Cardiac pacing: the state of the art

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Permanent cardiac pacing remains the only effective treatment for chronic, symptomatic bradycardia. In recent years, the role of implantable pacing devices has expanded substantially. At the beginning of the 21st century, exciting developments in technology seem to happen at an exponential rate. Major advances have extended the use of pacing beyond the arrhythmia horizon. Such developments include dual-chamber pacers, rate-response algorithms, improved functionality of implantable cardioverter defibrillators, combinations of sensors for optimum physiological response, and advances in lead placement and extraction. Cardiac pacing is poised to help millions of patients worldwide to live better electrically. We review pacing studies of sick-sinus syndrome, neurocardiogenic syncope, hypertrophic obstructive cardiomyopathy, and cardiac resynchronisation therapy, which are common or controversial indications for cardiac pacing. We also look at the benefits and complications of implantation in specific arrhythmias, suitability of different pacing modes, and the role of permanent pacing in the management of patients with heart failure.

Introduction

Permanent cardiac pacing is one of the most important medical innovations of the 20th century.[1] Although originally designed for management of Stokes-Adams attacks (in patients with complete heart block), sick-sinus syndrome is now the most common indication for permanent pacemaker implantation. In the USA, sinus-node dysfunction is probably the primary indication for pacemaker implantation in over 50% of patients.[2] Cardiac pacing remains the only effective long-term treatment for symptomatic bradycardia.[3]

Recent technical advances in cardiac pacing have included dual-chamber devices, rate-response algorithms, and progressive refinement of antibradycardia-pacing function in implantable cardioverter defibrillators (ICDs). Indications have expanded beyond symptomatic bradycardia, and now include neurocardiogenic syncope, hypertrophic obstructive cardiomyopathy, and cardiac resynchronisation therapy (CRT, biventricular pacing) for congestive heart failure. The role of atrial pacing in the prevention of atrial fibrillation is being explored.

Pacing modes

The generic pacemaker code of the North American Society of Pacing and Electrophysiology and the British Pacing and Electrophysiology Group is used to describe various pacing modes. The first letter denotes the chamber or chambers that are paced (A=atrial, V=ventricular, D=dual [atrial and ventricular]). The second letter describes which chambers detect (sense) electrical signals. The third letter represents the response to sensed events (I=inhibition, T=triggering, D=dual [inhibition and triggering]). A fourth letter, R, denotes activation of rate-response features. The most commonly used pacing modes are: AAI(R) single-chamber atrial pacing without (or with) rate response, VVI(R) single-chamber ventricular pacing without (or with) rate response, and DDD(R) dual-chamber pacing without (or with) rate response. In the latest version of the code,[4] a fifth position denotes the chamber or chambers in which multisite pacing is delivered.

Single-chamber right atrial pacing might be adequate for patients with sinus-node dysfunction and intact atrioventricular conduction. The disadvantage of this pacing modality is that atrioventricular block develops in 0·6–5·0% of patients with sick-sinus syndrome every year.[1,5,6] Atrial pacing would be inadequate for this type of acquired (natural or ablation-induced) atrioventricular block. To upgrade to a dual-chamber pacing system is often more complicated (venous thrombosis/fibrosis, pocket fibrosis) and might entail more morbidity than a de novo dual-chamber implant. In patients with sinus-node dysfunction, the presence of bundle-branch block at implantation is a better predictor of subsequent atrioventricular block than the atrial rate (Wenckebach cycle length), where Mobitz type I atrioventricular block occurs.[7,8]

Single-chamber right ventricular pacing can be associated with symptoms of pacemaker syndrome. During VVI pacing, this syndrome is most common in patients with normal (or near normal) left ventricular function and intact retrograde ventriculoatrial conduction.[9]

Search strategy and selection criteria

We undertook a comprehensive MEDLINE search using the MeSH term "pacemaker, artificial" from 1985, to December, 2003. Book chapters from cardiovascular disease or cardiac pacing texts published between 1985 and 2003 were searched by hand. Articles or book chapters published in English or Spanish were reviewed. A hand search of abstracts published in *Circulation, J Am Coll Cardiol, Pacing Clin Electrophysiol*, and *Heart* from 1998 to 2003 was also undertaken. The World Wide Web was used to provide information from the US Food and Drug Administration and as a source of information on late-breaking clinical trials. References deemed to provide important insights or that had further reading value were cited.

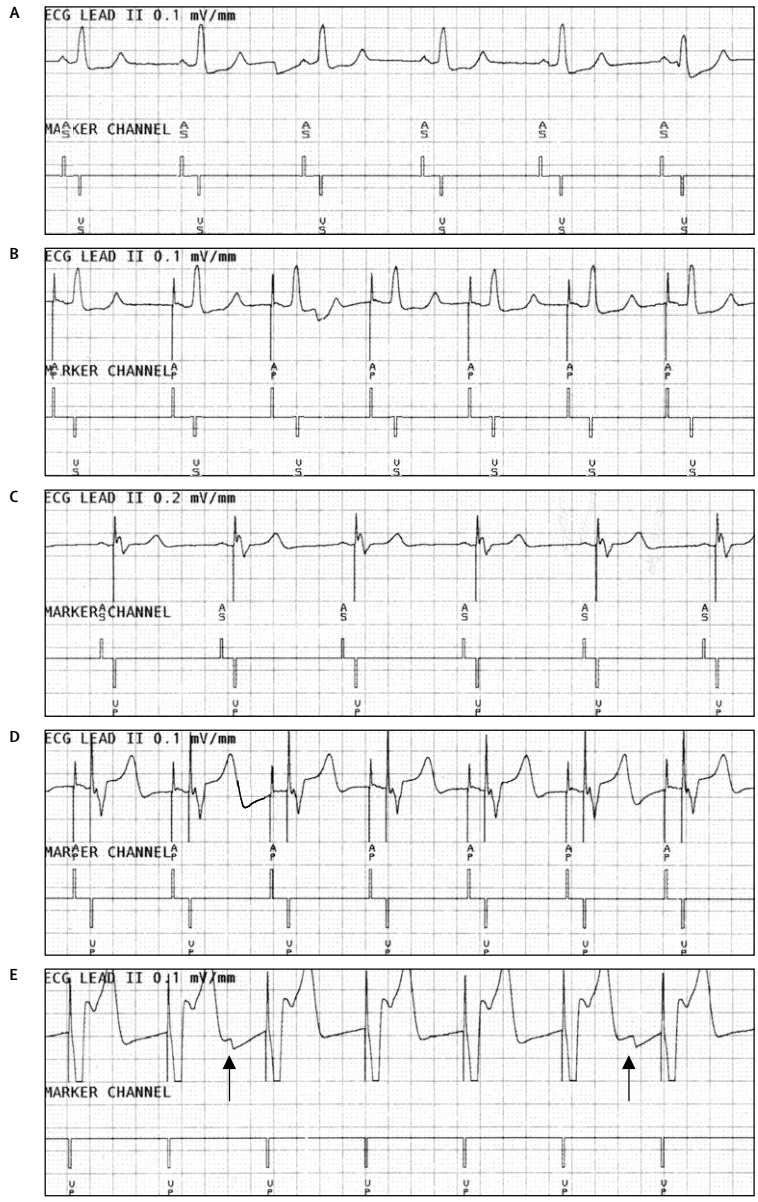

Figure 1: **ECG patterns of dual-chamber devices**
(A) Complete inhibition (sinus rhythm is present with intact atrioventricular conduction). (B) Atrial pacing with intact atrioventricular conduction. (C) Ventricular tracking of a sensed atrial rhythm (P-synchronous ventricular pacing). (D) Atrioventricular sequential pacing. (E) Single-chamber right ventricular pacing. Arrows point to smaller deflections occurring at a slower rate, which might represent P waves or baseline artifact. AS=sensed intrinsic atrial rhythm. VS=sensed intrinsic ventricular rhythm. AP=paced atrial rhythm. VP=paced ventricular rhythm.

Dual-chamber pacemakers that are programmed correctly assure maintenance of atrioventricular synchrony. Based on pacemaker programming and the intrinsic rhythm, patients with dual-chamber devices can show complete inhibition, atrial pacing with intact atrioventricular conduction, ventricular tracking of a sensed atrial rhythm (P-synchronous ventricular pacing), or atrioventricular sequential pacing (figure 1).

Loss of atrioventricular synchrony might reduce resting cardiac output by 20–30%.[9] Retrograde ventriculoatrial conduction might also cause a negative atrial kick, and could result in atrial distention and an autonomically mediated vasodepressor response. Atrial contraction against closed atrioventricular valves results in systemic and pulmonary venous regurgitation and congestion, which might precipitate heart failure.[9]

Symptoms of pacemaker syndrome include headache, disturbed mentation, neck pulsations, dyspnoea, chest discomfort, heightened cardiac awareness (transition from spontaneous to paced beats), fatigue, lethargy, exercise intolerance, and postural hypotension (lightheadedness, near-syncope, syncope).[9,10]

Dual-chamber pacing is traditionally accomplished by lead placement in the right atrial appendage and right ventricular apex. Development of active fixation technology has allowed lead placement at various sites within the right heart chambers. Pacing in the right atrial septum seems to be antiarrhythmic. Haemodynamics can be improved by pacing in the right ventricular outflow tract;[11] however, in short-term randomised studies, clinical benefits from outflow tract versus apical pacing have not been shown.[12]

In VDD pacing, the atrium is sensed but not paced, which is useful for patients with atrioventricular block and intact sinus nodal function. The main advantage of VDD pacing is atrioventricular synchrony with a single lead (incorporation of tip electrodes for ventricular sensing and pacing plus floating atrial electrodes for P-wave sensing). However, there has been concern that long-term stability of atrial sensing is not as reliable as in DDD systems and about VDD function under real-life conditions (atrial sensing might be variable). During atrial undersensing, a VDD system functions as a VVI system. Several recent studies suggest these concerns are not completely justified.[13,14] Investigators[15,16] have shown maintenance of atrioventricular synchrony during exercise. Another series of 13 children and 24 adults followed up for a mean of 3·5 years showed atrial electrogram stability and effective atrial sensing.[17] Present technology does not allow reliable atrial pacing via floating electrodes. This accomplishment could become feasible in the future.

