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Upgrading from ventricular to physiological pacing: is it worth it?

See page 490, doi:10.1053/euhj.2001.2817 for the article to which this Editorial refers

The paper by C. J. Hoijer et al. in this issue[1] raises a major fundamental problem that may be out of date. Apart from a few specific situations, is there a point in upgrading patients to physiological pacing, who have long been paced with single-chamber ventricular VVI(R) pacemakers?

The question has to be asked in those terms as it is known that in many European countries (including Belgium, Denmark, France, The Netherlands and Sweden[2] in particular), the level of primary implantation of physiological pacemakers (atrial or dual-chamber) was between 62% and 72% in 1997. This clearly shows that the majority of patients who were eligible for physiological pacing, i.e. those with preserved sinus rhythm and whose physiological condition permits that option, have effectively benefited from this treatment over the last few years. Discussions about secondary upgrading should therefore be almost unnecessary in the above countries.

In reality, the situation in these ‘rich’ countries may not be representative. In a number of European countries, even in Western Europe, such as Greece,
Spain or the United Kingdom, the proportion of physiological pacemakers is much lower (45%–46%). In these countries, the issue of possible secondary upgrading remains valid.

Regardless of economic aspects and cost–benefit analysis,[3] contrasting results from four currently completed multicentre controlled studies on pacing mode selection: the Danish trial, the PASE study, the CTOPP study and the recently reported MOST study would have justified prudence in pacemaker selection during primary implantation.

What have we learnt from controlled studies on pacing mode selection?
Andersen et al.[4–7] were the first to publish prospective data on pacemaker mode selection in 225 patients with sinus node dysfunction, but without any significant atrioventricular conduction abnormality. Patients were randomized to either AAI (n=110) or VVI (n=115) pacing. The initial report[4] with a mean follow-up time of 3·3 years, showed that atrial pacing was associated with significantly less atrial fibrillation and thromboembolic events, whereas mortality and heart failure were the same in both treatment groups. After extending the mean follow-up duration to 5·5 years, the incidence of atrial fibrillation and thromboembolism again decreased significantly in the atrial-paced group; but interestingly, the incidence of congestive heart failure[6] and of all-cause and cardiovascular mortality[5] was clearly and significantly higher in the ventricular-paced group. Finally, it is worth noting that atrioventricular conduction remained stable in the AAI group[6]. Atrioventricular block requiring upgrading to dual-chamber pacing occurred in only four patients, i.e. a 0·6% annual incidence.

The Pacemaker Selection in the Elderly (PASE) study[8] was a single-blind, randomized, controlled comparison of dual-chamber and ventricular pacing in 407 patients aged >65 years, who required permanent pacemakers for traditional pacing indications (49% atrioventricular block, 43% sinus-node dysfunction . . .). The primary end-point was the effect of pacing mode on health-related quality of life using the SF-36 questionnaire. One month after the implantation of a DDDR pacemaker, patients were randomized to be programmed in either VVIR or DDDR pacing mode. The average follow-up duration was 3 years. The primary end-point was stroke or all-cause mortality. Secondary end-points included health-related quality of life, cost-effectiveness, atrial fibrillation and development of pacemaker syndrome. No significant differences were observed between the pacing modes for all-cause and cardiovascular mortality and the combined primary end-point. But interestingly, statistically significant differences were observed in favour of dual-chamber pacing for health-related quality of life (P<0.001), atrial fibrillation (P=0.008 in the overall population, and P<0.001 in the subgroup of patients with a previous history of atrial tachyarrhythmia), and hospitalizations for heart failure (P=0.01).

The Canadian Trial of Physiological Pacing (CTOPP) was also a multicentre, randomized, controlled study of pacemaker mode selection[10]. Like PASE, CTOPP included all patients with preserved sinus activity scheduled for pacemaker implantation to correct symptomatic bradycardia, and compared ‘physiological’ (atrial or dual-chamber) with ventricular pacing. But contrary to PASE, where all patients received a DDDR pacemaker and were randomized to be subsequently programmed in either VVIR or DDDR pacing mode, patients in CTOPP were ran-
domized to receive either a ventricular single-chamber (VVI or VVIR) pacemaker or a physiological (AAI(R) or DDD(R)) device. The primary end-point was stroke or cardiovascular death. Secondary end-points were death from any cause, documented atrial fibrillation and hospital admission for heart failure. Two thousand five hundred and sixty-eight (2568) patients, mean age 73 years, were included. Atrioventricular block was the leading pacing indication (60%). Due to different randomization ratios between centres, 1474 were randomized to ventricular pacing and 1094 received a 'physiological' pacemaker. No statistically significant differences were observed between the two study groups for the primary combined end-point, all-cause and cardiovascular mortality, and heart failure-related hospitalizations. The only but slightly significant difference \( (P=0.05) \) in favour of physiological pacing was the lower annual rate of atrial fibrillation with an 18% relative risk reduction. As in other studies\[4,5\], this favourable effect became apparent only 3 years after the implantation.

