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Guidelines for cardiac pacing and cardiac resynchronization therapy

The Task Force for Cardiac Pacing and Cardiac Resynchronization Therapy of the European Society of Cardiology. Developed in Collaboration with the European Heart Rhythm Association

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Preamble

Guidelines and Expert Consensus Documents summarize and evaluate all currently available evidence on a particular issue with the aim to assist physicians in selecting the best management strategies for a typical patient, suffering from a given condition, taking into account the impact on outcome, as well as the risk–benefit ratio of particular diagnostic or therapeutic means. Guidelines are no substitutes for textbooks. The legal implications of medical guidelines have been discussed previously.

A great number of Guidelines and Expert Consensus Documents have been issued in recent years by the European Society of Cardiology (ESC) as well as by other societies and organizations. Because of the impact on clinical practice, quality criteria for development of guidelines have been established in order to make all decisions transparent to the user. The recommendations for formulating and issuing ESC Guidelines and Expert Consensus Documents can be found on the ESC website (http://www.escardio.org/knowledge/guidelines/rules).

In brief, experts in the field are selected and undertake a comprehensive review of the published evidence for management and/or prevention of a given condition. A critical evaluation of diagnostic and therapeutic procedures is performed including the assessment of the risk/benefit ratio. Estimates of expected health outcomes for larger societies are included, where data exist. The level of evidence and the strength of recommendation of particular treatment options are weighed and graded according to pre-defined scales, as outlined in *Tables 1* and *2*.

The experts of the writing panels have provided disclosure statements of all relationships they may have which might be perceived as real or potential sources of conflicts of interest. These disclosure forms are kept on file at the

Table 1 Classes of recommendations

Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, and effective
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy
Class IIb	Usefulness/efficacy is less well established by evidence/opinion
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective and in some cases may be harmful

Table 2 Levels of evidence

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, and registries

European Heart House, headquarters of the ESC. Any changes in conflict of interest that arise during the writing period must be notified to the ESC. The Task Force report was entirely supported financially by the ESC and was developed without any involvement of the industry.

The ESC Committee for Practice Guidelines (CPG) supervises and coordinates the preparation of new Guidelines and Expert Consensus Documents produced by Task Forces, expert groups, or consensus panels. The Committee is also responsible for the endorsement process of these Guidelines and Expert Consensus Documents or statements. Once the document has been finalized and approved by all the experts involved in the Task Force, it is submitted to outside specialists for review. The document is revised, and finally approved by the CPG and subsequently published.

After publication, dissemination of the message is of paramount importance. Pocket-sized versions and personal digital assistant-downloadable versions are useful at the point of care. Some surveys have shown that the intended end-users are sometimes not aware of the existence of guidelines or simply do not translate them into practice so this is why implementation programmes for new guidelines form an important component of the dissemination of knowledge. Meetings are organized by the ESC and directed towards its member National Societies and key opinion leaders in Europe. Implementation meetings can also be undertaken at national levels, once the guidelines have been endorsed by the ESC member societies, and translated into the national language. Implementation programmes are needed because it has been shown that the outcome of disease may be favourably influenced by the thorough application of clinical recommendations.

Thus, the task of writing Guidelines or Expert Consensus documents covers not only the integration of the most recent research, but also the creation of educational tools and implementation programmes for the recommendations. The loop between clinical research, writing of guidelines, and implementing them into clinical practice can then only be completed, if surveys and registries are performed to verify that real-life daily practice is in keeping with what is recommended in the guidelines. Such surveys and registries also make it possible to evaluate the impact of implementation of the guidelines on patient outcomes. Guidelines and recommendations should help the physicians to make decisions in their daily practice; however, the ultimate judgement regarding the care of an individual patient must be made by the physician in charge of his/her care.

Introduction

Cardiac pacing has been used in the treatment of bradyarrhythmias for more than 50 years and during that time both clinical practice and an impressive body of research have proved its effectiveness objectively, in terms of parameters that includes the patient's quality of life, morbidity, and mortality. There can also be no doubt that the related technology has made great strides over the same period.[1–4]

Today, thanks to developments in microelectronics, the devices are smaller, the programming options wider, and the pacing leads thinner but longer lasting than before. All these developments, in both hardware and software, have aimed at the primary goal of appropriate electrical correction of pulse and conduction defects in such a way as to simulate the natural, inherent electrical function of the heart as closely as possible and to satisfy the patient's needs while minimizing side effects. In addition, increased device longevity and the elimination of major and minor complications resulting from treatment have also been the constant aims of both manufacturers and physicians.

During the last 12 years, electrical stimulation has advanced further, into the realm of ventricular resynchronization as an adjunctive therapy for patients with drug-refractory heart failure and ventricular conduction delay. It must be remembered that cardiac pacing for both bradyarrhythmia and cardiac resynchronization therapy (CRT) was first used clinically in Europe.[4,5,264,265]

The guidelines for the appropriate use of pacemaker devices presented in this document, a joint European Society of Cardiology (ESC) and EHRA initiative, aim to provide for the first time in Europe an up-to-date specialists' view of the field. The guidelines cover two main areas: the first includes permanent pacing in bradyarrhythmias, syncope, and other specific conditions, whereas the second refers to ventricular resynchronization as an adjunct therapy in patients with heart failure.

Pacing in bradyarrhythmia, syncope, and other specific conditions

The recommendations for pacing in bradyarrhythmias were based on an extensive review of the literature, old and new, with a view to reaching evidence-based conclusions. Where the literature is lacking, mainly with regard to conditions where no other therapy could replace pacing, the recommendations are based on expert consensus. The guidelines that follow concern patients who have permanent and irreversible disturbances of the systems for generation and conduction of the cardiac stimulus. The text will often make reference to the fact that the decision to implant a device depends on the accurate judgement of the treating physician, who must determine whether the damage is of a permanent and irreversible nature.

When the pathophysiology of the condition is judged to be fully reversible, for example, in the case of drug effects (digitalis intoxication) or electrolyte disturbances, or most likely reversible, such as in inflammatory or ischaemic myocardial disease, the bradyarrhythmic condition should be treated initially without permanent implantable device therapy. Of course, in daily practice, the nature of the disturbances of stimulus production and conduction is often ambiguous and the permanence of the condition is unclear.

As mentioned above, the focus of these guidelines is the appropriate use of pacemakers in patients with bradyarrhythmias. Obviously, the work of the committee would be

incomplete if it limited itself only to recommendations concerning indications for pacing and failed to include consideration of the proper pacing mode in each case. It was therefore considered essential to cover in this report the proposed pacing modes for each condition.

On the other hand, the committee decided that the document should not include recommendations for the choice of pacing leads or for their extraction or replacement. These subjects will be covered by forthcoming EHRA documents.

Cardiac resynchronization therapy

Cardiac pacing as an adjunct therapy for heart failure began to be the subject of scientific research at the start of the 1990s. The first pacing modality to be examined was dual-chamber pacing with a short atrioventricular (AV) delay, in patients with heart failure but without the classical bradyarrhythmic indications for pacing. The first studies in this area gave promising results. Acute and short-term improvements resulted from the optimization of left ventricular (LV) filling and a reduction in pre-systolic mitral regurgitation. Unfortunately, the initial results were not confirmed by subsequent studies and the early hopes raised by dual-chamber pacing with a short AV delay for heart failure patients were not fulfilled.

In contrast, atrio-biventricular pacing for patients with symptomatic heart failure and intra- or interventricular conduction disturbances has proved beneficial. During the last decade, a number of studies have established a theoretical basis for this new therapy and have drawn related conclusions regarding the importance of resynchronization in terms of improving symptoms, morbidity, and mortality in these patients.

This document presents the recommendations of the committee concerning indications for CRT based on the most recent studies.

1. Pacing in arrhythmias

1.1. Sinus node disease

Sinus node disease, also known as sick sinus syndrome, designates a spectrum of sinoatrial dysfunction that ranges from the usually benign sinus bradycardia to sinus arrest or to the so-called bradycardia–tachycardia syndrome.[6] The latter is characterized by the development of paroxysmal atrial tachyarrhythmias in patients with sinus bradycardia or sinoatrial block. Some patients with frequent, repetitive, long-lasting episodes, or atrial fibrillation (AF) may remodel their atrial myocardium, including the sinoatrial region, and are prone to systemic embolism.[7]

In patients with sinus arrest, there may be an ectopic atrial or AV junctional escape rhythm. Some patients with sustained AF or flutter may have an underlying sinus node dysfunction that becomes patent after cardioversion of the atrial tachyarrhythmia. An additional manifestation of sinus node dysfunction is the lack of an adequate chronotropic response to exercise. Sinus node disease, as a clinical entity, encompasses not only disorders of the sinus node impulse formation or its conduction to the right atrium, but also a more widespread atrial abnormality that is the substrate for the development of atrial tachyarrhythmias. In addition, some patients with signs of sinus node dysfunction may also present AV conduction abnormalities.

We lack adequately controlled pathological studies to define the structural basis of the sick sinus syndrome and its various clinical and electrocardiographic manifestations. Future studies must compare the structural changes in the sinoatrial region of patients with various forms of sinus node disease, who otherwise have normal hearts, with appropriate controls matched for age and gender. To attribute specific pathological meaning to structural findings observed in anecdotal necropsy reports on patients with sick sinus syndrome is openly speculative. To conduct pathological studies on the sinus node region is not a simple task because of the complexity of this area.[8] The sinus node tissue is widely distributed at the junction between the superior vena cava and the right atrium, which probably implies that for the development of significant sinus node disease, an ample atrial architectural disorder is needed.

The most dramatic symptom of the disease is syncope or near syncope, due to sinus arrest or sinoatrial block, which may often be reflex in nature.[9]

Sinus pauses may sometimes be followed by atrial tachyarrhythmias that are sufficiently rapid to prolong the hypotension, causing syncope or dizziness. Apart from the above, it is not uncommon for the symptoms of the disease to be limited to fatigue or dyspnoea, reduced exercise capacity, and cognitive impairment, as a consequence of exaggerated bradycardia ($<$40 b.p.m.) and chronotropic incompetence.[10,11] The latter is characterized by an impaired heart rate response to exercise and is generally defined as failure to achieve 85% of the age-predicted maximum heart rate.[10,11]

The diagnosis of sinus node disease is based on relating a variety of electrocardiographic findings with the symptoms. In some patients with syncope of undetermined origin, the underlying mechanism is a symptomatic paroxysmal sinus node dysfunction that cannot be easily demonstrated by conventional 24 or 48 h Holter monitoring. In such patients, an implantable loop recorder may be the only way of establishing the correct diagnosis. We should also take into consideration the interaction between sick sinus syndrome and neurally mediated syncope. Apart from syncope caused by prolonged pause following the termination of tachycardia in the brady–tachy syndrome, the vast majority of the other syncopes are due to, or favoured by, an abnormal reflex. Moreover, if a persistent bradycardia clearly defines sick sinus syndrome, the meaning of intermittent bradycardia and sinus arrest is less clear. Indeed, the same event (i.e. intermittent sinus arrest) may be diagnosed by one physician as intermittent sick sinus syndrome and by another as cardioinhibitory neurally mediated syndrome. In general, the same syncope is diagnosed as neurally mediated if not documented, whereas if there is the fortuitous documentation of a pause, it is diagnosed as sick sinus syndrome.

Electrophysiological evaluation of sinus node function includes the measurement of the corrected sinus node recovery time and the sinus node conduction time. It is beyond the scope of these guidelines to review the sensitivity, specificity, and diagnostic accuracy of the various cut-off points that have been advanced during the last 25 years for these two sets of parameters.

1.1.1. Indications for pacing in sinus node disease

Once sinus node disease, mild or severe, is diagnosed, the question arises whether to implement permanent pacing or not.

Long experience, together with a number of studies, has shown that pacing in sinus node disease contributes more to relieving symptoms and reducing the episodes of AF[12–16] than to reducing mortality in these patients.[17–19]

The indications for pacing in sinus node disease, on the strength of evidence in the available older and modern literature, are given in *Table 1.1.1*. It is important to note here that when sinus node disease is diagnosed, atrial tachyarrhythmias are likely, even if not recorded, so that apart from pacing serious consideration should be given to oral anticoagulation therapy if not contraindicated.[20]

Table 1.1.1 Recommendations for cardiac pacing in sinus node disease

Clinical indication	Class	Level of evidence
1. Sinus node disease manifests as symptomatic bradycardia with or without bradycardia-dependant tachycardia. Symptom–rhythm correlation must have been: spontaneously occurring drug induced where alternative drug therapy is lacking	Class I	C
2. Syncope with sinus node disease, either spontaneously occurring or induced at electrophysiological study		
3. Sinus node disease manifests as symptomatic chronotropic incompetence: spontaneously occurring drug induced where alternative drug therapy is lacking		
1. Symptomatic sinus node disease, which is either spontaneous or induced by a drug for which there is no alternative, but no symptom rhythm correlation has been documented. Heart rate at rest should be $<$40 b.p.m.	Class IIa	C
2. Syncope for which no other explanation can be made but there are abnormal electrophysiological findings (CSNRT $>$ 800 ms)		
1. Minimally symptomatic patients with sinus node disease, resting heart rate $<$40 b.p.m. while awake, and no evidence of chronotropic incompetence	Class IIb	C
1. Sinus node disease without symptoms including use of bradycardia-provoking drugs	Class III	C
2. ECG findings of sinus node dysfunction with symptoms not due directly or indirectly to bradycardia		
3. Symptomatic sinus node dysfunction where symptoms can reliably be attributed to non-essential medication		

When sinus node disease is diagnosed, atrial tachyarrhythmias are likely even if not yet recorded, implying that serious consideration should be given to anticoagulant therapy.

1.1.2. Choice of the pacing mode for patients with sinus node disease

During the last two decades, several clinical endpoint trials, as well as developments in pacing devices, have increased our knowledge and expanded the possibilities for optimal pacing therapy in patients with symptomatic sinus node disease. The principal endpoints of those trials, comparing atrial with ventricular based pacing, were mortality, AF, frequency of thrombo-embolic episodes and stroke, heart failure, pacemaker syndrome, and the patients' quality of life.

The first randomized trial to address these matters was by Andersen *et al.*[21] They studied 225 patients with sinus node disease and intact AV conduction, who were assigned randomly to either atrial or ventricular pacing. At the end of a 5.5-year period, the patients who were paced in AAI mode had significantly lower incidences of AF, thrombo-embolic events, heart failure, cardiovascular mortality, and total mortality, compared with those paced in VVI mode. Two things were unique about that study: it was the only randomized study to date that compared pure AAI and VVI modes over a long follow-up period and it was also the only one to show a clear benefit in terms of all the clinical parameters examined, and primarily in mortality, for patients who had atrial pacing.

The following studies examined the role of VVI compared with DDD mode in this patient population. Lamas *et al.*,[22] in the PAcemaker Selection in the Elderly (PASE) trial, studied 407 patients who were paced for a variety of indications, including 175 who suffered from sinus node dysfunction. All patients received a dual chamber, rate adaptive system, which was randomly programmed to either VVIR or DDDR mode, and were studied prospectively for 2.5 years. The results showed no statistically significant difference between the two modes of pacing as regards the incidence of thrombo-embolic episodes, stroke, AF, or the patients' quality of life, for the patient population as a whole. There was a non-significant trend favouring atrial-based pacing in the subgroup with sinus node disease. However, the short follow-up of the study, the very large crossover from VVIR to DDDR and the problem of intention to treat analysis must be taken into consideration.

The Canadian Trial of Physiological Pacing (CTOPP),[23] a prospective, randomized study, compared the clinical outcomes in 2568 patients who were randomized to atrial based or ventricular pacing for a mean follow-up period of 3.5 years. The study found no significant difference between the two treatment groups in the combined incidence of stroke or death or in the likelihood of hospitalization for heart failure. However, after 2 years of follow-up, physiological pacing was associated with an 18% relative reduction in the development of chronic AF. A subgroup of patients who were paced for sinus node dysfunction showed no trend towards a benefit from atrial-based pacing in terms of mortality or stroke.

Finally, the Mode Selection Trial (MOST)[24] in sinus node dysfunction studied prospectively 2010 patients who were randomized to either DDDR or VVIR mode and were followed for a mean period of 2.7 years. There were no statistically significant differences between the groups in the incidence of death or stroke, but there was a 21% lower risk of AF, a 27% lower risk of hospitalization for heart failure and a better quality of life in the DDDR group, compared with those paced in VVIR mode. Importantly, the study also

showed that of the patients initially randomized to VVIR pacing, 37.7% were later switched to DDDR, most usually because of pacemaker syndrome.

The occurrence of bradycardia-dependent and other atrial tachyarrhythmias may cause symptoms and may, therefore, lead to consideration of pacing. In the case of bradycardia-dependent atrial tachyarrhythmias, which are typical of sinus node disease, pacing has been proven to be effective in their prevention. This was seen in the first Danish trial[21] and reinforced by the results of CTOPP,[23] MOST,[24] and the DANPACE pilot study.[25] When atrial arrhythmias are not suppressed simply by raising the atrial rate both at rest and, if necessary, on effort, recent pacemaker designs offer a host of atrial antitachycardia preventive and therapeutical pacing algorithms that have been shown to have benefit in some patients. However, the available clinical trials[26–31] have not proven their efficacy in the sinus node disease population. The picture may be complicated by the use of Class I antiarrhythmic drugs or amiodarone, which may not only affect sinus node automaticity but also depress atrial conduction, the latter resulting in potential pro-arrhythmic effects.

Summarizing the results of the above prospective, randomized studies, as well as two review papers,[32,33] we can conclude that in patients with sinus node disease the incidence of AF is lower in those who are given atrial or dual-chamber pacemakers than in those treated with ventricular pacing alone. Moreover, in the Cochrane review, which included five parallel and 26 crossover randomized controlled trials, there was a statistically significant trend towards dual-chamber pacing being more favourable in terms of exercise capacity and pacemaker syndrome.[34]

However, as far as stroke, heart failure and mortality are concerned, the findings are conflicting and we cannot draw significant conclusions regarding atrial based vs. ventricular pacing.