Clinical benefits of physiological (AAI or dual-chamber) pacing

Despite the apparent advantages of physiological pacing, recommendations that favoured dual-chamber over single-chamber ventricular pacing in patients with sick-sinus syndrome or atrioventricular block were mainly based on observational data and expert opinion, until recently. A retrospective study of patients with sick-sinus syndrome showed that development of chronic atrial fibrillation and stroke was strongly determined by clinical variables and secondarily by ventricular pacing modality.[18] In some instances, atrial fibrillation might be

Study (number of patients)	Inclusion criteria	Intervention or outcome	Length of follow-up	Crossover	Main findings	Comments
Sgarbossa et al[18] (n=507)	SSS	CAF/stroke	CAF: 59, 38 months Stroke: 65, 37 months	n/a	Ventricular pacing mode predicted CAF in patients with PAF (p<0·001) and was an independent predictor of stroke (p=0·008)	..
Sgarbossa et al[19] (n=507)	SSS	Retrospective, non-randomised Mortality (atrial *vs* ventricular) Ventricular (22%); atrial (4%); dual (74%) implanted	66 months	n/a	Ventricular pacing was associated with >40% increased risk of total (p=0.053) and cardiovascular death (p=0·15)	Non-significant or inconclusive mortality data
Sgarbossa et al[20] (n=507)	SSS	New or worsened CHF	65, 37 months	n/a	19% new or worsened CHF; independent predictors of CHF were left ventricular dysfunction (p<0·001) and complex ventricular arrhythmia (p<0·001)	Ventricular pacing not associated with increased incidence of CHF
Andersen et al[21,22] (n=225)	SSS	Randomised/ Atrial (n=110) *vs* ventricular pacing (n=115)	40, 18 months[21] 5·5, 2·4 years[22]	n/a	Higher frequency of atrial fibrillation in ventricular group. Thromboembolic events occurred in 20 patients in ventricular group and in 6 patients in atrial group (p=0·0083).[21] Atrial pacing associated with significantly higher survival, less atrial fibrillation, fewer thromboembolic complications, less heart failure, and low risk of atrioventricular block.[22]	..
PASE[23] (n=407)	Age ⩾65 years Dual chamber pacer Sinus rhythm	Single-blind, randomised Ventricular *vs* dual-chamber pacing QOL/SF-36 Cardiac (death, stroke, CHF, AF)	550 days	26% from ventricular to dual-chamber pacing because of pacemaker syndrome	QOL improved after implantation (p<0·001), but no overall difference between ventricular and dual pacing and cardiac endpoints; some improvement in QOL, functional status, and clinical endpoints with dual pacing, in patients with sinus-node dysfunction	..
CTOPP[25] (n=2568)	No CAF Pacer indicated	Randomised / Ventricular (n=1474) *vs* physiological (n=1094) pacemaker Primary: stroke or cardiac death Secondary: death, AF, CHF admission	3 years	3% from ventricular at year 3 13% from physiological at year 3	Primary: ventricular *vs* physiological (5·5% *vs* 4·9%; p=0·05). AF significantly lower in physiological group (5·3% *vs* 6·6%; p=0·05)	Benefits of physiological pacing for AF not seen until 2 years after initial implantation
MOST[29] (n=2010)	SSS	Randomised/ Dual-chamber (n=1014) *vs* ventricular (n=996) pacing Primary: death or non-fatal stroke Secondary: composite (death, stroke, or CHF admission), AF, QOL, CHF score, pacemaker syndrome	33·1 months (median)	31% randomised to ventricular programmed to dual-chamber pacing at last follow-up	Primary: dual (21·5 %) *vs* ventricular (23%) (p=0·48) Risk of AF was lower in dual chamber (p=0·008) Dual-chamber pacing had lower risk of AF (p=0·008) and a small increase in QOL	Stroke-free survival not improved by dual-chamber pacing
ADOPT[30] (n=288)	Bradycardia-tachycardia	Randomised DDDR alone *vs* DDDR with atrial dynamic overdrive pacing Primary: symptomatic AF burden	6 months	n/a	Atrial dynamic overdrive pacing reduced AF burden by 25% compared with DDDR alone	Absolute reduction small (2·5% DDDR alone *vs* 1·87% DDDR with atrial dynamic overdrive pacing)

SSS=sick-sinus syndrome. CAF=chronic atrial fibrillation. n/a=not applicable. PAF=paraoxysmal atrial fibrillation. CHF=congestive heart failure. QOL=quality of life. SF-36=short form-36. AF=atrial fibrillation. Length of follow-up are mean, SD, or mean alone, unless indicated otherwise.

Table 1: **Pacing trials for sick-sinus syndrome**

promoted by ventricular pacing. Data from the same patient population revealed inconclusive mortality results, and showed that ventricular pacing did not increase the frequency of progressive or new onset heart failure compared with physiological pacing.[19,20]

Andersen and associates[21,22] published the first randomised study comparing pacemaker modes in patients with sick-sinus syndrome. By contrast with the studies noted earlier, patients assigned to atrial pacing had lower rates of atrial fibrillation, heart failure, thromboembolic events, and cardiovascular and total mortality than did ventricularly-paced patients. In the Pacemaker Selection in the Elderly (PASE) study,[23] very little benefit in quality of life from dual-chamber pacing was shown in elderly patients. However, patients with sick-sinus syndrome (but not atrioventricular block) had improvement in quality of life and higher functional status with dual-chamber pacing.[23] Ellenbogen and colleagues[24] reviewed several variables at pacemaker implantation in patients from the PASE trial[23] who were randomly assigned to the VVIR mode. Significant decreases in systolic blood pressure during ventricular pacing at implantation, β-blocker use at the time of randomisation, and non-ischaemic cardiomyopathy were

the only variables that predicted crossover to DDDR pacing in the Cox multivariate regression model.

In the Canadian Trial of Physiologic Pacing (CTOPP), physiological pacing (AAI or DDD) provided little benefit over ventricular pacing in prevention of stroke or cardiovascular death.[25] Further analysis of this large study showed that physiological pacing significantly reduced the frequency of chronic atrial fibrillation.[26] Patients assigned to physiological pacing had a 27% relative risk reduction for development of chronic atrial fibrillation compared with those assigned to ventricular pacing.[27] The yearly event rate for cardiovascular death or stroke rose steadily with decreased intrinsic heart rate in the ventricular pacing group. There was no event rate change in the physiologically-paced group, suggesting a benefit for pacemaker-dependent patients.[28] The Mode Selection Trial in sinus-node dysfunction (MOST)[29] showed no difference between dual-chamber and ventricular pacing in all-cause mortality or non-fatal strokes. In the Atrial Dynamic Overdrive Pacing Trial (ADOPT),[30] patients with bradycardia-tachycardia syndrome who were randomly assigned to DDDR with atrial dynamic overdrive pacing had a significantly higher frequency of atrial pacing than those in the DDDR pacing alone group (table 1).

In the UK Pacing and Cardiovascular Events study[31] dual-chamber pacing did not reduce all-cause mortality compared with single-chamber ventricular pacing (fixed or adaptive) in patients over age 70 years with high-grade atrioventricular block. Secondary endpoint data also showed no difference in stroke or transient ischaemic attack, heart failure, and myocardial infarction. Analyses of quality of life, exercise tolerance, and other secondary endpoint data are pending.

These studies consistently showed a decreased frequency of atrial fibrillation with atrial-based pacing in patients with sinus-node dysfunction (table 1). The findings suggest that some time might be needed to see potential biological (remodelling) effects of right atrial pacing for atrial fibrillation prevention. Contrary to all expectations, a reduction in stroke, heart failure, and mortality has not been consistently shown. High crossover rates (from single-chamber ventricular to dual-chamber pacing) seen in MOST and PASE might have limited the value of data assessed by an intention-to-treat analysis.

Rate-responsive pacing

Inadequate rate response to exercise (chronotropic incompetence) could be a sign of sick-sinus syndrome. The syndrome might also be precipitated by drugs (eg, β blockers) used in the management of coronary disease or heart failure. Rate-responsive (adaptive) pacing uses sensors to detect physical or physiological indices and mimic the rate response of the normal sinus node. A rate-control algorithm affects the overall rate-adaptive characteristics of the pacing system. Although some features of rate-adaptive pacing are automatic, physicians need to programme one or more variables to achieve the clinically desired rate response.[32] Benefits of rate-adaptive pacing for patients with chronotropic incompetence (eg, sick-sinus syndrome or atrial fibrillation with advanced heart block) are well established. Many sensors have been developed to modulate pacing rate (according to metabolic needs) and correct chronotropic incompetence. Activity, minute-ventilation, QT-interval, and stroke-volume sensors are commercially available in the USA and Europe.

The large number of sensors in clinical or investigational pacemakers suggests that none is ideal. Characteristics of an ideal sensor include: compatibility with standard pacing leads, rapid response, proportionality to workload, sensitivity to non-exercise physiological stimuli (eg, emotional stress, postural changes, meals, fever), and specificity to physiological stimuli. Among commonly used sensors, activity sensors have the fastest response, but have poor proportionality (eg, faster rates when going downstairs than upstairs), and specificity (eg, inappropriately fast rates when riding over a bumpy road). Minute ventilation and QT-interval pacemakers have good proportionality but slow speed of response. Only QT-interval systems respond to emotional stress. Processing of raw sensor data by refined algorithms reduces but does not eliminate these limitations. Sensor strengths and limitations are summarised in table 2.[32]

Sensors using special lead technology might be unreliable and difficult to implant. Sensors in the pulse generator are more dependable and only require conventional implant techniques. Hence, commonly used clinical devices use accelerometers, activity, QT-interval, and minute-ventilation sensors.

