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REVIEW

Evolving Indications for Conventional Pacing

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KEY WORDS: *permanent pacemakers, atrioventricular block, vasovagal syncope, hypertrophic cardiomyopathy, atrial fibrillation*

ABBREVIATIONS
ACC = American College of Cardiology
AHA = American Heart Association
AV = atrioventricular
AVI = AV interval
ICD = implantable cardioverter defibrillator
LPRI = long PR interval
LV = left ventric-le(-ular)
LVOT = left ventricular outflow tract
MI = myocardial infarction
NASPE = North American Society of Pacing & Electrophysiology (now renamed: Heart Rhythm Society-HRS)
OHCM = obstructive hypertrophic cardiomyopathy
PVARP = post-ventricular atrial refractory period
RV = right ventricle

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ABSTRACT

Official guidelines for the indications of conventional permanent pacing are being updated periodically as the indications evolve continually. Also nontraditional indications for pacing emerge, such as marked first-degree AV block, malignant vasovagal syncope, obstructive hypertrophic cardiomyopathy, and paroxysmal atrial fibrillation. A critical review and analysis of these indications is undertaken in this review article.

INTRODUCTION

The indications for conventional pacing evolve continually with periodic upgrading of the well-known ACC/AHA/NASPE guidelines[1] and the development of nontraditional indications such as marked first-degree AV block, malignant vasovagal syncope, obstructive hypertrophic cardiomyopathy, and paroxysmal atrial fibrillation.[1-4] Rapid advances in pacemaker technology have provided improved systems to match the needs of patients in the aforementioned special situations.

2002 ACC/AHA/NASPE GUIDELINES

COMPLETE AV BLOCK

The 2002 ACC/AHA/NASPE guidelines designate, like the previous ACC/AHA recommendations, *asymptomatic* complete AV block (in the absence of co-morbidity) with ventricular escape rates >40 bpm as a class II indication for pacing. The rate criterion of >40 bpm is arbitrary and unnecessary. It is not the escape rate that is critical to stability, but rather the site of origin of the escape rhythm (junctional or ventricular). Rate instability may not be predictable or obvious. Irreversible acquired complete AV block should be a class I indication for pacing.[2]

TYPE I SECOND-DEGREE AV BLOCK

The 2002 ACC/AHA/NASPE guidelines state that type I second-degree AV block is usually due to delay in the AV node irrespective of QRS width.[1] Type I second-degree AV block with bundle branch block (far less common than narrow QRS type I block) must not be automatically labeled as AV nodal on the basis of this statement.

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With associated bundle branch block, type I block occurs in the His-Purkinje system in 60-70% of cases.[5] Infranodal type I block carries a poor prognosis with a substantial risk of progression to complete heart block.[5] Indeed, it is widely believed that type I and type II infranodal block carry the same prognosis. Consequently, most authorities recommend an electrophysiological study in *asymptomatic* patients with type I block and bundle branch block to determine the site of block.[5] The 2002 ACC/AHA/NASPE guidelines do not fully endorse this concept in the recommendation that "type I second-degree AV block at intra- or infra-His levels found at electrophysiology study performed for *other indications*" is a class IIa indication for pacing.[1] A more aggressive approach to this problem would be preferable because type I second-degree AV block in the His-Purkinje system represents diffuse conduction system disease and should be a class I indication for permanent pacing even in an asymptomatic patient.

TYPE II SECOND-DEGREE AV BLOCK

The definition of type II second-degree AV block continues to be problematic over 35 years since the advent of His bundle recordings and invasive cardiac electrophysiology.[6] In the 1998 ACC/AHA guidelines,[7] the definition of type II block was incomplete and subject to misinterpretation ("no progressive prolongation of the PR intervals before a blocked beat"). Note that "beat" was singular and conformed to the widely accepted criterion of a single blocked beat in the definition of type II block.[6,8,9] The 2002 ACC/AHA/NASPE guidelines state that "type II second-degree AV block is characterized by fixed PR intervals before and after the blocked beats." The pleural "beats" implies block of more than one beat that may create confusion with "advanced AV block" defined in the guidelines as block of 2 or more P waves. The 2002 ACC/AHA/NASPE guidelines as in the past, fail to mention the importance of a stable sinus rate in the diagnosis of type II second-degree AV block (Stability of the sinus rate is an important diagnostic criterion of type II block because a vagal surge can cause simultaneous sinus slowing and AV nodal block, generally a benign condition that can superficially resemble type II block.[6,10] Furthermore, vagally-induced AV block may occasionally exhibit an unchanged PR interval after a single blocked beat. It is also important to remember that when the PR interval after a single blocked impulse is shorter or the P wave is missing (if preempted by an escape complex), the diagnosis of type II block cannot be made regardless of the constancy of *all* the PR intervals before the single nonconducted P wave.[6] Such an arrangement should be considered as unclassifiable in terms of type II block.[6]

The 2002 ACC/AHA/NASPE guidelines introduced a new classification of type II second-degree AV block: wide QRS type II block (which makes up 65-80 % of type II blocks) with a class I indication for pacing and narrow QRS type II block with a class II indication for permanent pacing.[1] This differentiation is strange because there is no evidence that narrow QRS type II block is less serious than wide QRS type II block. The statement that "type II block is usually infranodal especially when the QRS is wide" may be the basis for this potentially misleading distinction. Type II block according to the strict definition is always infranodal and should be a class I indication regardless of QRS duration, symptoms or whether it is paroxysmal or chronic.[2,6]