Selection of pacing for sinus node disease must always depend on symptoms, although these have broadened from only syncope and dizziness to include malaise, some of

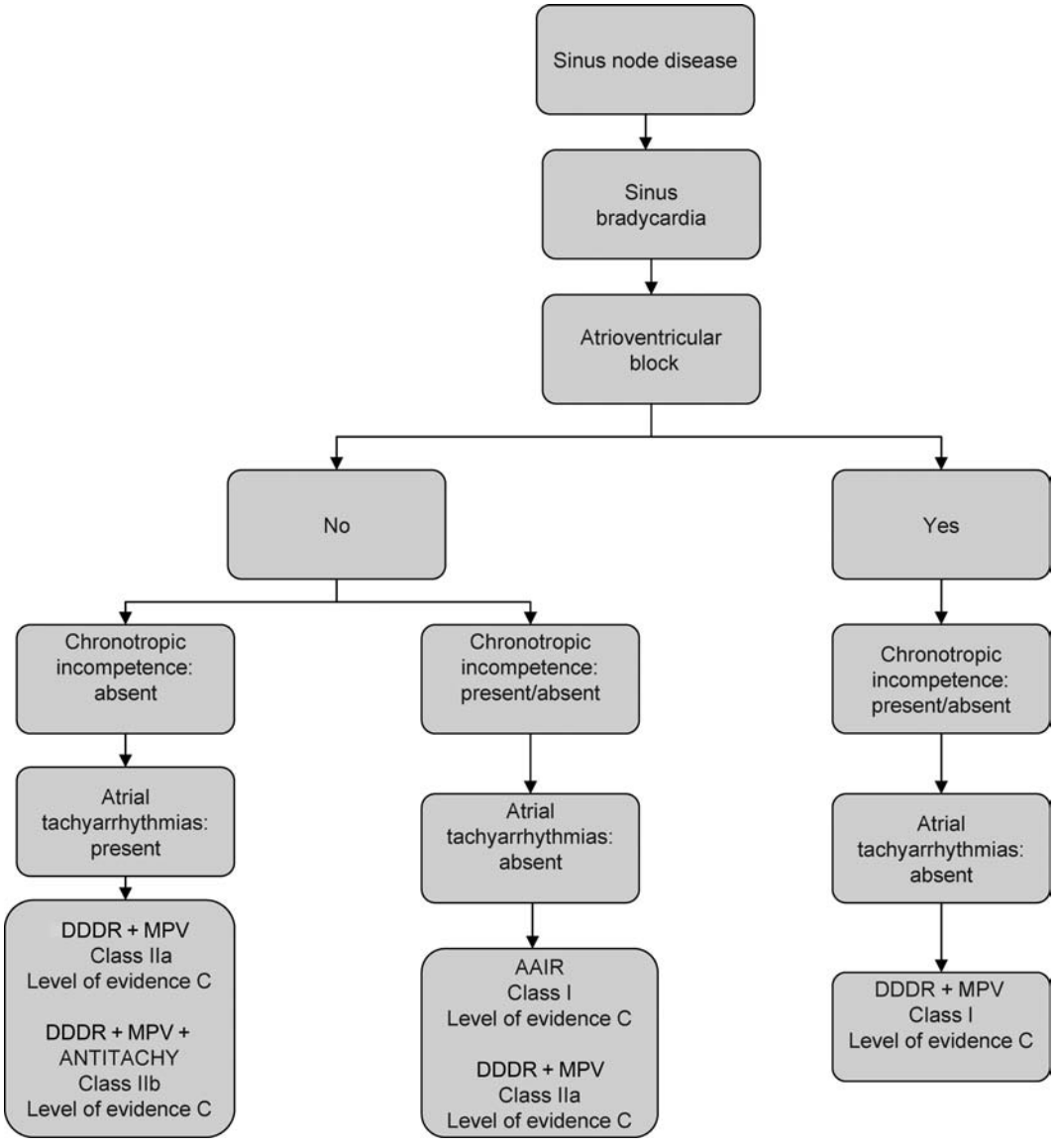

Figure 1 Pacemaker mode selection in sinus node disease. ANTITACHY = antitachycardia algorithms in pacemaker; MPV = minimization of pacing in the ventricles. *Note*: In sinus node disease, VVIR and VDDR modes are considered unsuitable and are not recommended. Where atrioventricular block exists, AAIR is considered inappropriate.

which is drug induced, and palpitations. Selection of pacing mode and device is more complex, but the trend is towards dual-chamber pacing with minimization of right ventricular stimulation (in order to avoid changes leading to desynchronization of the ventricles as a result of their being depolarized from the right ventricular apex), rate modulation (RR), and a panoply of antitachycardia algorithms possibly combined with stimulation of the atria from the septum rather than the appendage (*Figure 1*). However, no consistent data from large randomized trials support the use of alternative single-site atrial pacing, multisite right atrial pacing, or biatrial pacing in sinus node disease patients. Ventricular pacing alone can no longer be recommended, and furthermore, dual-chamber pacing increases quality-adjusted life expectancy at a cost that is generally considered acceptable.[34] Regarding the choice of AAI or DDD pacemaker implantation, we should take into consideration that although DDD is more expensive, there is a possibility, albeit small ($\sim$1% of annual incidence), of the future development of AV block.[35,36]

1.2. Atrioventricular and intraventricular conduction disturbances

In AV block, atrial activation is conducted to the ventricles with a delay, or is not conducted at all, during a period when the AV conduction pathway (AV node or His-Purkinje system) is not expected to be refractory. Traditionally, on the basis of the electrocardiographic criteria, AV block is classified as first, second, or third degree, and depending on the anatomical point at which the conduction of the activation wavefront is impaired, it is described as supra-Hisian, intra-Hisian, or infra-Hisian.

In the first-degree AV block, every atrial stimulus is conducted to the ventricles, but the PR interval is prolonged to $>$200 ms. The conduction delay may occur at the level of the AV node or at the His-Purkinje system. If the QRS complex is narrow, the conduction delay is usually in the AV node and rarely within the His bundle. If the QRS is wide, the conduction delay may be either in the AV node or in the His-Purkinje system and only a His bundle electrogram can locate it precisely.

A second-degree AV block is characterized by the fact that one or more atrial stimuli are not conducted to the ventricles. It is divided into type I, or Wenckebach, or Mobitz I, and type II, or Mobitz II AV block. In type I, the electrocardiogram (ECG) shows a progressively increasing PR interval until an atrial stimulus fails to be conducted to the ventricles. Often, the increase in the PR interval is subtle in the last cardiac cycles before the blocked P wave and can only be recognized in comparison with the shortest PR interval, which usually follows the blocked P wave. The delay is usually in the AV node and deterioration to a higher degree of AV block is uncommon. However, in cases with a wide QRS complex, an electrophysiological study is required to determine the level of the block. In type II AV block, provided there is normal sinus rhythm, the PR interval is constant before and after the blocked P wave. In this type, the conduction block is usually in the His-Purkinje system, especially in the case of a wide QRS.

In complete (third-degree) AV block, no atrial stimulus is conducted to the ventricles and the ventricles are depolarized by an escape rhythm. Although the escape rate may have significance for the development of symptoms, the site of escape rate origin is of major importance for patients' safety (i.e. in the AV node, intra- or infra-Hisian).

AV block was the first indication for pacing, and today, it remains one of the most common reasons for pacemaker implantation. Nevertheless, because of the lack of large, comparative, randomized studies, there are still open questions about the indications for pacing, others that concern the pacing mode, and numerous issues regarding the lead implantation site. The decision to implant a pacemaker is based, to a large extent, on the presence of symptoms that are directly related to the bradycardia caused by the AV block. The situation may become even more complex when the conduction disturbance is intermittent. In such a case, the information provided by the surface ECG is limited and a 24 h Holter ECG recording, or even longer rhythm recordings using an external or implantable loop recorder, may be required.

1.2.1. Indications for pacing

In the case of complete AV block, there are a number of non-randomized studies showing that permanent cardiac pacing improves survival, especially in patients who experience episodes of syncope.[37–42] In type I second-degree AV block, the indications for permanent pacing are controversial, unless the conduction delay occurs below the AV node or there are symptoms.[43,44] However, some authors suggest that pacemaker implantation should be considered even in the absence of symptomatic bradycardia or organic heart disease, because survival is significantly better for paced than for unpaced asymptomatic elderly patients, especially when type I second-degree AV block occurs during diurnal hours.[45]

In type II second-degree block, especially when there is also a wide QRS, progression to complete heart block and the appearance of symptoms are common;[43,46,47] thus pacing is recommended. In patients with first-degree AV block, cardiac pacing is not recommended unless the PR interval fails to adapt to heart rate during exercise and is long enough (usually $>$300 ms) to cause symptoms because of inadequate LV filling, or an increase in wedge pressure, as the left atrial systole occurs close to or simultaneous with the previous LV systole. In such cases small, uncontrolled studies have shown an improvement in patients' symptoms.[48,49]

It should be noted that before the decision for permanent pacing is made, it should be checked whether the AV block is due to a reversible cause, such as acute myocardial infarction, electrolytic disturbances, drugs that can be discontinued (digoxin, non-dihydropyridine calcium channel blockers, beta-blockers, and so on), sleep apnoea, peri-operative hypothermia, or inflammation or vagotonia arising from factors that can be avoided.

1.2.2. Acquired atrioventricular block in special cases

Distal AV block may be observed during effort and, if not due to ischaemia, it is probably caused by damage to the His-Purkinje system and has a poor prognosis.[50,51] In this case, permanent pacing is recommended, as it is also in patients who suffer from a progressively deteriorating condition such as amyloidosis, sarcoidosis, or neuromuscular diseases.[52–58] Pacing is also recommended in patients developing permanent AV block as a complication of a catheter

Table 1.2.1 Recommendations for cardiac pacing in acquired atrioventricular block

Clinical indication	Class	Level of evidence
1. Chronic symptomatic third- or second-degree (Mobitz I or II) atrioventricular block	Class I	C
2. Neuromuscular diseases (e.g. myotonic muscular dystrophy, Kearns–Sayre syndrome, etc.) with third- or second-degree atrioventricular block[52–58]	Class I	B
3.Third- or second-degree (Mobitz I or II) atrioventricular block: (i) after catheter ablation of the atrioventricular junction (ii) after valve surgery when the block is not expected to resolve	Class I	C
1. Asymptomatic third- or second-degree (Mobitz I or II) atrioventricular block	Class IIa	C
2. Symptomatic prolonged first-degree atrioventricular block	Class IIa	C
1. Neuromuscular diseases (e.g. myotonic muscular dystrophy, Kearns–Sayre syndrome, etc.) with first-degree atrioventricular block[52–58]	Class IIb	B
1. Asymptomatic first-degree atrioventricular block	Class III	C
2. Asymptomatic second-degree Mobitz I with supra-Hisian conduction block		
3. Atrioventricular block expected to resolve		

ablation procedure, although there are no controlled studies regarding this.[59,60] It is also recommended in patients developing AV block after heart valve surgery, because its progression is unpredictable (*Table 1.2.1*).[61] Congenital AV block, or AV block after myocardial infarction, and AV block due to enhanced vagal tone are discussed in separate sections.

1.2.3. Pacing for chronic bifascicular and trifascicular block

The term 'bifascicular block' refers to an electrocardiographic picture of complete right bundle branch block with anterior or posterior left hemiblock or of complete left bundle branch block alone. The term 'trifascicular' block means impaired conduction in all three branches at the same time, or at different times, although it has also been used to describe bifascicular block together with first-degree AV block. The term 'alternating bundle branch block' refers to electrocardiographically demonstrated block of all three branches on the same or successive ECG recordings. The prevalence of bundle branch block has been found to increase with age and is estimated at $\sim$1% of the population aged $>$35,[62,63] whereas it is higher at $\sim$17% at age 80 years.[64] In addition, we know that patients with bundle branch blocks often have other cardiac diseases, mainly coronary artery disease and hypertensive heart disease, which explains their higher mortality rate (2–14%).[65–68] Syncope is usually seen in patients with delayed conduction in the bundles of the left and right branches, although the risk of progression to high-degree AV block varies. The annual incidence of progression to high-degree AV block in unselected patients is estimated to be 1–4%,[65,68–71] although syncope has been found to be the sole predictive factor. The annual incidence of progression is 5–11% in syncopal patients, but just 0.6–0.8% in patients without syncope.[66,72]

1.2.4. Indications for pacing

In patients without syncope, the rate of progression to high-degree AV block is low and there is no non-invasive technique with a high predictive value. The results of studies that employed an electrophysiological study have shown that the finding of an HV interval $>$100 ms, or the demonstration of intra- or infra-Hisian block during incremental atrial pacing at a pacing rate $<$150 b.p.m., is highly predictive for the development of high-grade AV block, but the prevalence of these findings is very low, and thus their sensitivity is low.[71,73–75] Thus, in asymptomatic patients with bifascicular or trifascicular block, permanent pacing is considered appropriate only in those who exhibit intermittent second- or third-degree AV block, or signs of a severe conduction disturbance below the level of the AV node (HV $>$100 ms, or intra- or infra-Hisian block during rapid atrial pacing) during an electrophysiological study carried out for a different reason. It is unknown whether, apart from preventing future symptoms, pacing improves survival in these patients; however, to date, pacemaker treatment has been found to have no beneficial effect on survival.[66,71,76]

In patients with syncope and bundle branch block, the demonstration of definite abnormalities of the His-Purkinje conduction predicts the development of stable AV block in some 87% of patients.[77–79] These patients should undergo pacemaker implantation (Class I, level of evidence C). In patients with bundle branch block and a normal electrophysiological study, the use of an implantable loop recorder has shown that most syncopal recurrences are due to prolonged asystolic pauses, mainly attributable to sudden-onset paroxysmal AV block.[80] Because of the high, short-term incidence of AV block in patients with syncope and bundle branch block who have a normal HV conduction time, an acceptable strategy could be to implant a pacemaker rather than a loop recorder (Class IIa, level of evidence C). An electrophysiological study is considered normal in the absence of one of the following: (i) abnormal sinus node recovery time; (ii) baseline HV interval $\geq$70 ms; (iii) second- or third-degree His-Purkinje block demonstrated during incremental atrial pacing, or high-degree His-Purkinje block elicited by intravenous administration of ajmaline; (iv) induction of sustained monomorphic ventricular tachycardia with programmed electrical stimulation; (v) induction of rapid, haemodynamically unstable, supraventricular tachycardia, particularly if the spontaneous symptoms are reproduced.

Finally, it should be noted that in patients with neuromuscular disease and any degree of fascicular block, with or without symptoms, cardiac pacing may have a place, in view of the unpredictable progression of AV conduction disease.[52–58]

Pacemaker mode selection in chronic bifascicular and trifascicular block is summarized in *Figure 2* (see also *Table 1.2.2)*.

Table 1.2.2 Recommendations for cardiac pacing in chronic bifascicular and trifascicular block

Clinical indication	Class	Level of evidence
1. Intermittent third-degree atrioventricular block 2. Second-degree Mobitz II atrioventricular block 3. Alternating bundle branch block 4. Findings on electrophysiological study of markedly prolonged HV interval ($\geq$100 ms) or pacing-induced infra-His block in patients with symptoms	Class I	C
1. Syncope not demonstrated to be due to atrioventricular block when other likely causes have been excluded, specifically ventricular tachycardia[66,69,71,74,76,78,79]	Class IIa	B
2. Neuromuscular diseases (e.g. myotonic muscular dystrophy, Kearns–Sayre syndrome, etc.) with any degree of fascicular block	Class IIa	C
3. Incidental findings on electrophysiological study of markedly prolonged HV interval ($\geq$100 ms) or pacing-induced infra-His block in patients without symptoms	Class IIa	C
None	Class IIb	
1. Bundle branch block without atrioventricular block or symptoms[66,71] 2. Bundle branch block with first-degree atrioventricular block without symptoms[66,71]	Class III	B

1.2.5. Choice of pacing mode for patients with atrioventricular block

In patients with AV block, pacing and sensing of the ventricles are essential. Suitable pacing modes are VVI and DDD or alternatively single-lead VDD (*Figure 2*). Recent prospective, randomized studies of patients in sinus rhythm compared ventricular with AV pacing, having endpoints such as mortality, quality of life, and the occurrence of AF, stroke, or thrombo-embolic episodes. In the CTOPP study, where 60% of the patients had AV block, the primary endpoint, the occurrence of either stroke, or death from cardiovascular cause did not differ significantly between VVI and DDD.[81,82] Nor was there any difference in the annual rates of death from all causes, of stroke, or of hospitalization for congestive heart failure (CHF). The only significant difference found was in the annual incidence of AF. A subgroup analysis carried out as part of the same study found a trend for younger patients ($<$74 years) to benefit from physiological pacing, in terms of the risk of stroke or death from cardiovascular causes. Nonetheless, it should be noted that a later analysis of the CTOPP study found that pacemaker-dependent patients gained a significant benefit from DDD pacing when compared with VVI, as regards cardiovascular death or stroke, cardiovascular death, and total mortality.[83] Another prospective, randomized study (PASE) found no difference in quality of life, cardiovascular events, or death between patients with AV block, who were paced in DDD or VVI mode.[84] Similar results were noted in the UKPACE study in elderly patients, in whom the rate of death from all causes or the incidence of cardiovascular events was not affected by the pacing mode.[85] These studies found that a high percentage, ranging from 5 to 26% of these patients, developed pacemaker syndrome when paced in the VVI mode. Regarding the use of single-lead VDD pacing in cases with normal sinus node function, recent studies have shown that it is equivalent to DDD pacing, reducing the implantation and follow-up costs.[86–89]

Patients with AV block or bundle branch block and an indication for permanent pacing are of special concern if their LV ejection fraction (LVEF) is depressed ($\leq$35%). The DAVID trial has shown that, in patients requiring an implantable cardioverter defibrillator (ICD) without an indication for permanent pacing, DDDR stimulation at 70 b.p.m. is worse than VVI backup pacing at 40 b.p.m. in terms of a combined endpoint including mortality and worsening of heart failure.[90] In this patient population, the physician should take into consideration several important points, such as whether the patient is a candidate for conventional pacing or an ICD and/or a biventricular device for cardiac resynchronization. In addition, small studies have shown that upgrading AV pacing systems to biventricular systems improves LV systolic function,[91,92] whereas in a recent study, it was found that in patients with LV dysfunction who need permanent pacing for conventional indications, biventricular stimulation is superior to right ventricular pacing with regard to LV function, quality of life, and maximal as well as submaximal exercise capacity.[93] These matters will be further discussed in detail in the cardiac resynchronization section.