In AAI and VVI models, single-chamber pacing takes place when the sensed atrial or ventricular rate falls below a programmed lower rate limit. When rate response is activated, a sensor-driven rate is recorded. If the sensor-driven rate exceeds both the intrinsic rate and the lower rate limit, rate-adaptive pacing occurs. A programmed maximum sensor rate determines the fastest pacing that can occur.

In dual-chamber devices programmed in the DDDR mode, rate adaptation might result from ventricular tracking of the atrial rhythm or be sensor driven (atrial or atrioventricular sequential pacing). Maximum ventricular tracking and sensor rates can be programmed

	Speed	Proportionality	Specificity	Sensitivity
Activity	H	L	L	L
Minute ventilation	M	H	H	L
QT interval	L	M	M	H

H=high, L=low, M=medium. Adapted from reference 32, with permission.

Table 2: **Sensor strengths and limitations**

separately. If a fast atrial rate during exercise is assumed to be more likely to represent sinus tachycardia than a fast atrial rate at rest, a maximum sensor rate (that is programmed faster than the maximum ventricular tracking rate) helps provide faster ventricular rates during exertion and limits the ability to track atrial tachyarrhythmias. Dual-chamber devices also allow rate-responsive atrioventricular delays to be programmed (which simulates normal shortening of the PR interval).

Rate-response features could be adapted to individual patients. For instance, activity sensors can be programmed to various thresholds (high, medium, low), which can trigger rate-responsive pacing. The slope of acceleration and deceleration of pacing rate might also be programmed. Recently, different sensors have been combined to provide a more physiological response to exercise. Sensor combination aims to improve the speed of rate response, proportionality to workload, sensitivity to changes induced by exercise-related and non-exercise-related requirements, and specificity in rate adaptation.[32]

Combinations of sensors, which exploit strengths and counteract weaknesses of individual sensors, are a logical step toward optimisation of rate-responsive pacing. Clinically available combinations include activity/minute ventilation, accelerometer/minute ventilation, and activity/QT sensors. Combinations have included a fast reacting activity sensor with a more proportional and specific metabolic sensor. Initial dual-sensor systems needed time-consuming tailoring of the individual sensors and their interactions for every patient. Present systems allow for the automated tailoring of rate response, via self-learning rate-response algorithms (Vitatron, Arnhem, the Netherlands), or programming of a target rate histogram on the basis of the patient's activity level and frequency of exercise (Medtronic, Minneapolis, MN, USA).[32]

Benefits of rate-adaptive pacing are difficult to gauge in the usual pacemaker recipient. Most patients already have a quality of life similar to that of age-matched controls. VVIR pacing seems to be better than VVI pacing in terms of symptoms.[32,33] In one study, DDD pacing offered a better quality of life in all patient subgroups than did dual-sensor VVIR pacing.[34] There is little evidence to support a major clinical difference between sensors and their combinations. Cowell and colleagues[35] reported evidence (in one patient) of potential benefit of a dual-sensor compared with a single sensor.

Rate modulation is available in almost all modern pulse generators. In the USA, rate modulation and atrioventricular synchrony are given to pacemaker recipients whenever possible. Many sophisticated rate-adaptive features are poorly understood by clinicians and not well programmed. We believe that rate response is highly beneficial on occasion, although automated features are rarely an adequate substitute for careful physician input.

Permanent bradycardia pacing via implantable cardiac defibrillators

Previously, 15–20% of ICD recipients needed separate pacemakers. Strict criteria for dual-chamber pacing are present in 11–29% of recipients.[36–38] This percentage seems certain to rise as biventricular pacing for heart failure becomes increasingly common. Present ICDs capable of dual-chamber and triple-chamber, rate-responsive pacing provide state-of-the-art treatment. Shortcomings in early-generation devices have been corrected. However, addition of full-featured pacing is technically complex, and the final product is not merely the sum of a DDDR or DDDRV pacemaker and a tiered-therapy ICD. A tiered-therapy ICD includes antitachycardia pacing, cardioversion, and defibrillation capabilities. Emphasis on safe and reliable defibrillation can result in suboptimum pacemaker function.

If present and future trials expand indications for prophylactic defibrillator implantation, a large number of patients needing pacemakers for bradycardia or heart failure might instead receive (at least in the most developed countries) an ICD.[39,40] Cost considerations aside, substituting ICDs would have a profound effect on how cardiac rhythm management devices are designed, marketed, implanted, and followed up. Panel 1 shows the limitations of ICDs as pacemakers.

Frequent right ventricular pacing could be detrimental to ICD patients without indications for antibradycardia pacing. In the Dual chamber and VVI Implantable Defibrillator (DAVID) trial,[41] dual-chamber ICDs were programmed VVI 40 beats per minute or DDDR with a lower rate limit of 70 beats per minute. 1-year survival free of the composite endpoint (time to death or first admission for heart failure) was 89·3% in the VVI-40 group compared with 73·3% for the DDDR-70 group ($p \leq 0{\cdot}03$). Although the VVI-40 group had less congestive heart failure and death than did the DDDR-70 group, these differences for these individual endpoints were not significant. Nearly 60% of ventricular beats were

***Panel 1:* Limitations of ICD pacing function**

- Increased incidence of hardware and software design problems
- Uncertain long-term reliability of presently available defibrillation leads (compared with standard pacing leads)
- Increased current drain that reduces device longevity
- Heightened susceptibility to oversensing of endogenous (eg, diaphragmatic myopotentials) or exogenous (eg, electromagnetic interference) signals
- Pacing at rapid rates might delay or prevent detection of ventricular tachyarrhythmias
- Complicated pacing algorithms could result in inappropriate detection of ventricular tachyarrhythmias by ICDs[38]

paced in the DDDR-70 group compared with 1% in the VVI-40 patients. Andersen and colleagues[22] noted an improvement in cardiovascular and total mortality with AAI pacing. Dual-chamber pacing has not shown similar benefits.[23,25,29,31] Data from MOST[42] suggested that increased admission for heart failure was not associated with pacing mode, but with a prevalence of right ventricular pacing exceeding 40%. DAVID investigators suggested that right ventricular pacing (and the resultant left ventricular conduction delay) increases heart failure by creating ventricular desynchronisation.[41]

From the DAVID trial, single-chamber ICDs seem to be the device of choice. However, many ICD recipients will develop sinus-node dysfunction and atrial tachyarrhythmias. The diagnostic and therapeutic features of dual-chamber devices would be more suitable for these patients. Instead, the message from the DAVID trial should be that, when a dual-chamber ICD is chosen, the programming of a long atrioventricular delay (to reduce or avoid right ventricular pacing) should be considered for patients with intact atrioventricular conduction and narrow QRS complexes.

Pacing to terminate ventricular tachyarrhythmias

Antitachycardia pacing might terminate, accelerate, or have no effect on ventricular tachycardia. Because acceleration can turn a haemodynamically stable tachyarrhythmia into lethal ventricular fibrillation, this treatment requires backup defibrillation capabilities via an ICD. ICD treatment aims to prevent syncope and sudden death with minimum shock delivery. Antitachycardia pacing has traditionally been used to treat monomorphic ventricular tachycardias with rates up to 200 beats per minute. Only re-entrant monomorphic ventricular tachycardia (usually associated with clinically significant structural heart disease) can be ended by antitachycardia pacing. Ventricular tachycardia rates exceeding 200 beats per minute might be more likely to be accelerated by antitachycardia pacing and deteriorate into ventricular fibrillation. Adjuvant antiarrhythmic treatment might slow ventricular tachycardia rates and help with pace termination.[43] Various pacing techniques can be used or combined to find a regimen that works consistently without arrhythmia acceleration (figure 2).

Antitachycardia pacing requires pacing faster than each tachycardia. Figure 2A shows burst pacing at 290 ms (fixed rate of 207 beats per minute), which terminates ventricular tachycardia. In scanning burst pacing (figure 2B), successive bursts are paced at fixed and faster rates. The second attempt ends another ventricular tachycardia. More aggressive ramp pacing (rate increase or cycle length decrement between beats) is required to terminate the tachyarrhythmia in figure 2C.

Termination success rates of 80% or more can be achieved in heart disease. Termination rates of induced ventricular tachycardia with biventricular or right ventricular antitachycardia pacing are much the same.[44] Careful programming can result in acceleration rates as low as 1%. Almost all slow ventricular tachycardia episodes are pace terminable. However, in some patients antitachycardia pacing is unsuccessful and low-energy shocks are effective. Both treatments have comparable success, failure, and acceleration rates.[43,45] Almost all patients describe shocks of 1 J or more as uncomfortable. By contrast, effective and painless pacing can be achieved with μJ and is therefore more tolerable and less energy-consuming than cardioversion. Additionally, appropriately delivered pacing is unlikely to result in atrial proarrhythmia.[43]

Antitachycardia pacing treatment might be guided by electrophysiological test results or chosen empirically. New data suggest that ventricular tachycardia faster than 200 beats per minute can respond to empirical antitachycardia pacing.[46]

Pacing to prevent ventricular tachyarrhythmias

Algorithms that prevent ventricular tachyarrhythmias use continuous or intermittent (rate smoothing or stabilisation) pacing (with ventricular capture) to suppress triggering of ectopic beats, prevent re-entry, decrease dispersion of refractoriness, and eliminate pauses that might induce tachyarrhythmia. Various pacing techniques have been thought to prevent ventricular tachyarrhythmias; most are not very effective.[47] In the acquired long-QT syndrome, torsades de pointes is invariably preceded by pauses or bradycardia.