INTRAVENTRICULAR CONDUCTION BLOCKS

The 2002 ACC/AHA/NASPE guidelines do not fully address certain types of AV block that require provocative maneuvers for diagnosis. Most of these situations like non-physiologic second- or third-degree His-Purkinje block induced by a "stress test" (that involves gradually increasing the rate of atrial pacing) should be class I indications irrespective of symptoms.[11] These conditions include: 1) The "fatigue" phenomenon in the His-Purkinje system induced only after abrupt cessation of rapid ventricular pacing (with or without the concomitant administration of a type IA antiarrhythmic agent in selected cases).[12,13] This challenge is usually performed after an unremarkable response to an atrial pacing "stress test." 2. Bradycardia-dependent (phase 4) block (not bradycardia-associated as in vagally-induced AV block). Phase 4 block is always *infranodal* and can be diagnosed with His bundle recordings and pauses following electrically-induced atrial or ventricular premature beats.[14]

ACUTE MYOCARDIAL INFARCTION

The ACC/AHA/NASPE 2002 guidelines advocate "persistent and symptomatic AV block" after acute myocardial infarction (MI) as a class I indication for pacing.[1] This vague statement ignores the simple fact that any form of AV block in acute MI can be symptomatic before it resolves completely.

The 2002 ACC/AHA/NASPE guidelines recommend that an electrophysiological study may be necessary if the site of block is uncertain in transient advanced (second- or third-degree) AV block and bundle branch block, a possible class I indication. However, the guidelines provide no information how to interpret the data from an electrophysiological study in the decision process to implant a permanent pacemaker.[2]

The 2002 ACC/AHA/NASPE guidelines continue to classify "persistent AV nodal block" as a class II indication without defining the term "persistent." The latitude of this recommendation may promote the unnecessary implantation of pacemakers in patients with inferior MI and narrow QRS AV block where permanent pacing is almost never required.[15] The term "persistent" has been interpreted by some workers to mean 14-16 days, a cut-off point that seems satisfactory. [15] On the basis of the 14-16 day criterion the need for permanent pacing in survivors of inferior MI who develop second- and/or third-degree AV block should not exceed 1-2% of the entire AV block group whether or not they are treated with throm-

bolytics or primary angioplasty.

SPECIAL SITUATIONS

FIRST-DEGREE AV BLOCK

The hemodynamic disturbance produced by marked first-degree AV block (>0.30 sec) has been called the "pacemaker syndrome without a pacemaker" because inadequate timing of atrial and ventricular systole forms the basis of the pacemaker syndrome.[16,17] Both sinus rhythm with a very long PR interval and VVI pacing with retrograde ventriculoatrial conduction share the same pathophysiology with P waves too close to the preceding ventricular complexes (Figures 1, 2). The 2002 ACC/AHA/NASPE guidelines for pacemaker implantation state that "first- or second-degree AV block with symptoms similar to pacemaker syndrome" constitutes a class IIa indication.[1] This recommendation was logically extended in the latest version to patients with type I second-degree AV block (even without bradycardia) who experience hemodynamic compromise due to loss of AV synchrony.[1,2] This recommendation for a dual chamber pacemaker with a more physiologic AV interval, applies primarily to patients with well-preserved left ventricular (LV) function. Patients with a poor LV fraction ≤35% should be considered for biventricular DDDR pacing especially in the setting of congestive heart failure. Invasive hemodynamic measurements may be helpful in questionable cases but need not be routine in the decision process to implant a pacemaker.[1] The diagnosis is obvious when the long PR interval does not shorten during an exercise test in association with effort intolerance and dyspnea.

A DDD pacemaker can restore a relatively normal AV interval, but it necessarily produces a paced sequence from the right ventricle (RV) which produces LV desynchronization that adversely affects cardiac hemodynamics, and LV myocardial perfusion and function.[18] Thus, in the individual patient with a long PR interval (LPRI) as an isolated abnormality, the clinician must decide whether there will be a net benefit provided by 2 opposing factors: a positive effect from AV delay optimization with a shorter AV delay and a negative inotropic effect produced by pacing- induced aberrant ventricular depolarization.[18] This determination can sometimes be made clinically and noninvasively but a hemodynamic study with temporary pacing may be required in selected cases (Fig. 2). In this respect, Iliev et al.[19] compared the AAI and DDD modes in patients with sick sinus syndrome (DDD pacemakers) and native but long AV conduction in otherwise normal hearts. At a pacing rate of 70 ppm at rest, there was no overall difference in the aortic flow time velocity integral (which reflects cardiac output) during AAI and DDD pacing. However when the patients were divided according to the AV interval (AVI), those with AVI <270 ms showed a higher aortic flow velocity integral during AAI pacing. When the AVI was >270 ms, the aortic flow velocity integral was higher during DDD pacing. Thus during DDD pacing the increments in cardiac output were greater with the longer native AV intervals. Conversely with a normal or near normal PR interval, a higher cardiac output was found during AAI pacing with a conducted QRS complex and spontaneous ventricular depolarization. Not surprisingly these workers found that at a pacing rate of 90 ppm, DDD was superior to AAI pacing. These data provide an important guideline in the management of patients with LPRI in that the hemodynamic improvement with pacing outweighs the negative impact on LV function when the PR interval >0.28 sec. Despite these hemodynamic considerations the long-term consequences of RV pacing on LV function in the LPRI syndrome are unknown.

