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REVIEW

First-degree atrioventricular block

Clinical manifestations, indications for pacing, pacemaker management & consequences during cardiac resynchronization

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Abstract Marked first-degree AV block (PR ≥ 0.30 s) can produce a clinical condition similar to that of the pacemaker syndrome. Clinical evaluation often requires a treadmill stress test because patients are more likely to become symptomatic with mild or moderate exercise when the PR interval cannot adapt appropriately. Uncontrolled studies have shown that many such symptomatic patients with normal left ventricular (LV) function improve with conventional dual chamber pacing (Class IIa indication). In contrast, marked first-degree AV block with LV systolic dysfunction and heart failure is still a Class IIb indication, a recommendation that is now questionable because a conventional DDD (R) pacemaker would be committed to right ventricular pacing (and its attendant risks) virtually 100% of the time. It would seem prudent at this juncture to consider a biventricular DDD device in this situation. Patients with suboptimally programmed pacemakers may develop functional atrial undersensing because the P wave tends to migrate easily into the postventricular atrial refractory period (PVARP). Retrograde vetriculoatrial conduction block is uncommon in marked first-degree AV block so a relatively short PVARP can often be used at rest with little risk of endless loop tachycardia. The usefulness of a short PVARP may be negated by special PVARP functions in some pulse generators designed to time out a long PVARP at rest and a gradually shorter one with activity. First-degree AV block during cardiac resynchronization therapy (CRT) predisposes to loss of ventricular resynchronization during biventricular pacing because it favors the initiation of electrical "desynchronization" especially in association with a relatively fast atrial rate and a relatively slow programmed upper rate. Patients with first-degree AV block have a poorer outcome with CRT than patients with a normal PR interval, a response that may involve several mechanisms. (1) The long PR interval may be a marker of more advanced heart disease. (2) Patients with first-degree AV block may experience more episodes of undetected "electrical desynchronization". (3) "Concealed resynchronization" whereupon ventricular activation in patients with a normal PR interval may result from fusion of electrical wavefronts coming from the right bundle branch and the impulse from the LV electrode. The resultant hemodynamic response may be superior because the detrimental effects of right ventricular stimulation (required in the setting of a longer PR interval) are avoided.

Keywords Cardiac pacing · First-degree atrioventricular block · Cardiac resynchronization · Biventricular pacing · Heart failure · Atrial undersensing

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1 Clinical manifestations and indications for pacing

First-degree atrioventricular (AV) block, often considered a relatively benign arrhythmia, can occasionally be associated with severe symptoms. Although there is little evidence to suggest that pacemakers improve survival in patients with isolated first-degree AV block, it is now recognized that marked (PR ≥ 0.30 s) first-degree AV block (the cutoff for this discussion) can lead to symptoms similar to those in the pacemaker syndrome even in the absence of higher degrees of AV block [1–8]. Uncontrolled trials have shown that many symptomatic patients with a PR interval ≥ 0.30 s can be improved with dual chamber pacing especially in patients with normal left ventricular (LV) function [1–8].

1.1 Echocardiography

Prolonged AV conduction is not uncommon in patients with congestive heart failure (CHF). In this situation, atrial systole occurs too early in diastole causing an ineffective or decreased contribution of atrial systole to the cardiac output. The subsequent decrease in cardiac output is poorly tolerated in CHF patients. Atrial contraction begins in early diastole resulting in atrial contraction becoming superimposed upon the early LV filling phase and much earlier than the onset of left ventricular (LV) systolic pressure. There is therefore delay of the E wave with resultant fusion between the E and A waves producing shortening of the LV diastolic filling time (Fig. 1). The delay in AV conduction induces diastolic mitral regurgitation [9–14] (Fig. 2). In a normal heart, atrial systole occurs immediately before ventricular systole. In the setting of a long AV delay, the atrium begins to relax and atrial pressure drops after atrial systole. The mitral valve remains open because LV contraction is delayed. With the mitral valve open, the LV end-diastolic pressure (LVEDP) rises and exceeds left atrial pressure thereby producing diastolic mitral regurgitation, a decrease in preload (LVEDP) at the onset of LV systole and, ultimately, a decrease in LV dP/dt max and cardiac output. Such mitral regurgitation appears inconsequential in the normal heart but may be important in patients with severe LV dysfunction. Programming an optimal AV/PV delay helps to eliminate diastolic mitral regurgitation.

1.2 Pacemaker-like syndrome

AAI(R) pacing with a very long PR interval is a well-known cause of pacemaker syndrome [15]. This form of pacemaker syndrome has resurfaced recently in patients with intermittent marked first-degree AV block during managed ventricular pacing to minimize right ventricular pacing. In this pacing mode, the device permits the establishment of very long PR intervals without the emission of a ventricular output [16].

A long PR interval (≥0.30 s) without a pacemaker shares the same pathophysiology as VVI pacing with retrograde VA conduction or an AAI-induced pacemaker syndrome