We reviewed publications of acquired torsades de pointes in patients with permanent pacing. Studies providing documentation of tachycardia onset and pacemaker programming were included in our analysis, and events occurring less than 1 month after atrioventricular nodal ablation were excluded. 18 cases were identified. No patients developed the tachyarrhythmia with an effective pacing rate of more than 70 beats per minute. Programmed lower rates of up to 70 beats per minute were not protective. At programmed lower rates of over 70 beats per minute, torsades de pointes occurred only by programmable pause-promoting features or oversensing. Whether rate-smoothing algorithms can prevent the condition when the baseline rate is programmed to less than 70 beats per minute remains to be seen.[48] Viskin and colleagues[49] reported most pauses leading to torsade de pointes were unequivocally longer than the preceding basic cycle length (ventricular rate). The shortest culprit pause was 760 ms. They recommended pacing at a cycle length of 750 ms (ventricular rate of 80 beats per minute). We agree that this is reasonable. A detailed review of pacing in the long-QT syndrome has been published.[50]

Acute and chronic congestive heart failure contribute to the need for tachyarrhythmia treatment in ICD recipi-

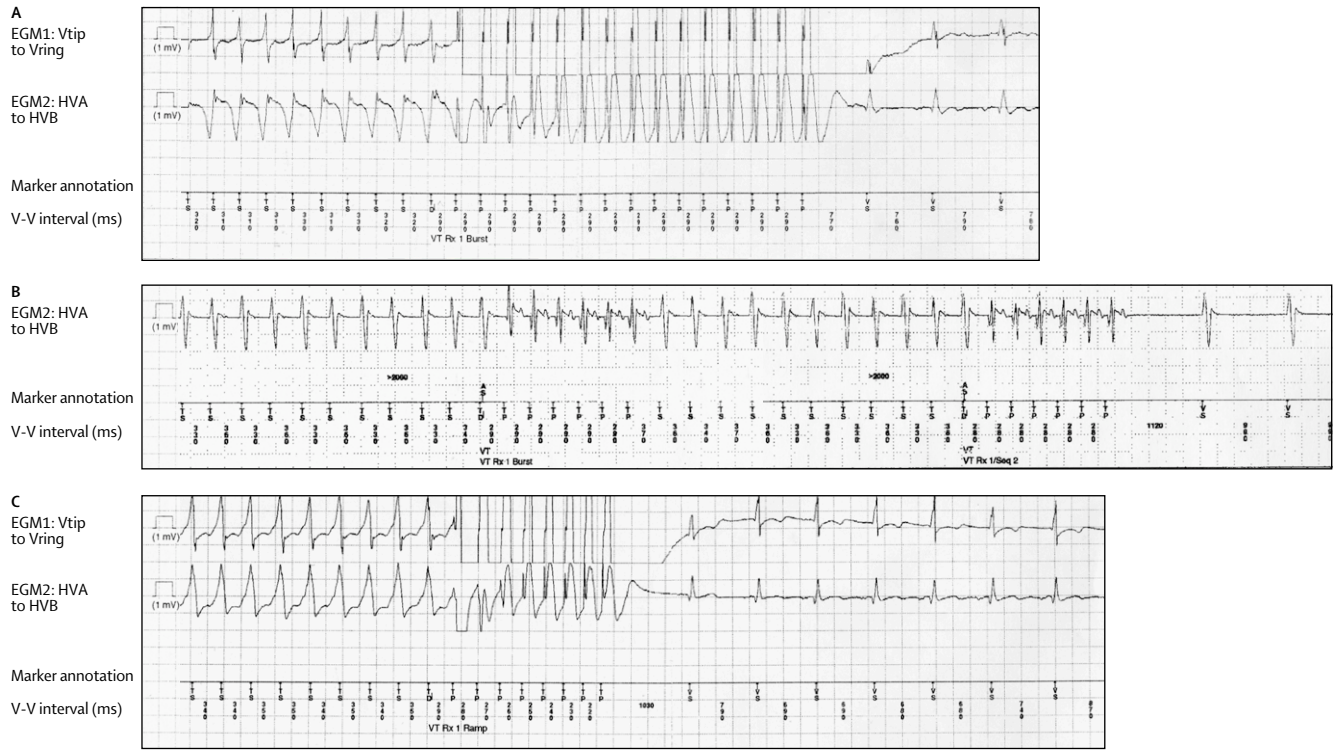

Figure 2: **Antitachycardia pacing for ventricular tachycardia**
(A) Ventricular tachycardia at cycle lengths of 310–20 ms (188–94 beats/minute). (B) Simulated ventricular tachycardia (courtesy of Medtronic) with cycle lengths of 330–70 ms (162–82 beats/minute). (C) Ventricular tachycardia at cycle lengths of 340–50 ms (rate 171–76 beats/minute). EGM1 Vtip to Vring=intracardiac ventricular electrogram recorded from pacing electrodes. EGM2=intracardiac ventricular electrogram recorded from high voltage (shock electrodes). TS=tachycardia sensing. TD=tachycardia detection. TP=tachycardia pacing. VS=sensing of intrinsic ventricular rhythm. V-V interval=ventricular cycle length (ms).

ents. Although small trials (93 patients in total) have shown that biventricular pacing treatment diminished ventricular arrhythmias, these results were not confirmed in larger trials.[44,51–55]

Pacing for neurally-mediated syncope

Case history, physical examination, and a 12-lead electrocardiogram (ECG) are most important in the assessment of a patient with syncope. With these investigations, the diagnosis can be ascertained or suspected in 40% of patients. Although echocardiography is commonly requested, little evidence supports its use if the physical examination and ECG are normal. Myocardial ischaemia rarely causes syncope, and stress testing is low yield unless there is a high index of suspicion (ie, angina pectoris). Holter monitoring is also low yield. If another diagnosis is not established or suspected, patients without evidence of structural heart disease are generally referred for assessment of neurally-mediated syncope (carotid sinus massage, head-up tilt table testing [HUT]). Those with structural heart disease or known cardiac arrhythmias are usually referred for electrophysiological testing.[56]

Benefit from pacing in patients with severe symptoms or unexplained falls and evidence of cardioinhibitory carotid sinus hypersensitivity has been recorded.[57] Carotid hypersensitivity is common in elderly patients with unexplained falls. Although empiric pacing is generally used, whether bradycardia causes these episodes is uncertain.[58,59] The Syncope and Falls in the Elderly—Pacing and Carotid Sinus evaluation (SAFE-PACE)[60] randomly selected patients to clinical observation or pacemaker implantation. After follow-up, paced patients had a lower incidence of recurrent falls than did controls. A second study (SAFE-PACE 2)[61] is an ongoing multicentre trial in which similar patients are randomly assigned to permanent pacing or an implantable loop recorder. Table 3 summarises the pacing trials for carotid sinus hypersensitivity.

The role of permanent pacing in management of neurocardiogenic (vasovagal) syncope remains controversial. A predominant cardioinhibitory (bradycardic <40 beats per minute or asystolic) response during HUT testing has been proposed as a means to identify patients with neurocardiogenic syncope who may respond to permanent pacing.

Maloney and colleagues[62] described a patient who had 73 s of asystole provoked by HUT. After the investigators acknowledged that vasovagal spells were usually benign,

Study (number of patients)	Inclusion criteria	Intervention or outcome	Length of follow-up	Crossover	Main findings	Comments
Brignole et al[57] (n=60)	Symptomatic CSH	Prospective, randomised No treatment (n=28) *vs* pacing (n=32 [VVI 18; DDD 14])	No pacing: 36 months No treatment: 34 months	68% of non-pacing group needed pacemaker implants for severe symptoms	Less syncope in pacing group (9% *vs* 57%; p=0·0002)	..
Shaw et al[59] (n=274)	Age ⩾65 years Dementia and cognitive impairment Falls	Multifactorial intervention Randomised	1 year	n/a	No difference in falls between intervention and control groups Cardiac diagnoses such as cardioinhibitory and vasodepressor CSH, orthostatic hypotension, and vasovagal syncope common	..
SAFE-PACE[60] (n=175)	Age >50 years Non-accidental fall Cardioinhibitory CSH Normal cognition	Randomised Consecutive patients Pacing (n=87) *vs* control (n=88)	159 completed 1 year	n/a	Paced patients less likely to fall than controls (OR 0·42; 95% CI 0·23, 0·75). Pacing benefit was similar for paced patients with a single fall and recurrent falls No difference in syncope between paced group and controls	Median of two falls before index presentation

CSH=carotid sinus hypersensitivity. n/a=not applicable. OR=odds ratio.

Table 3: **Pacing trials for carotid sinus hypersensitivity**

they defined long episodes (that could alter lifestyle or threaten health) of cardiac standstill during vasovagal spells as malignant vasovagal syncope. Even with a dual-chamber pacemaker, the patient had severe symptomatic hypotension on repeat HUT. Maloney and co-workers[62] recommended permanent dual-chamber pacing as adjuvant treatment for such patients. Sra and colleagues[63] subsequently assessed 22 patients with bradycardia (or asystole) and hypotension provoked by HUT. Temporary pacing did not prevent a substantial decline in mean arterial pressure during repeat HUT. During long-term follow-up (median 16 months), of 19 patients treated with drugs alone, 18 did not have presyncope or syncope. Sra and co-workers concluded that drug treatment was often effective for prevention of cardioinhibitory neurocardiogenic syncope, whereas permanent pacing was not. Baron-Esquivias and colleagues[64] reported a study including 1322 patients and concluded that neither pacing nor drug treatment affected the outcome of patients with tilt-induced asystole. They also concluded that the patients' clinical course was affected mainly by the frequency of pretreatment events.

Two new pacing modalities—search hysteresis and rate-drop response—could be more effective than conventional pacing.[65–68] Search hysteresis allows the patient's heart rate to fall to a low value before pacing begins at a much faster rate. When search hysteresis is turned on, the escape interval automatically continues for an extra cycle to allow spontaneous sinus rhythm to resume. In rate-drop response, a substantial drop in spontaneous rate triggers rapid pacing (90–100 beats per minute) for a programmable period. In the Vasovagal Syncope International study,[65] dual-chamber permanent pacing with search hysteresis was compared with no treatment. During follow-up, syncope occurred significantly more often in untreated patients than in those with permanent pacing.