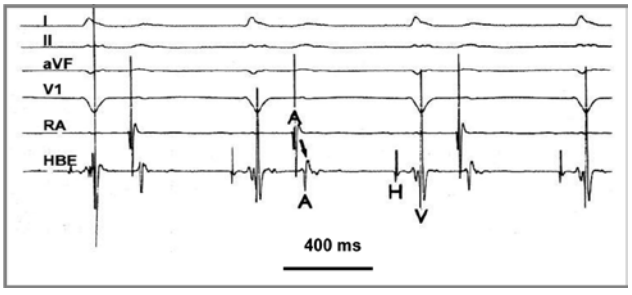

FIGURE 1. Surface ECG and intracardiac recording from a patient with symptomatic marked first-degree AV block. RA = high right atrial electrogram, HBE= electrogram at site of His bundle recording. Note the sequence of atrial activation (RA to HBE) is consistent with sinus rhythm and rules out retrograde atrial activation. The AH interval is markedly prolonged.

Pacemaker programming

An increase in the sinus rate coupled with a long PR interval can push the P wave continually into the postventricular atrial refractory period (PVARP) of a dual chamber pacemaker where it cannot be tracked.[20] This form of functional atrial undersensing can often be corrected or reduced by shortening the PVARP and AV delay. A relatively short PVARP (that would otherwise predispose to endless loop tachycardia) can often be used in the LPRI syndrome because retrograde VA block is common in these patients. In refractory cases of functional undersensing, AV junctional ablation should be considered. A recently developed algorithm used in cardiac resynchronization devices could be useful in the treatment of functional atrial undersensing in patients with LPRI syndrome. This algorithm restores 1:1 atrial tracking (provided the rate is slower than the programmed upper rate) by detecting the atrial event in the PVARP, whereupon it temporarily shortens the PVARP and permits sensing of the P wave outside the PVARP to promote the return of atrial tracking.

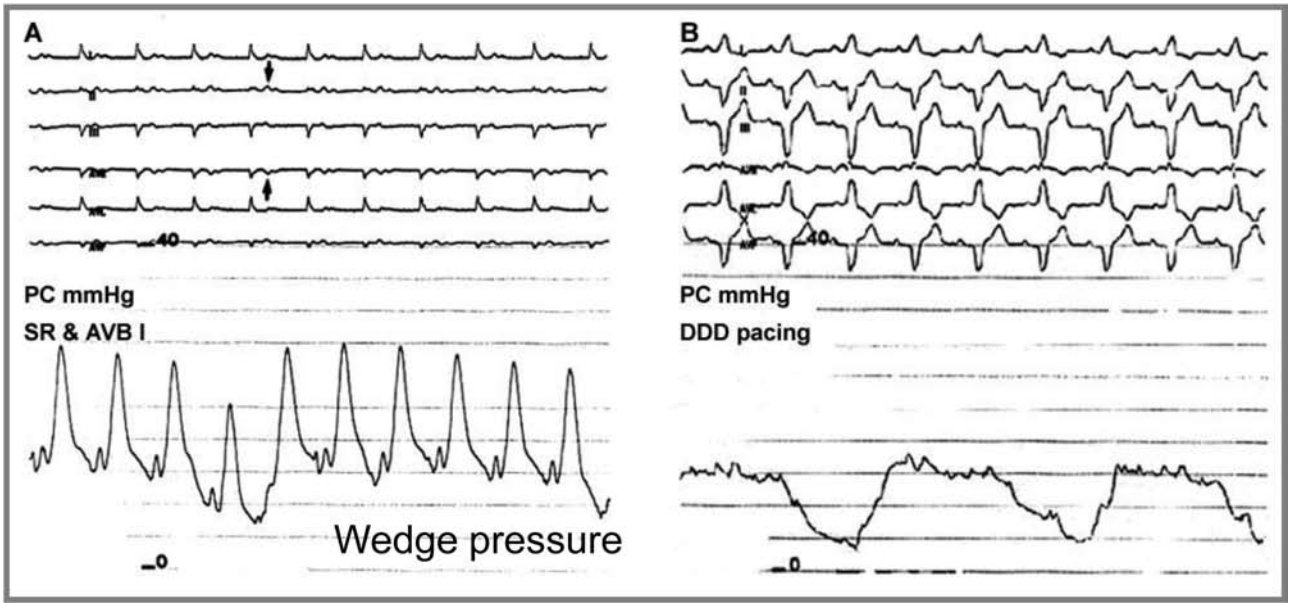

FIGURE 2. Same patient as Figure 1. A. Pulmonary capillary wedge pressure shows large cannon waves during sinus rhythm with a very long PR interval (Scale 0-40 mmHg). B. Note the normal pulmonary capillary wedge pressure after temporary dual chamber pacing with a physiologic AV delay (Scale 0-40 mm Hg).

VASOVAGAL SYNCOPE

Most patients with vasovagal syncope develop varying degrees of bradycardia during syncope. There is always a variable degree of vasodilatation. The value of pacing has therefore been questioned because vasodilatation often accompanies bradycardia at the time of fainting. In about 30% of the patients, the predominant manifestation is a vasodepressor reaction with hypotension without significant bradycardia. Pacing is obviously inappropriate in this group.

