

Physiologic versus Non-Physiologic Pacing in View of Recent Studies

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Summary

Recently published studies indicate that physiologic pacing (atrial or atrioventricular sequential pacing) is an efficient, and in the long term, a cost-effective mode of pacing in patients with the sick-sinus-node disease. Data support the effectiveness of physiologic pacing not only in improving quality of life, but also in reducing mortality and as an antiarrhythmic therapy (prevention of atrial fibrillation). Current prospective, randomized studies should have a major impact on our knowledge and on our practice of pacing mode selection.

Key Words

Atrial pacing, rate-responsive pacemaker, arrhythmia prevention

Introduction

Pacemaker therapy of bradyarrhythmias has a history of more than forty years. The first devices were only able to stimulate the ventricle. Rapid advances in technology led to the development of dual-chamber and rate-responsive pacemakers.

Atrio-ventricular sequential pacing has many advantages over the non-physiologic ventricular pacing, like enabling proper ventricular filling, higher cardiac output and higher exercise capacity. It also prevents pacemaker syndromes, thus improving the patient's quality of life. Recent studies indicate that physiologic pacing reduces the incidence of atrial fibrillation, stroke and cardiac failure, as well as mortality in certain cases.

Cost effectiveness and physiologic pacing

Despite the fact that physiologic pacing is indicated in every case but chronic atrial fibrillation [1,2], dual-chamber pacing is used much less frequently than expected. There are two reasons for this: first, dual chamber pacing is more expensive, and second, results of large, randomized studies on this subject are not yet available [3].

Costs of dual-chamber pacing are 75-94% higher than costs of ventricular pacing [4,5]. Additional costs are more frequent follow-up visits, shorter duration of battery life and a two- to threefold higher incidence of

complications requiring intervention [6]. Pacemaker-electrode dislodgment occurs in 2% of single-chamber pacemakers and in 5% of dual-chamber devices [6]. Lead fracture, vein thrombosis and retained leads are also more frequent in patients with dual-chamber pacemakers [7].

Cost-benefit was assessed using a computer model meta-analysis by Sutton and Bourgeois, evaluating a ten-year period and taking into account costs of treating atrial fibrillation, stroke and cardiac failure as well as mortality [8]. Comparing DDD and VVI pacing mode, mortality at ten year follow-up was 57% vs. 71% in patients with sick sinus syndrome, 51% vs. 61% in patients with AV block, disability due to stroke was 8% vs. 36% in patients with sick sinus syndrome, 3% vs. 22% in patients with AV block, whereas cardiac failure developed in 60% of the patients in both pacing modes. Cumulative costs of DDD pacing were higher in the first three years following implantation. Later the VVI pacing mode became more expensive and after ten years, its costs were 13-fold higher than the costs of DDD pacing in patients with sick sinus syndrome and 7-fold higher in patients with AV block.

Although there are only few data regarding the costs of atrial pacing, it appears to be the most cost-effective pacing mode even with the DDD upgrading in cases where a complete AV block develops [9].

	No. of patients	Diagnosis	Mode	Exercise tolerance improvement	QOL Improved with DDD
Rediker [10]	19	mixed	VVI	18%	yes
Perrins [11]	13	AVB	VVI	27%	yes
Kristensson [12]	44	AVB	VVI	14%	yes
Fananapazir [13]	14	AVB	VVI	44%	no data
Menozzi [14]	14	AVB	VVIR	NS	yes
Oldroyd [15]	10	AVB	VVIR	NS	no
Sulke [16]	22	AVB	VVIR	no	yes

Table 1. Effect of VVI/VVIR vs DDD pacing mode on exercise capacity and quality of life.