Two controlled studies compared permanent pacing with drug treatment in patients with vasovagal syncope. In the North American Vasovagal Pacemaker Study (VPS),[66] a large treatment effect for permanent pacing with rate-drop response versus medical treatment resulted in the study finishing early: a greatly reduced risk of syncope was seen in paced patients. Syncope Diagnosis and Treatment[67] compared dual-chamber permanent pacing (with rate-drop response) with atenolol treatment in patients with recurrent vasovagal syncope. This study was also ended early after an interim analysis showed significant benefit from permanent pacing. Rate-drop response seems to be more effective than search hysteresis.[68] New syncope sensors such as monitoring QT interval, right ventricular pressure, and other indicators of contractility are under investigation.[1]

Results of the second Vasovagal Pacemaker Study (VPS II)[69] were not as encouraging as the first VPS: cumulative risk of recurrent syncope did not differ significantly in patients with dual-chamber pacemakers with either ODO (control group, not actively pacing) or DDD (with rate-drop response). Because of a lower than expected event rate in the control group, the study lacked sufficient statistical power to prove that pacemaker treatment prevents recurrent vasovagal syncope.[69] This unexpectedly low event rate could represent a placebo effect that resulted from device implantation in the control group. Flevari and associates[70] recently compared the effects of propranolol, nadolol, and placebo in 30 patients with recurrent vasovagal syncope and positive HUTs. All three treatments significantly reduced spontaneous presyncope and syncope, although no differences in recurrence rates were seen between

treatment arms. The vasovagal syncope and pacing trial (SYNPACE)[71] randomised 29 patients to pacemaker on versus pacemaker off modes and was unable to show a benefit from active pacing in prevention of recurrence in patients with severe recurrent tilt-induced syncope.

We believe that neurocardiogenic syncope is generally a benign condition and can usually be managed without permanent pacing. Pure or predominantly vasodepressor episodes do not need pacing. At present, we believe that dual-chamber pacing should be regarded as an adjunctive treatment for patients with frequent and severe cardioinhibitory spells, especially for those who are drug refractory or intolerant or have asystole exceeding 5 s that can be shown clinically or during HUT.

Pacing in hypertrophic obstructive cardiomyopathy

Dual-chamber pacing has been proposed as an alternative to septal myotomy-myectomy for patients with hypertrophic obstructive cardiomyopathy (that is refractory to drug treatment). DDD pacing is used because patients with the condition often cannot tolerate loss of atrioventricular synchrony.[72,73] Placement of the right ventricular electrode at the apex pre-excites the right-sided septum. Reduced inward septal motion (during systole) augments left ventricular outflow tract diameter and diminishes obstruction, which allows further systolic emptying.[72,74,75]

Appropriate timing of the atrioventricular interval is essential for effective pacing. The programmed delay must be less than the native PR interval (to ensure full ventricular capture), but long enough to allow adequate atrial contribution to ventricular filling (to avoid falls in cardiac output and systemic blood pressure).[72,76,77] Paced, sensed, and rate-adaptive atrioventricular delays help to maintain optimum atrioventricular intervals during daily activities. Correctly programmed dual-chamber pacing results in a 30–60% acute reduction in the left ventricular outflow tract gradient without systemic compromise.[72, 78–81]

Several investigations have been undertaken to assess the clinical benefits of pacing in hypertrophic obstructive cardiomyopathy (table 4).[78–83] These studies have generated much controversy. Some investigators have suggested that responders tend to be older and more symptomatic than non-responders.[72,79] The balance between gradient reduction and impaired diastolic relaxation during ventricular pacing might determine clinical response. Pacing might be more favourable in patients with slight (or well compensated) diastolic dysfunction.[72] Attempts to objectively assess functional capacity could be frustrated by the intrinsic heterogeneity of disease in hypertrophic obstructive cardiomyopathy. Much attention has been drawn to the consistent placebo effect noted in randomised pacing trials.[72]

Surgery is still regarded as the gold standard intervention for medically refractory hypertrophic obstructive cardiomyopathy. Patients should be aware that percutaneous transluminal septal myocardial ablation (PTSMA) is a treatment option. These procedures are associated with a risk of atrioventricular block, which needs subsequent permanent pacing.[84] Permanent dual-chamber pacing might be considered in patients who are not candidates for surgery or PTSMA. Pacing might also be a reasonable adjunct for patients who use drugs that greatly impair their native conduction system.[71]

Pacing to palliate, prevent, and interrupt atrial fibrillation

Complete atrioventricular junction ablation and permanent pacing was introduced in 1982 as an alternative treatment for patients with medically refractory supraventricular tachycardia.[85] When radio-frequency currents were used as the energy source for ablation, this technique became a popular and effective method for palliative treatment of atrial fibrillation with a rapid ventricular response.[86] In atrioventricular nodal modification, radio-frequency current is used to reduce ventricular rates. Energy is initially delivered to the posterior atrioventricular nodal imputs (near the ostium of the coronary sinus) and, if needed, gradually applied anteriorly (toward the compact atrioventricular node and bundle of His) until the desired effect is achieved. Attempts to modify the atrioventricular node have been successful in achieving long-term rate control in over 70% of patients. Inadvertent high-grade atrioventricular block (that needs permanent pacing) is seen in 10–20% of patients.[87,88] Both nodal ablative techniques substantially improve symptoms, left ventricular function, and quality of life. However, complete atrioventricular junction ablation had a significantly greater effect on frequency of major symptoms and quality of life than did node modification.[89]

Use of these palliative techniques has waned, as curative procedures (ie, pulmonary vein isolation and left atrial ablation) continue to develop. Atrioventricular junction ablation and permanent pacing might still be useful in elderly patients with clinically significant underlying structural heart disease, and those with persistent or chronic atrial fibrillation.

Atrial pacing has been investigated for prevention (and reduced frequency) of atrial fibrillation. Theoretical explanations are: (1) prevention of bradycardia-induced dispersion of refractoriness, which reduces the likelihood for re-entry; (2) overdrive suppression of spontaneous atrial ectopy that could trigger atrial fibrillation; and (3) change in atrial excitation patterns and prevention of intra-atrial re-entry, in response to premature atrial beats.[90] As previously noted, the benefit of atrial-based pacing (compared with ventricular-based pacing) in reduction of atrial fibrillation (over time) in patients with sick-sinus syndrome has been well established in several randomised studies.

Study (number of patients)	Inclusion criteria	Intervention or outcome	Length of follow-up	Crossover	Main findings	Comments
Jeanrenaud et al[76] (n=8)	Dual-chamber pacing	Clinical and echocardiography parameters	Up to 62 months	n/a	Dual-chamber pacing at optimum atrioventricular interval reduced angina and dyspnoea Echocardiography showed decrease in obstructive gradient	..
Kappenberger et al[79] (n=83)	Medically refractory HOCM	Randomised, double-blind, crossover Pacemaker activated *vs* non-activated	12 weeks	12 weeks of pacing	After active pacing, pressure gradient (p<0·001) and symptoms (p<0·007) improved QOL improvement noted	..
Nishimura et al[80] (n=21)	Symptomatic HOCM Rest LVOT gradient >30 mm Hg NSR Able to treadmill exercise	Randomised, double-blind, crossover DDD/AAI pacing (2–3 months each) LVOT gradient QOL score, exercise duration Peak oxygen consumption	About 6 months	19 randomised HOCM patients had both DDD and AAI pacing	LVOT gradient decreased with DDD *vs* both baseline and AAI (p<0·05) After DDD (but not AAI) pacing, QOL score and exercise duration better than baseline No change in peak oxygen consumption (baseline, DDD, AAI)	DDD pacing beneficial in some; others had no change or worsened Question of placebo effect as symptom benefit without haemodynamic benefit noted
Slade et al[81] (n=53)	Drug refractory HOCM	Temporary pacing for atrioventricular optimisation Permanent DDD pacing	11 (mean) 11 months (SD)	n/a	Symptomatic improvement after DDD pacing	Discrepancy between perceived symptomatic benefit and modest objective improvement
Fananapazir et al[82] (n=84)	Consecutive HOCM patients Medically refractory HOCM	DDD devices implanted Symptoms, clinical data recorded	2·3 (mean) 0·8 years (SD)	n/a	Symptoms (p<0·0001) and LVOT gradient (p<0·0001) improved	Baseline pacing studies not necessary to identify candidates
Maron[83] (n=48)	Medically refractory HOCM ⩾50 mm Hg basal gradient	Randomized, double-blind, crossover DDD *vs* AAI-30 (3 months, then crossover, followed by uncontrolled and unblinded pacing for 6 months	12 months	As per protocol after 3 months	No significant benefit to pacing (symptoms, exercise capacity, NYHA Class, QOL, treadmill time, peak oxygen consumption) Modest reduction in LVOT gradient in most patients Small subset of patients (age ⩾65 years) showed a beneficial clinical response	Pacing is not a primary treatment for HOCM Placebo effect present in randomised group Uncontrolled pacing period showed (but not objective) improvement in cardiac parameters

HOCM=hypertrophic obstructive cardiomyopathy. n/a=not applicable. LVOT=left ventricular outfllow tract. NSR=normal sinus rhythm. QOL=quality of life. NYHA=New York Heart Association.

Table 4: **Summary of hypertrophic obstructive cardiomyopathy studies**

Clinical data have suggested that right atrial pacing is less effective for atrial fibrillation prevention in patients with right atrial conduction delays or increased dispersion of refractoriness. Site-specific pacing from the atrial septum or Bachmann's bundle could shorten atrial conduction time and help to prevent atrial fibrillation.[90]

Intra-atrial conduction delay can be diagnosed in the presence of P waves longer than 120 ms. Right atrial pacing could produce delayed left atrial activation with a suboptimum left-sided atrioventricular conduction time, which could result in left atrial mechanical systole close to, or simultaneous with, left ventricular systole. Loss of the atrial contribution to left ventricular filling could be haemodynamically deleterious. Simultaneous biatrial pacing (right atrium and proximal or distal coronary sinus), manifested by normalisation of P-wave configuration and duration, improves haemodynamics.[91]

Multisite atrial pacing has been investigated for prevention of atrial flutter and fibrillation. Some investigators have combined high right atrial and distal coronary sinus pacing.[90] Saksena and co-workers[92,93] paced the right atrium and the coronary sinus ostium. In another small study,[1] no difference was recorded in atrial fibrillation frequency or duration between right atrial and dual-site atrial pacing. Long-term results of multisite atrial pacing in heterogeneous atrial fibrillation populations have not been uniformly favourable.[91] Benefits of dual-site pacing over right atrial pacing seem to be, at best, modest and clinical enthusiasm for this technique has waned.