A further issue that must be addressed is the choice of pacing site or combination of sites in the right ventricle. What is clear so far is that the right ventricular apex, although easily accessible and ideal for electrode stability with low sensing and pacing thresholds, does not achieve the best possible haemodynamic result,[94] while in the long-term it may have an adverse effect on LV function and lead to structural remodelling as well as disturbances of LV perfusion and innervation.[95–101] However, conflicting results have emerged from studies that investigated the acute and chronic effects of alternative pacing sites, such as the right ventricular outflow tract or the combination of outflow tract and apex, compared with pacing from the apex alone. Acute haemodynamic studies generally found that outflow tract or dual-site pacing was superior, whereas most of the controlled studies with permanent pacing found it to be equivalent to right ventricular apical pacing.[100,102–111] Septal pacing could be more valuable, as two small controlled studies have recently shown that it preserved LV function better in the mid-to-long term when compared with apical pacing.[100,114] His-bundle pacing or para-Hisian pacing could be also of interest for patients with narrow QRS. It appears both feasible and safe, compared with conventional right apical pacing, and may allow an improvement in functional and haemodynamic parameters over long-term follow-up.[112] In such patients, biventricular stimulation is superior to right ventricular apical pacing in terms of contractile function and LV filling.[113] However, no recommendation can be proposed concerning the location of the right ventricular pacing site.

Pacemaker mode selection in acquired AV block is summarized in *Figure 2*.

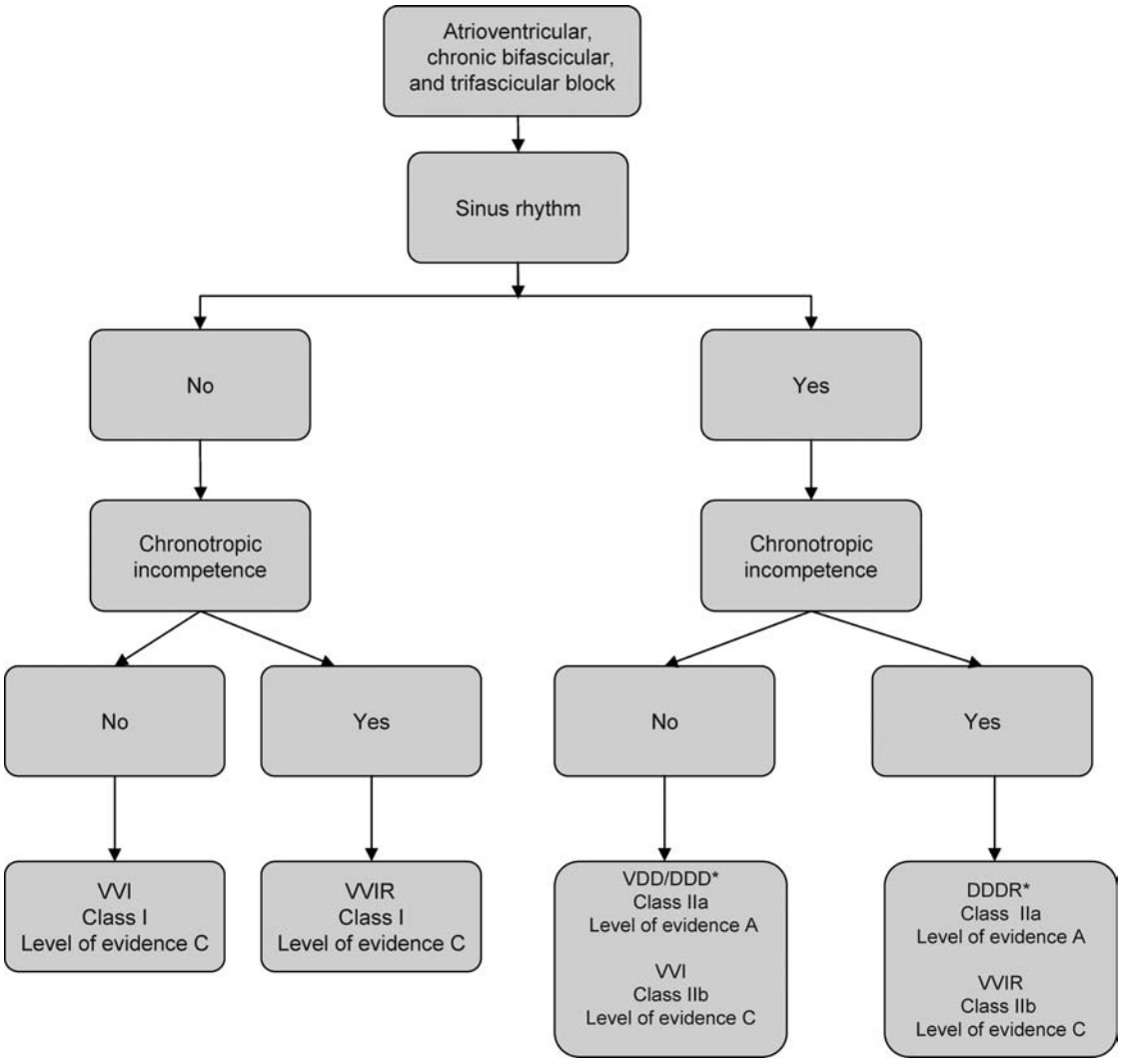

Figure 2 Pacemaker mode selection in acquired atrioventricular, chronic bifascicular, and trifascicular block. When atrioventricular block is not permanent, pacemakers with algorithms for the preservation of native atrioventricular conduction should be selected. *VVIR could be an alternative, especially in patients who have a low level of physical activity and in those with a short expected lifespan.

1.3. Recent myocardial infarction

1.3.1. Pacing in conduction disturbances related to acute myocardial infarction

The major conduction abnormalities associated with acute myocardial infarction include AV block and intraventricular conduction disturbances.[115–118] They are the result of both autonomic imbalance and ischaemia or necrosis of the conduction structure.

Despite the development of new methods for the management of acute myocardial infarction (including thrombolysis and percutaneous coronary intervention), the incidence of intraventricular conduction disturbances has not changed significantly, whereas the incidence of AV block has decreased but remains still high.[115,116,119–122]

Data from 75 993 patients enrolled in four large, randomized, clinical trials (GUSTO-I, GUSTO-IIb, GUSTO-III, and ASSENT-II) suggest that AV block occurs in almost 7% of cases of acute myocardial infarction.[119] Patients with periinfarction AV block have higher in-hospital and late mortality than do those with preserved AV conduction.[119]

Similarly, data regarding the incidence of intraventricular conduction abnormalities in patients with an acute myocardial infarction treated with thrombolytic agents suggest that the incidence of bundle branch block has not been altered significantly by thrombolytic therapy, occurring in a transient form in up to 18.4% of patients and in a persistent form in up to 5.3%.[122]

Conduction disturbances carry a poor prognosis, with a significant increase in the mortality rate even in the thrombolytic era.[115–122] The increase in mortality risk is largely seen within the first 30 days in the setting of both an inferior and an anterior myocardial infarction. However, when AV or intraventricular conduction block complicates acute myocardial infarction, the long-term prognosis for survivors is related primarily to the extent of myocardial injury, the degree of heart failure, and the higher incidence of haemodynamic complications.[115–123]

The location of the infarct influences the type of conduction disturbances in the setting of an acute myocardial infarction. AV block associated with inferior wall infarction is located above the His bundle in the vast majority of

patients, whereas AV block associated with anterior wall myocardial infarction is more often located below the AV node.[124] Thus, the former is usually associated with transient bradycardia, with a narrow QRS escape rhythm above 40 b.p.m. and low mortality, whereas the latter is associated with an unstable, wide QRS escape rhythm and extremely high mortality (up to 80%) due to the extensive myocardial necrosis. Intraventricular conduction disturbances are more commonly developed in the setting of an anterior-anteroseptal infarction as a result of specific blood supply conditions.[118,124] Their presence during an acute myocardial infarction is associated with an unfavourable short- and long-term prognosis and an increased risk of sudden cardiac death (SCD).

The nature and prognosis of conduction disturbances following an acute myocardial infarction are somewhat distinct from other forms of conduction abnormalities. Moreover, indications for permanent pacing after acute myocardial infarction are related to the coexistence of AV block and intraventricular conduction defects.[40,125,126] We must keep in mind that in patients with an inferior wall infarction conduction abnormalities may be transient (resolution within 7 days) and are often well tolerated.[127,128] Therefore, in such circumstances, there is generally no need for pacemaker implantation. Recommendations for cardiac pacing in persistent conduction disturbances (more than 14 days) related to acute myocardial infarction are summarized in *Table 1.3.1*.

In the context of thrombolysis and revascularization, data on persistence of conduction abnormalities and prognosis are lacking. Arbitrary definitions of transience and persistence have been proposed. Mobitz II with bundle branch block and third-degree AV block with wide QRS in post-myocardial infarction patients are considered to have a similarly poor prognosis.

Table 1.3.1 Recommendations for permanent cardiac pacing in conduction disturbances related to acute myocardial infarction

Clinical indication	Class	Level of evidence
1. Persistent third-degree heart block preceded or not by intraventricular conduction disturbances[115,125,126,128]	Class I	B
2. Persistent Mobitz type II second-degree heart block associated with bundle branch block, with or without PR prolongation[125–128]		
3. Transient Mobitz type II second- or third-degree heart block associated with new onset bundle branch block[127,128]		
None	Class IIa	
None	Class IIb	
1. Transient second- or third-degree heart block without bundle branch block[125,128]	Class III	B
2. Left anterior hemiblock newly developed or present on admission[128]		
3. Persistent first-degree atrioventricular block[128]		

1.4. Reflex syncope

Reflex syncope includes a wide spectrum of different entities that share common mechanisms (vasodilation and/or bradycardia). It is considered to be the consequence of a reflex that, when triggered, induces an acute, inappropriate response mediated by the autonomic nervous system. The main causes of reflex syncope are shown in *Table 1.4.1*. In this pathology syncope is the only symptom that may justify pacemaker implantation. This excludes dizziness, light-headedness and vertigo, which are beyond the scope of pacing therapy even in patients with an abnormal response to tests considered to be diagnostic of reflex syncope. Syncope should be diagnosed according to the definition in the syncope guidelines published by the ESC,[129] as follows: 'Syncope is a symptom, defined as a transient, self-limited loss of consciousness, usually leading to falling. The onset is relatively rapid, and the subsequent recovery is spontaneous, complete, and usually prompt. The underlying mechanism is transient global cerebral hypoperfusion'.

Although some patients with orthostatic hypotension or situational syncope have been treated by implantation of a permanent pacemaker, the series is too limited and the results too contradictory[130–133] to warrant separate consideration in the present guidelines. These autonomic diseases, which cause syncope mainly via major hypotension and/or bradycardia, are not presently a recognized indication for pacing, even though some individuals might benefit.[130,134] This discussion will be restricted to the role of pacing in patients with carotid and vasovagal syndromes, with a mention of adenosine sensitive syncope.

1.4.1. Carotid sinus syndrome

It has long been observed that pressure at the site where the common carotid artery bifurcates produces a reflex that leads to a slowing of heart rate and a fall in blood pressure (BP). Some patients with syncope exhibit an abnormal response to carotid massage.[135,136] A ventricular pause lasting 3 s or more and a fall in systolic BP of 50 mmHg or more is considered abnormal and define carotid sinus hypersensitivity.[137–139] Carotid sinus massage is a tool used to demonstrate carotid sinus syndrome in patients with syncope; its precise methodology and results are reported in the guidelines for syncope.[129] It should be emphasized that the reproduction of symptoms during the massage is necessary to diagnose carotid sinus syndrome, whereas

Table 1.4.1 Main causes of reflex syncope (adapted from Brignole *et al.*[129])

Vasovagal syncope (common faint)
Carotid sinus syncope
Situational syncope
Acute haemorrhage (or acute fluid depletion)
Cough and sneeze
Gastrointestinal stimulation (swallowing, defecation, and visceral pain)
Micturition (post-micturition)
Post-exercise
Post-prandial
Others (e.g. brass instrument playing and weightlifting)
Glossopharyngeal neuralgia

without this the diagnosis is carotid hypersensitivity.[140] Although carotid sinus syndrome is recognized as a potential cause of spontaneous syncope, it is still under investigation in the current clinical practice and is therefore probably underestimated.

1.4.1.1. Indications for pacing in carotid sinus syndrome

The first reports of the abolition of syncope in carotid sinus syndrome by permanent pacing appeared in the 1970s.[141,142] Subsequent investigations,[143,144] including non-randomized comparative studies,[145] showed that pacing in such patients could significantly reduce the number of syncopal episodes, and in the mid-1980s, pacing became the approved treatment. The first randomized trial comparing pacing and no pacing was reported in the 1990s.[146] This study included 60 patients: 32 were included in the pacemaker arm (18 patients with VVI and 14 patients with DDD pacemaker) and 28 in the 'no treatment' group. After a mean follow-up of 36 ± 10 months, syncope recurred in 9% of the pacemaker group, compared with 57% in the untreated patients ($P < 0.0002$). In another study, patients with a cardioinhibitory response to carotid sinus massage received a pacemaker that was designed to record asystolic episodes. Long pauses (>6 s) were detected in 53% of the patients during 2 years follow-up, suggesting that a positive response to carotid massage predicts the occurrence of spontaneous long ventricular pauses[147] and that pacing therapy is able to prevent the symptoms of these long pauses. Since drug therapy for cardioinhibitory carotid sinus syndrome has been abandoned,[148] cardiac pacing appears to be the sole beneficial treatment for these patients,[143–146] in spite of there being only one positive randomized trial with a relatively small number of patients.[147] Recommendations for cardiac pacing in carotid sinus syndrome are summarized in *Table 1.4.2*.

Table 1.4.2 Recommendations for cardiac pacing in carotid sinus syndrome

Clinical indication	Class	Level of evidence
Recurrent syncope caused by inadvertent carotid sinus pressure and reproduced by carotid sinus massage, associated with ventricular asystole of more than 3 s duration (patient may be syncopal or pre-syncopal), in the absence of medication known to depress sinus node activity	Class I	C
Recurrent unexplained syncope, without clear inadvertent carotid sinus pressure, but syncope is reproduced by carotid sinus massage, associated with a ventricular asystole of more than 3 s duration (patient may be syncopal or pre-syncopal), in the absence of medication known to depress sinus node activity[145–149]	Class IIa	B
First syncope, with or without clear inadvertent carotid sinus pressure, but syncope (or pre-syncope) is reproduced by carotid sinus massage, associated with a ventricular asystole of more than 3 s duration, in the absence of medication known to depress sinus node activity	Class IIb	C
Hypersensitive carotid sinus reflex without symptoms	Class III	C

1.4.1.2. Choice of the pacing mode in carotid sinus syndrome

Although it has been argued that single-chamber ventricular pacing may be sufficient in those relatively infrequent cases where there is neither a marked vasodepressor component to the reflex nor a so-called 'ventricular pacing effect',[149] when pacing is prescribed dual-chamber cardiac pacing is preferred.[144,150] Some dual-chamber pacemakers with sophisticated algorithms were specially designed to limit the effects of hypotension consequent to vasodilation. The algorithms were based on acceleration of the pacing rate when intrinsic heart rate suddenly decreases. Although acute results were in favour of these algorithms,[151] there is no well-designed trial demonstrating that they are superior to simple rate hysteresis during long-term pacing.

1.4.2. Vasovagal syncope

Vasovagal syncope accounts for ~50% of all the cases of patients admitted for this symptom.[152–154] In the vast majority, the clinical history is sufficiently typical to warrant the diagnosis without additional investigations. However, in some cases, tilt testing remains the key investigation used to diagnose the vasovagal origin of syncope. The methodology, complications and criteria for a positive response to tilt testing have already been reported in detail.[129] Many studies have assessed the role of tilt testing in treatment selection, including pacing for vasovagal syncope. Data from controlled trials showed that 50% of patients with a baseline positive tilt test became negative when the test was repeated, whether the patient was receiving treatment or placebo.[155–157] Moreover, acute studies were not predictive of the long-term outcome of pacing therapy.[156] Finally, the mechanism of tilt-induced syncope was frequently different from that of spontaneous syncope recorded by an implantable loop recorder.[158] These data show that tilt testing is of little or no value for assessing the effectiveness of treatments, particularly pacing.

1.4.2.1. Non-pacing therapy in vasovagal syncope

Despite vasovagal syncope being the most frequent of all causes of fainting, present treatment strategies are based on an incomplete understanding of the pathophysiology of the faint. In the majority of cases, patients who seek medical advice after having experienced vasovagal syncope mainly require reassurance and education regarding the benign nature of the condition. In particular, based on a review of their medical history, patients should be informed of the likelihood of syncope recurrence. Initial counselling should also include advice about adequate hydration and pre-monitory symptoms that may allow individuals to recognize an impending episode, so that they may take measures, such as lying down or using isometric manoeuvres, to avert or limit the consequence of a loss of consciousness. Pharmacological treatments in patients with vasovagal syncope,

generally effective in non-randomized trials, have been consistently disappointing in randomized series.[159,160]

1.4.2.2. Indications for pacing in vasovagal syncope

Non-randomized trials. The rationale behind pacing for patients with vasovagal syncope is based upon the frequent observation of spontaneous, or tilt-induced, long ventricular pauses in those patients. However, head-up tilt findings have generally shown that pacing fails to prevent syncope, although it may prolong the prodrome.[161,162] Nevertheless, pacing has been the object of a number of both small and large observational studies, either in single or multiple centres,[161–164] demonstrating effectiveness in highly selected patient populations.

Randomized trials. The effectiveness of pacing has been studied in five multi-centre, randomized, controlled trials:[165–169] the three non-blinded trials[165–167] produced positive findings, whereas the two blinded studies[168,169] had negative results. The strongest supportive evidence was provided by the North American Vasovagal Pacemaker Study (VPS)[166] and the European VASIS trial.[165] In the randomized, controlled Syncope Diagnosis and Treatment Study (SYDIT),[167] the control arm patients were treated with atenolol and the pacemaker was superior to the beta-blocker in preventing recurrences of syncope. After the publication of these three trials, pacing was considered to be a tenable treatment for patients with frequent vasovagal syncope. However, both the VPS II[168] and the Vasovagal Syncope and Pacing Trial (Synpace)[169] produced contradictory findings. They differed from the previous trials because patients in the control arm received a permanent pacemaker that was switched off. Although there was a 30% reduction in syncope recurrence rate (95% CI −33 to 63%), the VPS II study failed to demonstrate a significant superiority for pacemaker therapy. In the Synpace study, syncope recurred in 50% of patients assigned to an active pacemaker and in 38% of patients assigned to an inactive pacemaker. As reported in the European guidelines for syncope,[129] if the results of the five trials are put together, 318 patients were evaluated and syncope recurred in 21% (33/156) of the paced patients and in 44% (72/162) of the unpaced patients ($P < 0.001$). However, all the studies had weaknesses and further follow-up studies addressing many of these limitations, in particular the pre-implant selection criteria of patients who might benefit from pacemaker therapy, need to be completed before pacing can be considered an effective therapy in selected groups of patients with recurrent vasovagal syncope.