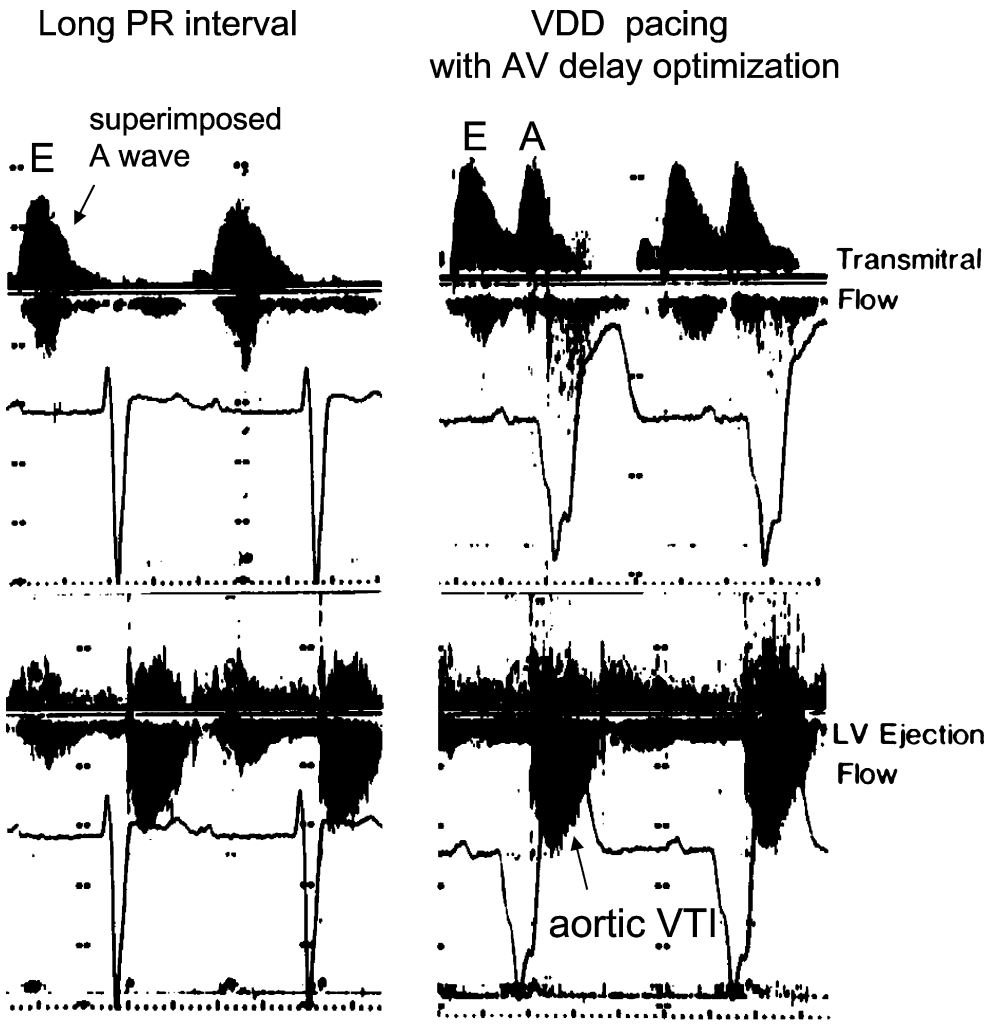

Fig. 1 Pulsed wave Doppler echocardiography coupled with the surface ECG in a patient with a long PR interval. *Left panel*: the E and A waves are superimposed due to the very late diastole resulting from a very delayed ventricular activation. *Right panel*: dual chamber pacing results in shortening of the AV interval (from atrial sensing to onset of ventricular pacing). The E wave now occurs well before the A wave (atrial contraction). This increases the left ventricular filling time and the aortic velocity–time integral (VTI). (Reproduced with permission from Garrigue S. Optimization of cardiac resynchronization therapy: the role of echocardiography in atrioventricular, interventricular and intraventricular delay optimization. In: Yu CM, Hayes DL, Auricchio A (Eds), Cardiac Resynchronization Therapy, Malden, MA, Blackwell-Futura, 2006:310–328)

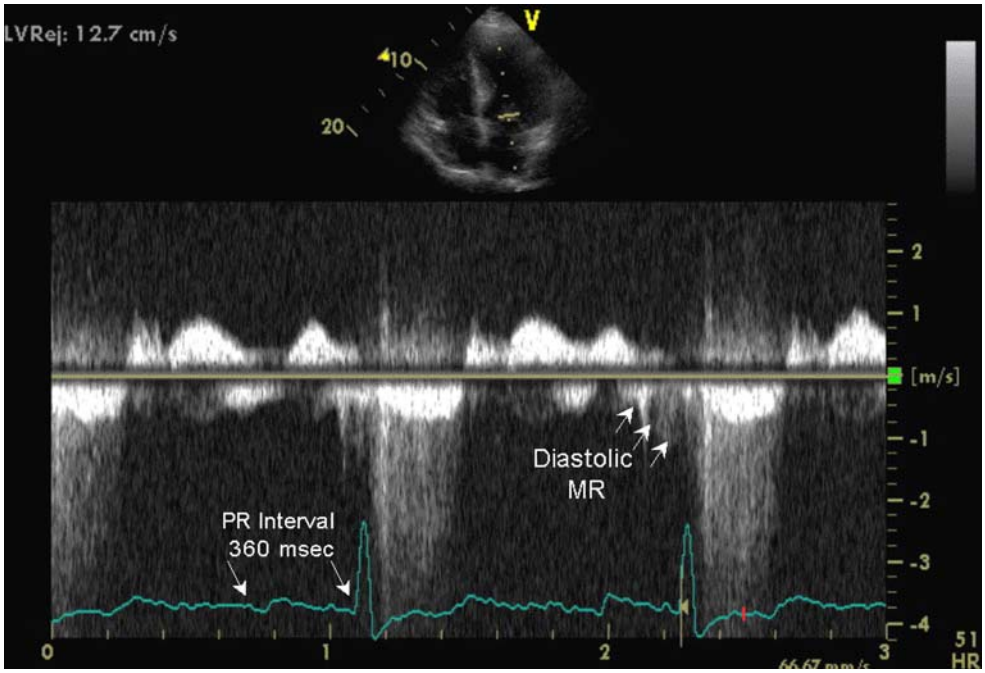

Fig. 2 Continuous-wave Doppler echocardiographic recording of transmitral blood flow velocity demonstrating diastolic mitral regurgitation in a patient with first-degree AV block with a markedly prolonged PR interval of 360 ms. The low velocity regurgitant signal is seen in diastole following the atrial filling wave and prior to the onset of systolic mitral regurgitation

[17]. Some workers have called the hemodynamic disturbance produced by marked first-degree AV block a "pacemaker syndrome without a pacemaker" [1], and others have labeled this entity as "pseudopacemaker syndrome" [4]. Unfortunately, these characterizations are potentially confusing. The term "pacemaker-like" syndrome is probably more appropriate [18].

Although patients with symptomatic marked first-degree AV block (≥0.30 s), and normal LV function can benefit from dual chamber pacing, some patients with a long PR interval (LPRI) and delayed interatrial conduction time (manifested by a prolonged P wave) may be hemodynamically compensated because they have an appropriately timed mechanical left AV synchrony, a situation where improvement would not be expected with pacing [19].

1.3 Clinical evaluation

It is incumbent upon the clinician to try to establish that in symptomatic patients with a LPRI (as an isolated abnormality), the benefit of pacing with optimized AV synchrony (with a shorter AV delay) will outweigh the impairment of LV function produced by right ventricular pacing with resultant LV dyssynchrony but this determination may be difficult or impossible [20–22] (Fig. 3). An acute determination of the clinical status and need for permanent pacing can often be made noninvasively. Occasionally a therapeutic decision may be facilitated with data from an invasive hemodynamic study with temporary right atrial and ventricular pacing to assess the hemodynamic response to AV interval optimization. Such a study coupled with echocardiography may reveal pacing-induced mitral regurgitation or its aggravation, findings predictive of long-term mitral valve dysfunction. However, an acute hemodynamic improvement with a more physiologic AV delay does not guarantee long-term benefit in these patients because of the risk of harmful long-term effects of continual right ventricular pacing.

Patients with LPRI may or may not be symptomatic at rest. They are more likely to become symptomatic with mild or moderate exercise when the PR interval does not shorten appropriately and atrial systole shifts progressively closer towards the preceding ventricular systole. The long PR interval itself may occasionally become manifest only on exercise. In this respect, Mabo et al. [23] reported five patients who demonstrated paradoxical prolongation of the PR interval on exercise from 220 ± 19 ms at rest to 286 ± 80 ms thereby canceling the benefit of atrial systole. Adaptation of the PR interval on exercise is unlikely in patients with a PR interval ≥ 0.30 s.

Patients with subtle symptoms should also undergo a treadmill stress test to determine the hemodynamic disadvantage of the LPRI (defined as ≥ 0.30 s in this review). The necessity and appropriateness of a diagnostic temporary AV pacing study in LPRI patients are questionable, especially if the PR interval is very long at rest (≥0.30 s), and does not shorten or even lengthens on exercise. During a resting pacing study it may not be possible to demonstrate symptomatic improvement, and the execution of exercise studies with temporary dual-chamber pacemaker in place is difficult. Therefore it is reasonable to recommend a permanent pacemaker in many symptomatic LPRI patients without a temporary pacing study that would add unnecessary risk and cost.