The value of atrial pacing to prevent atrial fibrillation in patients without bradycardia remains controversial. Trials have been small and undertaken in individuals with frequent, drug-refractory atrial fibrillation and in populations in which effective treatments are difficult to find. In the Atrial Pacing Peri-Ablation for Prevention of

Atrial Fibrillation study,[94] the investigators concluded that in patients with drug–refractory, paroxysmal fibrillation who were candidates for ablation, right atrial pacing did not prevent atrial fibrillation. In a subsequent randomised crossover comparison of DDDR and VDD pacing modalities in patients with paroxysmal atrial fibrillation, the time to first recurrence did not differ between groups and the atrial fibrillation burden (h/day) increased significantly over time in both.[95] In the New Indications for Pacing Prevention of Atrial Fibrillation study,[96] although time to first recurrence was extended by dual-site pacing compared with high right atrial pacing in conjunction with a consistent atrial-pacing algorithm, total atrial fibrillation burden was much the same in the two groups.

New pacemaker pulse generators will include antitachycardia pacing modalities. Studies in patients receiving dual-chamber ICDs show that atrial tachyarrhythmias are common. Antitachycardia or high-frequency burst pacing could end two-thirds of these episodes. Whether these episodes indicate true pace termination will need further investigation. Although we are skeptical that atrial fibrillation can be reliably pace-terminated, arrhythmias that trigger atrial fibriallation (such as atrial flutter or tachycardia) can be readily pace-terminated.[90,97]

Pacing for heart failure

Two small studies[98,99] have suggested that DDD pacing with a short atrioventricular delay might benefit patients with dilated cardiomyopathy and a prolonged baseline PR interval. CRT refers to pacing techniques that alter the degree of atrial or ventricular electromechanical asynchrony in patients with major conduction disorders, and is usually done by pacing more than one atrial or ventricular site (biatrial or biventricular pacing, respectively). Bifocal pacing refers to two sites in the same anatomic cardiac chamber (ie, right ventricular apex and outflow tract). CRT can also be achieved by pacing from an atypical site (such as single-site left ventricular pacing).[91] The Pacing Therapies in Congestive Heart Failure II study group[100] showed that left ventricular pacing significantly improved exercise tolerance in patients with left ventricular systolic dysfunction, chronic heart failure, and a QRS duration of more than 150 ms. At least 20–30% of class III and IV chronic heart failure patients have major left ventricular conduction disorders that make them potential candidates for ventricular CRT.[91,101]

Ventricular CRT has had far greater effect on improvement of heart failure than biatrial pacing has had on atrial fibrillation. Several studies[102–108] have shown beneficial effects from biventricular or left ventricular pacing in patients with severe left ventricular systolic dysfunction and major left-sided intraventricular conduction disorders, such as complete left bundle-branch block. These conduction delays result in inefficient left ventricular contraction, shortened diastole (or overlap of systole and diastole), and worsened functional mitral regurgitation. CRT improves the sequence of left ventricular contraction and reduces functional mitral regurgitation. By contrast to inotropic agents, this treatment reduces myocardial oxygen consumption.[91]

Atrioventricular optimisation might be needed to ensure continuous ventricular pacing. Patients with chronic atrial fibrillation might respond to biventricular pacing.[109] Atrioventricular junction ablation might be needed to maintain pacemaker-controlled ventricular depolarisation. Biventricular pacing is technically complex. Until recently, CRT was accomplished with modified use of conventional hardware.[110–113] The left ventricular lead is usually placed over the epicardial left ventricular surface via a tributary of the coronary sinus. Lateral and posterolateral cardiac veins seem to provide the best haemodynamic benefit (figures 3, 4),[114] but could result in diaphragmatic (phrenic nerve) stimulation.[91] Access to these lateral veins might be limited by variation in anatomy.

Success rates of implantation are dependent on experience, and experienced implanters achieve initial success in about 90% of patients. Median time for implantation has been reported to be 2·7 h.[115] Lead dislodgment occurs in 5–10% of cases.[116] Other potential complications include: increased left ventricular pacing thresholds, cardiac sinus dissection, cardiac tamponade, and various sensing problems. As mentioned earlier, cardiac venous anatomy is more variable than coronary

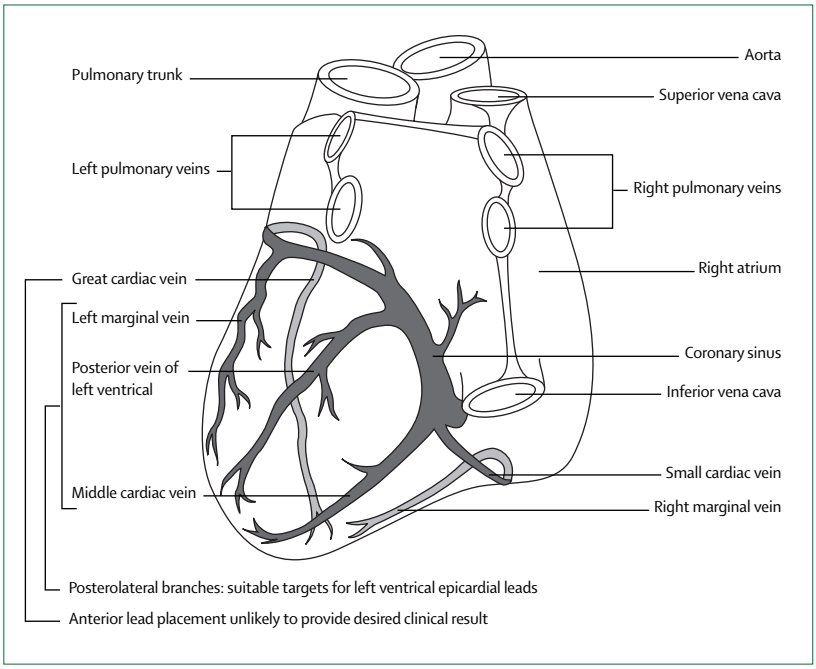

Figure 3: **Diagrammatic presentation of heart showing positions for coronary venous lead placement**
Adapted from reference 110, with permission.

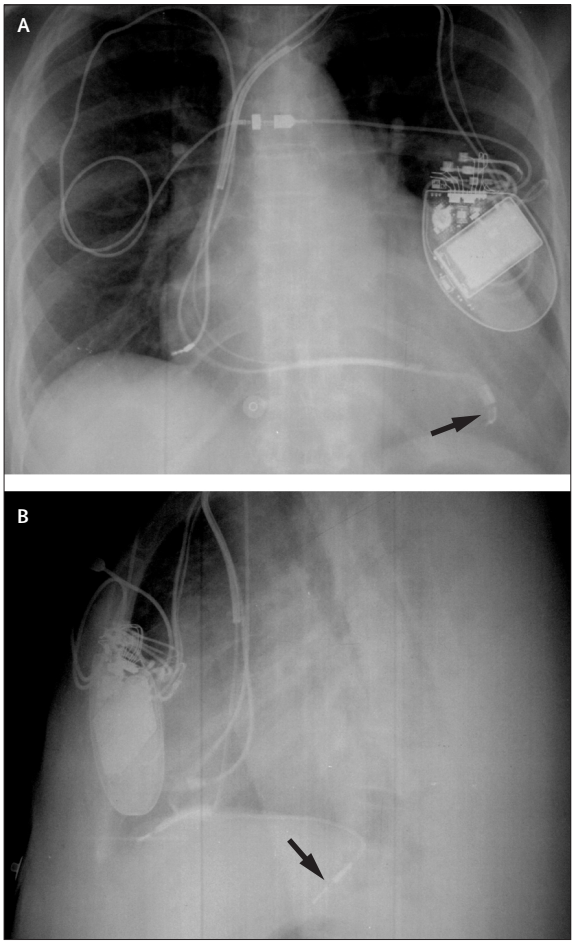

Figure 4: **Chest radiographs showing lead placements**
(A) Posteroanterior and (B) lateral chest radiographs showing tip of a left ventricular lead (arrows) in a tributary of the middle cardiac vein. Despite proximity of the lead to the left hemidiaphragm, phrenic nerve stimulation did not take place. The right ventricular lead points anteriorly toward the rib cage.

artery anatomy. Leads and lead delivery systems likewise vary in length, shape, and stiffness. We can now choose from an increasing variety of catheters, sheaths, guidewires, and leads, to assist left ventricular epicardial pacing. Recent addition of leads designed specifically for cardiac venous pacing (including models that can be advanced over wires used for percutaneous transluminal coronary angioplasty) helps to reduce procedure times and increase success rates. Some older biventricular pacing ICDs might sense every conducted QRS twice, because ventricular activation is detected at different times by the right and left ventricular leads. In newer devices, detection of tachyarrhythmias based on right ventricular sensing prevents the triggering of inappropriate shocks related to sequential ventricular sensing.

In several trials,[91,101,111,113] CRT has improved 6-min walking distance, quality of life score, left ventricular ejection fraction, functional class, exercise time, and peak oxygen consumption.