The inadequate effectiveness of pacing should not be surprising, since pacing can be expected to correct ventricular pauses but it cannot prevent hypotension due to vasodilation, which is frequently the dominant mechanism leading to loss of consciousness in vasovagal syncope. A recent study using the implantable loop recorder[158] concluded that only about half of the patients had an asystolic pause recorded at the time of spontaneous syncope. The role of the implantable loop recorder in the selection of patients who may possibly benefit from cardiac pacing was evaluated in the ISSUE 2 study,[170] which confirmed earlier data[158] indicating that patients selected on the basis of asystolic spontaneous syncope on implantable loop recorder can benefit from pacing. In any case, it must be underlined that the decision to implant a pacemaker needs to be kept in the clinical context of a benign condition, which frequently affects young patients in whom pacemakers and leads for several decades may be associated with complications. Thus, cardiac pacing should be confined to an extremely select small group of patients affected by severe recurrent vasovagal syncope and prolonged asystole during Holter recording and/or tilt testing. Recommendations for cardiac pacing in vasovagal syncope are summarized in *Table 1.4.3*. If pacing is judged desirable for the treatment of vasovagal syncope, the device used should be one that has the capacity for programming modes that pace the ventricle whenever mandatory, from one cycle to the next (DDIR+hysteresis, DDD/AMC, DDD+AVD hysteresis),[165] and control abrupt rate drops (rate drop response, rate smoothing, flywheel, etc.).[166,167] It has been shown in small series that pacemakers with haemodynamic sensors (intracardiac impedance and peak endocardial acceleration) have the capability to diagnose the vasovagal episode earlier than at the moment of rate drop. AAI-like algorithms are contraindicated.

Table 1.4.3 Recommendations for cardiac pacing in vasovagal syncope

Clinical indication	Class	Level of evidence
None	Class I	
1. Patients over 40 years of age with recurrent severe vasovagal syncope who show prolonged asystole during ECG recording and/or tilt testing, after failure of other therapeutic options and being informed of the conflicting results of trials	Class IIa	C
2. Patients under 40 years of age with recurrent severe vasovagal syncope who show prolonged asystole during ECG recording and/or tilt testing, after failure of other therapeutic options and being informed of the conflicting results of trials	Class IIb	C
1. Patients without demonstrable bradycardia during reflex syncope	Class III	C

1.4.3. Adenosine-sensitive syncope

Many series that included extensive evaluation have shown that 20–30% of patients with syncopal episodes have no precise diagnosis.[153,171] This observation has led to new tests for the investigation of patients with syncope of unknown origin. Among these, injection of an intravenous bolus of 20 mg adenosine was considered useful and has gained some acceptance.[172,173] The methodology and positive criteria of the test have been reported.[129,172,173] Although there was no agreement as to the positive criteria, there was a decrease in the number of patients without a diagnosis at the end of an extensive workup (probably between 5 and 10%). The only abnormal finding was an abnormally long ventricular pause during the adenosine injection. This long pause, lasting more than 6[173] or >10 s[172] was due to the sudden onset of AV block. Patients selected on the grounds of that finding underwent implantation of a permanent pacemaker. The therapy was tested

in one randomized series of 20 patients.[175] The results were in favour of pacing: after a mean follow-up of 52 months, no patient had recurrences in the paced group, whereas syncope was reported by six patients in the 'no pacing' group ($P < 0.02$). Assessment of these favourable results was complicated by the observation of cardiac rhythm during a syncopal recurrence registered by an implantable loop recorder: only 50% of the patients had bradycardia.[174,176,177] Finally, so far, there has been no well-designed randomized study able to determine the utility of pacing in patients with a positive ATP test,[129] thus no definitive recommendations can be made.

1.5. Paediatrics and congenital heart diseases

The indications for permanent cardiac pacing in children and adolescents, despite their similarities with those for adults, comprise a separate heading, under which a number of determining factors must be taken into account before the decision is made to implant a permanent pacing device[178–180] (*Table 1.5.1*).

The logic behind the decision to pace will be based on the patient's age and symptoms, the kind of disease and its natural history, and the possible coexistence of structural, congenital heart disease. The main indications for pacing in patients of this age are symptomatic bradycardia, bradycardia–tachycardia syndrome, congenital third-degree AV block, surgical or acquired, advanced second- or third-degree AV block, and long QT syndrome.

In any case, the decision to pace an infant, child, or adolescent is not an easy one, since apart from the technical peculiarities that are often associated with the procedure, concerns may often arise regarding the inadequacy of the pacing system with the growth of the child and the psychological issues raised by the patient or family. Nevertheless, at the same time, it is clear nowadays that any unreasonable postponement of the decision to pace, which leaves the patient with slow nodal or ventricular escape rhythms, often leads to further structural and functional heart problems and may expose the patient to the risk of sudden death.

Table 1.5.1 Recommendations for cardiac pacing in paediatrics and congenital heart disease

Clinical indication	Class	Level of evidence
1.Congenital third-degree atrioventricular block with any of the following conditions: Symptoms Ventricular rate <50–55/min in infants Ventricular rate <70/min in congenital heart disease Ventricular dysfunction Wide QRS escape rhythm Complex ventricular ectopy Abrupt ventricular pauses >2–3× basic cycle length Prolonged QTc Presence of maternal antibodies-mediated block[188–198]	Class I	B
2. Second- or third-degree atrioventricular block with Symptomatic bradycardia[a] Ventricular dysfunction	Class I	C
3. Post-operative Mobitz type II second- or third-degree block which persists at least 7 days after cardiac surgery[199,200]	Class I	C
4. Sinus node dysfunction with correlation of symptoms[184–186]	Class I	C
1. Asymptomatic sinus bradycardia in the child with complex congenital heart disease and Resting heart rate <40/min or Pauses in ventricular rate >3 s[184–186]	Class IIa	C
2. Bradycardia–tachycardia syndrome with the need of antiarrhythmics when other therapeutical options, such as catheter ablation, are not possible[187]	Class IIa	C
3. Long QT syndrome with 2:1 or third-degree atrioventricular block Symptomatic bradycardia[a] (spontaneous or due to beta-blocker) Pause-dependent ventricular tachycardia[201–203]	Class IIa	B
4. Congenital heart disease and impaired haemodynamics due to sinus bradycardia[a] or loss of atrioventricular synchrony	Class IIa	C
1. Congenital third-degree atrioventricular block without a Class I indication for pacing[188–198]	Class IIb	B
2. Transient post-operative third-degree atrioventricular block with residual bifascicular block	Class IIb	C
3. Asymptomatic sinus bradycardia in the adolescent with congenital heart disease and Resting heart rate <40/min or Pauses in ventricular rate >3 s[184–186]	Class IIb	C
4. Neuromuscular diseases with any degree of atrioventricular block without symptoms	Class IIb	C
1. Transient post-operative atrioventricular block with return of atrioventricular conduction within 7 days[199,200]	Class III	B
2. Asymptomatic post-operative bifascicular block with and without first-degree atrioventricular block	Class III	C
3. Asymptomatic type I second-degree atrioventricular block	Class III	C
4. Asymptomatic sinus bradycardia in the adolescent with minimum heart rate >40/min and maximum pause in ventricular rhythm <3 s[184–186]	Class III	C

[a]Clinical significance of bradycardia is age-dependent.

1.5.1. Sinus node dysfunction and bradycardia–tachycardia syndrome at young ages

Sinus node disease, although uncommon, is increasingly recognized in paediatric and adolescent patients, especially after atrial surgery for congenital heart diseases.[178,180–183] In the young patient with sinus bradycardia, the criterion that carries most weight in the decision to pace is the symptoms (i.e. syncope or inappropriate weakness or dyspnoea), rather than absolute heart rate criteria.[184–186] The clinical significance of bradycardia depends on age, since a low rate (<50/min) may be normal in a trained adolescent but not in an infant.

Bradycardia–tachycardia syndrome is often encountered in patients following surgery for congenital heart disease. The syndrome is manifested by periods of bradycardia that are often associated with atrial tachycardia or atrial flutter. The mixed nature of the syndrome makes treatment difficult or ineffective and often requires a complex therapeutic approach, combining antiarrhythmic medication, catheter ablation, or special anti-tachycardia pacing algorithms, with conventional ventricular pacing to treat episodes of excessive bradycardia.

Long-term medication with antiarrhythmic drugs such as amiodarone or sotalol, although it may be effective in the treatment of atrial tachycardias and atrial flutter, often leads to a worsening of the bradycardia episodes, necessitating permanent ventricular pacing as a backup, adjunctive therapy.

The clinical results from prospective, multi-centre anti-tachycardia pacing trials using devices equipped with special algorithms suggest reasonable efficacy (54%) in selected groups of patients.[187] In these cases, it must be kept in mind that anti-tachycardia pacing may lead to a further acceleration in the atrial arrhythmia, 1:1 AV conduction, and sudden death. To avoid this eventuality, the concomitant use of AV node blocking agents is strongly recommended.

In recent years, a wealth of experience, together with advanced new electro-anatomical mapping systems, has contributed to an increase in the success of catheter ablation in the treatment of atrial tachycardias and atrial flutter that develop in patients with congenital heart disease.[178] Nevertheless, despite the therapeutic alternatives available, bradycardia–tachycardia syndrome continues to be an intractable problem with uncertain outcome for the young patient.

1.5.2. Congenital atrioventricular block

Congenital AV block is a relatively rare entity that is due to abnormal embryonic development of the AV node, or is the embryonic result of maternal lupus erythematosus.[188,189] Congenital heart diseases, such as corrected transposition of the great arteries and ostium primum atrial and ventricular septal defects, may be associated with third-degree AV block. Nowadays, our ability to carry out a diagnostic study of the embryo in the womb allows detection of the problem between the 18th and 20th months of gestation.

As a clinical problem in infants and children, isolated congenital AV block is mainly marked by an unusually slow heart rate, rather than by the symptoms it causes.[188,190] The ECG usually reveals a third-degree AV block with a stable narrow QRS-complex escape rhythm.[188,190] The natural history of the disease in paced children is quite well known today, on the basis of a number of observational studies.[190–195] This knowledge of the development of the disease as revealed by modern diagnostic techniques, as well as developments in the field of pacing, has changed our views concerning the indications for and the timing of pacing. Nowadays, it is clear that the child's symptomatology is not the main criterion for pacing: the prevailing view now recognizes that early pacing based on a number of criteria (average heart rate, pauses in the intrinsic rate, exercise tolerance, presence of maternal antibodies-mediated block, and heart structure) is the recommended treatment of choice.[178,191–198] The latest prospective studies have shown that early pacing (at diagnosis) offers the advantages of improving survival, limiting the likelihood of syncopal episodes, and halting progressive myocardial dysfunction and mitral regurgitation in a significant number of patients.

1.5.3. Atrioventricular block and cardiac surgery

AV heart block is one of the major complications of surgery for congenital heart disease and occurs in 1–3% of operations. Pacemaker implantation is recommended in patients with persistent post-operative heart block lasting for 7 days. Late recovery of AV conduction following pacemaker implantation for post-surgical block is found in a significant percentage of patients. However, it has not been possible to identify clinical predictors related to patient characteristics, type of block, or type of repair.[199,200]

1.5.4. Long QT syndrome

The long QT syndrome is an arrhythmogenic, familial disease with high risk of SCD due to torsade de pointes and ventricular fibrillation. Cardiac pacing is indicated in patients with coincidence of AV block or evidence of symptomatic bradycardia (spontaneous or due to beta-blocking therapy) or pause-dependent ventricular tachycardia[201] (*Table 1.5.1*).

After pacemaker implantation beta-blockers should be continued. Dorostkar *et al.*[202] reported the largest cohort of long QT syndrome patients (37 patients) treated with combined beta-blocker and pacemaker therapy and followed over a mean period of 6.3 years. They revealed that the incidence of sudden death, aborted sudden death, or syncope was unacceptably high (24%). Therefore, in high-risk long QT patients, especially cardiac arrest survivals, implantation of a cardioverter defibrillator should be recommended.[201,203]

1.5.5. Adults with congenital heart disease

Adults with congenital heart disease are part of an expanding patient population. As a consequence of the ability to surgically repair or palliate patients with congenital heart disease, 85% of those born with congenital defects will survive to adulthood. Many of them have a lifelong need for pacing as a result of surgery, but others may come to require pacing later in life to provide anti-tachycardia pacing or to facilitate drug therapy of tachyarrhythmias (*Table 1.5.1*). In the current era, the incidence of surgical AV block after repair of septal defects and tetralogy of Fallot has decreased but has been offset by an increase in pacing after repair of complex defects. An important group of patients requiring pacemaker therapy includes those who undergo atrial manipulation and suturing, e.g. in the Fontan, Mustard, and Senning procedures.[178–180,204] Bradyarrhythmias and tachyarrhythmias may be seen in the early post-operative period or during late follow-up. Recently, Walker *et al.*,[204] in a retrospective study, presented long-term outcomes after pacemaker implantation

in 168 adults with congenital heart disease. Forty-five per cent of patients required pacing peri-operatively. The indication for pacemaker implantation was AV block in 65%, sinus node dysfunction in 29%, and long QT or tachycardia in the remainder. At first implant, 63% of patients were paced endocardially. Difficulty with vascular access was found in 15% of patients as a consequence of anomalous veins, previous surgery, or venous obstruction. A dual-chamber pacemaker was used for the initial implant in 42% of patients, whereas 14% were upgraded in the follow-up. In this cohort of patients, 45% of them remained at risk for atrial arrhythmias regardless of pacing mode.

1.5.6. Device and mode selection

In patients with AV block and normal ventricular function or in small children, ventricular rate-responsive demand pacing (VVIR) is sufficient for maintaining good cardiac function in most patients. In small children, the presence of two leads in the subclavian vein or superior vena cava might cause a high risk for thrombosis and venous occlusion. In adolescence and young adulthood, the system may be upgraded to a dual-chamber one. Ventricular dysfunction or overt heart failure, pacemaker syndrome, and other symptoms related to chronic asynchrony between atrial and ventricular contraction are common indications for conversion to a dual-lead pacing system.[178–180,204–208] Single-lead VDD pacing is possible in growing children with third-degree AV block. It provides atrial synchronous endocardial pacing without the need for a two-lead system and is recommended for young patients with impaired AV conduction as a viable alternative to a dual-lead pacing system.

New data show that DDD and VDD pacing may have the long-term detrimental effect of asynchronous electromechanical activation induced by apical right ventricular pacing, resulting in deleterious LV remodelling. Alternative sites of pacing should be considered.[209]

The higher heart rate level in infants and children compared with adults results in an increase in current drain, especially in the presence of high pacing thresholds. In these patients, especially automatic pacing threshold determination and subsequent output regulation increases pacing safety, decreases current drain, and prolongs battery life.[210]

In children and adolescents, AV and intraventricular conduction delay is frequently observed after complex congenital heart surgery; in some of them, CHF is present. In such selected cases and also in patients with dilated cardiomyopathy when substantial LV dyssynchrony is present, CRT seems to be feasible and effective.[211–213] Clinical experience with CRT in young patients remains very limited to date. Recently, Dubin *et al.*[212] presented a review of retrospective multi-centre experience in 52 patients from 13 institutions. They found that CRT appears to offer benefit in a paediatric and congenital heart disease population.

1.6. Cardiac transplantation

The aims of permanent pacing in cardiac transplant patients are three-fold:

- chronotropic support;
- coordination of cardiac chambers to improve mechanical performance;
- rejection monitoring.

Bradyarrhythmias are common in the early post-transplant period and are encountered in up to 64% of recipients.[214–216] Permanent pacemaker implantation rates vary from 2.8 to 29% based on the criteria used.[215,217] However, the surgical technique has been shown to have an important impact on the occurrence of sinus node dysfunction.[218,219] For example, a shift from standard atrial anastomosis to bicaval anastomosis has significantly reduced the need for pacemaker implantation.[218,219]

Sinus node dysfunction is the most frequent indication for permanent pacing in cardiac transplant patients.[216,219] Possible causes of sinus node dysfunction include surgical trauma, sinus node artery damage, or ischaemia and prolonged cardiac ischaemic times.[215,219] AV block is less common and is probably related to inadequate preservation of the donor heart.[216,219]

Following standard orthotopic heart transplantation, chronotropic incompetence is inevitable because of the loss of autonomic control. The heart rate response to exercise is characterized by a delayed onset, a reduced rate of rise, and a lower maximal rate at peak exercise. Following exercise, the heart rate increases further and then slows down gradually over time. The chronotropic response improves after the third week and remains unchanged after 6 months, probably as a result of the inadequate innervation of the donor sinus node.[220]

Sinus node and AV node function, however, improve during the first few weeks after transplantation.[217] Therefore, delaying pacemaker implantation will allow spontaneous recovery of the sinus node and more appropriate patient selection.

Since there are no established criteria to identify patients who may need a pacemaker, the optimal timing for permanent pacemaker implantation after transplantation is unclear. There is expert consensus that patients in whom bradycardia persists after the third post-operative week, despite treatment with theophylline, require permanent pacemaker implantation. Pacing restores the chronotropic

Table 1.6.1 Recommendations for cardiac pacing after cardiac transplantation

Clinical indication	Class	Level of evidence
Symptomatic bradyarrhythmias due to sinus node dysfunction or atrioventricular block 3 weeks after transplantation	Class I	C
Chronotropic incompetence impeding the quality of life late in the post-transplant period	Class IIa	C
Symptomatic bradyarrhythmias between the first week and third week after transplantation	Class IIb	C
1. Asymptomatic bradyarrhythmias and tolerated chronotropic incompetence 2. Monitoring of cardiac rejection alone 3. Bradyarrhythmias during the first week of transplantation	Class III	C

competence and improves exercise capacity. Since the preservation of AV synchrony results in an increased cardiac output, a DDDR mode with minimized ventricular pacing, or AAIR in the case of intact AV nodal conduction, is recommended.[219] Pacing recommendations after cardiac transplantation are summarized in *Table 1.6.1*.