The results of observational nonrandomized studies suggest that dual chamber pacing may benefit patients with vasovagal syncope often in combination with drug therapy [21,22] single chamber (atrial or ventricular) pacemakers and dual chamber devices without atrial stimulation are contraindicated because they do not fully address the pathophysiology. Three randomized unblinded trials (2 multicenter controlled trials and one comparing beta-blocker therapy with pacing) suggested the efficacy of dual chamber pacing in a highly selected patient population with predominant cardioinhibitory syncope.[23-25] However, the fourth and last trial (2003) which was randomized and blinded (VPS II) showed no real benefit of pacing.[26] The study compared DDD (rate-drop response) vs ODO (sensing only). After 6 months, there was a trend towards pacing increasing the time to recurrence with a relative risk reduction of 30% which was not quite statistically significant (data presented in 2004 at the Heart Rhythm Society meeting indicated the same results after 1 year). At this juncture, pacing remains controversial and certainly capable of providing a placebo effect. The role of pacing needs further investigation because the VPS II study included only 100 patients, the eligibility criteria did not demand the same degree of bradycardia as in other randomized studies and the follow-up was relatively short.

Pacing seems to work in selected patients but is it worth it? Dual chamber pacing should not be first-line therapy for vasovagal syncope because many patients respond to drug therapy and/or training measures. The selection of candidates for pacing therapy is still unclear but it should be carefully considered in highly symptomatic patients with demonstrable (relative) bradycardia refractory if a reasonable course of medical therapy (at least 3 medication attempts) fails to prevent syncope. It is difficult to recommend a device (no-return therapy) for the following reasons: 1. Most patients are young and otherwise healthy. 2. The ability to discern the relative contributions of cardioinhibitory and vasodepressor features may be difficult. 3. Spontaneous vasovagal events may not always exhibit the same pathophysiologic features in a given individual and 4. Syncopal episodes may be clustered and sporadic. The decision to implant a pacemaker is easier in the older population. The 2002 ACC/AHA/NASPE guidelines for pacemaker implantation now recommend pacing carefully prescribed on the basis of tilt table testing as a class IIa indication, an unjustified promotion from a class IIb indication in the 1998 ACC/AHA guidelines.[1,7] However a conservative approach is wise because of the basically benign course of the

disease. The role of pacing is therefore likely to remain small and used only in highly selected patients: those with frequent episodes of syncope, in the setting of poor quality-of-life, risk of injury, occupational hazard, and in the absence of warning.[27] The implantation rate should be less than 0.5-1% of all the patients with this condition though it is unsurprising that about 2% of patients eventually referred to tertiary centers receive pacemakers.

Pacing attenuates the hemodynamic manifestations of vasovagal syncope and attenuates the fall in blood pressure. A more gradual drop in blood pressure during the attacks can be perceived thereby enabling the patient to take appropriate measures: lying down or stop driving a car. In patients with significant bradycardia during syncope, pacing may reduce or prevent episodes of syncope and significantly prolong the time from onset of symptoms to loss of consciousness. Thus dual chamber pacing with appropriate algorithms for vasovagal syncope can retard the appearance of symptoms. There is some evidence that a hysteresis rate-drop algorithm is superior to conventional pacing.[22] This algorithm works with a programmable heart-rate change-time duration "window" to quickly detect abrupt cardiac slowing (diagnosis) whereupon it activates a short period of selectable high rate pacing for a programmed duration (therapy). Pacemakers are being developed with special sensors to detect vasovagal pathophysiology in its early phase so that pacing therapy can begin earlier than with present devices that detect only bradycardia. The results of the randomized trials[27] may reflect the fact that we may be presently pacing the wrong way and that better technology and an earlier response may produce better results.

OBSTRUCTIVE HYPERTROPHIC CARDIOMYOPATHY

Many observational studies have suggested that dual chamber pacing can be effective therapy for symptomatic relief in patients with obstructive hypertrophic cardiomyopathy (OHCM).[28-32] Pacing reduces the LV outflow (LVOT) gradient by about 50% in most patients. However, data from controlled crossover randomized trials (that involved only 3 relatively small studies discussed below) are far less impressive and even controversial.[33-35] In the European Pacing In Hypertrophic Cardiomyopathy study (PIC study), 83 patients with OHCM (refractory or intolerant to drug therapy) and a resting LVOT gradient >30 mmHg underwent a randomized, cross-over study between AAI (at 30 ppm) and DDD pacing with short AV interval, each for a 12 week period.[33] Seventy-nine of the 83 patients (95%) preferred DDD pacing. Subsequent follow-up of patients for one year showed that pacing was beneficial on pressure gradient and symptoms in 72 patients (87%).[36] Subgroup analysis of the PIC data showed that improvement depended upon age, with a marked improvement between the ages of 60 and 70 which was statistically significant compared to other decades.

On the other hand, the M-PATHY study, which randomized 48 patients with resting LVOT ≥50 mmHg to receive 3 months of DDD and 3 months of AAI pacing, showed that the symptoms were not improved but when the patients were unblinded and followed for an additional 6 months, patients in the DDD phase were symptomatically improved.[34] This response suggests a strong placebo effect of pacing. In a subgroup of 6 elderly patients (>65 years), more striking clinical improvement was noted. In a smaller study with a similar double-blind randomized crossover design (21 patients with 19 completing the study), Nishimura et al[35] showed that pacing produced no symptomatic response despite significant reduction of LVOT tract gradient when DDD pacing was compared to AAI backup pacing (30/min) an observation consistent with a placebo effect.

The mixed findings in the 3 randomized trials are difficult to explain. Observations by Linde et al suggest that improvement with pacing is probably based on more than a placebo effect.[37] OHCM is a complex heterogeneous disease with variable symptoms and gradients so that an intervention such as pacing is liable to produce variable results. Furthermore changes in exercise capacity and NYHA class are not necessarily associated with a reduction in LVOT gradient.

