Who Needs Physiologic Pacing and Why?

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Various pacing technologies have been developed during the past 50 years since the first pacemaker was implanted in 1958. Dual-chamber pacing, rate responsiveness, programmable and rate-responsive atrioventricular (AV) intervals, alternative-site pa0cing, and new multichamber pacing devices are all attempts to mimic normal cardiac physiology as much as feasible. The categories of alternative-site and multichamber pacing will not be addressed in this review. The term physiologic pacing refers to dual-chamber (DDD and DDDR) and atrium-based pacing (AAI and AAIR) in contrast to the ventricle-based mode of pacing (VVI and VVIR). Both AAI/R and DDD/R pacing preserve the synchrony of atrial and ventricular contraction, and therefore resemble the normal cardiac function more closely than does VVI/R pacing. Despite this physiological superiority of AAI and DDD pacing, VVI pacemakers are still used in a large proportion of patients with sick sinus syndrome. Physician's reluctance toward implantation of more physiological pacemakers may be related to difficulties with implantation of an atrial lead, the higher device cost of DDD units, and the more complex programming and follow-up of such pacemakers. Moreover, the lack of large-scale prospective randomized trials to document which pacing mode is superior probably also contributes significantly.

Key Words: Artificial pacemaker • Sick sinus syndrome • Atrioventricular block

HEMODYNAMICS OF CARDIAC PACING

Challenge to the cardiovascular system, such as exercise or emotion, usually results in an increase in cardiac output, which is determined by heart rate and stroke volume. The cardiovascular demands incurred with exercise are met primarily by an increase in heart rate and secondarily by increases in stroke volume. Maximally, the heart rate may increase by two to three folds in responding to vigorous exercise. Stroke volume may increase by 60% maximally during exercise.

The earliest indication for pacing was complete heart block, and ventricular pacing was the only pacing mode available. With fixed rate ventricular pacing, a stable ventricular rhythm was lifesaving and overshadowed the fact that normal cardiac function was not reestablished. It has been reported that some patients experienced hemodynamic decline with this mode of pacing. This may attribute to one of the major drawbacks of fixed-rate ventricular pacing, which include 1) AV dissociation or ventriculoatrial (VA) conduction, 2) lack of AV synchrony and 3) lack of chronotropic competence. AV dissociation or VA conduction may result in symptoms of hypotension and heart failure that constitute pacemaker syndrome. The prevalence of pacemaker syndrome has been reported to be in the range of 7% to 10%.[1] AV synchrony is estimated to increase stroke volume by as much as 50% in normal heart and increase cardiac index by as much as 25% to 30%.[2] It is generally believed that chronotropic competence is the most important contributor to cardiac output, especially at moderate or extreme degrees of exercise (Figure 1). At rest and at lower levels of activity, AV synchroniza-

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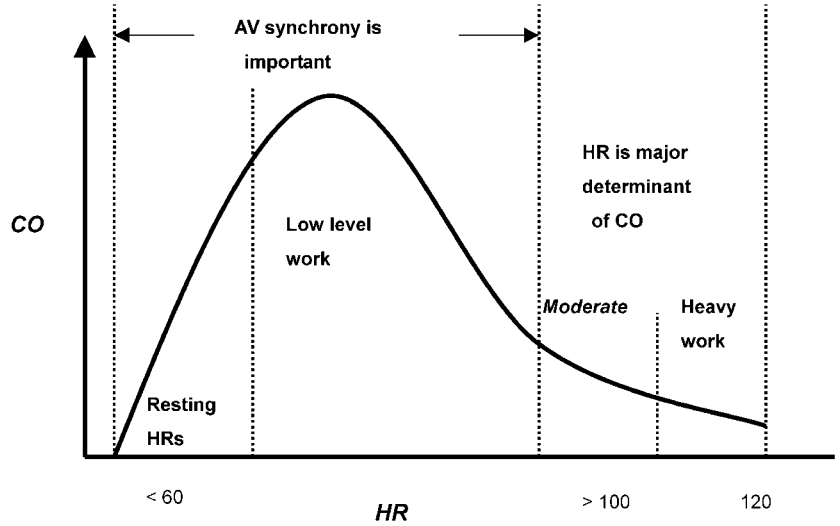