These global analysis results, neutral or negative depending on stand-points, must however be weighted with those from a recently published subgroup analysis\[11\] that compared patients with and without 'pacemaker dependency', as assessed by temporarily programming the pacemaker to VVI 40 beats \( \text{min}^{-1} \) at the first follow-up visit. Of the 2244 patients tested, 1245 had an intrinsic heart rate \( \leq 60 \text{ beats } \text{min}^{-1} \) and were defined as 'pacemaker-dependent'. The other 999 patients had an intrinsic heart rate > 60 beats \( \text{min}^{-1} \) and were presumed to be paced infrequently. This may mean that in 45% of patients included in the CTOPP study, the pacemaker worked principally as a back-up. Comparing the two pacing modalities in the two subgroups of patients revealed a marginally significant trend \( (P=0.06) \) for the primary combined end-point, and a significant decrease in cardiovascular \( (P=0.005) \) and all-cause \( (P=0.0008) \) mortality with dual-chamber pacing in the subgroup of pacemaker-dependent patients only. As logically expected, these data suggest that patients with a low intrinsic heart rate will probably be paced frequently and are likely to benefit from physiological pacing. In contrast, non-pacemaker-dependent patients may not benefit from physiological pacing.

In total, although apparently contrasting, the results from those controlled studies are definitely consistent. In patients with preserved sinus activity and who, because of frequent or permanent bradyarrhythmia by whichever electrophysiological mechanism, will be paced permanently or most of the time, physiological pacing significantly improves long-term clinical outcome in comparison with classic ventricular pacing.

In patients who were implanted for sinus-node dysfunction, the results from the Danish trial, the PASE substudy and the MOST trial are consistent and prove that physiological pacing, either atrial single-chamber (Danish trial), or dual-chamber (PASE, MOST) significantly improves the health-related quality of life, the incidence of atrial fibrillation and of hospital admissions related to heart failure. Mortality data are more controversial. In any case, in this group of patients representing nearly half of permanent cardiac pacing indications\[3\], the main question is no longer whether physiological pacing is better than traditional ventricular pacing: obviously, it is! The question remains of which physiological pacing mode to choose. Acute haemodynamic studies with temporary pacing\[12,13\] have demonstrated the superiority of the AAI mode, which preserves both atrioventricular synchrony and a normal ventricular activation pattern, on dual-chamber pacing which most often requires otherwise useless ventricular capture. The highly positive results from the Danish trial, despite a limited population, argue in favour of atrial single-chamber pacing whenever possible, i.e. in patients with normal atrioventricular conduction. In any case, additional prospective randomized study comparing atrial with dual-chamber pacing in patients with sick sinus syndrome, appears necessary\[14\].

Conversely, all remains to be proven in patients who were implanted for atrioventricular block. There is no current evidence for the superiority of atrial-synchronized ventricular pacing modes (VDD or DDD) on the VVIR mode, which also corrects the ventricular chronotropic incompetence that characterizes high-degree atrioventricular blocks. The only data available are those reported by the subgroup analysis of PASE\[8\]: they do not favour dual-chamber pacing. Will the UKPACE study\[15\] results, which are expected to be published in 2003, provide a clear answer to that question? This prospective randomized trial will randomly allocate 2000 patients \( \geq 70 \) years with second- or third-degree atrioventricular block and undergoing first pacemaker implantation to receive VVI (25%), VVIR (25%) or DDD (50%) pacemakers. All patients will be followed-up for at least 3 years. The only end-point will be all-cause mortality.

Beside expecting a higher level of evidence, especially in patients who were implanted for high-degree atrioventricular block, other arguments may plead for a still wider use of ventricular pacing, either in VVI mode in patients in need of a mere back-up, or in VVIR mode in patients with permanent or frequent bradycardia. Single-chamber ventricular pacemakers are less expensive, easier and faster to implant, less subject to lead malfunction and longer-lived than
dual-chamber devices. In that respect, the CTOPP study[10] experience was particularly instructive; that study incorporated 33 highly unequally sized Canadian centres, thus reflecting the ‘real life’ of cardiac pacing. The incidence of perioperative complications was only 3·8% in the ventricular pacing group as compared to 9% in the ‘physiological’ group (P<0·001). The rate of lead dislodgement requiring reoperation was three times higher in the physiological pacing group (4·2% vs 1·4%, P<0·001). No controlled study had so far provided this type of data, which are very useful to decision making in clinical practice.