2. Pacing for specific conditions

2.1. Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy is a genetically transmitted heart disease characterized by ventricular hypertrophy and myofibrillar disarray. In about 25% of patients with familial hypertrophic cardiomyopathy, asymmetrical interventricular septal hypertrophy leads to a dynamically variable pressure gradient between the apical LV and the outflow tract (LVOT).[221] The narrowing of the outflow tract is caused both by protrusion of the hypertrophied septum and by the systolic anterior motion of the mitral valve toward the asymmetrically hypertrophied interventricular septum. Mitral valve regurgitation is frequent. Early acute pacing studies indicated that right ventricular pacing could reduce the LVOT gradient by 30%.[222–224]

2.1.1. The rationale for short atrioventricular delay DDD pacing in hypertrophic obstructive cardiomyopathy

Pre-excitation of the right ventricular apex changes the ventricular contraction pattern, creating regional dyssynchrony (desynchronization). The altered LV activation pattern with late activation of the basal part of the septum and decreased LV contractility[225–227] increases the LV systolic diameter and reduces the systolic anterior motion of the mitral valve which as a net effect leads to a lowering of the LVOT gradient. Similar effects have also been shown in patients with symmetric hypertensive hypertrophy and distal cavity obliteration.[227] Pre-excitation of the right ventricular apex is achieved by short AV delay DDD pacing. The atria are sensed and trigger right ventricular pacing ahead of spontaneous AV conduction. In addition to an altered ventricular contraction pattern, pacing results in redistribution of wall stress, probably causing modification of coronary blood flow.[228–230] In the absence of mitral valve disease, DDD pacing reduces mitral incompetence,[231] which in turn can be expected to help maintain the atrial contribution to ventricular filling. These beneficial effects of pacing can be counteracted by potentially negative effects of short AV delay DDD pacing, since pacing may raise left atrial pressure[232,233] while simultaneously reducing filling and associated pressures in the LV.[227] Thus, the benefits of lowering LVOT gradient and an increase in end-systolic volume by 45% might be counterbalanced by a reduction in ventricular relaxation as a result of pacing.[234,235] One study suggests that the negative effect on diastolic function occurs mainly in patients with no previous diastolic dysfunction.[236] In contrast, in those with more severe diastolic dysfunction, DDD pacing causes no further deterioration in diastolic function.

After a year of pacing, the reduction in gradient is maintained when pacing is discontinued, which suggests ventricular remodelling resulting from pacing.[237,238] There is, however, no evidence that pacing reduces septal thickening.

2.1.1.1. Clinical effects of short atrioventricular delay DDD pacing in hypertrophic obstructive cardiomyopathy

Uncontrolled studies have indicated that short AV delay DDD pacing reduces the LVOT gradient and relieves severe symptoms in patients with hypertrophic obstructive cardiomyopathy (HOCM).[239–241] One randomized crossover study of 83 patients with an LVOT gradient of at least 30 mmHg at rest demonstrated that short AV delay DDD pacing reduced the LVOT gradient, improved New York Heart Association (NYHA) functional class and relieved symptoms with sustained effects over 3 years.[242,243] Exercise tolerance was only improved in subjects with a reduced baseline exercise duration, in whom a 21% improvement was seen during the DDD pacing period.

These results were not supported by two smaller randomized crossover studies.[244,245] In one study of 54 patients with an LVOT gradient of at least 50 mmHg, after 3 months of pacing, a benefit of pacing compared with controls could only be seen in patients aged over 65 years.[244] In this study, the LVOT gradient was significantly reduced already within 3 months, with a sustained effect over 12 months. Symptomatic improvement, in terms of quality of life and functional class, was only seen after 12 months of DDD pacing. These results illustrate the lack of direct correlation between a reduction in LVOT gradient and symptomatic relief. In addition, pacemaker implantation caused a placebo effect that became apparent after 3 months of pacing.[246] However, the long-term results from the same study suggest that the treatment effect remains after a year of treatment when the placebo effect can be expected to have waned.[243,247] One study suggests similar beneficial effects from pacing in patients without a significant LVOT gradient at rest.[248]

Although there is clear evidence that some patients derive a benefit from pacing, there is to date no certain way to predict the response. A reduction in LVOT gradient does not correlate with symptomatic improvement.[242–244] In one retrospective study with 12 months follow-up, patients with disturbed diastolic function were generally older and more likely to derive benefit from pacing in terms of NYHA class than those with normal diastolic function.[236] Although this observation is derived from a single study, it is substantiated by the subgroup analysis of another,[244] indicating that older patients might derive a benefit from pacing.

2.1.2. Therapy delivery and programming

Factors of crucial importance for therapeutic results are the position of the right ventricular lead in the right ventricular apex,[249] the full right ventricular apical pre-excitation, and optimal diastolic filling of the LV. Since diastolic function is disturbed in HOCM, the AV delay is crucial to ensure a full atrial contribution to ventricular filling. The optimal AV delay is defined as the longest AV delay which results in full pacing-induced ventricular pre-excitation (wide QRS) without disturbing LV filling. The sensed AV delay needs to be shorter than the PR interval to achieve ventricular pacing. In some HOCM patients with a very short inherent PR interval, AV nodal ablation as adjunct therapy can enable the programming of an optimal AV delay, maintaining diastolic function and enhancing the therapeutic effect of pacing.[250,251] The upper rate limit should be programmed higher than the fastest sinus rate achievable during exercise

Table 2.1.1 Recommendations for cardiac pacing in hypertrophic cardiomyopathy

Clinical Indication	Class	Level of evidence
None	Class I	
Symptomatic bradycardia due to beta-blockade when alternative therapies are unacceptable	Class IIa	C
Patients with drug refractory hypertrophic cardiomyopathy with significant resting or provoked LVOT gradient[240–242] and contraindications for septal ablation or myectomy	Class IIb	A
1. Asymptomatic patients 2. Symptomatic patients who do not have LVOT obstruction	Class III	C

LVOT = left ventricular outflow tract.

to ensure permanent ventricular pacing even during brisk exercise.

2.1.3. Indications for pacing in hypertrophic obstructive cardiomyopathy

DDD pacing partially reduces the LVOT gradient and improves NYHA class and quality of life in patients with HOCM, as evidenced by one randomized study with a 3-year follow-up.[242,243] However, compared with septal ablation and myectomy, the improvement in LVOT gradient and symptoms is of lesser magnitude.[252] The advantages of pacing are the relative simplicity of the procedure compared with septal ablation or myectomy. The lack of large randomized trials makes the indications for pacing controversial. Currently, there is no evidence to suggest that pacing alters disease progress or reduces mortality. Therefore, DDD pacing can only be considered in patients with contraindications for septal ablation or myectomy, or those requiring pacing for bradycardia or with an indication for an ICD. Pacing may, therefore, be an option primarily in elderly patients with drug-refractory HOCM.[242,243] Pacing recommendations for HOCM are summarized in *Table 2.1.1*.

2.2. Sleep apnoea

The sleep apnoea/hypopnoea syndrome is a very common respiratory disturbance affecting 4% of middle-aged men and 2% of women.[253] It is defined as a total or partial interruption of inspiratory airflow during sleep, leading to a reduction in oxyhaemoglobin saturation and to sleep fragmentation. The syndrome is classified as either central or obstructive. In the former type, the respiratory disturbance is due to the interruption of diaphragm activity because of dysfunction of the central regulation mechanisms for respiratory control and is very common among patients with CHF. In the latter, the muscle tone in the upper airways is insufficient to maintain their patency. Both types are associated with increased cardiovascular morbidity and mortality.[254,255] The diagnosis of the syndrome is based on overnight polysomnography, whereas the treatment of choice is the application of continuous positive airway pressure.[256]

In a recently published study,[257] it was found that atrial overdrive pacing at a rate of 15 b.p.m. higher than the mean nocturnal heart rate had a positive effect on sleep apnoea, reducing both obstructive and central apnoeic episodes in patients who were already paced for conventional indications. Most patients had predominantly central sleep apnoea, whereas in those with predominantly obstructive sleep apnoea, the percentage of episodes of central type was high. These positive results, however, were not confirmed by other studies that included patients with pure obstructive sleep apnoea.[258–262] Thus, more studies are needed to clarify the possible effect of atrial pacing on sleep apnoea and to determine in which subgroups of patients this approach might be beneficial. Finally, cardiac resynchronization with atrio-biventricular pacing has been found to improve central sleep apnoea, sleep quality, and symptomatic depression in patients with CHF and intraventricular asynchrony, mainly by improving the pump function of the heart.[263,264]

3. Cardiac resynchronization therapy in patients with heart failure

3.1. Introduction

The first descriptions of the short-term haemodynamic effects of left or of simultaneous right and LV stimulation were published over 35 years ago.[265–268] However, the clinical applications of the stimulation technique known as CRT began in 1994, when Cazeau *et al.*,[269] in France, and Bakker *et al.*,[270] in the Netherlands, described the first cases of atrio-biventricular pacemakers implanted in patients with severe CHF and no conventional indication for cardiac pacing. This concept was mainly based on the frequent observation of intraventricular conduction delays in patients with chronic CHF, due to ventricular systolic dysfunction. In such patients, a QRS duration $\geq$120 ms is prevalent in 25–50%, and left bundle branch block is found in 15–27%.[271] In addition, AV dyssynchrony, as indicated by a prolonged PR interval on the surface ECG, is present in up to 35% of severe CHF patients.

3.1.1. Rationale of cardiac resynchronization

AV and intraventricular conduction delays both further aggravate LV dysfunction in patients with underlying cardiomyopathies. Notably, left bundle branch block alters the sequence of LV contraction, causing wall segments to contract early or late, with redistribution of myocardial blood flow, non-uniform regional myocardial metabolism, and changes in regional molecular processes, such as calcium handling and stress kinase proteins.[272–276] Intraventricular dyssynchrony partly favours mitral valve incompetence and shortening of LV filling. In addition to intraventricular conduction, delays in AV timing also influence the mechanical function of the four cardiac chambers, in which optimal timing of the atrial systole is linked to an increase in cardiac output and the duration of diastolic filling and a decrease of pre-systolic mitral regurgitation. Thus, dyssynchrony seems to represent a pathophysiological process that directly depresses ventricular function, causes LV remodelling and CHF, and as a consequence causes a higher risk of morbidity and mortality.

Table 3.1.1 Inclusion criteria of the randomized studies on pacing in heart failure

Study	Patients (*n*)	NYHA class	LVEF (%)	LVEDD (mm)	SSR/AF	QRS (ms)	ICD
MUSTIC-SR[281]	58	III	≤35	≥60	SSR	≥150	No
MIRACLE[282]	453	III, IV	≤35	≥55	SSR	≥130	No
MUSTIC AF[311]	43	III	≤35	≥60	AF	≥200	No
PATH CHF[283]	41	III, IV	≤35	NA	SSR	≥120	No
MIRACLE ICD[286]	369	III, IV	≤35	≥55	SSR	≥130	Yes
CONTAK CD[285]	227	II, IV	≤35	NA	SSR	≥120	Yes
MIRACLE ICD II[287]	186	II	≤35	≥55	SSR	≥130	Yes
COMPANION[288]	1520	III, IV	≤35	NA	SSR	≥120	Yes/no
CARE HF[289]	814	III, IV	≤35	≥30 (indexed to height)	SSR	≥120	No

NYHA = New York Heart Association; LVEF = left ventricular ejection fraction; LVEDD = left ventricular end-diastolic diameter; SSR = stable sinus rhythm; AF = atrial fibrillation; ICD = implantable cardioverter defibrillator; NA = non applicable.

3.1.2. Evidence-based clinical effects of cardiac resynchronization therapy

State-of-the-art management of CHF, besides alleviating symptoms, preventing major morbidity, and lowering mortality, increasingly strives to prevent disease progression, particularly the transition between asymptomatic LV dysfunction and overt CHF. The clinical effects of long-term CRT were first evaluated in non-controlled studies, in which a sustained benefit conferred by biventricular pacing was measured.[270,277–280] Randomized multi-centre trials with crossover or parallel treatment assignments were subsequently conducted to ascertain the clinical value of CRT in patients with advanced CHF and in sinus rhythm, with or without indications for an ICD.[281–289] Meta-analyses were also published.[290–292] The usual study enrolment criteria were: (i) CHF in NYHA functional class III or IV, despite optimal pharmacological treatment (OPT); (ii) LVEF < 35%, LV end-diastolic diameter >55 mm, and QRS duration ≥120 or 150 ms (*Table 3.1.1*).

3.1.2.1. Impact of cardiac resynchronization therapy on symptoms and exercise tolerance

All the randomized trials have confirmed a significant alleviation of symptoms and increase in exercise capacity conferred by CRT. Mean NYHA functional class decreased by 0.5–0.8 points, the distance covered during a 6 min walk increased by a mean of 20%, and peak oxygen consumption during symptom-limited cardiopulmonary exercise increased by 10–15%. Quality of life, usually measured with the 'Minnesota Living with Heart Failure' questionnaire, was significantly improved in all trials. The magnitude of clinical improvement was similar to or greater than that observed in trials of pharmaceuticals. Furthermore, cumulative improvements were noted when CRT was added to the standard medical management of CHF. An important limitation in these studies was their short follow-up (3–6 months). However, the clinical benefits observed after the 3-month crossover phases of MUSTIC remained stable at 1 and 2 years of follow-up over time in surviving patients.[293] This durable efficacy was recently confirmed in CARE-HF, where the clinical benefits conferred by CRT were sustained during a mean follow-up of 29 months.[289]

3.1.2.2. Impact of cardiac resynchronization therapy on heart failure-related major morbidity

The early randomized trials were designed with symptoms and functional capacity as primary endpoints. Though they were not powered to detect significant effects on morbidity and mortality, these trials showed a clear trend toward lower rates of hospitalization for management of CHF in patients assigned to active therapy. In the MUSTIC trial, the monthly rate of hospitalization for CHF during delivery of CRT was seven-fold lower than that in the absence of CRT,[293] whereas in the MIRACLE trial, the number of hospitalized days was lower by 77% in the group of patients assigned to CRT.[282] In a meta-analysis of all studies completed by 2003, Bradley *et al*.[290] found a 30% reduction in the total number of hospitalizations for management of CHF, attributable to CRT. In the COMPANION trial, CRT with or without cardioverter-defibrillator lowered the combined endpoint of total mortality and rehospitalization for CHF by 35–40%, a proportion mainly driven by the 76% lower rate of rehospitalizations.[288] In CARE-HF, CRT lowered the proportion of unplanned hospitalizations for worsening CHF by 52% and the number of unplanned hospitalizations for major cardiovascular events by 39%.[289]

3.1.2.3. Impact of cardiac resynchronization therapy on mortality

CARE-HF and COMPANION were trials designed to examine the effects of CRT on combined primary endpoints of morbidity and mortality.[288,289] COMPANION included 1520 patients randomly assigned in a 1:2:2 ratio into three treatment groups: OPT, OPT combined with CRT (CRT-P), and OPT combined with CRT-ICD (CRT-D). CRT-P and CRT-D were both associated with a 20% reduction in the primary combined endpoint of all-cause mortality and all-cause hospitalization ($P < 0.01$). However, only CRT-D was associated with a significant decrease in total mortality (relative risk ratio: 36%; absolute decrease: 7%; $P = 0.003$), whereas the 24% relative reduction (absolute: 4%) in mortality associated with CRT-P was nearly statistically significant ($P = 0.059$). COMPANION, however, had three important methodological limitations. First, the high rate of crossover. Secondly, the premature termination of the study after a median follow-up of 14 months that exaggerated the benefits of the treatment causing cessation (CRT-D) but disadvantaged other interventions (CRT-P). Thirdly, there was no prespecified analysis to compare CRT-D and CRT-P, precluding the demonstration of the superiority of one CRT strategy over the other.[288]

The CARE-HF trial enrolled 813 patients. CRT plus standard pharmacological treatment for heart failure was

compared with OPT alone. At the end of a mean follow-up of 29 months, a 37% relative risk reduction in the composite endpoint of death and hospitalization for major cardiovascular events ($P < 0.001$) and 36% in the risk of death (absolute: 10%, $P < 0.002$) were observed. The effect on mortality was mainly due to a marked reduction in CHF-related deaths. It is, however, noteworthy that the extension study[294] showed a delayed but highly significant 46% reduction in the risk of sudden death with CRT.

Thus, one large, randomized trial[289] with more than 2 years follow-up indicates that CRT-P significantly lowers total mortality, whereas two trials demonstrate a reduction in morbidity.

3.1.2.4. Impact of cardiac resynchronization therapy on cardiac function and structure

Cardiac remodelling is now viewed as an important target in the treatment of CHF. A positive relationship between reverse ventricular remodelling and outcome has been demonstrated with drugs such as angiotensin-converting enzyme-inhibitors, angiotensin-receptor blockers, and beta-adrenergic blockers, with a parallel improvement in ventricular geometry and function and reduction in morbidity and mortality. Results of several non-controlled studies indicate that CRT reverses LV remodelling, decreases LV end-systolic and end-diastolic volumes, and increases LVEF. These benefits were attributed to CRT, since discontinuation of pacing resulted in loss of improvement in cardiac function.[295] A consistent finding in the randomized trials designed with up to 6 months of follow-up has been up to 15% absolute reduction in LV end-diastolic diameter and up to 6% increase in LVEF following CRT.[293–297] These effects were significantly greater in patients with non-ischaemic than in those with ischaemic heart disease.[295,297]

Finally, the reverse remodelling process was sustained. In the CARE-HF study, the mean reduction in LV end-systolic volume increased from 18.2% after 3 months to 26% after 18 months of CRT. Similarly, mean LVEF increased from 3.7% at 3 months to 6.9% at 18 months.[289] These observations provide consistent evidence of a large, progressive, and sustained reverse remodelling effect conferred by CRT.

3.1.3. Cost-effectiveness issues

Extensive cost-effectiveness analyses were done in the COMPANION[298] and CARE-HF[299] studies. CRT was associated with increased total costs when compared with standard medical treatment. Over a mean follow-up of 29.6 months in CARE-HF,[299] the mean €4316 overcost was mainly attributable to the device itself, with an estimated cost of €5825. The mean incremental cost-effectiveness ratio per life year gained was €29 400[299] and $28 100[298] with CRT-P and $46 700 with CRT-ICD.[298] Extending the analysis to a patient life perspective, the mean incremental cost gained per quality-adjusted life year (QALY) was €19 319[299] and $19 600[298] for CRT-P, whereas it was more than twice as high ($43 000) for CRT-ICD.[298] These data suggest that the clinical benefits of CRT are economically viable and can be achieved at a reasonable cost in most European countries. As cost-effectiveness of CRT-ICD compared with CRT-P is age-sensitive, expected longevity should help determine whether to use CRT-P or CRT-ICD in the individual patient.[300]

3.1.4. Unresolved issues

3.1.4.1. Patient selection: electrical or electromechanical dyssynchrony criteria to select patients for cardiac resynchronization therapy?