Figure 1. *Schematic representation of the contribution of atrioventricular synchrony and rate response to cardiac output (CO) at various levels of activity. At rest and low levels of activity, maintenance of atrioventricular synchrony makes a proportionately greater contribution to cardiac output. At higher exercise levels, heart rate (HR) clearly contributes more to cardiac output.*

tion has a greater role in maintaining an appropriate cardiac output. Because most of the pacing population is at the lower levels of activity most of the time and a significant proportion of these patients are also dependent on adequate preload because of decreased ventricular compliance, AV synchrony is perhaps just as important as rate responsiveness for achieving optimal cardiovascular hemodynamics in the typical patient. Therefore, restoration of both rate responsiveness and AV synchrony should be the goal of physiologic pacing and should be viewed as complementary achievement.

EFFECT OF PACING MODE ON MORBIDITY AND MORTALITY

Retrospective studies

In addition to the pacemaker syndrome in patients with VVI pacemakers, many retrospective studies showed higher morbidity and mortality in such patients as well. An early study by Rosenqvist[3] lead the way for clinical interest in and clinical trial on the effects of pacing mode in these regards. At 4 years of follow-up in patients with sick sinus syndrome, atrial fibrillation had occurred in 47% of the patients receiving VVI pacing but in only 7% of those receiving AAI pacing ($p < 0.0005$); congestive heart failure occurred in 37% of the VVI group and in 15% of the AAI group ($p < 0.005$); and mortality was 23% in the VVI group and 8% in the AAI group ($p < 0.025$). In the largest long-term observational study comparing physiologic pacing with VVI pacing in patients with sick sinus syndrome, Sgarbossa et al. found that VVI pacing was an independent predictor of chronic atrial fibrillation and stroke,[5] whereas there was no difference in mortality[6] or heart failure[7] between the two groups. In spite of the inherent weakness of retrospective analyses, many other retrospective reviews disclosed similar finding among all the studies of significantly lower mortality, though less consistent, with DDD or AAI pacing than with VVI pacing and significant lower incidences of atrial fibrillation.[4] However, as cardiac pacemakers have gained in sophistication, changes have become evolutionary, and the most plausible expected benefit is small to moderate in magnitude. Thus, observational analyses have failed to yield conclusive results on the value of evolutionary advances such as dual-chamber pacing, rate modulation, and mode switching. During the past decade, it has become increasingly clear that large scale randomized trials were necessary to reliably measure the benefit, if any, of progressively more expensive and complex pacemakers. The interpretation of observational studies requires an understanding of their unique strengths and their limitations. Case-controlled and cohort studies provide reliable data for

relatively large effect sizes (i.e., > 50%). When effect sizes are small (i.e., < 30%), the amount of uncontrolled and uncontrollable confounding inherent to such designs is as large as the postulated effect size. Small effect sizes are clinically worthwhile and can have important public policy implication but are far more difficult to reliably detect.

Prospective studies

Currently, several prospective clinical trials are available for evaluating the effect of pacing mode on the clinical outcome in terms of mortality, atrial fibrillation, stroke, heart failure and quality of life. Some of them are still going on. In this section, three major trials will be reviewed.

Danish trial

In 1994, the first prospective randomized trial comparing AAI and VVI pacing was reported by Andersen.[8] There were 225 patients (mean age 76 years) with sick sinus syndrome, normal AV conduction and a narrow QRS complex. After a mean follow-up of 3.3 years, AAI pacing was associated with less atrial fibrillation and thromboembolism than VVI pacing, whereas there was no statistically significant difference in mortality or heart failure between the two treatment groups. After an extended follow-up to a mean of 5.5 years, the differences between the AAI and VVI groups had enhanced substantially in favor of AAI pacing.[9] Total mortality was significantly less in the AAI group (relative risk 0.66, $p = 0.045$). The excess mortality in the VVI group was due to cardiovascular deaths. Moreover, atrial fibrillation, chronic atrial fibrillation, thromboembolic events and heart failure were reduced in the AAI group. AV conduction was always a concern in sick sinus syndrome with AAI pacing, which was stable, and AV block occurred in 4 of 110 patients (0.6% annual incidence).[10]