The less impressive results from the CONTAK CD study might relate to less stringent QRS duration and New York Heart Association (NYHA) functional class requirements.[44,91] The US Food and Drug Administration felt that the CONTAK CD study[110,111] did not fully establish the effectiveness of CRT as a treatment for heart failure. In the Focused Confirmatory Study,[110,111] 127 patients with class III or IV heart failure received the CONTAK CD system. In about half the patients, only the defibrillator component was turned on. In the other half, both defibrillator and CRT components were turned on. These results established the effectiveness of CRT for heart failure. Additional supporting evidence showed reduced left ventricular intracavitary dimensions and improved left ventricular ejection fraction in patients on CRT.[110] In the InSync ICD trial,[117,118] patients given CRT had significantly improved quality of life, NYHA functional class, peak VO_2 (oxygen consumption), exercise duration, left ventricular intracavitary dimensions, and ejection fraction.[44]

In a meta-analysis[44] of four controlled CRT studies (Multisite Stimulation in Cardiomyopathy trial [MUSTIC],[101] CONTAK CD,[110,111] InSync ICD [MIRACLE ICD],[117,118] and MIRACLE;[112,113] 1634 patients) CRT significantly reduced death from progressive heart failure and admission for heart failure, at follow-up. Total mortality was reduced by 23%, although this was not significant. In a meta-analysis,[116] nine CRT trials were analysed for efficacy. All-cause mortality was significantly reduced by 21%. This result was largely driven by a reduction in progressive heart failure. A non-significant increase in sudden cardiac death was noted. A metaregression showed no difference in all-cause mortality benefit between CRT patients an CRT-D patients. Data from the Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure trial (COMPANION)[120] were not included in the metaregression. The COMPANION trial was stopped prematurely because of the significant benefit of CRT and CRT defibrillators (CRT-D) in the combined primary endpoint of all-cause mortality and admission.[44,119,120] The investigators recorded a non-significant 24% relative reduction in all-cause mortality with CRT alone. However, a significant relative reduction in all-cause mortality with CRT-D was reported.[120]

The MIRACLE ICD trial[118] showed that at 6 months, patients assigned to CRT-D had a greater improvement in quality of life and functional class than controls. Treadmill exercise duration increased in the CRT-D group and decreased in the control group. No significant changes in left ventricular size or function, survival, or rates of admission were noted. Proarrhythmia was not seen and arrhythmia termination was likewise not impaired.

Which patients are the best candidates for CRT? Presently, those with drug-refractory NYHA class III or IV congestive heart failure, left ventricular ejection

fraction up to 35%, left ventricular end-diastolic diameter equal to or more than 55 mm, and a major left-sided conduction delay (QRS duration ⩾130 ms) seem to be reasonable candidates to offer biventricular pacing. The underlying rhythm should be sinus or atrial fibrillation with a ventricular response slow enough to allow continuous biventricular stimulation and capture.[91,115] We believe that CRT is rapidly becoming invaluable in the management of severe heart failure. We almost always offer CRT-D rather than CRT alone. Although some researchers maintain that the benefits of CRT and CRT-D are similar,[116] we have seen CRT reduce the burdensome multidrug treatment that looms as a crisis during management of patients with heart failure.[121] The most striking examples include elimination of the need for intermittent inotropic infusions.

Because right ventricular pacing might lead to ventricular asynchrony, patients who are dependent on ventricular pacing are candidates for biventricular pacing.[41,115] Preliminary data from a subanalysis of the biventricular pacing after ablate compared with right ventricular study (PAVE)[122] suggests that CRT might benefit patients with left ventricular ejection fractions of 35% or less and chronic atrial fibrillation who undergo ablation of the atrioventricular junction. Controversy exists over whether patients with right bundle-branch block should be candidates for CRT. Few with this condition have been included in clinical trials. Some cardiac electrophysiologists believe that the type of bundle-branch block does not predict clinical response and advocate biventricular pacing for advanced heart failure and any QRS duration of 130 ms or longer. Others have suggested that there might be a benefit in patients with right bundle-branch block accompanied by a substantial concomitant left-sided intraventricular conduction delay (assessed by echocardiography).[90,94]

We cautiously offer biventricular pacing to patients with right bundle-branch block after counselling them that the benefits for their patient group are uncertain. Achilli and co-workers[123] have shown that CRT might be helpful in patients with severe heart failure and narrow and incomplete left bundle-branch block QRS complexes who show echocardiographic evidence of intraventricular and interventricular asynchrony. Larger studies will be needed to confirm these preliminary results. A recent analysis of CRT cost-effectiveness suggested that CRT should not be considered in patients with comorbidities that are likely to reduce life expectancy.[124] Table 5 summarises some of the data from CRT studies.

Percutaneous lead extraction

Advances in cardiac pacing have spurred the use of percutaneous techniques for permanent lead extraction. Formal methods for transvenous extraction of permanent pacing leads have been available since 1988.[125] Although new methods are still being developed, currently available techniques are generally safe and very effective.

All lead extractions need some degree of direct traction (pulling). Simple direct traction on the proximal portion of the lead might be sufficient to remove newly implanted leads. Some evidence has shown that infected leads respond to direct traction alone more often.[126] The tensile strength of fibrous lead encapsulation increases over time. Passive fixation leads are generally more difficult to remove than active fixation leads. Traction alone is often ineffective and unsafe in leads implanted for more than 4–6 months. A variety of locking stylets (inserted into the proximal conductor coil and bound to its tip at the distal pacing electrode) has greatly simplified the application of direct traction.

Most operators begin with a superior vena caval (subclavian) approach and switch to an inferior vena caval (transfemoral) approach if needed. The ability to use snares and basket catheters makes the inferior venal caval approach more versatile than the superior approach. A transfemoral approach is recommended when a subclavian insertion site is grossly infected and when leads are broken or free-floating.

Many sheath systems are available for extraction. Sheaths provide counterpressure (forward movement to break adhesions) as they are advanced, and countertraction (opposition to movement of the myocardial wall) as the extractor pulls to remove the lead. The Pacemaker Lead Extraction with the Excimer Sheath trial[127] showed that excimer laser sheaths (which vaporise fibrous adhesions) improved the effectiveness of lead extraction and reduced procedure time. Complete lead removal was achieved in 94% of patients with laser sheaths compared with 64% of those using conventional telescoping non-laser sheaths. In a more recent study, extraction of 2561 pacing and defibrillator leads was attempted with three sizes of laser sheaths. Complete removal took place in 90% of leads, 3% were partially removed, and the remaining 7% were failures. Multivariate analysis showed that implant duration was the only preoperative independent predictor of failure; female sex was the only multivariate predictor of complications.[128] Indications for lead extraction are evolving. We believe that decisions on lead removal should be guided by parallel hierarchies that assess procedural timing (emergent, urgent, elective) and the risk benefit ratio (ie, whether extraction is mandatory, necessary, or discretionary; panel 2).[129] Success is inversely related to duration of implantation and patient age.

Major complications of lead extraction can be expected in up to 2% of patients, and happen more often during an operator's early experience.[128] These problems include low cardiac output, lead breakage, pulmonary embolism, lead migration (consequences depend on size and ultimate destination of the debris),[130,131] avulsion of veins or myocardial tissue, venous or myocardial tears (resulting in haemothorax, cardiac tamponade, or death), and failure to remove an infected lead.[125,128] The US extraction database enrolled 4090 patients between

Study (number of patients)	Inclusion criteria	Intervention or outcome	Length of follow-up	Crossover	Main findings
MUSTIC[101] (n=58)	LVEF≤35 % NYHA Class III LVEDD >60 mm NSR QRS >150 ms	Single-blind, randomised, crossover CRT (biventricular pacing) active (3 months) *vs* inactive (VVI-40 for 3 months) pacing Primary: 6-min walk Secondary: QOL, mortality, CHF admissions, patient preference, peak oxygen consumption	6 months	48 patients completed study	Active CRT pacing resulted in 23% increase in distance walked (p<0·001) QOL (p<0·001), peak oxygen uptake (p<0·03), admissions (p<0·05), and patient preference (p<0·001) all improved with biventricular pacing active
MIRACLE[113] (n=453)	LVEF≤35% NYHA Class III or IV LVEDD≥55 mm QRS ≥130 ms 6-min walk ≤450 m	Randomised, double-blind NYHA Class, QOL, 6-min walk	6 months	10 patients in control group	Biventricular pacing improved 6-min walk distance (p=0·005), NYHA Class (p<0·001), QOL (p=0·001)
MIRACLE ICD[118] (n=369)	LVEF≤35% NYHA Class III or IV LVEDD≥55 mm QRS ≤130 ms ICD indication	Randomised, double-blind ICD activated in both groups CRT pacing on (n=187) or off (n=182) NYHA Class, QOL, 6-min walk	6 months	Pacing on: n=10 Pacing off: n=14	At 6 months, pacing resulted in improved QOL (p=0·02) and NYHA Class (p=0·007) Although treadmill exercise duration increased by 56 s in CRT group and decreased by 11 s in controls (p<0·001), the two groups were not different in the change in distance walked in 6 min (p=0·36)
Bradley et al[44] (n=1634)	Randomised trials of biventricular pacing *vs* control	Meta-analysis of 11 reports of four randomised trials Mortality from CHF	3–6 months	n/a	Pooled CRT data showed 51% reduction in death from CHF *vs* controls (OR 0·49; 95% CI 0·25–0·93) CRT reduced heart-failure admissions by 29% (0·71, 0·53–0·96) Trend toward reduction of all-cause mortality was recorded
COMPANION[120] (n=1520)	LVEF≤35% NYHA Class III or IV LVEDD=60 mm QRS=120 ms NSR, PR ≥150 ms heart failure admission within previous year No heart-failure admissions hospitalisation within previous month	Randomised, open label (three arms) OPT OPT plus CRT OPT plus CRT-D Primary: composite of time to first all-cause mortality/admission Secondary: all-cause mortality, cardiac morbidity	About 15–16 months	Not published	At 12 months, both CRT and CRT-D were beneficial *vs* OPT for composite of time to first all-cause mortality/admission (both RR=20%; p=0·008 for CRT and p=0·007 for CRT-D) CRT-D reduced all-cause mortality *vs* OPT (RR=36 %; p=0·003)

LVEF=left ventricular ejection fraction. LVEDD=left ventricular end-diastolic diameter. OPT=optimal pharmacological theraphy. CHF=congestive heart failure. NSR=normal sinus rhythm. QOL=quality of life. n/a=not applicable. RR=risk ratio .

