CARDIAC PACEMAKERS

When Clinical Evaluation Lags Behind Technological Progress

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Abstract

Objective: The rise in the number of implantations of cardiac pacemakers is of some concern to decision makers in the health sector. We assessed the intrinsic and relative clinical efficacy of cardiac pacemakers in current clinical indications to find out whether scientific or clinical arguments might justify differences in market prices.
Methods: We retrieved papers on cardiac pacing (January 1993–April 1998) from five databases (MEDLINE, HealthSTAR, EMBASE, Cochrane Library, and PASCAL). The citations in these papers were used to seek further articles. We selected the articles that met the criteria of evidence-based medicine (EBM) (randomized and nonrandomized controlled trials) and classified them according to clinical indication and type of evaluation (either of the intrinsic efficacy of a pacemaker versus a control or of the relative efficacy of different pacing modes).
Results: A total of 542 references were retrieved, but under 10% met our EBM criteria. Very few were comparative studies versus controls; most were recent and tended to use endpoints other than survival. Clinical efficacy was not proven on the basis of EBM criteria, even in common indications (e.g., sick sinus syndrome). Studies comparing different pacing modes were rarely randomized and did not provide consistent evidence for the superiority of any pacing mode in a given indication.
Conclusions: Knowledge of the natural history of the diseases for which cardiac pacing is indicated is scarce. There is an approximately 20-year gap between technological progress and clinical evaluation that cannot be easily bridged because of methodologic difficulties and ethical issues. Current guidelines on pacemaker use either rely on expert opinion or highlight present inadequacies and make recommendations for future work. Available clinical efficacy data do not justify the wide differences in the price of cardiac pacemakers.

Keywords: Pacemaker, Cardiac pacing, Randomized controlled trial, Evidence-based medicine, Cost

Since 1992 the number of primary implantations of cardiac pacemakers in Europe has increased by 3% each year, and the rate of increase will probably soon reach 4% to 5% (22;59). In 1993 about 600 cardiac pacemakers were implanted annually per million inhabitants in France and in the United States (26;35). The clinical indications for implantation and the preferred pacing modes differ by country; in 1995, depending upon the country, sick sinus syndrome accounted for as few as 21% or as many as 53% of all implantations. Wide variations were also noted for other indications, such as atrioventricular block (33–62%) and

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atrial fibrillation (10–20%) (23). In 1996 single-chamber pacemakers accounted for 18% to 60% of all implantations and dual-chamber pacemakers for 40% to 59%, according to country (41).

There are, no doubt, many reasons for these wide variations, including differences in pacemaker availability, in the cost of different models, and in habits. However, we questioned whether the root of the discrepancies might not lie in the simple fact that the best evidence published for implantation in all indications is not sufficient, by today's standards, to provide a sound basis for objective decisions. A lack of evidence would imply heavy reliance on expert opinion, and experts often tend to disagree. Moreover, rising numbers of implantations can easily—and also mistakenly—be taken as a sign of improved medical care. A "snowball" effect would accelerate the increase.

Because cardiac pacemakers are an accepted technology dating back to the 1960s (31), it may seem paradoxical to question their intrinsic efficacy and utility today. However, they were introduced on the basis of clinical data from case series at a time when the focus was not yet on randomized controlled trials (RCTs) nor on evidence-based medicine (EBM). Not only has the technology progressed considerably, but the indications for permanent pacing have also evolved. Is the clinical data available for justifying their use, or has the notion of intrinsic efficacy been largely superseded by technological comparisons of the relative efficacy of different models?

In this paper, we provide an overview of the best available evidence for the use of cardiac pacemakers. The trials have been classified in two categories: a) those that provide direct proof of intrinsic clinical efficacy; and b) those that are technological comparisons. The study was prompted by the National French Public Health Insurance system (*Sécurité Sociale*), which reimburses cardiac pacemakers. They wished to know whether there were any scientific or clinical reasons to justify the wide differences in the price of pacemakers in France. These prices vary from 1,528 to 4,624 Euro dollars (Euro) and are not stratified according to pacemaker type. The price of pacemakers of the same type from different manufacturers can vary up to 200%.