Another subgroup analysis showed further long-term advantages of AAI pacing in terms of heart failure and echocardiographic changes.[11] After a mean follow-up of 5.5 years, NYHA class was significantly lower in the AAI group compared with the VVI group. The difference in heart failure class was supported by the dose of diuretics, which was lower in the AAI group than in the VVI group ($p = 0.033$). Left atrial diameter increased significantly in both groups, but the increase was significantly lower in the AAI group ($p < 0.0005$). Left ventricular fractional shortening decreased significantly in the VVI group but not in the AAI group. A final report[12] in 1999 assessed whether thromboembolic events could be predicted by pacing mode, occurrence of atrial fibrillation, or echocardiographic findings. Thromboembolic events occurred less frequently in the AAI group ($p = 0.0083$). Patients in the AAI group, in whom atrial fibrillation never occurred, had less risk of thromboembolic events compared to those in the VVI group ($p = 0.013$). Left atrial size did not predict the occurrence of thromboembolism.

The Danish trial and its reanalyses suggest that in the long-term, clinical outcomes including all-cause and cardiovascular mortality, incidence of thromboembolism, incident and chronic atrial fibrillation, clinical and echocardiographic indicators of heart failure occur less frequently with atrial pacing as compared with ventricular pacing. Furthermore, the trial suggested that the advantages of AAI pacing became more evident with longer follow-up. However, the results of this trial of small sample size have to be interpreted cautiously. The number of patients and events in this trial were insufficient to detect small to moderate benefits of either pacing mode. Thus, the observed differences between groups could have occurred by chance. The randomized patients were highly selected, thus, the results may be applicable only to the subset of patient with sick sinus syndrome and intact AV conduction. Finally, although the results of this trial have been debated for years, it is indisputable that the landmark Danish trial spurred and molded the design and execution of trials of larger sample size, to detect more reliably the more plausible small to moderate differences in clinical outmodes.

The canadian trial of physiologic pacing (CTOPP)

Connolly et al[13] reported the results of CTOPP in 2000, in which 2568 patients with symptomatic bradycardia (sick sinus syndrome and AV block) requiring permanent pacing were randomized to physiological (AAI/AAIR and

DDD/DDDR) or ventricular pacing (VVI/VVIR) and followed for an average of 3 years. Each clinical center was allowed to choose one of five different ratios of ventricular to physiologic pacing, but mode assignment occurred randomly within each ratio. The overall ratio of ventricular to physiologic pacing was 57:43; so 1474 patients were assigned to ventricular pacing and 1094 to physiologic pacing. The combined primary endpoint of stroke or cardiovascular death was not significantly different between pacing modalities, with an annual rate of death or stroke of 4.9% for physiologic pacing and 5.5% for ventricular pacing (p = 0.33). The annual rate of atrial fibrillation was lower in the physiologic pacing group (5.3%) as compared with ventricular pacing (6.6%) (p = 0.05). This constituted a relative risk reduction of 18% and absolute risk reduction of 3.9% for physiologic pacing. This reduction was observed only after a 2-year follow-up. Other secondary endpoints, like hospitalization for heart failure, stroke and total mortality, did not differ significantly between groups. The effect of pacing mode on the quality of life in CTOPP was reported to be null between physiologic pacing and ventricular pacing.[17] The occurrence of pacemaker syndrome was rare. As CTOPP was a generator randomization trial, the relative complication rates of implanting dual-chamber compared with ventricular pacemakers could be determined. There were more perioperative complications with physiologic (9%) than with ventricular pacing (3.8%) (p < 0.001). These included lead dislodgement and inadequate pacing or sensing; however, pneumothorax, hemorrhage, and device malfunction did not differ significantly.

Subgroup analysis of CTOPP showed that patients < 75 years of age were more likely to benefit from physiologic pacing compared to ventricular pacing (hazard ratio for cardiovascular death/stroke 0.62, 95% CI of 0.44-0.89), whereas older patients did not (HR 1.02, 95% CI 0.08-1.29).[20] Patients with AV block as an indication for pacing also tended to have a lower mortality/stroke incidence (HR 1.03, 95% CI 0.77-1.4), but there was only borderline difference on statistical significance (p = 0.06).