Effects of pacing mode on exercise capacity and quality of life

DDD and VVI pacing were compared in many small crossover studies (Table 1). Physiologic pacing resulted in 18-44% higher exercise capacity when compared with VVI pacing [10-13]. No significant difference could be shown in exercise capacity between rate-responsive ventricular pacing and DDD pacing [14-16]. Most retrospective studies indicate a better quality of life in patients with a DDD pacemaker than either VVI or VVIR pacemaker. Yet, these results require careful interpretation [10-16].

The first prospective, randomized study to assess the quality of life was the PASE study (Pacemaker Selection in the Elderly) [17]. Four hundred and seven patients older than 65 years underwent a DDDR pacemaker implantation and were randomized to either DDDR or VVIR pacing mode. The pacemaker implantation itself produced a marked improvement in quality of life. There was no difference between the two pacing modes in patients with AV block, while the dual-chamber pacing mode was somewhat more favorable in patients with a sick sinus syndrome. Mortality and cardiovascular events in the two pacing-mode groups were similar in patients with AV block and tended to be favorable in the DDDR group in patients with sick sinus syndrome, but the difference did not reach statistical significance ($p = 0.09$ and 0.07 , respectively to mortality and cardiovascular events). These results can be explained by the randomization, since there was no randomization in the previous studies and therefore, the older, more severe patients received ventricular pacemakers. However, the PASE study should be criticized for crossing over 26% of patients with sick sinus syndrome from ventricular pacing mode to dual chamber pacing to eliminate pace-

maker syndrome [18]. Without that cross-over, incidence of atrial fibrillation and stroke would have been higher in the VVIR group. Furthermore, the follow-up period of 30 month was too short to detect a possible significant difference in cardiovascular events.

Effects of pacing mode on atrial fibrillation, stroke and mortality

Atrial fibrillation frequently develops in patients with sick sinus syndrome. Many studies indicate that ventricular pacing promotes the development of atrial fibrillation, whereas atrial or sequential pacing may prevent atrial fibrillation. In patients with atrial fibrillation, the annual incidence of stroke is 5%. With the use of chronic anticoagulant treatment, this can be reduced to 1.5% [19].

Based on many observational studies, atrial or atrio-ventricular sequential pacing reduces the development of atrial fibrillation by 2/3 and mortality due to atrial fibrillation by 1/3. In a study by Rosenquist in 1988 [20], atrial fibrillation and mortality was significantly lower during a four-year follow-up in patients with atrial pacing than in patients with ventricular pacing (1.8% vs. 12.1% per year, and 2.2% vs. 5.5% per year, respectively).

In a study by Hesselton, 665 patients received a DDD and 285 patients received a VVI pacemaker and were followed for 7 years [21]. There was a significant difference between the two groups in terms of both atrial fibrillation (8.9% vs. 13.6% per year) and mortality (1.6% vs. 5.3% per year). The results of some retrospective studies are shown in Table 2. Those non-randomized studies indicate that the risk of the development of atrial fibrillation can be reduced by 39-100% and the risk of mortality by 35-65% using atrial pacing in patients with sick sinus syndrome.

	Follow-up patients		AF (% / year)		Death (% / year)	
	DDD/AAI	VVI	DDD/AAI	VVI	DDD/AAI	VVI
Santini [22]	661	332	1.9	11.9	3.1	7.7
Bianconi [23]	561	738	4.8	7.9	3.8	6.3
Rosenquist [20]	326	309	1.8	12.1	2.2	5.9
Stangl [24]	367	308	1.8	6.9	5.1	9.8
Hesselson [21]	1662	1045	1.6	5.3	8.9	13.6

Table 2. Effect of mode of pacing on the development of atrial fibrillation and death in some nonrandomized studies.