METHODS

We retrieved the English and French literature on cardiac pacemakers (January 1993 to April 1998) using five databases (MEDLINE, HealthSTAR, EMBASE, Cochrane Library, and PASCAL). The search strategy was designed to identify papers on clinical practice guidelines, consensus conferences, decision analyses, literature reviews, and meta-analyses. The main keywords were "pacemaker, artificial" OR "cardiac pacing, artificial" OR "artificial heart pacemaker" OR "pacemaker" (a total of 542 references). This search was then refined by associating keywords relating to: a) controlled or randomized studies; b) technical aspects of pacemakers; c) databases on pacemakers; d) indications; e) quality control studies; and f) assessment and follow-up studies. We used the reference lists of retrieved articles to find articles published before 1993. The process was reiterated until we felt confident that we had recovered key articles and those most frequently cited by the profession.

An in-house clinician (BC) analyzed the retrieved medical literature using ANAES grids for levels of scientific evidence (34) analogous to those of McMaster University Health Sciences Centre (Canada) (17). The ANAES report was submitted to a panel of 11 experts (10 cardiologists and 1 biomedical engineer) chosen from lists supplied by professional societies. Two discussion meetings and a phone conference were convened over 6 months, during which the experts compared published evidence with current practice. Their conclusions were included in the final report validated by the Scientific Council of the ANAES and published in French in 1999 (available upon request from the ANAES).

RESULTS

Fewer than 10% of all the articles we retrieved met the criteria of an evidence-based approach (Table 1).

Evidence for the Clinical Efficacy of Cardiac Pacemakers

We retrieved only 10 state-of-the-art studies comparing pacing to medical treatment or absence of treatment in several clinical indications (Table 2).

Acquired Atrioventricular Block and Bifascicular Block. Atrioventricular (AV) block is an indication for cardiac pacing in adults that is based on 30 years of clinical experience. The main syndrome of AV block is bradycardia. Because there are no alternatives to watchful waiting for most bradycardias, no RCT is available. Nonrandomized studies suggest that permanent pacing improves survival in patients with third-degree acquired AV block (2;13;19;45;54). AV block can occur at the onset of an acute myocardial infarction, but the need for a pacemaker is usually temporary. Fewer than 1% to 2% of all AV block patients receiving thrombolytics for acute myocardial infarction of the inferior wall develop second and/or third degree AV block in the 14 to 16 days postinfarct and require permanent pacing (4). The incidence of bifascicular block was 130/100,000 in the Framingham study (52). Syncopal attacks, although common, tended not to be recurrent and were not linked to more sudden deaths. A nonrandomized study has suggested that pacing relieves transient neurologic symptoms but does not alter the risk of sudden death (46).

Sick Sinus Syndrome. We retrieved a single RCT that compared pacing (dual chamber) to appropriate controls (1). Syncopal attacks were significantly less frequent on pacing or drug administration than in the absence of treatment, but there was no significant difference between the two treatments. The incidence of paroxysmal or permanent atrial fibrillation and of thromboembolic events—other endpoints of sick sinus syndrome studies—did not differ in the three study arms. A nonrandomized controlled study found significantly improved survival in patients who were paced whether with a single-chamber (atrial-inhibited [AAI] or ventricular-inhibited [VVI]) or dual-chamber (DDD) pacemaker (51).