The implantation of dual-chamber pacing is not primary therapy and should not be considered as replacement for drug therapy. Pacing should be weighed against the risk and efficacy of surgical left ventricular myectomy and percutaneous transcoronary septal myocardial ablation with ethanol injection into the first septal artery (chemical myectomy).[38-40] There are no prospective randomized studies comparing pacing with other therapeutic strategies. The 2002 ACC/AHA/NASPE guidelines for implantation of pacemakers list medically refractory symptomatic HOCM with significant resting or provoked LV outflow obstruction as a Class IIb indication seemingly based on data from observational reports with favorable results derived mostly from retrospective uncontrolled studies.[1] The guidelines are vague on what constitutes a "significant resting or provoked gradient" in HOCM patients but they do say that patients with a resting gradient ≥30 mm Hg or a provoked LVOT gradient ≥50 mm Hg may derive the most benefit. Pacing is obviously indicated in patients who develop bradycardia secondary to successful pharmacologic therapy. In patients without bradycardia, pacing for HOCM should be considered only in drug-refractory patients (especially the elderly) in whom surgical myomectomy (superior to pacing in symptom relief and gradient reduction according to a recent comparison study) is either unwise, contraindicated, rejected (or are not optimal candidates). Such patients should be warned of the uncertainty of acute or long-term improvement.

PACEMAKER PROGRAMMING

A flexible dual chamber device and meticulous programming are essential for successful outcome. The pacemaker must be programmed with a short AV interval to avoid spontaneous ventricular depolarization at all times. One must ensure complete ventricular capture at rest and on exercise without any evidence of ventricular fusion resulting from partial activation via the normal pathways.[4] The optimal pacemaker AV delay should be determined under echo-Doppler control. An excessively short AV delay causes impaired LV filling and loss of the atrial contribution. A relatively long pacemaker AV delay defeats the very purpose of pacing. In some patients the PR interval is so short that the pacemaker cannot provide an hemodynamically beneficial AV delay shorter than the PR interval. Drugs may help by prolonging AV conduction. In refractory cases, the creation of complete AV block by radiofrequency ablation of the AV junction permits the establishment of pacemaker-controlled ventricular depolarization at all times and facilitates overall management.

FAILURE OF PACING TO IMPROVE SYMPTOMS AND RELIEVE OBSTRUCTION

The commonest cause of failure to improve symptoms or reduce the LVOT gradient is inappropriate pacemaker programming with the AV delay too short or too long.[4,28,29] A poor response may be due to a proximal RV pacing lead instead of the most distal apical site. Other causes include an inadequate trial period (months may be required), mitral regurgitation (primary or unrelated to OHCM), aberrant papillary muscle obstructing the LVOT, mid-cavity obstuction, inappropriate drug therapy and atrial and ventricular arrhythmias. [29,30]

MECHANISM OF IMPROVEMENT AND NATURAL HISTORY

Inverted LV activation and altered or paradoxical septal motion widens the LVOT in systole. This mechanism does not entirely explain the therapeutic benefit because there is a progressive reduction in the LVOT gradient with time.[4,30] Indeed some patients do not improve on a short-term basis but require several months or longer for optimal improvement. This suggests that factors other than altered septal motion, such as cellular and molecular modification of the myocardium account for the clinical improvement. The evidence for LV remodeling is controversial. The impact of pacing on the natural history and prevention of sudden death is unknown.

INDICATIONS FOR A DUAL CHAMBER DEFIBRILLATOR

Pacing does not reduce mortality or sudden cardiac death. The question arises as to whether it would be preferable to implant a dual chamber defibrillator (with DDDR pacing capability) in most or all patients in whom pacing is being considered because of OHCM patients are at risk of malignant ventricular tachyarrhythmias and sudden death. At this juncture a prophylactic defibrillator (ICD) should at least be considered in high risk patients (whether or not pacing is intended): family history of sudden death, recurrent syncope, abnormal blood pressure response to exercise, septal or LV thickness ≥30 mm, and Holter documented nonsustained ventricular tachycardia. In future genotyping might become an important marker in risk stratification.[41-44] Atrial tachyarrhythmias often result in serious hemodynamic consequences and an ICD with atrial defibrillation capability would also be a consideration. ICDs often remain dormant for prolonged periods before discharge (up to 9 years) emphasizing the unpredictability of arrhythmic sudden death, the long risk period and the need for extended follow-up.[45-47]

CONTROL OF PAROXYSMAL ATRIAL FIBRILLATION

Conventional dual chamber and AAI pacing reduces the incidence of chronic atrial fibrillation compared to single chamber ventricular pacing in patients with sick sinus syndrome.[48] The 1998 ACC/AHA guidelines for pacemaker implantation stated a class IIb for "prevention of symptomatic drug-refractory recurrent atrial fibrillation".[7] This vague statement was misleading and it has now been replaced by "prevention of symptomatic drug-refractory recurrent atrial fibrillation in patients with coexisting sinus node disease" also as a class IIb indication.[1] This new recommendation reflects the lack of evidence that pacing can prevent atrial fibrillation in patients without bradycardia. The complexity of pacing in atrial fibrillation depends on many factors: presence of bradycardia, left atrial size, interatrial conduction delay, underlying disease, substrate modification at precise sites, single or multiple algorithms addressing triggers, potentiation by drugs and the precise definition of endpoints.