The response rate to CRT is limited to 60–70% of patients and so there is a need for optimizing individual therapy delivery and for developing selection criteria for CRT.[271] Nonetheless, the evidence for a clinical benefit from CRT is derived from randomized studies using QRS $\geq$120 ms as a marker of ventricular dyssynchrony. Consequently, there is currently no evidence that CRT is indicated in CHF patients with QRS $<$120 ms. Electrical dyssynchrony does not always accompany mechanical dyssynchrony.[271] Conversely, mechanical ventricular dyssynchrony is not always linked to electrical dyssynchrony. For example, signs of intraventricular dyssynchrony have been reported by imaging techniques in a subset of patients with LV systolic dysfunction and a QRS $<$120 ms.[301–304] The mean QRS duration of heart failure patients enrolled in these studies ranged from 110 to 120 ms. In spite of positive results from observational studies of the benefit from CRT using mechanical dyssynchrony criteria to select patients,[304,305] the real value of the mechanical dyssynchrony criteria for patient selection remains to be determined in randomized studies. That is particularly true for the so-called 'narrow QRS' ($<$120 ms) patients.[306–308]

3.1.4.2. Patients with atrial fibrillation

The randomized studies of CRT to date have been almost exclusively restricted to patients in sinus rhythm. The prevalence of AF in patients with moderate-to-severe CHF, however, varies between 25 and 50%.[309] This high prevalence contrasts with the low percentage (2%) of patients with AF enrolled in randomized trials of CRT. Therefore, we have little knowledge of the clinical value of CRT in this population. The reasons for this lack of information are various. Patients suffering from CHF, AF, and ventricular dyssynchrony are typically older, have a higher prevalence of associated illnesses, and a worse prognosis than patients in sinus rhythm.[310] On the other hand, enabling incessant and complete ventricular capture may be inconvenient for the patient, since this often requires the prior creation of complete heart block by radiofrequency ablation of the AV junction. Finally, outcomes are more difficult to measure, since both heart rate control and CRT may contribute to the observed changes in clinical status. Thus far, a single small controlled study (MUSTIC-AF) has yielded negative results in the intention-to-treat analysis, whereas the per-protocol analysis showed a marginally significant functional improvement conferred by CRT.[311] However, the results of a recent large prospective observational study[312] clearly demonstrated that, over a long-term follow-up, combining CRT with AV junction ablation (thus obtaining 100% effective biventricular stimulation) conferred marked improvements in LV function and exercise capacity (comparable with those achieved in patients with sinus rhythm). In contrast, AF patients treated with CRT without AV junction ablation, in whom rate control was achieved by means of negative chronotropic drugs, performed very poorly. Two small trials, the OPSITE and PAVE trials, primarily focused on patients with fast drug-refractory AF[314,315] treated with AV junction ablation combined with different pacing modes. Only a subset of patients in both trials had LV

Table 3.1.2 Endpoints, design, and main findings of the randomized studies evaluating pacing in heart failure

Study	Endpoints	Design	Main findings
MUSTIC-SR[281]	6MWT, QOL, pVO_2, Hosp	Single-blinded, controlled, crossover, 6 months	CRT-P improved: 6MWT, QOL, pVO_2; reduced Hosp
MIRACLE[282]	NYHA class, QOL, pVO_2	Double-blinded, controlled, 6 months	CRT-P improved: NYHA, pVO_2, 6MWT
MUSTIC AF[311]	6MWT, QOL, pVO_2, Hosp	Single-blinded, controlled, crossover, 6 months	CRT-P (high drop-out rate): improved all; reduction of Hosp
PATH CHF[283]	6MWT, pVO_2	Single-blinded, controlled, crossover, 12 months	CRT-P improved: 6MWT; pVO_2
MIRACLE ICD[286]	6MWT, QOL, Hosp	Double-blinded, ICD vs. CRT-D 6 months	CRT-D improved all from baseline (not ICD)
CONTAK CD[285]	Mortality+Hosp HF+ VA, pVO_2, 6MWT, NYHA class, QOL, LVEDD+LVEF	Double-blinded, ICD vs. CRT-D 6 months	CRT-D improved: pVO_2, 6MWT; reduced LVEDD and increased LVEF
MIRACLE ICD II[287]	VE/CO_2, pVO_2, NYHA, QOL, 6MWT, LV volumes/EF	Double-blinded, ICD vs. CRT-D 6 months	CRT-D improved: NYHA, VE/CO_2; volumes, LVEF
COMPANION[288]	(1) All-cause death or Hosp (2) All-cause death	Double-blinded, controlled, OPT, CRT-D, CRT-P, about 15 months	CRT-P+CRT-D: reduced (1) Only CRT-D: reduced (2)
CARE-HF[289]	(1) All-cause death or Hosp for major CV event (2) Death from any cause	Double-blinded, controlled, OPT, CRT-P, 29 months	CRT-P reduced (1) and (2)

6MWT = 6 min walk test; QOL = quality of life; pVO_2 = peak oxygen consumption; Hosp = hospitalizations; CRT-P = biventricular pacemaker; CRT-D = biventricular pacer with a defibrillator; VE/CO_2 = ventilation/carbon dioxide ratio; LV = left ventricular; LVEF = left ventricular ejection fraction; OPT = optimal HF treatment arm; BV = biventricular.

dysfunction and were in NYHA classes II–III. The results of both trials remain inconclusive regarding the primary endpoints (measures of functional capacity and LVEF). Additional larger and better-designed studies are needed in this area.

3.1.4.3. Patients with mild heart failure or asymptomatic left ventricular systolic dysfunction (New York Heart Association classes I–II)

The main goals of treatment for patients in NYHA functional class I or II are: (i) to prevent the progression of disease and CHF; and (ii) to reduce cardiac mortality, mainly due to SCD. The assessment of the clinical value of a new therapy in this population requires the definition of specific endpoints (*Table 3.1.2*). The most relevant is probably a clinical composite of symptoms, morbidity and mortality,[316] and reverse remodelling. Although with LV remodelling develop progressively more severe CHF, the slowing or reversal of remodelling has only recently been recognized as a goal of treatment.[317] The clinical applications of CRT in patients in stable NYHA functional class I or II remain limited. In the CONTAK-CD trial, significant reverse remodelling was observed in the small subgroup of patients in NYHA functional classes I–II after 6 months of CRT, although the benefits were less prominent than in the much larger group of patients in NYHA functional classes III–IV.[285] Similar observations were made in the MIRACLE ICD II study.[287] This small trial randomly assigned patients to CRT vs. no CRT. At the end of the 6-month blinded period, there was no significant difference in peak VO_2 (the primary study objective), though a significant improvement in the clinical composite endpoint was observed in the group assigned to CRT compared with the control group. These preliminary observations suggest that CRT has a favourable impact on the outcome of patients with less advanced CHF and less severe LV systolic dysfunction and ventricular dyssynchrony. This issue now needs to be further examined in large randomized trials. No recommendation can be made at this time regarding this specific situation.

3.1.4.4. Pacing in heart failure in the paediatric population

Few studies[318–320] have addressed the possibility of pacing for heart failure in the paediatric population. For the most part, this approach has been adopted in paediatric patients after surgical repair of congenital heart defects and has yielded significant short-term improvements in symptoms and systolic function. Pacing for heart failure in this complex and heterogeneous subpopulation is supported by limited evidence and requires further investigation to identify who may benefit the most from which pacing modality (uni- or biventricular) in the long-term.[321]

3.1.4.5. Device selection: cardiac resynchronization therapy in combination with implantable cardioverter defibrillator therapy (CRT-D) or cardiac resynchronization therapy alone?

The typical CRT patient is a high-risk patient with an increased risk for sudden death that is significantly reduced[322] but probably not optimally prevented by CRT alone. Three randomized, prospective, controlled trials have shown the efficacy of the stand-alone ICD in the primary prevention of SCD in patients with a history of previous myocardial infarction and depressed EF.[323–325] Two relevant randomized, controlled trials have demonstrated that heart failure patients with LV dysfunction treated with an ICD have a reduced risk of death, regardless of the aetiology.[288,326] Both trials enrolled patients with ischaemic dilated cardiomyopathy (IDCM) and non-ischaemic dilated cardiomyopathy (NIDCM): (i) the COMPANION trial[288] has shown that, when compared with OPT alone, CRT-D

significantly reduces total mortality within the limits of a 14-month median follow-up; (ii) the SCD-HeFT trial[326] has also shown that ICD, and not amiodarone, in conjunction with OPT decreases mortality in mild heart failure patients.

The beneficial role of the ICD in the primary prevention of SCD in patients with NIDCM is more controversial.[288,326–329] The earlier studies enrolled small patient groups and were discontinued prematurely because of the low event rate which occurred in the control arm, therefore showing no significant benefit of ICD in the primary prevention of SCD in patients with NIDCM. Larger randomized trials with longer follow-up have shown a benefit in terms of survival in patients receiving an ICD compared with patients on OPT and showed no difference in benefit between ischaemic vs. non-ischaemic aetiology. Another trial[327] enrolled only heart failure patients with NIDCM and LVEF $<36\%$; these patients were randomized to either OPT or OPT plus ICD. Although there was a trend for total mortality reduction in the ICD group, statistical significance was not reached. On the other hand, arrhythmic mortality was significantly reduced by the ICD.

Whereas one study has advocated a protective role of CRT-P against SCD,[294] two meta-analysis pooling survival data from the major CRT trials have reported that CRT-P has either no significant effect on SCD[330] or even causes a moderate increase of such events.[291] Moreover, a recent prospectively defined registry also showed a large protective effect of CRT-D on SCD (MILOS registry).[331]

There exists some overlap between the indications for CRT-P and CRT-D; this renders the clinician's task in selecting the device a difficult one. The most recent Guidelines on SCD[322] have emphasized the importance of 'survival expectancy' in order to guide the use of an ICD in primary prevention of SCD. The concept of 'expectation of survival' englobes the general conditions of the patient, specifically based on biological age and the presence of important comorbidities which may have an impact on prognosis. These guidelines specifically state that the use of an ICD in primary prevention is indicated (Class I indication) in heart failure patients with severe LV dysfunction, regardless of underlying aetiology, 'who have a reasonable expectation of survival' (>1 year).[322]

Therefore, it is strongly recommended that the choice of the most appropriate device (whether CRT-P or CRT-D) for a patient be based upon careful evaluation of the following 2 points: (i) the patient's expectation of survival, which, when considering an ICD, should exceed 1 year; (ii) health care logistical constraints and cost considerations (see Section 3.1.3).

3.1.4.6. Biventricular pacing or left ventricular pacing alone?

Biventricular pacing is the preferable mode but LV pacing may be acceptable in selected patients. Pacing in heart failure may be achieved by means of two different pacing modalities: biventricular pacing or LV pacing alone. Most studies on CRT have used biventricular pacing, and thus, this pacing mode has been extensively studied and most widely used. Although indications for LV pacing must still be clearly defined, there is growing evidence suggesting that applying LV pacing is comparable with the biventricular mode in selected heart failure patients presenting left bundle branch block or echocardiographic evidence of significant mechanical delay at the level of the LV lateral wall.[284,332–336] One multi-centre randomized pilot trial (BELIEVE trial) has confirmed that there are no substantial differences in response between the two pacing modes.[332] Early experience of CRT based on LV pacing[336] was characterized by the technical limitation of not having devices with separate channels. The risk of LV lead dislodgement without right ventricular backup has limited LV pacing to patients who were not pacemaker-dependent or who had a concomitant indication for ICD implantation. The present availability of devices with separate channels allows the application of LV pacing while ensuring pacemaker or ICD backup on the right ventricular lead, thus eliminating the above-mentioned safety concerns. In selected cases who present left bundle branch block, conventional CRT indication, advanced age, and/or important comorbidities, without a bradycardiac indication for a pacemaker, in whom an improvement in quality of life is sought, it may be reasonable to consider LV pacing alone.

3.1.4.7. Patients with indication for permanent pacing for bradyarrhythmia, with heart failure symptoms and severely compromised left ventricular function

Studies specifically addressing this issue are lacking. It is important to distinguish what part of the clinical picture may be secondary to the underlying bradyarrhythmia rather than LV dysfunction. Once severe reduction of functional capacity as well as LV dysfunction have been confirmed, then it is reasonable to consider biventricular pacing for the improvement of symptoms.

Conversely, the detrimental effects of right ventricular pacing on symptoms and LV function in patients with heart failure of ischaemic origin have been demonstrated.[337,338] The underlying rationale of recommending biventricular pacing should therefore aim at avoiding chronic right ventricular pacing in heart failure patients who already have LV dysfunction.

3.1.4.8. Patients with a previously implanted conventional pacing device and severe left ventricular dysfunction

Chronic right ventricular pacing induces LV dyssynchrony with deleterious effects on LV function.[337,338] However, there are few data concerning the effects of device upgrading from only right ventricular to biventricular pacing.[313] Therefore, the consensus is that in patients with chronic right ventricular pacing who also present an indication for CRT (right ventricular paced QRS, NYHA class III, LVEF $\leq 35\%$, in optimized heart failure therapy) biventricular pacing is indicated. Upgrading to this pacing mode should partially revert heart failure symptoms and LV dysfunction.

3.1.4.9. Patients with indication for biventricular pacing who must undergo heart surgery

In this condition, heart surgery may be an opportunity for positioning an epicardial LV lead intraoperatively on the lateral epicardial surface of the LV. This procedure may overcome the possible failure of a transvenous approach. It is important to establish the degree to which the 'surgical' problem is responsible for LV dysfunction.

3.1.5. Programming recommendations

Device programming should specifically aim at ensuring atrial-synchronous (in sinus rhythm patients) permanent biventricular pacing by:

- performing AV interval optimization (echocardiographically guided[339] or using invasive haemodynamic[283] measurements);
- performing ventricular-ventricle (VV)[340,341] interval optimization;
- setting upper tracking limit (should be higher than the fastest sinus rate);
- setting automatic mode switch;
- setting protection against endless-loop tachycardias;
- setting rate responsiveness in case of chronotropic incompetence;
- setting diagnostic functions dedicated to detection of ventricular and atrial arrhythmias.

In permanent AF patients, the AV junction should be ablated[312] in patients whose native AV conduction is still present, with an intrinsic rhythm that interferes with biventricular pacing. VVIR mode should be selected and diagnostic functions dedicated to the detection of ventricular arrhythmias.

3.2. Recommendations

The following recommendations for pacing in heart failure have been subdivided according to the different clinical and technical characteristics of the single patient. These have obviously been formulated on the basis of evidence derived from large randomized trials; however, an effort has been made to identify ill-defined areas (such as heart failure patients with permanent AF or with previously implanted device) in order to provide a practical framework to indicate pacing in heart failure. In this way, the following recommendations also consider possible additional risks to which the patients may be exposed during an upgrading procedure.

Pacing for heart failure can be applied either by biventricular pacing or, in selected cases, by LV pacing alone.[332–334] The following recommendations consider cardiac pacing for heart failure delivered through biventricular pacing, since this mode is supported by the greatest body of evidence. This, however, does not preclude other pacing modes, such as LV pacing, to correct ventricular dyssynchrony.

Ventricular conduction delay continues to be defined according to QRS duration (QRS $\geq$ 120 ms). It is recognized that ventricular conduction delay may not result in mechanical dyssynchrony. Dyssynchrony is defined as an uncoordinated regional contraction–relaxation pattern. Although from the theoretical point of view it may be more appropriate to target mechanical dyssynchrony, rather than electrical conduction delay, no large controlled study has prospectively assessed the value of mechanical dyssynchrony in heart failure patients undergoing pacing for heart failure. Device selection and programming for pacing in heart failure are considered for each of the specific conditions. The recommendations are divided into subsections designed to guide the physician towards the most adequate treatment, based on specific patient characteristics.

3.2.1. Recommendations for the use of cardiac resynchronization therapy by biventricular pacemaker (CRT-P) or biventricular pacemaker combined with an implantable cardioverter defibrillator (CRT-D) in heart failure patients

Heart failure patients who remain symptomatic in NYHA classes III–IV despite OPT, with LVEF $\leq$ 35%, LV dilatation [LV dilatation/different criteria have been used to define LV dilatation in controlled studies on CRT: LV end-diastolic diameter $>$55 mm; LV end-diastolic diameter $>$30 mm/m^2, LV end-diastolic diameter $>$30 mm/m (height)], normal sinus rhythm and wide QRS complex ($\geq$120 ms).

- Class I: level of evidence A for CRT-P to reduce morbidity and mortality.[288,289,292,330]
- CRT-D is an acceptable option for patients who have expectancy of survival with a good functional status for more than 1 year; Class I: level of evidence B.[288]

3.2.2. Recommendations for the use of biventricular pacing in heart failure patients with a concomitant indication for permanent pacing

Heart failure patients with NYHA classes III–IV symptoms, low LVEF $\leq$ 35%, LV dilatation and a concomitant indication for permanent pacing (first implant or upgrading of conventional pacemaker). Class IIa: level of evidence C.[289,313]

3.2.3 Recommendations for the use of an implantable cardioverter defibrillator combined with biventricular pacemaker (CRT-D) in heart failure patients with an indication for an implantable cardioverter defibrillator

Heart failure patients with a Class I indication for an ICD (first implant or upgrading at device change) who are symptomatic in NYHA classes III–IV despite OPT, with low LVEF $\leq$ 35%, LV dilatation, wide QRS complex ($\geq$120 ms). Class I: level of evidence B.[286]

3.2.4 Recommendations for the use of biventricular pacing in heart failure patients with permanent atrial fibrillation

Heart failure patients who remain symptomatic in NYHA classes III–IV despite OPT, with low LVEF $\leq$ 35%, LV dilatation, permanent AF and indication for AV junction ablation. Class IIa: level of evidence C.[311,312]

Appendix A: pacemaker follow-up

Successful pacing therapy presupposes that a series of necessary conditions be satisfied. These are given in detail in *Table A.1*.