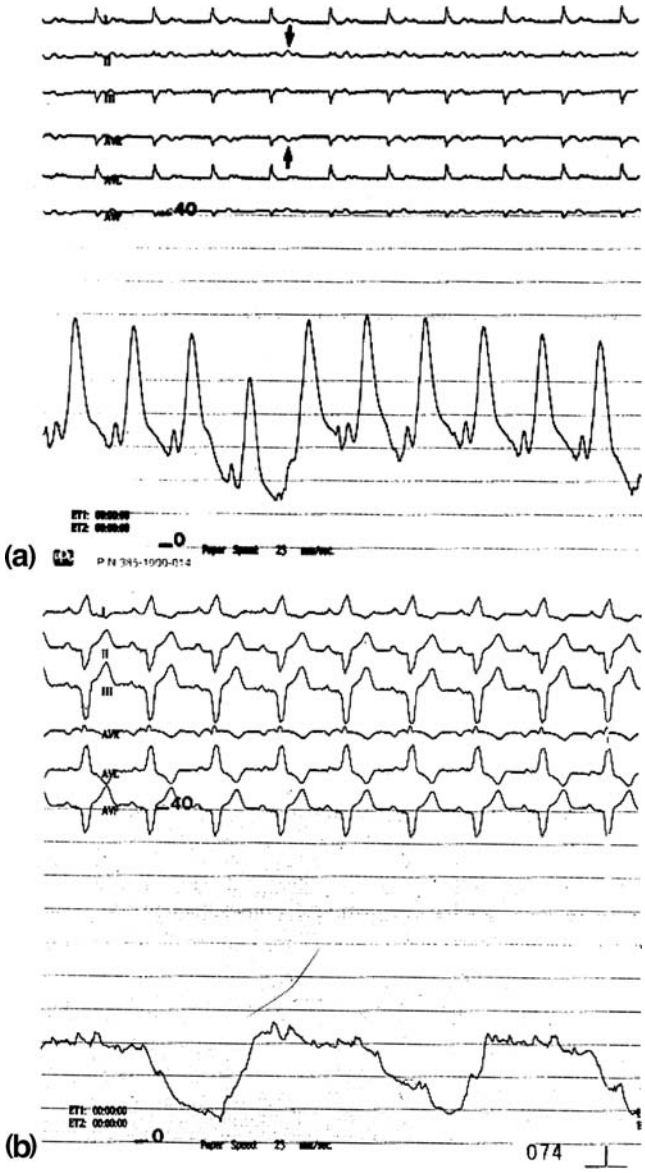

Fig. 3 Hemodynamic abnormalities in a symptomatic patient with marked first-degree AV block and hemodynamic improvement with temporary dual chamber pacing. (**a**). Pulmonary capillary wedge pressure shows large cannon waves during sinus rhythm with a very long PR interval (Scale 0–40 mm Hg). (**b**). Note the normal pulmonary capillary wedge pressure after temporary dual chamber pacing with a physiologic AV delay (Scale 0–40 mm Hg). (Reproduced with permission from Barold SS. Acquired atrioventricular block. In: Kusomoto FM, Goldschlager N (Eds), Cardiac Pacing for the Clinician, Philadelphia, PA, Lippincott Williams and Williams, 2001;229–251)

1.4 Asymptomatic patients

There are no data on the prognosis of asymptomatic patients with LPRI (≥0.30 s). Pacing is generally not recommended in truly asymptomatic patients with isolated LPRI even with abnormal hemodynamics though this recommendation may change in the future when more becomes known about the long-term prognosis of this condition.

1.5 Differential diagnosis

1. The diagnosis of LPRI can be overlooked when the PR interval is very long because the ECG may be misinterpreted to show a junctional rhythm with retrograde VA conduction (Figs. 4, 5). In questionable cases, sinus rhythm can be easily documented during an electrophysiologic study by delineating the pattern of right atrial activation which travels from high to low right atrium in sinus rhythm (Fig. 5).
2. Patients with a LPRI may respond to the deranged hemodynamics with sinus tachycardia which may be so fast as to be misinterpreted as supraventricular tachycardia because the P-wave is so close to the preceding QRS complex [24] (Fig. 6).

1.6 AV delay vs. asynchronous ventricular activation: Acute data

Iliev et al. [25] compared the AAI and DDD modes of pacing in patients with sick sinus syndrome 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 is proportional to stroke volume and the cardiac output when the heart rate remains constant) 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 time integral during AAI pacing. When the AVI > 270 ms, the aortic flow velocity time integral was higher during DDD pacing. Thus, during DDD pacing, longer native AV intervals were associated with larger increments in stroke volume and indirectly CO. Conversely with a normal or near normal PR interval, AAI pacing with a conducted QRS complex and spontaneous ventricular depolarization generated a higher CO (Figs. 7, 8). Knowing the physiology of the LPRI syndrome, it is not surprising that Iliev et al. [25] found that at a pacing rate of 90 ppm, DDD was superior to AAI pacing. These observations should be considered before and after pacemaker implantation to optimize the AV interval because in some patients deterioration of LV function secondary to paced (asynchronous) ventricular depolarization may outweigh the benefit of optimized AV synchrony. Programming a short AV delay for hemodynamic benefit requires periodic evaluation of LV function to evaluate the cumulative effect of right ventricular pacing [26]. On the other side of the coin, it may be unwise to program a slow pacing rate and a very long AV delay to avoid right ventricular pacing in a patient who remains symptomatic.