Modification of the atrial fibrillation substrate by dual site atrial pacing or pacing from single unconventional sites (high atrial septum near Bachmann's bundle or low atrial septum) can prevent atrial fibrillation in some patients with advanced interatrial conduction delay (P wave >120 ms).[49-54] Pacing appears less likely to provide an additive effect in patients with bradycardia but no interatrial conduction delay. The results are so far unimpressive and need to be confirmed in large-scale trials.[55,56] Furthermore, it is impossible to predict which patients will from these pacing modalities. When it works, pacing improves the atrial activation sequence and reduces atrial asynchrony related to slow conduction.[57,58] New pacemakers with sophisticated algorithms (delivering either dynamic overdrive suppression without a substantial increase in the pacing rate or reacting to atrial premature beats) designed to target potential triggers of atrial fibrillation are being investigated

for the prevention of atrial fibrillation mostly in patients with antibradycardia pacemakers.[57-59] Preliminary evidence suggests that dynamic overdrive suppression provide a modest benefit by reducing atrial fibrillation burden in patients with conventional antibradycardia devices but the effect may be attenuated by frequent ventricular pacing.[59,60] Many other complex algorithms are being investigated and a combination of several algorithms may ultimately prove more useful than a single one.[57,58] Finally, antitachycardia pacemakers are capable of terminating organized atrial tachyarrhythmias that predispose to atrial fibrillation.[61] All in all, the control of atrial fibrillation is difficult and often requires tailoring the treatment for individual patients employing so-called hybrid therapy with 2 or 3 strategies in the same patient, bearing in mind that pacing may potentiate the effect of antiarrhythmic therapy. Pacing should not replace pulmonary vein ablation in suitable candidates.

PACING FOR SLEEP APNEA

Sleep apnea is a common medical problem, and affects 2-4% of the middle-aged population of the United States. During apneic episodes there is a high incidence of asymptomatic cardiac arrhythmias amenable to treatment. As the patients are asleep, these arrhythmias are asymptomatic. Recent observations suggest that pacemakers with minute-ventilation sensors can make the diagnosis of sleep apnea in patients with congestive heart failure (CHF). In a recent publication, Garrigue et al[62] reported that pacing may reduce the incidence of apnea/hypopnea episodes. The patients were randomized to AAI pacing at >15 bpm over the nocturnal rate, or to VVI pacing at 40 bpm, each for 1 day. There was a significant reduction from 9 to 3 episodes/hour after pacing without changing the sleeping duration nor the overall pacing rate. So far, these observations have not yet been confirmed in follow-up studies.[63-65] No pacemaker has yet been implanted primarily for the treatment of sleep apnea but ongoing trials are evaluating this potential therapy in patients with sleep apnea who otherwise require antibradycardia pacing.

REFERENCES

1. Gregoratos G, Abrams J, Epstein AE, et al. ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/NASPE Committee to Update the 1998 Pacemaker Guidelines). *Circulation* 2002; 106:2145-2161.
2. Hayes DL, Barold SS, Camm AJ, et al. Evolving indications for permanent cardiac pacing. An appraisal of the 1998 ACC/AHA guidelines. *Am J Cardiol* 1998;82:1082-1086.
3. Hayes DL. Evolving indications for permanent pacing. *Am J Cardiol* 1999;83 (5B):161D-165D.
4. Barold SS. New and evolving indications for cardiac pacing. In Singer I (Ed), Interventional Electrophysiology, Williams, Wilkins, Lippincott, Baltimore, 2001:781.
5. Barold SS. Lingering misconceptions about type I second-degree atrioventricular block. *Am J Cardiol* 2001; 88:1018-1020
6. Barold SS, Hayes DL. Second-degree atrioventricular block: a reappraisal. Mayo Clin Proc. 2001; 76:44-57.
7. Gregoratos G, Cheitlin MD, Freedman RA, et al. ACC/AHA guidelines for implantation of cardiac pacemakers and antiarrhythmia devices; a report of the American College of Cardiology/American Heart Association task force on practice guidelines (Committee on pacemaker implantation). *J Am Coll Cardiol* 1998;31:1175-1209.
8. WHO/ISC Task Force. Definition of terms related to cardiac rhythm. *Am Heart J* 1978; 95:796-806.
9. Surawitz B, Uhley H, Borun R, et al. Optimal Electrocardiography. Tenth Bethesda Conference co-sponsored by the American College of Cardiology and Health Administration of the Department of Health, Education, and Welfare Task Force 1. Standardization of terminology and interpretation. *Am J Cardiol* 1878;41:130-144.
10. Massie B, Scheinman MM, Peters R, et al. Clinical and electrophysiologic findings in patients with paroxysmal slowing of the sinus rate and apparent Mobitz type II atrioventricular block. *Circulation* 1978;58:3305-314.
11. Petrac D, Radic B, Birtic K, et al. Prospective evaluation of infrahisal second-degree AV block induced by atrial pacing in the presence of chronic bundle branch block and syncope. *PACE* 1996;19:784-792.
12. Narula OS, Runge M. Accommodation of AV nodal conduction and "fatigue" phenomenon in the His-Purkinje system. In The Conduction System of the Heart. Wellens HJJ, Lie KI, Janse M (Eds). Leiden, Stenfert Kroese 1976:529-544.
13. Englund A, Bergfeldt L, Rosenqvist M. Pharmacological stress testing of the His-Purkinje system in patients with bifascicular block. *PACE* 1998;21:1979-1987.
14. Denes P, Murabit I, Ezri M et al. Tachycardia- and bradycardia-dependent block: observations regarding the mechanism of block. *J Am Coll Cardiol* 1987;9:446-449.
15. Barold SS. American College of Cardiology/American Heart Association guidelines for pacemaker implantation after acute myocardial infarction. What is persistent advanced AV block at the atrioventricular node? *Am J Cardiol* 1997;80:770-774.
16. Barold SS. Optimal pacing in first-degree AV block. *PACE* 1999;22:1423-1424
17. Mabo P, Cazeau S, Forrer A, et al. Isolated long PR interval as only indication of permanent DDD pacing (abstract). J Am Coll Cardiol 1992;19:66.
18. Barold SS. Adverse effects of ventricular desynchronization induced by long-term right ventricular pacing. *J Am Coll Cardiol* 2003;42:624-626.
19. Iliev II, Yamachika S, Muta K, et al. Preserving normal ventricular activation versus atrioventricular delay optimization