Hypersensitive Carotid Sinus and Neurally Mediated Syncope. Hypersensitive carotid sinus is an infrequent cause of syncope but provokes significant injuries in up to 25% of patients (43). Neurally mediated syncope is more frequent (36). We retrieved two RCTs comparing cardiac pacemakers to no treatment, one in each indication. Implantation of either a single- or dual-chamber pacemaker significantly diminished syncope recurrence in patients with hypersensitive carotid sinus (10). However, the reduced syncope recurrence noted in patients with neurally mediated attacks may not be meaningful because baseline characteristics of syncope frequency were not comparable in the groups with and without pacemaker (14). Although three RCTs have compared medical treatment to placebo in both indications (7;8;61), no RCT has compared pacing to medical treatment. Three nonrandomized controlled studies have been performed with significant results in favor of pacing in two studies (20;56).

Tachyarrhythmia. Atrial fibrillation is encountered in 2% of patients over 65 and 5% of patients over 75 (12). Junctional tachychardia and atrial flutter are successfully treated by radio-frequency ablation (42). Patients with paroxysmal or chronic atrial fibrillation that is ill tolerated and drug refractory are selected for pacing (11;21;39). We retrieved two RCTs comparing pacing after radio-frequency ablation versus second-line drug therapy: one in patients with severely symptomatic paroxysmal atrial fibrillation (6), and the other in patients with chronic atrial fibrillation and heart failure (9). In both studies, pacing led to significant improvements in symptoms but none in objective cardiac performance.

Table 1. Number of Retrieved and Selected Studies

Indication	Associated keywords	MEDLINE	HealthSTAR	EMBASE	Number of selected studies			
					RCT			
					AT	CCPM	NRCT	DT
Atrioventricular block	Heart block OR atrioventricular block OR heart bundle branch block OR heart right bundle branch block OR bundle branch block OR AV block OR bifascicular block OR trifascicular block	105	1	46	0	1	5	1
Sick sinus syndrome	Sinoatrial node OR sick sinus syndrome OR arrhythmia, sinus OR sinus node dysfunction	45	1	24	1	2	9	2
Carotid sinus hypersensitivity	Carotid sinus OR carotid sinus syndrome	44	0	0	2	2	5	1
Tachycardia	Tachycardia OR atrial fibrillation OR ventricular fibrillation OR heart atrium fibrillation	162	1	41	3	0	4	0
Cardiomyopathy	Cardiomyopathy, hypertrophic OR obstructive cardiomyopathy	42	2	4	1	0	3	0
Heart transplants	Heart transplantation	17	3	4	0	0	0	5

Abbreviations: RCT = randomized controlled trial; AT = comparison with alternative therapy; CCPM = comparison of cardiac pacemaker models; NRCT = nonrandomized controlled trial; DT = descriptive trial.

Table 2. Best-level Clinical Evidence Studies for the Use of Cardiac Pacemakers (CPM)

	Inclusions	Type of study	Mean follow-up	Main outcome
Sick sinus syndrome				
Sasaki et al. (51), Japan	NA	Nonrandomized controlled No CPM (n = 54) AAI (n = 12) VVI (n = 25) DDD (n = 12)	35 mo	Survival: Significantly improved with CPM
Alboni et al. (1), Italy	Jan 1991–Jun 1994	Randomized controlled Controls (n = 35) Drug (n = 36) DDDR (n = 36)	19 mo	Syncope: CPM < controls ($p = .02$); CPM < drug (not significant)
Hypersensitive carotid sinus				
Huang et al. (30), USA	Jan 1980–Jun 1986	Nonrandomized controlled No CPM (n = 8) With VVI (n = 9) or DDD (n = 4)	42 mo	Syncope recurrence: No CPM: 1/8 With CPM: 0/13
Fitzpatrick & Sutton (20), UK	Jan 1984–May 1988	Nonrandomized controlled No CPM (n = 13) With DDI (n = 40)	25 mo	Annual syncope rate: With CPM < no CPM ($p < .05$)
Brignole et al. (10), Italy	Nov 1986–May 1989	Randomized controlled No CPM (n = 28) VVI (n = 18) DDD (n = 14)	36 mo (without) 34 mo (with CPM)	Syncope recurrence: With CPM < no CPM ($p < .0002$)
Vasovagal syncope				
Sra et al. (56), USA	Oct 1989–Mar 1991	Nonrandomized controlled Drug (n = 22) AV sequential (n = 22)	16 mo	Negative tilt test: With drug: 19/22 With CPM: 2/22