Reanalysis of CTOPP showed the effect of pacing mode on the outcome in terms of pacemaker dependence.[14] 2244 patients were able to have pacemaker dependency test, assessed at the first follow-up visit. Patients were defined as pacemaker dependent, if they had lower spontaneous heart rate (< 60 beats/min). Non-pacemaker dependent patients had higher spontaneous heart rate and used the pacemaker only as a backup (Figure 2). The treatment effect of physiologic pacing in patients with a lower spontaneous heart rate

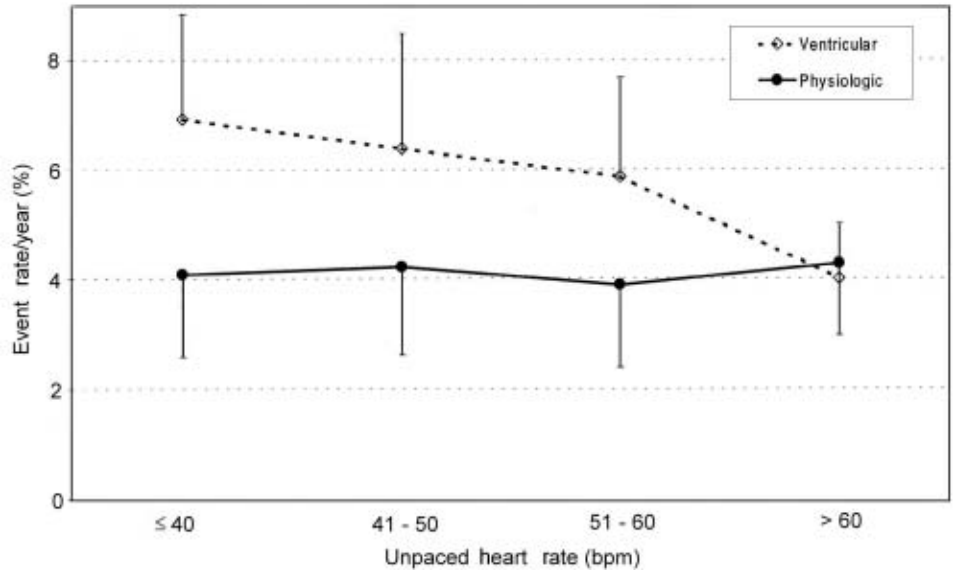

Figure 2. *Yearly event rates for the composite end point of cardiovascular mortality and stroke are plotted against (unpaced heart rate) UHR (Reference 14). The yearly event rate steadily increased with decreasing UHR in the ventricular pacing group, whereas the yearly event rate of the physiologic pacing group was essentially constant over UHR.*