Upgrading dual-chamber pacing after long-term ventricular stimulation

The issue discussed in the paper by C. J. Hoijer et al.[11] therefore remains up to date in a few European countries and probably for some time (years) yet. This crossover randomized study compared DDDR and VVIR pacing modes over two 2-month periods in 19 patients who were previously treated with ventricular pacing for a mean duration of 6·8 years, then were upgraded to dual-chamber pacing. The upgrade was motivated by poor ventricular pacing tolerance (pacemaker syndrome) in nine patients and was systematically implemented at the time of box change in the other 10 patients. To minimize the risks of carry-over or period effect, randomization began only after a long period under dual-chamber pacing, i.e. 2·2 years on average. Within the limitations of that study, i.e. the small number of patients and the short duration of crossover periods, the authors showed that the DDDR period was preferred by most patients (16/19; P<0·001) and that dual-chamber pacing significantly improves dyspnoea and activity scores, increases left ventricular end-diastolic diameter without altering the left ventricular endsystolic dimensions, decreases the left atrial size, and reduces plasma brain natriuretic peptide in comparison with VVIR pacing. These results complemented and confirmed those from a previous study[16] which compared VVI and DDD pacing modes in patients who were initially implanted for atrioventricular block. In this study, the absence of a rate-responsive function penalized ventricular pacing.

Although it has its own technical shortcomings, including the risk of chronic deep venous occlusion, secondary atrialization following ventricular pacing is worth discussing in certain patients. In whom? When? Two different situations can then be considered:

- marked intolerance to ventricular pacing, i.e. the invalidating forms of pacemaker syndrome. But these remain to be identified, because nothing is as imprecise as the definition of that syndrome, which is subjective in essence[17]. In that respect, it is worth comparing the crossover rates from ventricular to dual-chamber pacing, between the PASE and MOST trials and the CTOPP study, respectively. In the PASE and MOST studies, where crossover only required simple reprogramming of the dual-chamber pacemaker into DDDR mode, the crossover rate for pacemaker syndrome was high, 26% and 31%, respectively. Most reprogramming was carried out early: 44% before the end of the first month following randomization and 77% within 6 months in the PASE study. In contrast, in the CTOPP, where upgrading required reoperation for new lead placement and box change, crossover from ventricular to physiological pacing at 1, 3 and 5 years was only 2·1%, 2·7% and 4·3%, respectively. These data clearly illustrate the relativeness of the pacemaker syndrome notion.

- systematic upgrading at the time of elective box change in asymptomatic patients. Such an attitude could be discussed following the publication of results from two small controlled studies on that theme. But one should be prudent because in the study by Sulke et al.[16] the upgrading restored not only atrioventricular synchrony but also normal chronotropic function. In Hoijer et al.’s[11] study, only 10 of the 19 patients were upgraded on principle.

In conclusion, teachings from controlled studies on pacing mode selection and common sense would indicate that the debate on whether to upgrade from ventricular to physiological pacing will lose relevance in future. At present, it is mainly discussed in cases of marked intolerance to ventricular pacing or as a systematic measure at elective box change in patients in good physiological condition and whose atrial activity remained sinus and where a perspective of several months or years has revealed that pacing was very frequent or permanent.

J. C. DAUBERT
C. LECLERCQ

Département de Cardiologie et Maladies Vasculaires,
Centre Cardio-Pneumologique,
Hôpital Pontchaillou/CHU 35033
Rennes Cedex, France

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Clinical course after radiofrequency ablation of type I atrial flutter. Identification of patients who risk atrial arrhythmia recurrences

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There has been a strong increase in the indications for radiofrequency ablation in the treatment of type I atrial flutter; the technique is relatively easy to perform, relatively safe and is often effective immediately. However, the follow-up of these patients is still unclear. In clinical practice, the subsequent occurrence of atrial arrhythmias and particularly atrial fibrillation remains a significant problem. The identification of these patients is important, since it indicates the need for or maintenance of anticoagulation therapy.

Before radiofrequency ablation, the risks and the follow-up associated with atrial flutter were difficult to evaluate. For example, some authors had reported a risk of embolic events with this arrhythmia, which was previously considered only as at weak risk of thromboembolism[1]. However, the risk of stroke was principally noted in patients who develop an episode of atrial fibrillation[2]. The main problem in patients with atrial flutter is related to the confusion or the association of atrial flutter with other atrial arrhythmias.

The history of atrial flutter is generally associated with the history of atrial fibrillation. Both arrhythmias are frequently associated in the same patient. Several mechanisms are possible: the transformation of atrial flutter into atrial fibrillation seems to be rare[3]; the presence of an underlying heart disease...