Connolly et al. (14), USA	Jun 1995–Apr 1997	Randomized controlled No CPM (n = 27) DDDR (n = 29)	9.3 mo	Risk of syncope: With CPM < no CPM ($2p = .000022$)
Tachyarrhythmia				
Brignole et al. (6), Italy	NA	Randomized controlled Drug (n = 22) CPM + AVJA (n = 21)	6 mo	Quality of life: CPM + AVJP < drug ($p = .0006$)
Brignole et al. (9), Italy	NA	Randomized controlled Drug (n = 26) CPM + AVJA (n = 28)	12 mo	Quality of life: CPM + AVJP < drug (not significant)
Obstructive myocardiopathy				
Kappenberger et al. (32), Switzerland	NA	Randomized controlled (crossover) Nonactivated CPM (n = 83) Activated DDD/AAI (n = 83)	24 wk	Pressure gradient: Nonactivated > activated ($p < .001$)

Classifications: 1st letter = chamber that is paced; 2nd letter = chamber(s) where sensing occurs; 3rd letter = type of response.
Abbreviations: A = atrium; V = ventricle; D = dual; I = inhibited; R = rate-adaptive; AVJA = atrioventricular junction ablation; NA = not available.

Table 3. Technological Comparisons of Cardiac Pacemakers in Sick Sinus Syndrome

	Inclusions	Type of study	Mean follow-up	Main outcome
Tung et al. (58), USA	Jan 1969–Dec 1991	Descriptive VVI (n = 112) Dual (n = 36)	3.7 yr	Survival: 47%
Hesselson et al. (29), USA	Feb 1977–Aug 1989	Nonrandomized controlled VVI (n = 285) DVI (n = 84) DDD (n = 581)	7 yr	Survival VVI < DDD & DVI ($p = .025$)
Elshot et al. (18), Holland	Dec 1977–Oct 1980	Descriptive VVI (n = 41)	12.3 yr	Survival: 58%
Stangl et al. (57), Germany	Jan 1978–Dec 1986	Nonrandomized controlled AAI (n = 110) VVI (n = 112)	53 mo	Survival: Not significant
Markewitz et al. (38), Germany	Jan 1979–Dec 1985	Nonrandomized controlled AAI (n = 67) VVI (n = 87) DDI (n = 69)	From 13–51 mo according to CPM	Atrial fibrillation: VVI > AAI & DDI
Brandt et al. (5), Sweden	Aug 1979–Jul 1989	Descriptive AAI (n = 213)	5 yr	Survival: 89% at 5 yr 72% at 10 yr
Rosenqvist et al. (49), Sweden	Oct 1979–Dec 1983	Nonrandomized controlled AAI (n = 89) VVI (n = 79)	4 yr	Survival: VVI < AAI ($p = .048$)

Sgarbossa et al. (54), USA	Jan 1980–Dec 1989	Nonrandomized AAI (n = 19) VVI (n = 112) Dual (n = 376)	59 mo	Congestive cardiac failure: Not significant
Zanini et al. (60), Italy	Jan 1981–Dec 1988	Nonrandomized controlled AAI (n = 53) VVI (n = 57)	40 or 45 mo	Survival: Not significant
Santini et al. (50), Italy	NA	Nonrandomized controlled AAI (n = 135) VVI (n = 125) DDD (n = 79)	5 yr (2–10)	Overall mortality: VVI < AAI & DDD ($p < .001$)
Andersen et al. (3), Denmark	May 1988–Dec 1991	Randomized controlled AAI (n = 110) VVI (n = 115)	5.5 yr	Overall mortality: AAI < VVI ($p = .05$)
Lames et al. (33), USA	Feb 1993–Sep 1994	Randomized controlled VVIR (n = 85) DDDR (n = 90)	30 mo	Overall mortality: Not significant

See Table 2 for definitions of classifications and abbreviations.