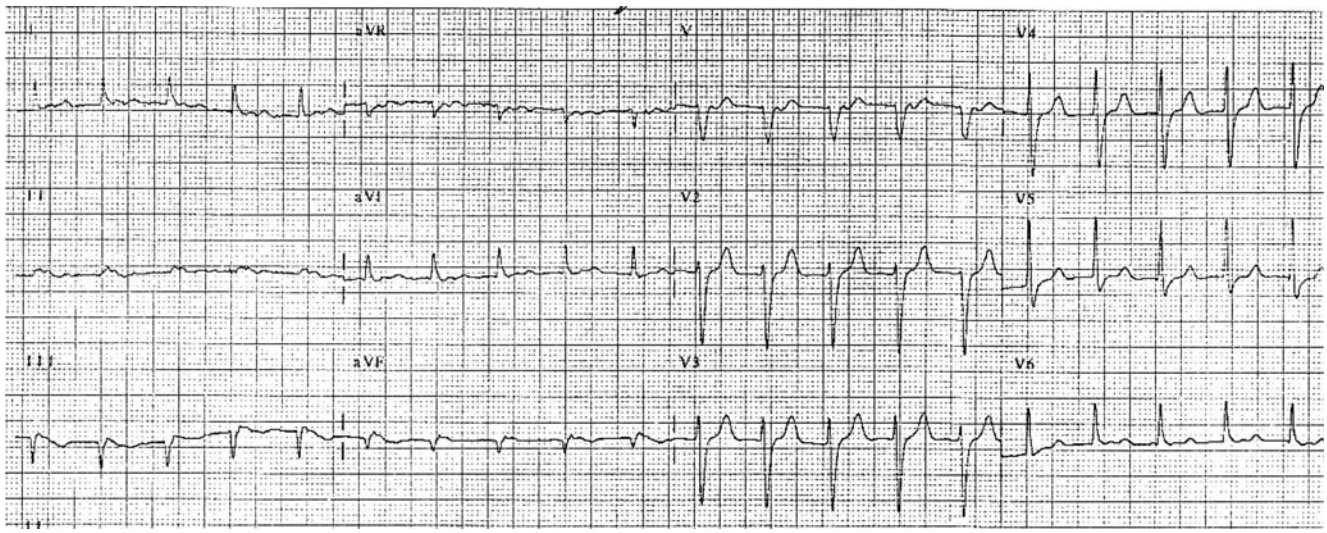

Fig. 4 Twelve-lead ECG in the same patient as in Fig. 3. During sinus tachycardia the sinus P wave is close to the preceding QRS complex on the initial portion of the ST-segment. This pattern mimics a reentrant supraventricular tachycardia. (Reproduced with permission from Barold SS. Acquired atrioventricular block. In: Kusomoto FM, Goldschlager N (Eds), Cardiac Pacing for the Clinician, Philadelphia, PA, Lippincott Williams and Williams, 2001;229–251)

1.7 Long PR interval, dilated cardiomyopathy and congestive heart failure

Over the last decade long-term studies with conventional DDD pacing and a short AV delay in heterogeneous groups of patients with LV systolic function and CHF of various etiologies have generally yielded disappointing results [27]. In a few patients with severe CHF and first-degree heart block, implantation of a conventional dual chamber pacemaker may occasionally improve cardiac performance but DDD pacing may also cause further long-term deterioration of LV function related to pacing-induced abnormal LV depolarization associated with mechanical dyssynchrony. In patients with first degree AV block, conventional DDD pacing abolishes presystolic mitral regurgitation and increases the time for forward flow. Elimination of diastolic mitral regurgitation plays as yet an undefined but probably small role in the overall hemodynamic benefit but it may result in more optimal hemodynamic performance because of a

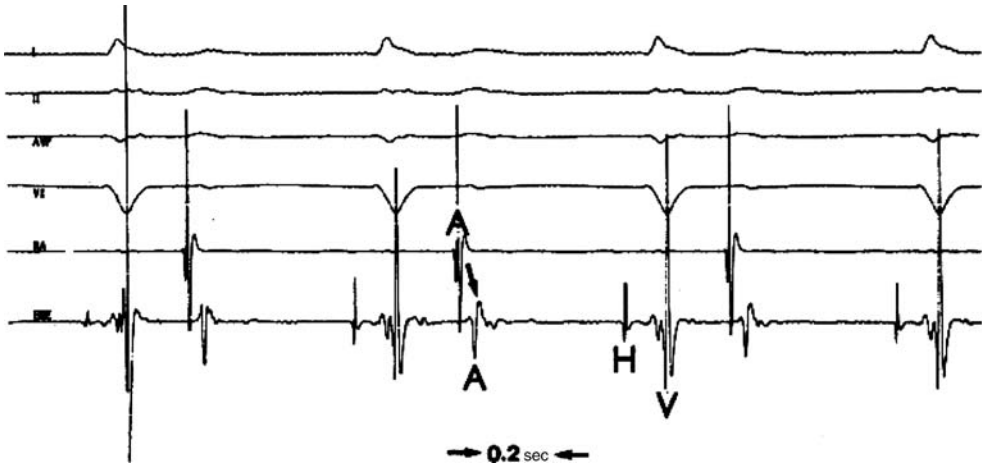

Fig. 5 Surface ECG and intracardiac recording from a patient with symptomatic marked first-degree AV block. Same patient as in Figs. 3 and 4. *RA* = high right atrial electrogram, *HBE* = electrogram at site of His bundle recording. Note the sequence of atrial activation (RA to HBE) is consistent with sinus rhythm and rules out retrograde atrial activation. The AH interval is markedly prolonged. (Reproduced with permission from Barold SS. Acquired atrioventricular block. In: Kusomoto FM, Goldschlager N (Eds), Cardiac Pacing for the Clinician, Philadelphia, PA, Lippincott Williams and Williams, 2001;229–251)

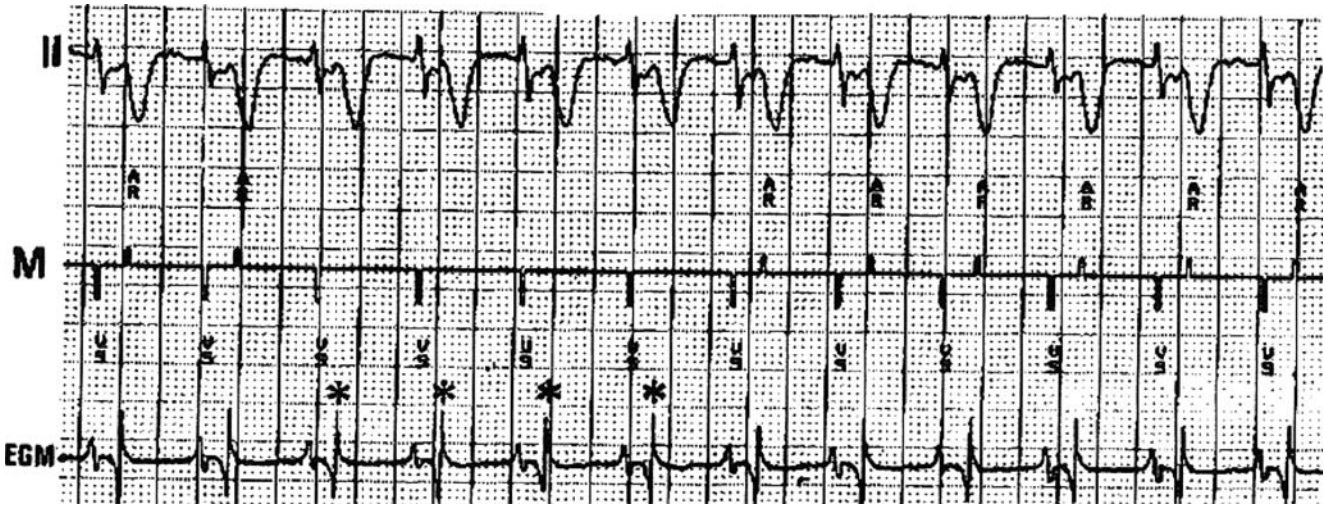

Fig. 6 Sinus tachycardia in a patient with a long PR interval and a DDD pacemaker. The ECG is on *top*, the markers in the *middle* and the atrial electrogram (EGM) at the *bottom*. Postventricular atrial refractory period (PVARP) = 360 ms. There is sinus tachycardia at a rate of 110 bpm. The R–P interval was about 150 ms. The pacemaker detects P waves in the 360 ms PVARP as AR events, but not when the R–P interval becomes shorter than the 150 ms postventricular atrial blanking period (no AR representation-asterisks). *AR* = atrial event sensed in the PVARP, *AS* = atrial sensed event, *EGM* = electrogram, *M* = markers, *VS* = ventricular sensed event. Paper speed = 25 mm/s. (Reproduced with permission from Reference [24])

lower left atrial pressure and higher LV preload at the onset of systole.