Apart from the successful placement of lead(s) and generator, today's advanced pacemaker technology, along with the increased cost of sophisticated devices, requires methodical long-term follow-up in order that the patient may receive the optimum pacing benefit and the treatment may be as cost-effective as possible.[342,343]

Long-term pacemaker follow-up itself, pacemaker troubleshooting, and the indications for device replacement represent an extensive area that is beyond the scope of this document. However, it was considered advisable for these

Table A.1 Main components of successful pacing therapy

1. Suitable choice of candidates for pacing, based on history, electrocardiographic findings, and/or specific electrophysiological characteristics
2. Detailed information provided to the patient about pacing therapy
3. High-quality surgical placement of lead(s) and generator
4. Meticulous determination of optimum acute sensing parameters and appropriate pacing threshold(s)
5. Thorough pre-discharge evaluation of the patient and appropriate pacemaker programming
6. Methodical long-term follow-up of the patient and proper pacemaker troubleshooting
7. Prompt detection of complications related to the pacing therapy
8. Psychological support of the patient when deemed necessary

Table A.2 Goals of a pacemaker clinic

1. Evaluation of the overall clinical condition of the paced patient
2. Timely recording of failures or abnormalities of the pulse generator, leads, and correction of any problems identified
3. Recording problems or complications related to the surgical procedure and placement of generator and lead(s)
4. Proper sensing tests and relevant optimum programming
5. Threshold testing and output programming, with a view to adjusting pacing to the needs of the patient and maximizing generator longevity
6. Non-invasive programming, utilizing the full range of programmable options in order to optimize device function for an individual's specific needs
7. Correct evaluation of the end of life of the pulse generator, avoiding unnecessary and premature replacement
8. Organization of a database containing details of each patient's pacing system, for monitoring the performance and reliability of the pulse generator and leads
9. Provision of education and support—medical and psychological—to the paced patient
10. Provision of education and training to doctors, technicians, and nurses with regard to permanent pacing

Table A.3 Logistical needs for a pacemaker follow-up clinic

Equipment:
1. Multi-channel electrocardiograph with real-time rhythm strip recording capability
2. Electronic device for the measurement and assessment of pulse duration and inter-stimulus interval
3. Magnet
4. Programmers corresponding to the devices monitored by the centre. The range should be more extensive if the clinic performs checks on transient patients (from other regions or countries)
5. A broad variety of pacemakers and programmer manuals
6. External defibrillator, transcutaneous pacing system, and resuscitation apparatus
7. Well-organized databases with telephone numbers of all relevant pacemaker providers and technicians

Facilities:
1. Easy access to an X-ray laboratory
2. A full spectrum of non-invasive cardiac diagnostics
3. Twenty-four hour telephone answering response

Table A.4 Functional aspects of a pacemaker clinic

1. Appropriately updated patient file including the following data: demographics, medical history, electrocardiographic and electrophysiological details, X-ray implantation features, and long-term changes in programmed sensing and pacing parameters
2. Archiving of information concerning generators, leads, and programmers
3. Editing of European pacemaker registration card for each patient
4. Up-to-date training for all clinical personnel
5. Periodic briefing and education of patients
6. Adequate briefing of all care physicians concerning the paced patient
7. Informing official national organizations about pacemaker implantations, failures, and recalls

guidelines to include a brief informatory description of certain topics of central importance, which are relevant to the long-term follow-up of a paced patient.

The main objectives, structure, and function of the pacemaker clinic

The long-term follow-up of a paced patient requires a well-organized pacing clinic, whose infrastructure, know-how, and staff are sufficient to ensure a reliable periodic assessment of the patient in general and the pacemaker function in particular. The goals of such a pacing clinic are shown in *Table A.2*.

The clinic should aim to maintain optimal pacemaker function matched to the patient's needs, to maximize device longevity, to identify any problems or complications related to the pacing system, and to ensure prompt recognition of battery depletion, enabling elective device replacement to be scheduled. It must be stressed that the follow-up should include a qualitative evaluation of the pacing result. Symptoms or signs, even secondary ones, that are sometimes associated with pacemaker syndrome or with an inappropriate response to the patient's needs should elicit a detailed analysis and solution.

The organization of the clinic requires a suitable space, adequate secretarial support, facilities for conventional and electronic archiving of patients' records, and the necessary equipment and facilities (*Tables A.3 and A.4*). The harmonious function of the clinic, especially nowadays when developments in device technology are rapid, depends on experienced staff, who make a point of staying well informed and thus steadily increase their knowledge. The staff should include well-trained nursing personnel, a part-time or full-time pacemaker technician, and of course a specialized cardiologist, experienced not only in device implantation but also in programming and pacing troubleshooting.

Pre-discharge assessment and long-term follow-up methodology

In general, patients who are not pacemaker-dependent and are free of complications stay in hospital for 24 h after the implantation procedure. In well-selected cases, modern technology permits an early discharge policy, where the paced patient leaves hospital after a few hours. A discussion of the benefits and concerns associated with this policy would require a more extensive document.

In the 24 h after implantation and before discharge, a careful examination protocol must be followed:

- evaluation of the wound and generator pocket;
- 12-lead ECGs;
- upright postero-anterior and lateral chest radiograph;
- appropriate programming of primary pacing and sensing parameters;
- adjustment of the full spectrum of available settings so as to ensure the optimum haemodynamic pacing effect and a positive cost–benefit result.

The schedule for long-term follow-up is strictly dependent on a range of parameters, such as the initial indication for pacing, the patient's overall clinical condition, the type of pacemaker implanted and any associated complications, and the post-implantation course. As a general rule, in the case of the simplest single-chamber pacemakers, the first follow-up visit may be scheduled after 4–6 months and the second after a similar interval. Thereafter, patients are followed annually until the first signs of battery depletion appear, after which examinations should be more frequent, say every 3 months, until device replacement.

For the more complex dual-chamber pacemakers, the suggested schedule is the same after discharge; however, from then on, it is preferable for examinations to continue on a 6-monthly basis, because it is likely that the multiple programming parameters will need to be adjusted to match the patient's needs.

As a supplement to the above, transtelephonic monitoring may be of value; despite its utility, it is currently little used in Europe. This service provides the opportunity for frequent assessment of the pacing system's performance, as well as allowing the pacing clinic to receive and record the cardiac rhythm during symptoms such as dizziness and palpitations. Transtelephonic monitoring is particularly useful for patients who live far away from the follow-up centres in remote areas or who have limited mobility. We may expect that these transtelephonic facilities—such as the rapidly developing remote, wireless, and patient-independent monitoring systems—will soon come to play an increasing role in pacemaker follow-up.

Wireless monitoring of pacemakers, or of more hybrid systems for cardiac rhythm management, as a service for improving care, enhancing patients' safety, and optimizing the allocation of human and financial health resources, will be the subject of an independent document.

Complications, failures, and side effects of pacemaker treatment

Pacemaker implantation, as an invasive procedure, entails a risk of complications and failures, not only in the perioperative period but also in the longer term. Furthermore, cardiac pacing as a complex therapy, with mechanical and electrical dimensions contributing to the support of a weakened cardiac physiology, is inevitably prone to a variety of possible types of failures or side effects, which are described in all the relevant textbooks. On the basis of their incidence and clinical significance, intraoperative pneumothorax, haematomas, lead dislodgement, and functional problems—such as pacemaker syndrome, pacemaker-mediated tachycardia, and crosstalk phenomena—have been selected for further mention in this section.

Intraoperative pneumothorax and haemothorax, which are far from rare and are rather serious complications, are due mainly to the common—and deprecated—practice of puncturing the subclavian vein in order to introduce the pacing leads through subclavian introducers. The complication requires prompt diagnosis so that proper therapeutic measures may be applied.

Haematoma in the region of the generator pocket occurs mainly in patients who are taking antiplatelet or anticoagulant medication. It is recommended that in such cases, the treatment should be interrupted 3–8 days pre-operatively and replaced by heparin. If that is not feasible and implantation must be performed, although the patient is under anticoagulant therapy, the procedure should be carried out by an experienced operator who will pay close attention to haemostasis in the area of the generator pocket.

Lead dislodgement, more usually of the atrial lead when screw-in technology is not used, represents one of the most common complications of this therapy. Careful electrocardiographic evaluation of the pacing result after the procedure, in combination with postero-anterior and lateral X-rays as routine practice, is sufficient to confirm such an occurrence. Of course, stability tests during electrode placement are essential in order to ensure the reliability of the pacemaker's acute sensing and pacing as well as the stability of the result.

Special issues related to the paced patient's life

The life of the paced patient and the pacemaker function are linked in a relationship of reciprocal interdependence, as is often apparent during the post-implantation period. The treating cardiologist, the follow-up centre, and the primary care physicians are often asked reasonable questions by paced patients concerning the kind of life they are able to lead after pacing, particularly in relation to sports, driving, and the possible effect of various sources of electromagnetic interference on pacemaker function.

The latest developments in the technology of pacing devices and leads permit paced patients to lead a normal active life, which can even include sports as long as there is no danger of injury or overstretching in the pacemaker region. Driving is also permitted, usually 1 week after device implantation, provided there are no additional disabling factors or unless there are local regulations that dictate otherwise.[344]

Electromagnetic interference from a variety of sources in today's rapidly developing technological environment is a potential cause of pacemaker dysfunction. This means that treating physicians must be aware of the problem, so that any possibility of undesirable events can be minimized. At the same time, they should reassure their patients that

the risk of electromagnetic interference might otherwise arouse, in order to avoid anxieties.

The sources of electromagnetic interference can be broadly divided into two categories: those that occur in the hospital environment, as a result of diagnostic or therapeutic procedures, and those encountered outside the hospital, such as cellular phones and electronic article surveillance equipment.[345–347]

The hospital environment undoubtedly presents the most serious risks of electromagnetic interference with pacemakers. Despite the effective shielding pacemaker devices possess, it is common for dysfunction to occur during certain procedures, such as electrocautery, lithotripsy, radio frequency ablation, and magnetic resonance imaging (MRI), so reprogramming and special monitoring may be necessary during a long-term follow-up.[348,349]

Electrocautery, a common technique during surgical procedures, needs to be singled out because it can result in numerous pacing responses, including reprogramming, inhibition, and noise reversion mode. It may also cause local heating of the electrode, resulting in damage to the myocardium that can lead to elevation of the pacing or sensing threshold, or both.[350,351] Care must therefore be taken that in paced patients undergoing electrocautery, its use and power output should be kept to the minimum required, with the application of short bursts that are not in close proximity to the device. Bipolar electrocautery systems are to be preferred, as they are less hazardous. In the case of the pacemaker-dependent patient, pre-operative reprogramming of the device to an asynchronous or a triggered mode should be considered. In all other cases, there must be provision for the activation of asynchronous, fixed-rate pacing immediately, through the use of a programmer or magnet, should pacemaker inhibition occur.

Similar considerations apply to catheter ablation, as almost all procedures nowadays are performed using radio frequency current at a frequency of 400–500 kHz.[352] Prior to radio frequency ablation, the implanted pulse generator should be interrogated and the settings recorded. On completion of the procedure, further interrogation of the device will determine whether reprogramming is necessary.

Lithotripsy, in the treatment of nephrolithiasis or cholethiasis, entails a risk arising from both electromagnetic interference and mechanical damage from the hydraulic shock wave that is generated. The procedure, however, is considered to be relatively safe, provided that the pacemaker is synchronized with the ECG and that dual-chamber devices have safety pacing enabled. If the patient is pacemaker-dependent and has a dual-chamber pacemaker, the device should be programmed to VVI, VOO, or DOO mode so as to avoid ventricular inhibition.[353]

MRI is particularly hazardous for the paced patient, as the procedure involves the generation of a powerful magnetic field that is modulated by a radio frequency electrical signal. This procedure is contraindicated for paced patients, but if it is considered essential, careful monitoring is required throughout the procedure and the pacemaker should be checked afterwards. The potential adverse effects of MRI on pacemakers have been demonstrated in a number of animal studies and include asynchronous pacing and dual inhibition by the radio frequency signal. Similar problems have been reported in humans and some deaths have been reported.[354] If MRI is considered absolutely essential and the patient is not pacemaker-dependent, the patient should be informed in detail about possible complications and written consent to the examination should be obtained. In such cases, the patient should be put on cardiac monitoring from the time the pacemaker is reprogrammed to yield non-capture until the completion of the procedure. Even these measures, however, cannot eliminate the risks of MRI, as there is the possibility, albeit a small one, that the magnetic field can cause heating of the conductor coil and electrode tip, resulting in damage where the electrode makes contact with the myocardium.

Although sources of electromagnetic interference outside the hospital pose a lesser threat to pacemaker function, the patient should nevertheless be made aware of them and encouraged to avoid areas with strong electromagnetic fields. The main sources of interference that have drawn attention are certain household devices, such as microwave ovens, electronic article surveillance equipment, and mobile telephones.[345–347] At our current state of technology, it has been shown that the ovens are no longer a significant source of interference. Electronic article surveillance equipment, which is used as a security measure in many libraries and shops, may also affect pacemaker function. However, the possibility of significant adverse effects is low if the patient passes rapidly through any electronic article surveillance field. For this reason, patients are advised to walk quickly through electronic article surveillance gates and avoid leaning on or standing near them.

Cellular phones also have the potential to affect pacemakers, and this potential is increased when they are placed directly over the device. However, clinically significant electromagnetic interference is unlikely during everyday use of cellular phones and most adverse effects are eliminated if the phone is held more than 15 cm from the pacemaker. Minimal interference has been detected when the patient uses the ear opposite to the site of the implant.[347]

Appendix B: technical considerations and requirements for implanting cardiac resynchronization therapy devices

According to the international guidelines, implantation of anti-bradycardia or anti-tachycardia devices consists of five distinct parts: (i) proper indications; (ii) the surgical element of implantation; (iii) venous access; (iv) intracardiac manipulation of leads and lead placement; and (v) electrophysiological interpretation during implantation.[355,356] Implantation of a CRT device is, however, more demanding than implantation of a conventional pacemaker or implantable cardioverter defibrillator. Thus, additional laboratory, operator, and technical support should be considered.

Requirements for implanting CRT devices have not previously been articulated in detail in guidelines. The following section outlines practical and technical aspects related to CRT and consists of six parts: (i) technical and human resources for a centre intending to perform CRT implants; (ii) pre-implantation scheduling; (iii) requirements for the operating room; (iv) personnel requirements during CRT implantation; (v) competence for implanting CRT devices; and (vi) practical CRT implant recommendations.

Technical and personnel requirements for centres intending to implant cardiac resynchronization therapy devices

It is recognized that CRT is very demanding of the operator. Thus, a high level of cardiological procedure experience should be obtained prior to commencement of training.

Experts feel that centres intending to perform CRT implantation and actively follow-up patients with CRT should fulfil the following conditions.

(i) Two or more cardiologists qualified for device implantation and management. At least one of these physicians should have competence in electrophysiology and in management of pacemaker and cardioverter-defibrillator devices.
(ii) All physicians should possess knowledge and experience in haemodynamic monitoring and administration of cardiovascular support, including positive inotropic drugs, experience in cardiovascular resuscitation, and handling of low output syndromes and life support.
(iii) Trained nurses and technical personnel: at least one of these professional figures should have competence in implantable device management.
(iv) Pacing system analyser and programmer of implanted device: electronic patient file is highly encouraged.
(v) A minimum case load of at least 20 CRT device implantations per year is strongly advised.[383,384]
(vi) Outpatient clinic or service for follow-up of patients implanted with CRT; consultancy with heart failure clinic or specialist with competence in echocardiography is strongly encouraged.
(vii) Continuing medical education for physician, nurses, and technician is mandatory.
(viii) Yearly quality control, including implantation failure, procedure-related death, and 30-day mortality, should be audited.

Scheduling patient for cardiac resynchronization therapy

Although the indication for CRT is based on the patient's history, NYHA functional class, underlying cardiac rhythm, and history of arrhythmias, co-morbidity should be closely considered. Depending on coagulation disorders, renal insufficiency, and electrolyte imbalance, appropriate pre-operative management of the patient should be undertaken.

ECG recording is mandatory at the present time before implantation of a cardiac resynchronization device. PR interval, QRS duration and morphology, and underlying rhythm should be evaluated for the most appropriate selection of device.

Echocardiographic evaluation is important for precise assessment of ventricular dimensions, presence of mitral regurgitation, and LVEF. Many echocardiographic criteria evaluating inter- and intra-ventricular dyssynchrony have been proposed. At the present time, there is no consensus about which echocardiographic parameters may best determine baseline dyssynchrony and which of these can predict response to CRT. The majority of studies on the evaluation of inter- or intra-ventricular delay was not randomized and enrolled limited patient populations with short follow-up.[357–369] A list of echocardiographic parameters is given in *Table B.1*.

Cardiopulmonary exercise testing is an important, yet not widely accepted, criterion for screening patients undergoing CRT. The testing is time-consuming, expensive, and requires great skill in cardiopulmonary physiology. However, it is a very helpful objective criterion for measuring the patient's exercise capacity.[370] As an alternative to cardiopulmonary testing, the 6 min walking distance may be helpful for assessing patient's physical ability. Six-minute hall walk testing[371] may have limited value in older and physically impaired patients, but presents the advantage of being easily performed even in an outpatient clinic follow-up.

Self-administered quality-of-life questionnaires are useful for measuring the patient's discomfort and quantifying the feeling of well being. However, their use in the screening of patients for CRT is limited.[372]

Characterization of coronary sinus anatomy

Precise assessment of coronary venous anatomy is mandatory in patients undergoing CRT. An angiogram of tributary veins to the coronary sinus may be obtained either by direct balloon-occlusive angiography or in the late phase of standard coronary angiography. The quality of direct angiography is usually higher and is mostly preferred. Angiography of the coronary sinus and coronary veins at the time of implantation is strongly encouraged. Also, non-invasive imaging, such as angio-CT scan or MRI, may be utilized for anatomical evaluation.

Preference for the implantation site is usually given to the lateral and the postero-lateral regions of the LV,[373] corresponding to regions B–D of the proposed schema (*Figure B.1*). Even more important is placing the LV lead in a basal or median section of these three regions, avoiding the apical section, which is too close to the right ventricular lead.

The best angiographic view of the target vein may vary considerably among patients. Three different views are suggested: right anterior oblique (RAO) 25°, left anterior oblique (LAO) 35°, and antero-posterior view. An additional view can be obtained on the basis of the target vein morphology and the origin of the vein.

Requirements for the operating theatre

A suitable operating room for CRT device implantation should have the equipment listed below.