during pacing: The role of intrinsic atrioventricular conduction and pacing rate. *PACE* 2000;23:74-80.
20. Bode F, Wiegand U, Katus HA, et al. Pacemaker inhibition due to prolonged native AV interval in dual-chamber devices. *PACE* 1999;22:1425-1431.
21. Raj SR, Sheldon RS. Permanent cardiac pacing to prevent vasovagal syncope. *Curr Opin Cardiol* 2002; 17:90-95.
22. Sheldon R, Koshman ML, Wilson W, et al. Effect of dual-chamber pacing with automatic rate-drop sensing on recurrent neurally mediated syncope. *Am J Cardiol* 1999;81:158-162.
23. Connolly SJ, Sheldon R, Roberts RS et al. The North American Vasovagal Study (VPS). A randomized trial of permanent pacing for the treatment of vasovagal syncope. *J Am Coll Cardiol* 1999;33:16-20.
24. Sutton R, Brignole M, Menozzi C, et al. Dual chamber pacing in the treatment of neurally-mediated tilt-positive syncope: pacemaker versus no therapy: a multicenter randomized study. The Vasovagal Syncope International Study (VASIS) Investigators. *Circulation* 2000;102:294-299.
25. Ammirati F, Colivicchi F, Santini M, et al. Syncope Diagnosis and Ttreatment Study Investigators. Permanent cardiac pacing versus medical treatment for the prevention of recurrent vasovagal syncope: a multicenter randomized controlled trial. *Circulation* 2001;104:52-57.
26. Connolly SJ, Sheldon R, Thorpe KE, et al. Pacemaker therapy for prevention of syncope in patients with recurrent severe syncope. Second Vasovagal Pacemaker Study (VPS II): a randomized trial. *JAMA* 2003;7:224-229.
27. Brignole M. Randomized clinical trials of neurally mediated syncope. *J Cardiovasc Electrophysiol* 2003; 14(9 Suppl):S64-S69.
28. Fananapazir L, Epstein ND, Curiel RV, et al. Long-term results of dual-chamber (DDD) pacing in obstructive hypertrophic cardiomyopathy. Evidence for progressive symptomatic and hemodynamic improvement and reduction of left ventricular hypertrophy. Circulation 1994;90:2731-2742.
29. Fananapazir L, Atiga W, Tripodi D, et al. Therapy in obstructive hypertrophic cardiomyopathy. The role of dual chamber (DDD) pacing in Barold SS, Mugica J (Eds). Recent advances in cardiac pacing. Goals for the 21st century. Armonk NY Futura Publishing Co. 1998;35-50.
30. Fananapazir L, McAreavey D. Therapeutic options in patients with obstructive hypertrophic cardiomyopathy and severe drug-refractory symptoms. *J Am Coll Cardiol* 1998;31:259-264.
31. Nishimura RA, Holmes DR Jr. Clinical Practice. Hypertrophic obstructive cardiomyopathy. *New Engl J Med* 2004;350:1320-1327
32. Elliot P, McKenna WJ. Hypertrophic cardiomyopathy. *Lancet* 2004;363:1881-1891
33. Kappenberger L, Linde C, Daubert C et al. Pacing in hypertrophic obstructive cardiomyopathy. A randomized crossover study. PIC Study Group. *Eur Heart J* 1997;18:1249-1256.
34. Maron BJ, Nishimura RA, McKenna WJ, et al. Assessment of permanent dual-chamber pacing as a treatment for drug-refractory symptomatic patients with obstructive hypertrophic cardiomyopathy. A randomized, double-blind, crossover study (M-PATHY). *Circulation* 1999;99:2927-2933.
35. Nishimura RA, Trusty JM, Hayes DL, et al. Dual-chamber pacing for hypertrophic cardiomyopathy: a randomized, double-blind, crossover trial. *J Am Coll Cardiol* 1997;29:435-441.
36. Gadler F, Linde C, Daubert C, et al. Significant improvement of quality of life following trioventricular synchronous pacing in patients with hypertrophic obstructive cardiomyopathy. Data from 1 year of follow-up. PIC study group. Pacing in Cardiomyopathy. *Eur Heart J* 1999;20:1044-1050.
37. Linde C, Gadler F, Kappenberger L. Placebo effect of pacemaker implantation in obstructive hypertrophic cardiomyopathy. PIC Study Group. Pacing in Cardiomyopathy. *Am J Cardiol* 1999;83:903-907.
38. Ommen SR, Nishimura RA, Squires RW, et al. Comparison of dual-chamber pacing versus septal myectomy for the treatment of patients with hypertropic obstructive cardiomyopathy: a comparison of objective hemodynamic and exercise end points. *J Am Coll Cardiol* 1999;34:191-196.
39. Firoozi S, Elliott PM, Sharma S, et al. Septal myotomy-myectomy and transcoronary septal alcohol ablation in hypertrophic obstructive cardiomyopathy. A comparison of clinical, haemodynamic and exercise outcomes. *Eur Heart J* 2002 Oct;23(20):1617-1624.
40. Nielsen CD, Killip D, Spencer WH 3rd. Nonsurgical septal reduction therapy for hypertrophic obstructive cardiomyopathy: short-term results in 50 consecutive procedures. *Clin Cardiol* 2003;26:275-279.
41. Maron BJ. Risk stratification and prevention of sudden death in hypertrophic cardiomyopathy. *Cardiol Rev* 2002;10:173-181
42. Maron BJ. Contemporary considerations for risk stratification, sudden death and prevention in hypertrophic cardiomyopathy. *Heart* 2003;89:977-978.
43. Monserrat L, Elliott PM, Gimeno JR, et al. Non-sustained ventricular tachycardia in hypertrophic cardiomyopathy: an independent marker of sudden death risk in young patients. *J Am Coll Cardiol* 2003;42:873-879
44. Maron BJ, McKenna WJ, Danielson GK, et al.Task Force on Clinical Expert Consensus Documents. American College of Cardiology; Committee for Practice Guidelines. European Society of Cardiology. American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy. A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. *J Am Coll Cardiol* 2003; 42:1687-713.
45. Maron BJ, Shen WK, Link MS, et al. Efficacy of Implantable cardioverter-defibrillators for the prevention of sudden death in patients with hypertrophic cardiomyopathy. *New Engl J Med* 2000;342:365-373.
46. Jayarilleke I, Doolan A, Ingles J, et al. Long-term follow-up of implantable cardioverter-defibrillator therapy for hypertrophic cardiomyopathy. *Am J Cardiol* 2004;93:1192-1194.
47. Begley DA, Mohiddin SA,Tripodi D, et al. Efficacy of implantable cardioverter-defibrillator therapy for primary and second-