1.8 Indications for pacing

The ACC/AHA/NASPE 2002 guidelines recommended pacing in the following circumstances [8]: 1. *Class IIa*. First- or second-degree AV block with symptoms similar to those of pacemaker syndrome. These same principles for first-degree AV block may also be applied to patients with type I second-degree AV block who experience hemodynamic compromise due to loss of AV synchrony, even without bradycardia. (*Level of Evidence: B*). 2. *Class IIb*. Marked first-degree AV block (>0.30 s) in patients with LV dysfunction and symptoms of CHF in whom a shorter AV interval results in hemodynamic improvement, presumably by decreasing left atrial filling pressure. (*Level of Evidence: C*). This recommendation is now questionable because a conventional DDD(R) pacemaker with an optimized AV delay would have to pace the ventricle virtually 100% of the time. Despite symptomatic and hemodynamic improvement, right ventricular pacing would carry the potential of long-term worsening of LV function and aggravating or developing moderate or severe functional mitral regurgitation. Long-term deterioration of LV function might be more likely in patients with initial evidence of LV dyssynchrony (determined by tissue Doppler imaging) either before pacing (despite a narrow QRS complex before device implantation) or immediately after the institution of RV pacing [28, 29]. The risk of long-term LV dysfunction is also higher in patients starting with a wide QRS (complex in the baseline unpaced ECG [30]. It would seem more prudent at this juncture to consider a biventricular DDD device especially if the LV ejection fraction is ≤35% bearing in mind that such a recommendation has not yet found its place in the official guidelines from learned societies [31, 32]. We suspect that future guidelines will recognize this problem and will eliminate the use of conventional pacemaker with a short AV delay in this situation.

2 Pacemaker management in patients with first-degree AV block

2.1 Functional atrial undersensing

Patients with first-degree AV block and pacemakers that are suboptimally programmed may develop functional atrial undersensing under certain circumstances when the P wave shifts into a relatively short or excessively long PVARP and also into the postventricular atrial blanking period where the P wave is not depicted by the marker channel [33–44] (Figs. 6 and 9). The most comprehensive study of this form of functional atrial undersensing in patients with first-degree AV block was undertaken by Bode et al. [33] who studied 255 patients with Holter recordings and found nine patients with atrial undersensing despite an adequate atrial signal. In these patients, the P waves fell continually within the PVARP of 276 ± 26 ms; no PVARPs functioned with automatic extension in response to ventricular extrasystoles). All nine patients exhibited substantial delay of spontaneous AV conduction (284 ± 61 ms, range 230–410 ms).

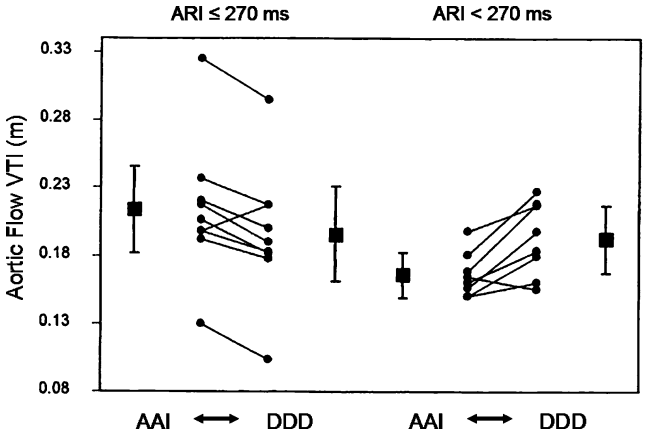

Fig. 7 Effect of AAI and DDD pacing modes on the aortic flow time velocity integral (TVI). The patients are divided according to stimulus-R interval in AAI mode (AR interval) in two groups: those with ARI ≤ 270 ms (*left*) and those with ARI ≥ 270 ms (*right*). (Reproduced with permission from Reference [25])

The combination of a relatively fast sinus rate and prolonged AV conduction provides the appropriate setting for the development of functional atrial undersensing (by pushing the P wave into the PVARP) during which the ECG shows sinus rhythm, a long spontaneous PR interval and conducted QRS complexes but no pacemaker stimuli. The conducted QRS complexes activate the ventricle while the P waves remain trapped in the PVARP. The pacemaker itself acts as a "bystander" in that it can initiate the pacemaker-like syndrome but the ECG then shows no pacemaker activity. Bode et al. [33] also observed that functional atrial undersensing could be initiated and terminated by appropriately timed atrial and ventricular extrasystoles [40]. Barring disruption of the self-perpetuating process by atrial or ventricular extrasystoles, and assuming no change in AV conduction, functional atrial undersensing should theoretically continue indefinitely as long as the atrial rate remains relatively fast and constant. It will, however, terminate when slowing of the sinus rate produces a P–P interval longer than the prevailing total atrial refractory period which is the sum of the intrinsic PR interval (not the programmed AV delay) and the programmed PVARP.

2.1.1 Influence of heart rate

A relatively fast sinus rate predisposes to functional atrial undersensing. This was shown by Bode et al. [33] who recorded a mean sinus rate of 105 ± 3 bpm during functional atrial undersensing because a relatively fast atrial rate facilitates displacement of the P wave toward the PVARP. Some patients with functional atrial undersensing develop marked sinus tachycardia probably as a response to the hemodynamic derangement created by the loss of optimal AV synchrony. The tachycardia often subsides quickly upon restoration of a physiologic AV delay by the pacemaker. A long PR interval almost never shortens significantly in situations causing sinus tachycardia. Therefore with a fixed PR interval, sinus tachycardia may create a vicious cycle because it pushes the P wave closer to the preceding ventricular complex and if this arrangement creates a more unfavorable VA relationship, it will in turn aggravate the sinus tachycardia.

2.1.2 Pacemaker-like syndrome

During functional atrial undersensing five of the nine patients reported by Bode et al. [33] developed complaints suggestive of the pacemaker-like syndrome. Bode et al. [33] prevented functional atrial undersensing in seven of their nine patients by shortening the PVARP and AV delay and previously symptomatic patients became asymptomatic. The other two patients exhibited less atrial undersensing.

2.2 Pacemaker programming

The pacing system must prevent migration of the P wave into the postventricular atrial refractory period (PVARP) where it cannot generate a programmed physiologic resulting in loss of AV synchrony. Functional atrial undersensing is rare in a correctly programmed pacemaker.