(i) High-quality fixed or mobile fluoroscopic equipment capable of performing oblique projections (RAO 25°, LAO 35°, and PA 0°) and offering easy-to-use image management in order to view, simultaneously, on separate or split screens, real-time as well as memorized images.
(ii) Complete monitoring of 12-lead ECG allows continuous monitoring of heart rhythm and rate and provides preliminary indications on acute electrical resynchronization by evaluating QRS duration, electrical axis, and QRS morphology. More specifically, leads AVL (typically negative with LV pacing), DIII (typically positive in the anterolateral region and negative in the postero-lateral region of LV), and V1 (typically first component positive with LV pacing) tend to have a

Table B.1 Echocardiographic criteria for predicting cardiac resynchronization therapy response

Author	Patients	Dyssynchrony criterion [method]	Aetiology	Follow-up months	Comment
		Inter-ventricular dyssynchrony			
Rouleau *et al.*[357]	35	(Q-Ao)-(Q-Pulm) and (Q-Mit)-(Q-Tri)→IMD [standard pulsed Doppler and Doppler tissue imaging] Mean IMD 77 ± 15 ms and 88 ± 26 for QRS>150 ms	IDCM/NIDCM	—	IMD correlates with wide QRS
		Intra-ventricular dyssynchrony			
Pitzalis *et al.*[358]	20	Septal-to-posterior wall motion delay (M-mode ≥130 ms)	IDCM/NIDCM	1	Septal-to-posterior wall motion index ≥130 ms predicts ↓ LVESV index (≥15%) after CRT
Sogaard *et al.*[359]	25	Delayed longitudinal contraction (% basal LV) [tissue Doppler imaging]	IDCM/NIDCM	6–12	↑ LVEF ↓ LV end-systolic/diastolic volumes
Breithardt *et al.*[360]	34	Difference in septal and lateral wall motion phase angles to establish dyssynchrony	IDCM/NIDCM	1	Acute benefit of CRT in patients with greater dyssynchrony
Yu *et al.*[361]	30	Systolic dyssynchrony index (time-to-peak systolic contraction 32.6 ms) [tissue Doppler imaging]	IDCM/NIDCM	3	After CRT: ↓ LVESV
Breithardt *et al.*[362]	18	Peak septum strain–peak lateral wall strain pre-CRT vs. peak septum strain peak lateral wall strain post-CRT	IDCM/NIDCM	Acute	CRT reverts strain patterns
Bax *et al.*[363]	85	LV dyssynchrony (≥65 ms, septal to lateral delay) [tissue velocity imaging]	IDCM/NIDCM	6	After CRT: ↓ NYHA class ↓ LVESV
Penicka *et al.*[364]	49	LV+LV–RV asynchrony (sum asynchrony ≥102 ms) [tissue Doppler imaging]	IDCM/NIDCM	6	After CRT: ↑ LVEF (25%) ↓ LV end-systolic/diastolic volumes
Gorcsan *et al.*[365]	29	Time-to-peak velocities of opposing ventric. wall ≥65 ms [tissue synch imaging]	IDCM/NIDCM	5 ± 2	After CRT: ↑ LVEF
Yu *et al.*[366]	54	Standard deviation of T_s time-to-peak myocardial velocity: 31.4 ms [tissue Doppler imaging]	IDCM/NIDCM	3	After CRT: ↓ LVESV
Bordachar *et al.*[367]	41	Intra-LV delay peak, intra-LV delay onset [tissue Doppler imaging]	IDCM/NIDCM	3	After CRT: ↓ LV volumes ↑ LVEF
Yu *et al.*[368]	141	10% reduction of LVESV, mortality, and heart failure events	IDCM/NIDCM	−6	10% reduction in LVESV predicts lower long-term mortality and heart failure events
Marcus *et al.*[369]	79	Evaluation of septal-to-posterior wall motion delay to predict CRT response	IDCM/NIDCM	6	Septal-to-posterior wall motion delay did not predict reverse remodelling or clinical improvement

Q-Ao = QRS onset to onset of aortic flow; Q-Pulm = QRS onset to onset of pulmonary flow; Q-Mit = QRS onset to onset of mitral annulus systolic wave; Q-Tri = QRS onset to onset of tricuspid annulus systolic wave; IMD = interventricular electromechanical delay; IDCM = ischaemic dilated cardiomyopathy; NICM = non-ischaemic dilated cardiomyopathy; LVESV = left ventricular end-systolic volume; LV = left ventricular; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

particular QRS morphology according to the site of LV stimulation.

(iii) Invasive and non-invasive continuous arterial BP monitoring. Equipment allowing invasive haemodynamic monitoring (i.e. dP/dt, pulse pressure), although not indispensable, is helpful in assessing a patient's pre-CRT haemodynamic status or in assessing acute haemodynamic effects of CRT.

(iv) Continuous monitoring of oxygen saturation (per cent).

(v) The products of more than one manufacturer available while performing the procedure offer a variety of implantation systems (i.e. device-types, guiding catheters, electrodes, stylets, and guide wires) and allow adequate tailoring of CRT according to individual patient's clinical characteristics and to individual coronary sinus anatomy.

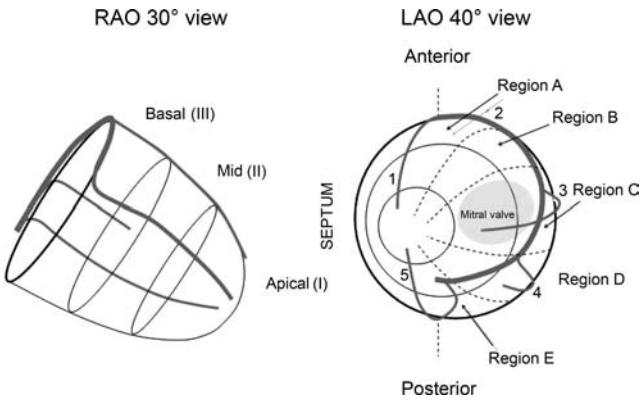

Figure B.1 On the left, the three segments (apical, mid, and basal) of the left ventricle are shown in the right anterior oblique 30° view. On the right, the left anterior oblique 40° view presents the possible venous tributaries of the coronary sinus: (1) anterior; (2) anterolateral; (3) lateral; (4) postero-lateral; and (5) posterior (middle cardiac vein). Coronary sinus venous anatomy allowing left ventricular lead tip should usually be positioned in a basal/mid-basal lateral (region C) or basal/mid-basal postero-lateral (region D) location, avoiding apical regions (too close to the right ventricular lead).

(vi) Knowledge of patient's coronary venous tree derived from previous angiographic procedures (coronary angiography or coronary sinus venography) is helpful in planning the implant procedure. This allows preliminary choices of adequate equipment to reach the target vein.
(vii) Availability of an external defibrillator with continuous monitoring of heart rate.
(viii) Availability of anaesthesiological support must be ensured for the management of critical clinical situations.
(ix) Easy and quick access to an intensive care unit must be available.
(x) When the transvenous approach fails, referral to a cardiac surgery unit that possesses adequate technical experience in positioning LV epicardial leads is useful. The cardiac surgery unit need not be within the same hospital structure, but must be easily accessible.

Personnel requirements during cardiac resynchronization therapy implantation

Usually two operators are required, especially during extraction/insertion of guidewires, handling of wires, sheaths, and stylets.

Ideally, two nurses are required. One nurse monitors patient status and manages all necessary impellent accesses, including the urine catheter and the intravenous administration of drugs. A second nurse provides implant assistance by:

(i) handing over sterile material;
(ii) positioning the ECG screen, with the above-described characteristics;
(iii) monitoring haemodynamic parameters invasively or with wristband;
(iv) monitoring oxygen saturation;
(v) monitoring defibrillator electrogram (EGM);
(vi) monitoring endocardial EGM.

Technical radiological assistance is strongly advised and in some countries is mandatory.

Continuous anaesthesiological support is not obligatory, but quick anaesthesiological assistance must be available if a critical clinical situation develops.

Clinical competence for implanting cardiac resynchronization therapy devices

Minimum training for competence

The manipulation of stylets, sheaths, guidewires, and guiding catheters derives from integrated experiences in different branches of invasive cardiology and should follow at least one of the three following practical lines of technical expertise for the commencement of training in the implantation of CRT devices:

(i) 'pure' electrophysiologists (more expert in cannulation of the coronary sinus) must have previously executed at least 200 electrophysiological studies/ablations (including cannulation of the coronary sinus);
(ii) interventional cardiologists [more expert in the execution of coronary angiography of percutaneous coronary intervention (PCI)] should have performed at least 200 angiographies/PCIs;
(iii) device implanters (more expert in the manipulation of catheters with stylets) should have performed at least 200 pacemaker/ICD implants (single or dual chamber);

or a combination of these amounting to at least 200 procedures.

Achieving adequate proficiency for implanting CRT devices is met by focusing training towards the acquisition of those skills that are not part of the original background of the operator and must include the following:

(i) thorough knowledge of the anatomy of the coronary sinus;
(ii) understanding of the principles of device management for CHF;
(iii) electrocardiographic interpretation of LV and biventricular pacing;
(iv) ability to interpret chest X-rays that include a coronary sinus lead.

Multi-centre studies have reported a success rate of CRT device implant of around 87–96%.[282,288,289] It is therefore reasonable to assume that performing 50 CRT implants fulfils the adequate learning curve in order to reach elevated success rates, above 90%. To start implanting CRT, participation as primary operator in at least 20 supervised CRT implants (this may include upgrades of existing pacemakers or ICD systems) is advised.

Alternatively, the acquisition of basic technical skills for physicians routinely involved in implanting pacemakers and ICDs should include all of the following criteria:

(i) observing at least 15 cases under the supervision of an experienced CRT implanting physician;
(ii) performing at least 20 implants in their own institution in the presence of an experienced proctor;

(iii) completing an approved didactic course on CRT or having performed a fellowship/stage at a recognized high volume institution.

Other technical and cognitive aspects involved in order to achieve clinical competence include:

(i) recognition of symptoms that suggest a system-related complication, e.g. tamponade, loss of biventricular capture, phrenic nerve stimulation, infection, and so on;
(ii) understanding of above-mentioned guidelines for CRT indications;
(iii) proper management of contraindications for and understanding of complications of CRT;
(iv) recognition and management of post-implantation complications, including LV repositioning;
(v) management of post-surgical complications related to device decubitus or pocket haematoma.

Maintenance of competence

A minimum number of cases are necessary for continued proficiency in quality of care. The operator should perform a minimum of 20 CRT implants per year to maintain skills and is advised to take $\geq$30 h of formal continuing medical education (level 1 category) every 2 years to remain up to date on developments in knowledge and technology related to CRT implantation.

Further practical cardiac resynchronization therapy implant recommendations

CRT implantation can be an extremely long procedure during the first phase of the learning curve; the longer the procedure, the higher the risks of complications observed (the status of the patient and the attention span of the operator tend to deteriorate during a lengthy procedure). The procedure should be interrupted after 4 h of unsuccessful attempts or after 60 min of X-ray exposure.[289] In such cases, careful re-evaluation is necessary, prior to repeating attempts.

Utilizing a 'stepwise' approach could be helpful. Repeating the procedure after careful examination of the coronary angiography and a new re-evaluation of the entire previously failed procedure and asking for the assistance of a more experienced operator can bring a higher and safer success rate.

The safety and efficacy of epicardial leads for biventricular pacing have not been assessed by large randomized trials. If transvenous coronary venous placement of the LV lead is unsuccessful, referral to a cardiac surgery unit qualified to do epicardial lead placement could be considered, but training guidelines are not within the purview of this document. Lead extraction requires special consideration, because this represents an important issue in CRT patients. However, it is also beyond the scope of this document.

Follow-up

There is a considerable number of patients who have minimal benefit or no improvement at all from CRT and are considered as non-responders.[282,283,286,288] In order to maximize the benefit of CRT, proper patient management and device follow-up are crucial.

CRT-P is a different therapy than classical cardiac pacing, as: (i) all CRT patients have advanced heart failure; (ii) the rationale of atrio-biventricular pacing is electromechanical resynchronization and not correction of bradycardia (most of the patients do not have conventional pacing indications); (iii) the devices are more sophisticated, with an additional lead; and (iv) a significant number of the patients have an ICD indication.

The follow-up objectives for a patient paced for heart failure include heart failure management and device follow-up. The latter incorporates standard technical interrogation (non-specific) and specific CRT-P or CRT-D device check-up. Guidelines and statements on anti-bradycardia pacemaker follow-up have been provided elsewhere.[339,374–377] Specific CRT follow-up should be initiated soon after implantation and should focus on the identification and correction of procedure-related complications and optimal device programming in order to ensure that appropriate biventricular therapy is being delivered. Pre-discharge management of the patient requires a clinical evaluation as well as programming of the CRT device, including assessment of optimal AV and VV intervals. Patients must be seen at 1 month post-discharge and from then on, regular visits at 3–6 month intervals should be scheduled.

Long-term follow-up

Long-term follow-up of the CRT requires coordination between the heart failure and the CRT management teams. Particularly, in CRT-D patients, the team should include a fully trained electrophysiologist. Institutions performing implantation of CRT and CRT-D devices should maintain facilities for inpatient and outpatient care, and support devices for all CRT and CRT-Ds used at that institution. Compliance with device follow-up should be discussed a priori with the patients, as it is of vital importance to ensure the efficacy of the therapy. Heart failure therapy has to be continued and optimized. Clinical response to CRT is evaluated by means of patient history and physical examination. Echocardiography and cardiopulmonary exercise test provide information about the effect of CRT on cardiac function.

A typical device follow-up includes the same sort of system testing one would expect for a normal pacemaker, such as interrogation of the pacing system, review of telemetry data, assessment of the underlying rhythm, sensing tests, atrial and left/right/biventricular pacing threshold, and proper programming to optimize device function and longevity. For CRT-D devices, follow-up also includes the detection of device-delivered therapies.

Important device features for heart failure include delivery of 100% biventricular stimulation, function assessment of three independent pacing and sensing channels, optimal programming of AV and VV intervals, atrial arrhythmia management, and monitoring of ventricular arrhythmias. Some device-derived features have been developed to monitor autonomous nervous system[378,379] and haemodynamic status[380] over time. Such monitoring parameters may be useful to assess responsiveness or, in contrast, to detect response failure early on before symptoms arise.

Echocardiographically guided AV and VV timing optimization is recommended mainly in patients with dubious response to therapy. Doppler evaluation of the transmitral flow has been widely used as a method of AV delay tuning.[339,381] The optimum AV delay is that which adjusts

the contraction sequence between left atrium and LV to optimize LV filling without truncating the atrial contribution.[339] Improper setting of AV delay may cause loss of pre-excitation, suboptimal atrial filling, and exacerbation of mitral regurgitation. Doppler estimation of the LV stroke volume utilizing the velocity time integral method has been used as a means of programming optimal VV timing. Although optimization of VV timing has been associated with an increase in the LV stroke volume in the acute phase,[340] chronic effects of optimized VV interval must still be assessed.

Approximately one-third of patients may experience intermittent or permanent loss of CRT during a long-term follow-up.[382] This interruption of therapy is mostly due to the occurrence of atrial tachyarrhythmias and is a common cause of hospitalization for worsening heart failure in these patients. However, successful re-institution of CRT may be achieved in the vast majority of patients.

Abbreviations

AF	Atrial fibrillation
ANTITACHY	Antitachycardia algorithms in pacemaker
AP	Antero-posterior
ATP	Adenosine triphosphate
AVB	Atrioventricular block
BP	Blood pressure
b.p.m.	Beats per minute
BV	Biventricular
CHF	Congestive heart failure
CPG	Committee for Practice Guidelines
CRT	Cardiac resynchronization therapy
CRT-D	Biventricular pacemaker combined with an ICD
CRT-P	Biventricular pacemaker
CSNRT	Corrected sinus node recovery time
CT	Computed tomography
ECG	Electrocardiogram
EF	Ejection fraction
EGM	Electrogram
EHRA	European Heart Rhythm Association
ESC	European Society of Cardiology
HOCM	Hypertrophic obstructive cardiomyopathy
Hosp	Hospitalizations
ICD	Implantable cardioverter defibrillator
IDCM	Ischaemic dilated cardiomyopathy
IMD	Interventricular electromechanical delay
LAO	Left anterior oblique
LV	Left ventricle
LVEDD	Left ventricular end-diastolic diameter
LVEF	Left ventricular ejection fraction
LVESV	Left ventricular end-systolic volume
LVOT	Left ventricular outflow tract
MPV	Minimization of pacing in the ventricles
NA	Non-applicable
NIDCM	Non-ischaemic dilated cardiomyopathy
OPT	Optimal pharmacological treatment
pVO_2	Peak oxygen consumption
QALY	Quality-adjusted life year
Q-Ao	QRS onset to onset of aortic flow
Q-Mit	QRS onset to onset of mitral annulus systolic wave
QOL	Quality of life
Q-Pulm	QRS onset to onset of pulmonary flow
Q-Tri	QRS onset to onset of tricuspid annulus systolic wave
RAO	Right anterior oblique
SCD	Sudden cardiac death
SSR	Stable sinus rhythm
VE/CO_2	Ventilation/carbon dioxide ratio
6MWT	6 min walk test

Clinical trial acronyms

ASSENT-II	Assessment of the Safety and Efficacy of a New Thrombolytic trial
BELIEVE	The Bi vs Left Ventricular Pacing: an International Pilot Evaluation on Heart Failure Patients with Ventricular Arrhythmias multicentre prospective randomized pilot study
CARE-HF	The Cardiac Resynchronization-Heart Failure trial
COMPANION	Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure trial
CTOPP	Canadian Trial of Physiological Pacing
DANPACE	Danish Multicenter Randomized Study on Atrial Inhibited versus Dual-Chamber Pacing in Sick Sinus Syndrome
DAVID	Dual Chamber and VVI Implantable Defibrillator trial
GUSTO-I	Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries-I
GUSTO-III	Global Use of Strategies to Open Occluded Coronary Arteries-III
ISSUE 2	International Study on Syncope of Uncertain Etiology 2
MILOS	Multicenter Longitudinal Observational Study
MIRACLE	Multicenter InSync Randomized Clinical Evaluation trial
MIRACLE ICD II	Multicenter InSync ICD Randomized Clinical Evaluation trial
MOST	Mode Selection Trial
MUSTIC	Multisite Stimulation in Cardiomyopathy study
OPSITE	Optimal Pacing SITE study
PASE	Pacemaker Selection in the Elderly trial
PATH CHF	Pacing Therapies in Congestive Heart Failure study
PAVE	Left Ventricular-Based Cardiac Stimulation Post AV Nodal Ablation Evaluation
SCD-HeFT	Sudden Cardiac Death in Heart Failure Trial
SYDIT	Syncope Diagnosis and Treatment study
SYNPACE	Vasovagal Syncope and Pacing trial
UKPACE	United Kingdom Pacing and Cardiovascular Events trial
VASIS	The Vasovagal Syncope International Study
VPS	North American Vasovagal Pacemaker Study

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