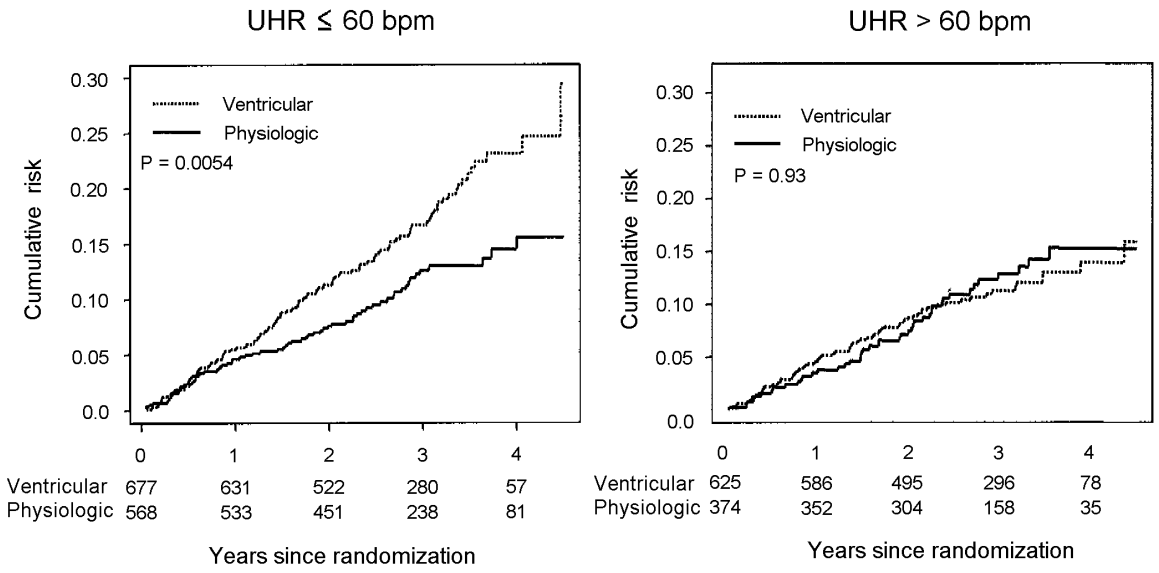

Figure 3. *Rate of stroke or cardiovascular death for the two spontaneous unpaced heart rate (UHR) subgroups in patients randomized to ventricular (n = 1474) or physiologic pacing during a mean follow-up of 3 years in CTOPP (Reference 14).*

was marked, with a relative reduction of death or stroke of 35.5% for spontaneous heart rate ≤ 60 beats/min, while in patients with spontaneous heart rate > 60 beats/min, there was no trend towards benefit from physiologic pacing. The yearly event rate in patients in the ventricular pacing group increased with decreasing spontaneous heart rate, while in patients in the physiologic pacing group, the event rate remained constant with decreasing spontaneous heart rate. When patients were divided into two subgroups according to spontaneous heart rate ≤ 60 beats/min compared with that > 60 beats/min, there was a positive effect for the primary endpoint from physiologic pacing that became evident after 1 year only in patients with lower spontaneous heart rate (Figure 3).

The mode selection trial (MOST)

Instead of using generator selection, MOST[15] adopted mode selection with the same dual-chamber generator in both groups. 2010 patients were randomized into either VVIR or DDDR mode and followed an average of 2.7 years. The median age of the patients was 74 years, all patients had sick sinus syndrome, including 21% with concomitant AV block. The primary endpoint was a composite of nonfatal stroke or death from any cause. Secondary endpoints included a composite endpoint of death, first occurrence of stroke or hospitalization for heart failure, and atrial fibrillation, death from any cause, and death from cardiovascular causes.

The primary endpoint occurred in 22.2% of the patients, and no significant difference was found between the two treatment groups. Among secondary endpoints, stroke occurred in 4.5% of the population, death in 20.1%, cardiovascular death in 8.9% and the combined endpoint of death, stroke, or hospitalization for heart failure in 28.8%. With multivariate analysis, a difference of borderline significance ($p = 0.05$) was observed in the secondary endpoint of death, stroke, or hospitalization for heart failure favoring dual-chamber pacing. Atrial fibrillation occurred in 24.2% of the patients and was significantly less frequent in the dual-chamber pacing group ($p = 0.008$). Progression to chronic atrial fibrillation occurred in 15.2% of the dual- chamber pacing group and in 26.7% with ventricular pacing ($p = 0.001$). The heart failure score was lower in the dual-chamber pacing group compared with the ventricular-paced group ($p = 0.0001$) at one year. A total of 18.3% of ventricular pacing patients met the criteria of pacemaker syndrome; however, crossover from ventricular to dual-chamber pacing occurred in 31.4% of patients.

Cautious interpretation of the CTOPP and MOST data lead to the conclusion that, when compared to ven-

tricular pacing, dual-chamber pacing does not improve survival or reduce the incidence of stroke. However, dual-chamber pacing does reduce incident and chronic atrial fibrillation, and, in patients with sick sinus syndrome, reduces symptoms of heart failure and leads to somewhat better quality of life.

Pacing and stroke

CTOPP and MOST together with another trial, PASE,[16] did not observe a significant reduction in stroke in patients receiving a physiologic pacemaker. This contrasts with the observations of the Danish trial that found a significant reduction in stroke in patients receiving an AAI pacemaker compared to those receiving a VVI pacemaker. This difference may be explained by more appropriate use of anticoagulant therapy in the more recent trials, because of overall incidence of stroke was much lower in STOPP than in the Danish trial. However, at the time of randomization, warfarin use was 11% in CTOPP and only 2% in PASE. The proportion of patients in CTOPP and PASE who ultimately received warfarin is unknown. In the Danish trial, over half the patients who lapsed in persistent atrial fibrillation did not receive warfarin therapy. Thus, if patients at risk of systemic thromboembolism from atrial fibrillation were appropriately treated, physiologic pacing would not be expected to have substantial impact on the incidence of stroke in atrial fibrillation population, even though the incidence of that is higher in the ventricular-paced patients.