2.2.1 Significance of PVARP duration and extension

In the past, functional atrial undersensing was possible with a short PVARP whenever a ventricular premature complex (VPC) activated an automatic PVARP extension. In this

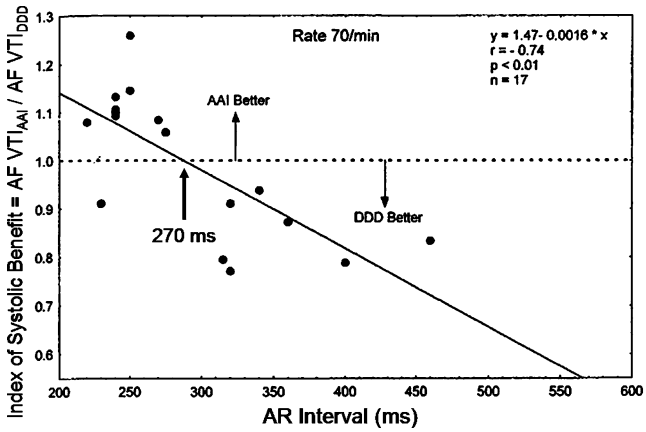

Fig. 8 Plot of the index of systolic benefit (defined as the ratio of aortic flow time velocity (AFTVI) under AAI and DDD modes) versus stimulus-R interval in AAI mode (AR interval) for each patient for pacing rate 70/min. The *thick line* represents a regression line. *Above the dashed horizontal line drawn* at level 1 is the zone of AAI benefit, *below* is the zone of DDD benefit. (Reproduced with permission from Reference [25])

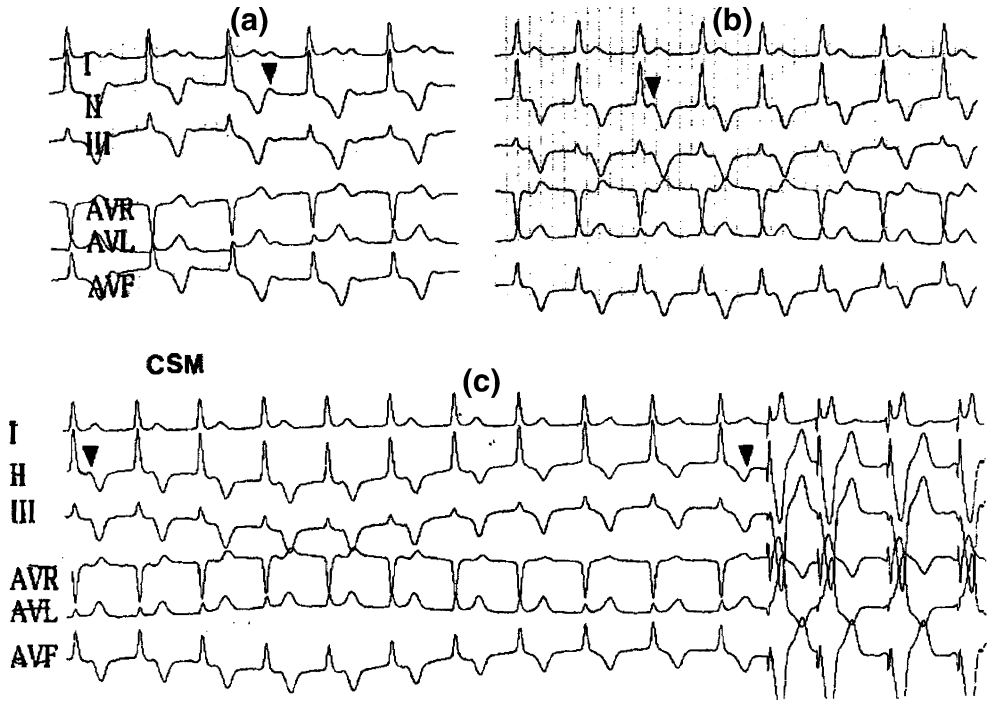

Fig. 9 Six-lead ECG in a patient with marked first-degree AV block and a DDD pacemaker showing loss of dual chamber pacing (Same patient as Fig. 6). The postventricular atrial refractory period (PVARP) was 360 ms. The *arrow heads* point to sinus P waves. (**a**) Sinus rhythm at a rate of 88 bpm with an R–P interval of approximately 360 ms. Note the positive P wave near the end of the T wave in leads I, II, III, and aVF. (**b**) Sinus tachycardia at a rate of 112 bpm and a longer PR interval than in panel (**a**). The R–P interval now measures only 150 ms. At that time the PVARP was shortened to 200 ms but the sinus tachycardia continued. (**c**). Carotid sinus massage (CSM) caused a gradual slowing of the sinus rate with eventual restoration of AV synchrony. The *arrow head points* to a P wave beyond the 200 ms PVARP. The succeeding 2 ventricular stimuli occur after completion of the upper rate interval. The basic AV delay was 120 ms and the rate-adaptive function was programmed on. (Reproduced with permission from Reference [24] with permission)

situation an unsensed P wave within the extended PVARP gave rise to a conducted QRS complex which the pacemaker interpreted as a ventricular extrasystole whereupon it generated another PVARP extension. The extended PVARP was perpetuated from cycle to cycle as long as the pacemaker interpreted the conducted QRS as a ventricular extrasystole. Most contemporary pacemakers contain an algorithm that eliminates the PVARP extension whenever the pacemaker detects a P wave anywhere within the entire unblanked portion of the PVARP or within a specific window in the unblanked PVARP. In such a case, the subsequent sensed ventricular beat is not identified as a VPC. When a pacemaker senses two consecutive ventricular beats, PVARP extension after the second beat cannot be eliminated if no P wave occurs in the unblanked PVARP or if the P wave falls in the postventricular atrial blanking period where it cannot be detected. The automatic PVARP extension after a VPC should therefore be programmed off especially in patients with a device for cardiac resynchronization. Abbreviation of the postventricular atrial blanking period (without inducing far-field R wave oversensing) may occasionally improve the detection of the P wave, and prevent PVARP extension.

2.2.2 Prevention of functional atrial undersensing

Retrograde VA conduction block is uncommon in LPRI patients. Therefore, a relatively short PVARP can often be used at rest with little risk of endless loop tachycardia. A short PVARP, in turn, prevents functional atrial undersensing. Consequently, the PVARP programming maneuver is simple. Avoid sensor-varied and auto-PVARP functions (discussed later).

Noncompetitive atrial pacing is easily programmed and consists of the delivery of a premature but appropriately delayed atrial stimulus when the pacemaker senses activity in the PVARP. In this function an atrial stimulus is usually emitted 300 ms after the pacemaker senses atrial activity in the PVARP beyond the postventricular atrial blanking period. This process promotes AV resynchronization.

Ablation of the AV junction with resultant complete AV block should be considered in difficult situations as a last resort therapy where the symptomatic disturbances by first-degree AV block cannot be eliminated by reprogramming the pacemaker [4, 45]. Such drastic action is rarely needed.