The only prospective, randomized study so far on that subject was published in 1994 [25]. Patients (225) were randomized to atrial or ventricular pacing and were followed for a mean period of 3.3 years. Atrial fibrillation was more frequent among patients with VVI pacing mode, but the difference did not reach the level of significance (23% vs. 14%; $p = 0.12$). Thromboembolic complications occurred significantly less frequently among patients with AAI pacing (5% vs. 14%; $p = 0.0083$). No significant difference was observed in mortality and cardiac failure between the two groups. However, after an extended follow-up period, mortality was significantly lower in the AAI group (39% vs. 57%; $p = 0.045$). The higher mortality in the VVI group was due to an increase in cardiovascular mortality. The decrease in incidence of atrial fibrillation as well as the decrease of cardiac failure reached the level of significance after the extended follow-up period [26,27]. Thus, the results of that study are promising, but confirmation by a study with a larger population is necessary.

Current prospective randomized studies

The results of current randomized, prospective studies will have a major impact on the selection of the pacing mode. The PASE study [17] has already been presented in this paper. The Canadian Trial of Physiological Pacing (CTOPP) compares VVI(R) pacing mode vs DDD(R)/AAI(R) pacing mode in 2550 patients with sick sinus syndrome or AV block. Primary end-points are cardiovascular mortality and stroke. Preliminary data show no difference in terms of total and cardiovascular mortality [28]. Final data are expected in the near future. The UK-PACE multicenter study evaluates 2000 patients older than 70 years with AV block in Great-Britain. The patients receive ventricular or dual-

chamber pacemakers and are followed for 3 years. Primary end-point is total mortality. The Mode Selection Trial (MOST) studies the total mortality and stroke in 2000 patients with sick sinus syndrome randomized to ventricular or dual-chamber pacing [29]. Calculations indicate, that meta-analysis of these three large randomized studies will allow to demonstrate 20% decrease in mortality, 30% decrease in stroke and 25% decrease in cardiac failure in the group of physiologic pacing mode [30].

References

- [1] ACC/AHA Guidelines for Implantation of Cardiac Pacemakers and Antiarrhythmic Devices: Executive Summary. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Pacemaker Implantation) *Circulation*. 1998; 97: 1325-1335.
- [2] Clarke M, Sutton R, Ward D et al. Recommendation for pacemaker prescription for symptomatic bradycardia. *Br Heart J*. 1991; 66: 185-191.
- [3] Petch MC. Who needs dual chamber pacing? *Br Med J*. 1993; 307: 215-216.
- [4] de Belder MA, Linker NJ, Jones A et al. Cost implication of the British Pacing and Electrophysiology Group's recommendation for pacing. *Br Med J*. 1992; 305: 861-865.
- [5] Ray SG, Griffith MG, Jamieson S et al. Impact of the recommendation of the British Pacing and Electrophysiology Group on pacemaker prescription and immediate costs of pacing in the Northern Region. *Br Heart J*. 1992; 68: 531-534.
- [6] Parsonnet V. The cost-effectiveness of dual chamber pacing. *Eur Heart J*. 1996; 17: 495-496.
- [7] Mason JW, Hltaky MA. Do patients prefer physiologic pacing. *N Eng J Med*. 1998; 338: 1147-1148.
- [8] Sutton R, Bourgeois I. Cost benefit analysis of single and dual chamber pacing for sick sinus syndrome and atrioventricular block. An economic sensitivity analysis of the literature. *Eur Heart J*. 1996; 16: 574-582.
- [9] Clarke KW, Conelly MD, Charles RG. Single chamber atrial pacing: An underused and cost-effective pacing modality in sinus node disease. (abstract) *PACE*. 1998; 21 (Part II): 895.