Adverse effects of ventricular pacing

Ventricular pacing resulting in asynchronous contraction of ventricle may lead to myocardial remodeling contractile dysfunction and heart failure. The subgroup analysis of CTOPP[14] showed that pacemaker dependent patients received greater benefit from physiologic pacing compared with ventricular pacing, and that benefit of physiologic pacing could not be demonstrated for patients who were not pacemaker dependent. This observation appears to support a concept that the desynchronization of ventricular contraction that occurs with ventricular pacing is harmful, even in patients with preserved left ventricular function.

A subgroup analysis of MOST trial studied the effect of ventricular pacing on heart failure and atrial fibrillation.[18] In this 1339-patient, 6-year, randomized trial of DDDR versus VVIR pacing in sick sinus syndrome with narrow QRS-complex, cumulative percent ventricular paced (Cum%VP) was determined from stored pacemaker data. Cox models demonstrated that the time-dependent covariate Cum%VP was a strong predictor of heart failure hospitalization in both groups of pacing mode. The risk of atrial fibrillation increased linearly with Cum%VP from 0% to 85% in both groups. Based on these findings, ventricular desynchronization imposed by ventricular pacing even when AV synchrony is preserved may increase cardiovascular morbidities.

The Danish group also conducted a study to test the effect of ventricular desynchronization.[19] A total of 177 patients were randomized to treatment with one of 3 rate-adaptive pacemakers: AAIR (n = 54), DDDR with a short AV delay (< 150 ms, n = 60) (DDDR-s), or DDDR with a fixed long AV delay (300 ms, n = 63) (DDDR-l). The mean percent of ventricular pacing was 90% in the DDDR-s group and 17% in the DDDR-l group. After a mean follow-up of 2.9 years, the AAIR group showed no significant changes in left atrium or left ventricle diameters or left ventricular fractional shortening from baseline to last follow-up. In both DDDR groups, left atrium diameter increased significantly, and in the DDDR-s group, left ventricle fractional shortening decreased significantly. Atrial fibrillation was significantly less common in the AAIR group, 7.4% versus 23.3% in the DDDR-s group versus 17.5% in DDDR-l group. Mortality, thromboembolism, and congestive heart failure did not differ between groups.

These studies imply that ventricular desynchronization caused by right ventricular apical pacing in the DDDR mode may increase the risk of heart failure and atrial fibrillation and support AAIR pacing as the preferred pacing mode in sick sinus syndrome with intact AV conduction.

INDICATION FOR PHYSIOLOGIC PACING IN 21ST CENTURY

The majority of prospective randomized trials do not

support selection of a physiologic pacing system over a ventricular pacing system for mortality benefit. Patients with a life expectancy of < 3 years will not benefit substantially from physiologic pacing. However, younger patients (< 75 years) and perhaps those with AV block who are pacemaker dependent are more likely to benefit from physiologic pacing in terms of survival and prevention of stroke. Physiologic pacing is associated with a reduced risk of developing chronic atrial fibrillation. Again, younger patients and those without structural heart disease are more likely to benefit from the antiarrhythmic benefit of physiologic pacing. Importantly, the CTOPP and the Danish study suggest that the benefits of physiologic pacing are delayed for several years following implant.

The Danish investigators have shown that 20% of patients with sick sinus syndrome are suitable candidates for atrial pacing and that this pacing modality is effective over the long term. Atrial pacing is less costly than dual-chamber pacing, and should be more widely employed.

Currently, a simple approach for pacing mode selection is appropriate for most patients. For patients with chronic atrial fibrillation and a slow ventricular response in whom pacing is required, VVIR is the mode of choice. This is also the only clear-cut indication for ventricular pacing mode. Otherwise, pulse generator and mode selection should be individualized and as physiological as possible in terms of replicating the rate responsiveness of a normal sinus node, maintaining appropriate AV sequencing, and preserving rapid synchronous ventricular contraction when possible.

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