Table 5: **Summary of CRT studies**

January, 1994, and December, 1997. Major complications took place in 1·6% of patients (0·2% mortality rate). The 109 women who underwent removal of three or more leads had a 7·3% major complication rate.[125]

Complications of permanent pacing

Expanding indications and the relative ease of percutaneous implantation have fuelled enthusiasm for permanent pacing devices.[132] However, complications vary in clinical significance (and patient effect) from benign to life-threatening. An acute pacemaker implant might be associated with a complication rate of 4–5%.[132,133] Incidence of acute complications is related to operator experience. In MOST,[133] the incidence of late complications was 2·7%. Some investigators believe this incidence correlates with the number of leads implanted, but this opinion is debatable.[132] However, the direct correlation between procedure duration and the patient's risk for system infection is generally accepted.

Complications related to venous access include pneumothorax, haemothorax, and air embolism. In MOST,[133] the incidence of pneumothorax was 1·5%. Risk of pneumothorax is associated with the experience of the implanter, plus the number and difficulty of subclavian punctures. This risk can be eliminated by the cephalic vein cutdown technique. Pneumothorax is often small, asymptomatic, and noted incidentally on follow-up chest radiography; however, tension pneumothorax should always be part of the differential diagnosis when hypotension or pulseless electrical activity ensues during an implantation. Haemothorax results from trauma to the great vessels. Arterial puncture must be promptly recognised and treated with manual compression. Arterial cannulation (with a sheath or lead) can be avoided by advancing a guide wire to the inferior vena cava before any introducer insertion. Patients are surprisingly tolerant of air emboli. The air is filtered, absorbed in the lungs, and treatment is generally not needed. However, large emboli can result in respiratory distress, oxygen desaturation, and hypotension. Treatment with 100% oxygen, inotropic agents, or aspiration of the embolus from the right heart might be needed.[132]

Lead-related complications include perforation, dislodgment, diaphragmatic stimulation, and malposition.[132]

***Panel 2:* Assessment of risk benefit ratios for lead removal**

Mandatory

- Life-threatening condition, leads must be removed
- Indications include septicaemia (endocarditis), migration (causing emboli, arrhythmia, or perforation), device interference (ie, abandoned ICD lead), and occlusion of all usable vessels

Necessary

- Great potential for morbidity or mortality, leads should be removed
- Indications include pocket infection, chronic draining sinus, erosion, potential device interference, venous thrombosis, and lead replacement (extract and reimplant via thrombosed vein)

Discretionary

- Lead removal is optional
- Indications include pain, malignant disease, and replacement of leads abandoned for less than 3–4 years (not advisable to remove non-infected leads that have been implanted for more than 8–10 years)[129]

Perforation can involve the great vessels, right atrium, or right ventricle. Most perforations do not result in major sequelae. Cardiac tamponade, usually the result of chamber perforation, is the most ominous implant complication and should be suspected whenever hypotension occurs. The diagnosis is supported by enlargement of the cardiac silhouette and weak contractions, and can be confirmed by emergent 2D echocardiography. Definitive treatment via emergent pericardiocentesis should not be delayed. Surgical intervention might be needed if the bleeding persists and pericardial fluid reaccumulates. Trauma to the great vessels is more common with lead extraction than implantation and might result in direct bleeding into the mediastinum, which is an indication for emergent open chest surgery. Lead dislodgment takes place in 2·5% of implants, usually in the first 24–48 h postimplant.[133] If the patient is not dependent on pacing in that chamber, a different pacing mode could be reprogrammed to manage dislodgement. Definitive correction needs lead repositioning or replacement.

Diaphragmatic stimulation results from phrenic nerve stimulation. Right atrial leads can stimulate the right phrenic nerve, whereas right and left (cardiac venous leads) ventricular leads stimulate the left phrenic nerve and left hemidiaphragm. Screening for this complication by pacing at maximum outputs is a requisite part of correct implantation procedure.

Presence of an atrial or ventricular septal defect can allow passage of a lead to the left heart. Passage into the left heart is more common with ventricular leads. Confirmation of lead position by use of a left anterior oblique fluoroscopic projection of equal to or more than 40° should identify this problem during implantation. A lateral chest radiograph usually provides definitive diagnosis (figure 5).[134,135] A paced right bundle-branch block configuration on surface ECG might result from left ventricular pacing. However, this configuration can be present in up to 8% of patients with properly placed right ventricular leads. Coman and Trohman[136] have developed an algorithm to distinguish right versus left ventricular lead positions when pacing produces a right bundle-branch block configuration.

Pocket-related complications include haematoma, wound pain, pocket erosion, and infection. Haematomas are usually managed conservatively. Evacuation is required in 1–2% of implants.[132] Risk of bleeding is increased in anticoagulated patients, especially in those receiving heparin. Simple analgesics usually control wound pain. Pain that initially improves and then recurs or is temporally remote from the implant suggests infection.

The frequency of pacemaker implant infection ranges from 1–19%.[129,137] We believe that laboratory or surgical-suite infection rates greater than 7–8% suggest (potentially correctable) contamination or technical problems that need thorough investigation.

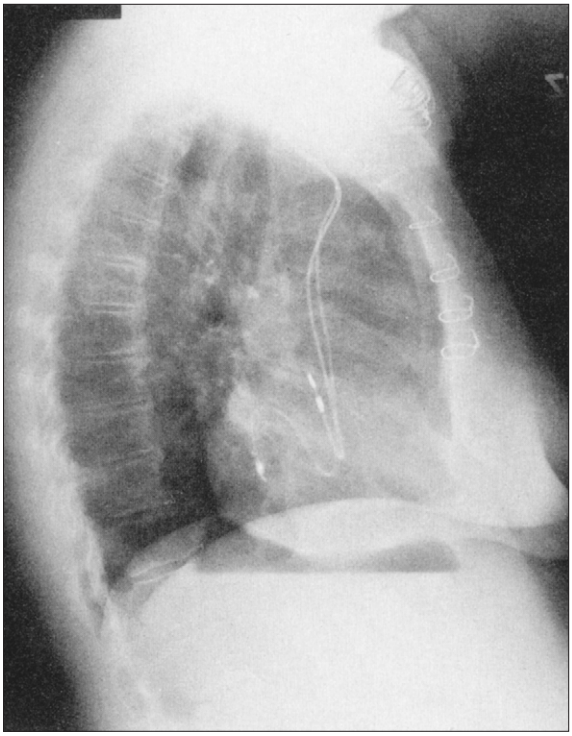

Figure 5: **Lateral chest radiograph of lead passing through atrial septum**
This ventricular lead points posteriorly and its tip is in the left ventricular endocardium. The lead passed through a patent foramen ovale, the left atrium, and the mitral valve into the left ventricle. This abnormal position is emphasised by comparison with figure 4B in which the right ventricular lead points anteriorly and the left ventricular epicardial lead points posteriorly. Adapted from reference 129, with permission from Blackwell.

Manifestations of pacemaker infection range from mild local pain and erythema to life-threatening septicaemia.[132,137] Early infection tends to be more clinically evident than the often indolent course of late infection. In one large series of patients with infected implantable antiarrhythmic devices,[137] the most common pathogens were coagulase-negative staphylococci (68%), *Staphylococcus aureus* (24%), and gram-negative enteric bacilli (17%). 16 of 123 (13%) infected patients had polymicrobial infections. When infection is strongly suspected, the entire system should be regarded as contaminated. The treatment of choice is complete system removal (pulse generator explant plus transvenous lead extraction), and antimicrobial therapy. Reimplantation should be undertaken at a different site. Morbidity due to persistent infection (ie, when infected leads are not removed) can be as high as 66%.[132] Erosion is associated with a high risk of infection and complete extraction of the device-lead system is likewise advised.

Delayed complications of permanent pacing leads include venous thrombosis, exit block, insulation failure, and conductor fracture. Late lead damage might be reduced by use of axillary or cephalic venous access. Symptomatic venous thrombosis takes place in up to 5% of patients. Treatments depend on the site and symptoms associated with thrombosis, and vary from heparin (followed by warfarin) or thrombolysis to angioplasty or open surgery. Exit block manifests as increased pacing thresholds. Insulation failure results in decreased lead impedance. Conduction fracture manifests as increased lead impedance. Definitive treatment for these complications is lead replacement.

We postulated that the design of bipolar coaxial leads from modern endocardial pacemakers might be susceptible to a high failure rate. We analysed[138] the long-term survival of bipolar coaxial leads and unipolar leads implanted at the Cleveland Clinic, OH, USA. At 5 years, the cumulative survival was 98·6% for both types. However, at 10 years, the survival of bipolar coaxial leads was only 92·4% compared with 98·6% of unipolar leads.[138] Silicone lead insulation has proved to be reliable for over 30 years. To improve handling, polyurethane (low coefficient of friction) was used for bipolar leads, but failed to show satisfactory insulation.[139] Pacing failure in bipolar systems with polyurethane-insulated leads can be frequent and might result in oversensing or failure to capture, or both. Failure is often due to chemical degradation (via oxidation) causing breakage in the inner insulation.[140,141] In one series,[142] overall lead failure occurred more often in the polyurethane group than in the silicone group. Most lead failures took place in the first 36 months after implantation.

Most modern pulse generators have an expected longevity of 5–9 years. Unexpected pulse generator (electrical) failure is rare.[143] Many problems discovered in new models can be corrected by software upgrades. Lead-related problems (increased thresholds, decreased impedance) resulting in increased current drain are the most common causes of premature battery depletion. Stepwise changes in pacing or magnet pacing rates, changes in pacing mode, pulse-width stretching, and telemetered battery voltages or impedances are clinical indicators used to measure the time for elective generator replacement and battery end-of-life.[144] Lithium-iodine batteries used in current pulse generators are not rechargeable and surgical replacement of the entire generator is needed.

Conflict of interest statement

R G Trohman and S L Pinski are paid consultants for Guidant Cardiac Rhythm Management (CRM) and are members of the Guidant CRM speakers' bureau. M H Kim is a paid consultant for Medtronic and member of the Medtronic speakers' bureau.

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