- [10] Rediker DE, Eagle KA, Homma S, et al. Clinical and hemodynamic comparison of VVI versus DDD pacing in patients with DDD pacemakers. *Am J Cardiol.* 1988; 61: 323-329.
- [11] Perrins EJ, Morley CA, Chan SL. Randomized controlled trial of physiological and ventricular pacing. *Br Heart J.* 1983; 50: 112-117.
- [12] Kristensson BE, Amman K, Segdard P, et al. Physiological versus single-rate ventricular pacing: a double-blind cross-over study. *PACE.* 1985; 8: 73-84.
- [13] Fananapazir L, Bennet DH, Monks P. Atrial synchronized ventricular pacing: Contribution of the chronotrop response to improved exercise tolerance. *PACE.* 1983; 6: 601-608.
- [14] Menozzi C, Brignole M, Moracchini P, et al. Inpatient comparison between chronic VVIR and DDD pacing in patients affected by high degree AV block without heart failure. *PACE.* 1990; 13: 1816-1822.
- [15] Oldroyd KG, Rae AP, Catre R, et al. Double-blind cross-over comparison of the effects of dual chamber pacing (DDD) and ventricular rate adaptive (VVIR) pacing on neuroendocrine variables, exercise performance, and symptoms in complete heart block. *Br Heart J.* 10991; 65: 188-193.
- [16] Sulke N, Chambers J, Dristas A, et al. A randomized double-blind crossover comparison of four rate-responsive pacing mode. *J Am Coll Cardiol.* 1991; 17: 696-706.
- [17] Lamas GA, Orav JE, Stambler BS, et al. Quality of life and clinical outcomes in elderly patients treated with ventricular pacing as compared with dual-chamber pacing. *N Engl J Med.* 1998; 338: 1097-1104.
- [18] Alt E, Schüller H. Letter to the Editor. *PACE.* 1999; 22: 141.
- [19] Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. *Arch Intern Med.* 1994; 154: 1449-1557.
- [20] Rosenquist M, Brandt J, Schuller H. Long-term pacing in sinus node disease: the effects of stimulation mode on cardiovascular morbidity and mortality. *Am Heart J.* 1988; 116: 16-22.
- [21] Hesselson AB, Parsonnet V, Bernstein AD, et al. Deleterious effect of long-term single chamber ventricular pacing in patients with sick sinus syndrome: the hidden benefits of dual chamber pacing. *Am J Cardiol.* 1992; 17: 1542-1549.
- [22] Santini M, Alexidu G, Ansalone G, et al. Relation of prognosis in sick sinus syndrome to age, conduction defects and mode of permanent cardiac pacing. *Am J Cardiol.* 1990; 65: 729-735.
- [23] Bianconi L, Boccomado R, DiFlorio A, et al. Atrial versus ventricular stimulation in sick sinus syndrome. (abstract) *PACE.* 1989; 12: 1236.
- [24] Stangl K, Steitz K, Wirtzfeld A, et al. Differences between atrial single chamber pacing (AAI) and ventricular single chamber pacing (VVI) with respect to prognosis and antiarrhythmic effect in patients with sick sinus syndrome. *PACE.* 1990; 13: 2080-2085.
- [25] Andersen HR, Thuesen L, Bagger JP, et al. Prospective randomized trial of atrial versus ventricular pacing in sick-sinus syndrome. *Lancet.* 1994; 344: 1523-1528.
- [26] Andersen HR, Nielsen JC, Thomsen PEB, et al. Long-term follow-up of patients from a randomized trial of atrial versus ventricular pacing for sick-sinus syndrome. *Lancet.* 1997; 350: 1210-1216.
- [27] Nielsen JC, Andersen HR, Thomsen PEB, et al. Heart failure and echocardiographic changes during long-term follow-up of patients with sick sinus syndrome randomized to single-chamber atrial or ventricular pacing. *Circulation.* 1998; 97: 987-995.
- [28] Sami M, Abdollah H, Conolly S. et al. Profile of Cardiovascular Mortality in the CTOPP study. (abstract) *PACE.* 1999; 22 (Part II): 195.
- [29] Lamas GA. Pacemaker mode selection and survival: A plea to apply the principles of evidence based medicine to cardiac pacing practice. *Heart.* 1997; 78: 218-220.
- [30] Conolly SJ, Kerr C, Gent M, Yusuf S. Dual-chamber versus ventricular pacing. Critical appraisal of current data. *Circulation.* 1996; 94: 578-583.