of these results will become clearer.

The magnitude of the treatment effect with physiologic pacing was modest. An absolute reduction of 1% per year translates into the prevention of CAF in one of every hundred patients per year undergoing physiologic permanent pacemaker implantation. Ninety-five percent of physiologic pacing in CTOPP was accomplished with dual chamber implants (13). Based on a significant incremental cost per implant of dual chamber pacing (estimated to be approximately $2,000 to $3,000 [U.S.] per implant for hardware and leads only), widespread use of dual chamber pacing to prevent the development of CAF appears to be a costly endeavor. However, given the fact that AF is exceedingly common (1,2) and is associated with substantial health care costs (3), physiologic pacing may prove to be a cost-effective therapy despite only modest reductions in AF burden. Selection of patients without significant coronary disease or LV dysfunction may further predict a subgroup that will derive greater and most cost-effective benefit from physiologic pacing.

Study limitations. Although part of the current analysis represents subgroup analysis, the end point of CAF was a prospectively defined secondary end point. Furthermore, the subgroup analysis was also prospectively planned, and relevant data was prospectively collected. Thus, due to the large study cohort, the estimation of benefit of physiologic pacing in preventing CAF and the subgroup analysis is important and likely valid.

The duration of AF determined to be chronic was brief. However, the definition was such that patients whose AF was paroxysmal and self-terminating were eliminated. Hence, it likely represents a clinically meaningful group. No attempt was made to document episodes of asymptomatic AF using loop recorders or pacemaker monitoring functions. There is no reason to believe that the methodology would document episodes of AF to a greater degree in one pacing group than in the other. Also, no attempt was made to classify patients into "persistent" versus "permanent" AF, as this involved judgements determined by the treating physician as to ability or desire to perform DC cardioversion.

Decisions about the use of medications were left to the treating physician. Data with respect to drug use were not systematically collected in the trial. However, 12% of the population was taking antiarrhythmic agents for prior AF at baseline equally distributed between the groups (14). As outlined in the original trial (14), 16.6% ($n = 427$ patients) developed AF and would have provided an opportunity for the influence of medication on the outcome in the current trial. As a history of prior AF is known to predict further episodes (annual risk of 9.6% in this trial), a large percentage of these patients would have developed their index arrhythmia on medications. As such, it is likely that the influence of medication in the current trial was small at best.

Finally, LV function was objectively determined by echocardiography or LV angiography in less than half of patients. In the remainder, investigators made presumptive assessments and determined LV function as "normal" or "abnormal." While this determination is less quantitative, it remains clinically relevant and easily applicable.

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