Obstructive Cardiomyopathy and Dilated Cardiopathy. Pacing might counter the increased left ventricular outflow gradient in patients with obstructive cardiomyopathy who either do not respond to drugs or do not tolerate their side effects. We retrieved a single RCT that compared patients with an activated or deactivated pacemaker (DDI or AAI) (32). Symptoms and quality of life significantly improved in a subset of patients with activated pacemakers, but objective parameters (duration of exertion) and survival were no better in paced than unpaced patients.

It has been recently suggested that pacemakers might improve symptoms and prognosis in patients with dilated cardiomyopathy (25), but this hypothesis is not supported by any RCT.

Cardiac Transplantation. Cardiac pacemakers are implanted after heart transplants to control early brady-arrhythmias due to sick sinus syndrome or atrioventricular block. The prognosis of patients with sinus node dysfunction is poor (37). Only descriptive studies on prognosis and survival have been published (27;28;44;48;53).

Other Indications. Preventive permanent pacing has been advocated in rare diseases such as long Q-T syndrome, myotonic muscular dystrophy, or Kearns-Sayre syndrome (25), but no in-depth clinical evaluations have been performed.

Evidence for the Relative Efficacy of Different Types of Cardiac Pacemakers

The majority of controlled studies on cardiac pacemakers address different pacing modes (Tables 3 and 4). Only four of the studies we retrieved were randomized. Most concerned sick sinus syndrome (Table 3), and the most frequent endpoint was survival or overall mortality. Only one RCT revealed a clearly significant difference between pacing modes, but this study did not concern mortality but rather the overall symptom score during the 14 days following AV block (16). A dual-chamber pacemaker was a marked improvement on a single-chamber pacemaker, but the study included few patients. The results of the nonrandomized controlled trials were often controversial. For instance, in sick sinus syndrome, a VVI pacemaker proved no better or worse than an AAI or a dual-chamber pacemaker, depending upon the study (38;49;50).

DISCUSSION

The first cardiac pacemaker was implanted in 1958. According to our literature review, the first controlled studies were performed in the 1980s. The first RCTs were initiated in the early 1990s, but we found only six RCTs comparing cardiac pacing to medical treatment or absence of treatment. Nonrandomized controlled studies, which provide complementary evidence to RCTs (40), were also scarce and tended to focus on comparisons of pacing modes rather than on evidence for clinical efficacy in a given indication. No RCT or longitudinal observational study has investigated whether pacing is preferable to watchful waiting in common indications such as syncopal attacks with suspected bradycardia and asymptomatic sick sinus syndrome or AV block. There are no convincing epidemiologic data on large populations of patients with sick sinus syndrome, syncopal attacks, or AV block with no or few symptoms.

How is it that the use of such a widespread technology is based on such limited external evidence? Most of the first patients to be implanted presented syncope due to complete AV block. They showed clear improvements in quality of life and survival that left little room for doubt as to the benefits of pacing. We do not contest the use of pacemakers in this indication. However, as new indications were introduced, signs of efficacy continued to be taken as proof of efficacy. A treatment designed for high-risk patients in specific indications

Table 4. Technological Comparisons of Cardiac Pacemakers in Indications Other Than Sick Sinus Syndrome