Sensor-varied and auto-PVARP The usefulness of a short PVARP may be negated by special PVARP functions

designed to time out a long PVARP at rest and a gradually shorter one with activity. Sensor-varied and auto-PVARP are designed to provide a dynamic and longer PVARP at slower rates to enhance protection against endless loop tachycardia but these functions should be used cautiously, if at all, in patients with first-degree AV block. Both these features are contained in the Medtronic Kappa series of pacemakers and subsequent ones derived from the same platform. In the DDDR, DDD, and VDD modes of some specific Medtronic devices, the sensor-varied PVARP (controlled by the sensor) is limited to 400 ms at low rates and the programmed PVAB at high rates. The function of the Medtronic Auto-PVARP feature is more complex. With auto-PVARP (controlled by the atrial rate), the pacemaker determines the duration of the automatic PVARP according to the current mean atrial rate (calculated over previous four beats). PVARP is continually adjusted such that 2:1 block point is maintained at 30 ppm over current mean atrial rate (which is an average of all A–A intervals except those starting with an atrial sensed or atrial refractory sensed event and ending with an atrial paced event). Auto-PVARP is set with a minimum adjustable 2:1 block rate of 100 ppm. Therefore, with a 120 ms AV delay initiated by atrial sensing, there is 480 ms left to complete the minimum adjustable 2:1 block interval of 600 ms (corresponding to a rate of 100 ppm). This produces a total atrial refractory period of 600 ms and a PVARP of 480 ms. PVARP will subsequently shorten if the atrial rate exceeds 70 ppm in order to maintain the 30 ppm "headroom" requirement mentioned above for the development of 2:1 block (>70 + 30 > 100 ppm). At an atrial rate >100 bpm, the PVARP then becomes less than 480 ms as long as sensed AV delay remains constant. The programmable Minimum PVARP parameter controls the minimum value to which the PVARP can be shortened. In this respect, Lau et al. [41] reported a case of functional atrial undersensing precipitated and terminated by a VPC [as in the report of Bode et al. [33]] in a patient with a Medtronic Kappa DR 733 pacemaker. They explained their observations in terms of a 480 ms PVARP (Fig. 10). The precise explanation for the 480 ms PVARP was not addressed in the report, but it seems that Auto-PVARP had been programmed. The response to auto-PVARP may produce quite a long PVARP at rest in patients with cardiac resynchronization devices are programmed with a short sensed AV delay.

3 First-degree AV block and cardiac resynchronization

3.1 First-degree AV block predisposes to loss of ventricular resynchronization in biventricular pacemakers

1. Delayed resumption of atrial tracking after exceeding the programmed upper rate with activity

When the atrial rate exceeds the programmed upper rate of a CRT device, the P wave is no longer tracked because it coincides with the PVARP where it labeled a refractory sensed event (AR). CRT patients can occasionally develop substantial increases in sinus rates with exercise or states of increased circulating catecholamines despite beta-blocker therapy or in patients intolerant of beta-blockade. In the absence of impaired AV conduction, AR conducts to the ventricle where it generates a sensed spontaneous QRS complex (VS) with resultant disruption of ventricular resynchronization. As the atrial rate slows, a CRT device may not assume 1:1 atrial tracking when the sinus rate drops immediately below the programmed upper rate [46]. The reason lies in the fact that AR-VS (spontaneous AV conduction) > programmed AS-VP interval where AS is an atrial sensed event and VP is a ventricular paced event. Therefore, the total atrial refractory period (TARP) during AR-VS operation, [(AR-VS) interval + PVARP must be longer than the programmed TARP which is equal to [(AS-VP) interval + PVARP]. The pacemaker will continue to operate with AR-VS cycles below the upper rate until the sinus interval drops below the duration of the TARP or [(AR-VS) interval + PVARP] interval when it allows escape of the sinus P wave out of the PVARP. In other words, biventricular pacing remains inhibited until either the occurrence of a non-refractory sensed atrial depolarization or delivery of an atrial pacing pulse outside the TARP. In this way restoration of ventricular resynchronization with biventricular pacing will occur at a rate slower than the programmed upper rate. In patients with a long PR interval resynchronization will occur at a slower atrial rate compared with the atrial rate of patients with a normal PR interval. This difference becomes more prominent during CRT compared to conventional DDDR pacing because the AS-VP delay is often quite short. These responses can often be prevented and CRT maintained by programming a relatively fast upper rate, an important consideration in CRT patients.

Let us examine an example in a CRT patient with a PR interval of 350 ms and a device with a sensed AV delay of 150 ms, a PVARP of 250 ms and an upper rate of 150 ppm. Loss of CRT will occur when the atrial rate exceeds 150 bpm. When the atrial rate drops below 150 bpm, AV synchrony and CRT will be reestablished when the total atrial refractory period becomes less than (PR interval + PVARP) or (350 + 250) or 600 ms corresponding to a rate of 100 ppm. Loss of CRT in this situation may be important hemodynamically and symptomatically.

2. Loss of resynchronization without attaining the programmed upper rate

AR-VS, AR-VS ....sequences containing trapped or locked P waves within the PVARP can also occur outside