ary prevention of sudden death in hypertrophic cardiomyopathy. *PACE* 2003;26:1887-1896.
48. Lamas GA, Ellenbogen KA. Evidence for pacemaker mode selection: from physiology to randomized trials. *Circulation* 2001;109:443-451.
49. Barold SS. Prevention of atrial fibrillation by multisite atrial pacing. *J Electrocardiol* 2001;34:49-52.
50. Saksena S, Prakash A, Ziegler P, et al. Improved suppression of recurrent atrial fibrillation with dual-site right atrial pacing and antiarrhythmic drug therapy. *J Am Coll Cardiol* 2002;40:1140-1150.
51. D'Allonnes GR, Pavin D, Leclercq C, et al. Long-term effects of biatrial synchronous pacing to prevent drug-refractory atrial tachyarrhythmia: a nine-year experience. *J Cardiovasc Electrophysiol* 2000;11:1081-1091
52. Daubert JC, Pavin D, Jauvert G, et al. Intra- and interatrial conduction delay: implications for cardiac pacing. *PACE* 2004;27:507-525.
53. Leclercq JF, De Sisti A, Fiorello P, et al. Is dual site better than single site atrial pacing in the prevention of atrial fibrillation? *PACE* 2000;23:2101-2107.
54. Padeletti L, Michelucci A, Pieragnoli P, et al. Atrial septal pacing: a new approach to prevent atrial fibrillation. *PACE* 2004;27:850-854.
55. Savelieva I, Camm AJ. The results of pacing trials for the prevention and termination of atrial tachyarrhythmias: is there any evidence of therapeutic breakthrough? *J Interv Card Electrophysiol* 2003;8:103-115.
56. Kok LC, Ellenbogen KA. Device therapy for atrial fibrillation. *Cardio Clin* 2004;22:71-86.
57. Israel CW, Barold SS. Pacing algorithms for prevention of atrial tachyarrhythmias. In: Israel CW, Barold SS (Eds), Advances in the Treatment of Atrial Tachyarrhythmias. Pacing, Cardioversion and Defibrillation. Armonk, NY, Futura 2002:139-171.
58. Israel CW, Hohnloser SH. Pacing to prevent atrial fibrillation. *J Cardiovasc Electrophysiol* 2003;14(9Suppl):S20-S26.
59. Carlson MD, Ip J, Messenger J, et al. Atrial Dynamic Overdrive Pacing Trial (ADOPT) Investigators. *J Am Coll Cardiol* 2003;42:627-633.
60. Gold MR, Fain E, Messenger J, et al. Frquent ventricular pacing attenuates the benefit of dynamic atrial overdrive for the prevention of atrial fibrillation (abstract). *Heart Rhythm* 2004;1(Issue 1S):S65-66.
61. Israel CW, Barold SS. Can implantable devices detect and pace-terminate atrial fibrillation? *PACE* 2003;26:1923-1925.
62. Garrigue S, Bordier P, Jais P et al. Benefit of atrial pacing in sleep apnea syndrome. *N Engl J Med* 2002;346:404-412.
63. Theres H, Melzer C, Duru C, et al. Nocturnal overdrive pacing does not reduce sleep apnea in pacemaker patients (Abstract). *Heart Rhythm* 2004;1(Issue 1S):S149-150.
63. Garrigue S, Defaye P, Poezevara Y, et al. Can atrial pacing prevent pure obstructive sleep apnea? (Abstract). *Heart Rhythm* 2004;1(Issue 1S):S81.
64. Luethje LGC, Unterberg C, Vollman D et al. Atrial overdrive pacing for the reduction of sleep apnea severity (Abstract). *Europace* 2004;16 (Suppl I):S118.