	Inclusions	Type of study	Mean follow-up	Main outcome
AV block				
Channon et al. (13), UK	NA	Randomized controlled (crossover) VVI (n = 16) DDD (n = 16)	14 days	Overall symptom score: DDD < VVI ($p < .006$)
Lamas et al. (33), USA	Feb 1993–Sept 1994	Randomized controlled VVIR (n = 102) DDDR (n = 102)	30 mo	Overall mortality: Not significant
Vasovagal syncope				
Peterson et al. (47), UK	1985–1991	Nonrandomized controlled Before DDI (n = 37) After DDI	50.2 mo	Improvement: 89%
Hypersensitive carotid sinus				
Morley et al. (43), UK	NA	Nonrandomized controlled AAI (n = 8) VVI (n = 55) DVI (n = 6) DDD (n = 1)	18 mo	Complete relief from symptoms: 77% AAI: 0/8 VVI: 85% DVI/DDD: 7/7

See Table 2 for definition of classifications and abbreviations.

began to be prescribed to less severely ill patients with other indications. The next 20 to 25 years thus saw a considerable increase in expertise but little in evidence. Currently, we are therefore having to decide whether to validate a backlog of 25 years of experience and, if so, how.

The lack of data derived from multiple RCTs involving a large number of individuals has already been recognized by the American College of Cardiology/American Heart Association guidelines on pacemaker implantation (24). In these guidelines, most of the evidence for efficacy in acquired AV block in adults, sinus node syndrome, hypersensitive carotid sinus syndrome, and neurally mediated syncope is considered to be of low or intermediate level. The guidelines nevertheless rank these indications as class I indications on the basis of the general agreement among experts that pacemakers are beneficial, useful, and effective. The provisional solution has been to rely on expert opinion.

Carrying out the missing RCTs raises obvious methodologic and ethical difficulties. How does one define a suitable control group? Crossover studies using deactivated pacemakers do not provide a true control, and the ethics of permanent implantation of a deactivated pacemaker are debatable. The ethics of going back to a study of the natural history of the diseases for which pacing is recommended are also debatable. Can one withhold treatment from patients if it is the consensus opinion of experts that the indication warrants pacing? The final decision can only be in the hands of the informed patient (15).

With time, the emphasis of studies on cardiac pacemakers has clearly shifted from the clinical to the technological scene, just as in the field of drugs it shifted from innovative to "me-too" drugs. Evaluating devices is even more complex than evaluating drugs. The shelf-life of drugs can exceed 20 years; devices tend to be superseded within 2 to 3 years. By the time a registration file is approved, a device can be obsolete. Drugs comply with fairly standard and invariant production and prescription measures; devices can be reprogrammed and individualized, and their efficient use depends on individual expertise. Most drugs are developed by multinational companies; devices are often manufactured by small, local companies with less internal clinical know-how and much lower profit margins for funding research and development. The cost of devices is such that, unlike drug samples, they can rarely be supplied free in clinical trials. In Europe, the EC mark (implemented in 1998 in France) is delivered to devices conforming to certain technical and safety standards, but evidence of efficacy from RCTs is not mandatory.

Clearly, national agencies are faced with a delicate task both as regards authorizing medical devices and issuing guidelines. While making sure that devices are safe, useful, effective, and reasonably priced, they also have to ensure that innovation is not suffocated by standardization, regulation, and no-risk policies. Because scientific evidence is often inadequate and expert opinion can be biased, they cannot establish cut-and-dried norms. Guidelines should therefore be taken for what they are—as recommendations that will evolve—and not as fixed tenets. National agencies should actively encourage validation of clinical indications in step with technological progress and also encourage the study of economic factors as soon as clinical trials are initiated.

POLICY IMPLICATIONS

In reply to the *Sécurité Sociale*'s concerns on the wide range of prices of cardiac pacemakers in France, the ANAES clinical and economic report concluded that there is, at present, no justification for these differences, at least on the basis of state-of-the-art clinical efficacy trials. The French government, which is currently reviewing its medical device reimbursement policies, is deliberating whether to discontinue reimbursing cardiac pacemakers according to brand and to reimburse them according to type instead. The anticipated decision of reimbursement by type is being challenged by the manufacturers, who fear hard-hitting reviews

of medical devices like those under way for pharmaceuticals. Moreover, they are concerned that further investment in research will be severely compromised.

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