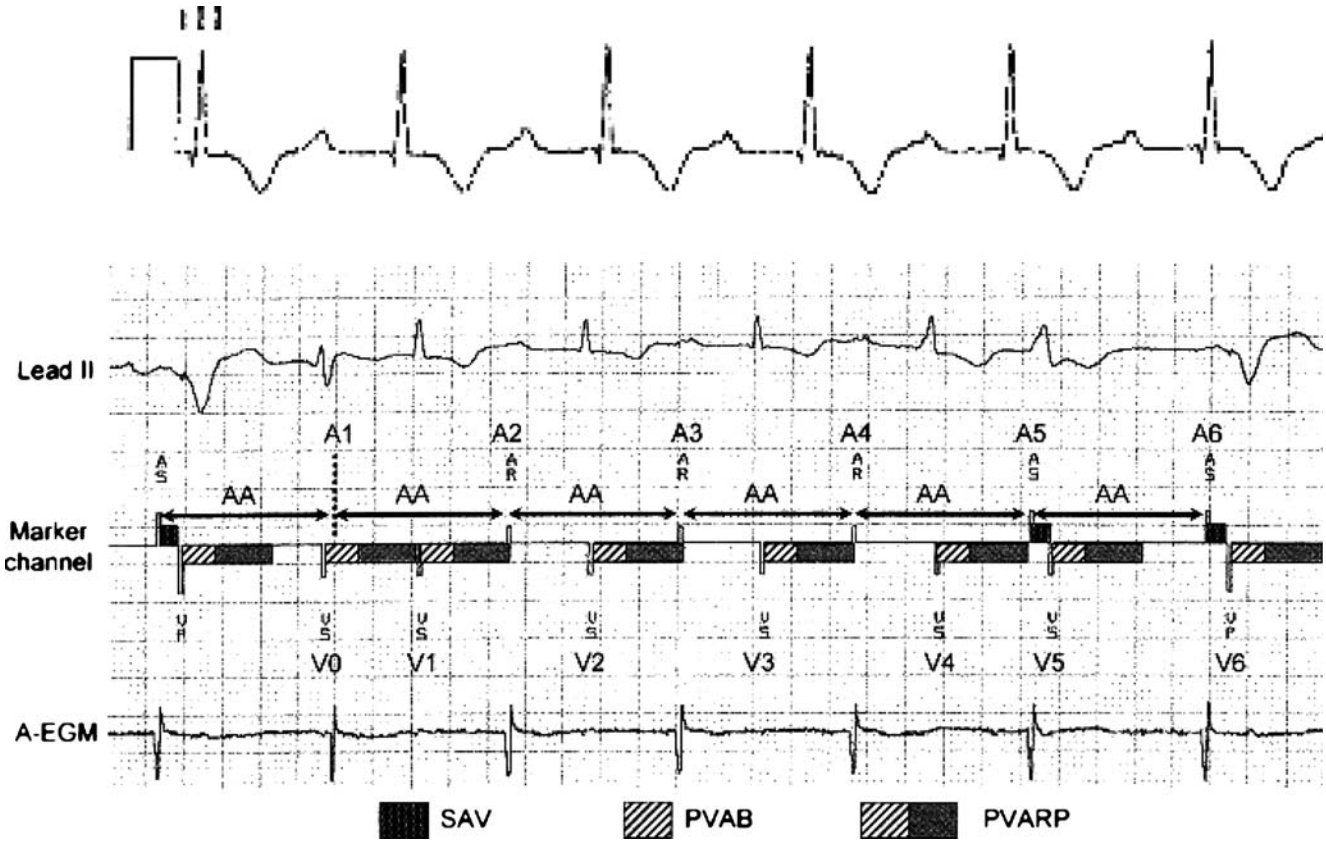

Fig. 10 Functional atrial undersensing caused by a long PR interval and a long PVARP in a patient with a Medtronic Kappa 733 dual chamber pacemaker. A VPC (V0) initiates a long PVARP. The subsequent P wave then falls in the 480 ms PVARP initiated by the preceding VPC. This P wave cannot trigger ventricular pacing. However, it is conducted to the ventricle (V1) with a very long PR interval (close to 400 ms). Ventricular beat V1 initiates a 480 ms PVARP so that the succeeding P wave falls again into the PVARP and again conducts to the ventricle with a very long PR interval. This process of functional atrial undersensing continues until a VPC (V5) disrupts the timing cycles by advancing the PVARP thereby restoring AV synchrony with P wave sensing and ventricular pacing. *VPC* = ventricular premature complex, *A-EGM* = atrial electrogram, *PVAB* = postventricular atrial blanking period *AR* = atrial event sensed in the PVARP, *PVARP* = postventricular atrial refractory period, *VS* = ventricular sensed event, *AS* = atrial sensed event, *SAV* = atrioventricular delay after a sensed atrial event, *VP* = ventricular paced event. See text for discussion of PVARP duration. (Reproduced with permission from Reference [40])

of situations related to a fast atrial rate > the programmed upper rate. There are many causes of desynchronization that can start at rates slower than the programmed upper rate [46]. For example, during sinus rhythm and synchronized biventricular pacing (below the upper rate), a ventricular premature complex (VPC) initiates a regular PVARP which shifts pacemaker timing so that the succeeding undisturbed sinus P wave now falls in the PVARP). Other ventricular sensed events such as T wave oversensing can produce the same effect (Figs. 11, 12(a)). The trapped P wave (AR) within the PVARP conducts to the ventricle producing a spontaneous QRS complex sensed by the device. The alteration in pacemaker timing will tend to keep sinus P waves trapped in the PVARP according the prevailing timing disturbance as long as the P–P interval < [(AR-VS) + PVARP]. The presence of first-degree AV block favors the initiation of electrical "desynchronization" especially in association with a relatively fast atrial rate and a relatively long PVARP. The first conducted P wave (such as AR after a VPC) with a long PR interval gives rise to a substantially *delayed* spontaneous QRS which then initiates a PVARP coinciding with the next sinus P wave which also becomes an AR event. This arrangement perpetuates the desynchronization process. Loss of atrial synchrony may extend over a period of time (e.g., seconds to hours) depending on the pacemaker's programmed rate settings and the patient's sinus rate. These forms of ventricular desynchronization (AR-VS sequences) are not uncommon in patients with first-degree AV block and may be symptomatic. They may also produce a reduction of cardiac resynchronization "dose."

3.1.1 Prevention of the "locked" P wave effect in patients with first-degree AV block

"Locking" of the P wave can often be prevented (barring reprogramming the device to eliminate the initiating mechanism e.g., T wave oversensing) with a shorter

PVARP and slowing the sinus rate with drugs. CRT permits the use of larger doses of beta-blockers but CRT with atrial sensing is generally superior to CRT with atrial pacing [47]. Special algorithms can be programmed to restore 1:1 atrial tracking at rates slower than the programmed upper rate [46]. These algorithms are activated whenever the device detects AR-VS, AR-VS... sequences suggestive of ventricular desynchronization where AR is an atrial event in the PVARP. The algorithm temporarily shortens the PVARP and therefore the intrinsic total atrial refractory period to permit sensing of the P wave beyond the PVARP so as to restore 1:1 atrial tracking (Fig. 12(b)). A P wave falling in the postventricular atrial blanking period (for pacing) cannot activate the special algorithm. These algorithms do not function when the atrial rate is faster than the programmed upper rate or during automatic mode switching. This algorithm may be useful in patients with sinus tachycardia and first-degree AV block in whom prolonged locking of the P waves inside the PVARP is an important problem. Refractory cases (usually associated with marked first-degree AV block) can be treated by AV junctional ablation to ensure continual CRT delivery.

3.2 Response to CRT

Pires et al. [48] studied the predictors of a CRT response in patients from the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) and MIRACLE-ICD trials. Patients with an improvement of > or =1 New York Heart Association (NYHA) class from baseline to the 6-month follow-up were considered responders and those who had no change or worse NYHA class or died were classified as nonresponders. Based on improvement of > or =1 NYHA class, less than two thirds of patients enrolled in the MIRACLE or MIRACLE-ICD trials responded to CRT. One hundred forty-three (64%) of 224 and 190 (61%) of 313 patients in the MIRACLE and MIRACLE-ICD trials, respectively, responded to therapy. Stepwise logistic regression methods identified several differing factors that predicted CRT response in the two trials. One of these factors was the absence of first-degree AV block that was associated with a response to CRT ($p = 0.005$). Tedrow et al. [49] who evaluated 75 consecutive CRT patients also found that patients with first-degree AV block have a poorer outcome than patients with a normal PR interval though the data was not quite statistically significant (Hazard ratio = 1.01, $p = 0.0650$).

3.2.1 Mechanism of altered CRT response

The reason patients with first-degree AV block do not fare as well with CRT as patients with normal AV conduction may involve several mechanisms. (1) The long PR interval may be a marker of more advanced heart disease. It is possible but as yet unproven that there may be a higher incidence of inter- and intraatrial conduction delay and left atrial dysfunction in patients with marked first-degree AV block. (2) Patients with first-degree AV block may have experienced more episodes of undetected electrical desynchronization to which they are predisposed (as already described) induced by devices without appropriate restorative algorithms. (3) Enhanced hemodynamic response in patients with normal AV conduction by concealed resynchronization or fusion as suggested by Kurzidim et al. [50]. These workers studied 22 CHF patients, all in sinus rhythm with temporary multisite pacing prior to implantation of a CRT system. LV systolic function was evaluated invasively by the maximum rate of LV pressure increase (dP/dt max). Sequential biventricular pacing was performed with preactivation of either ventricle at 20–80 ms. In 60% (6/10) of patients with a normal PR interval (≤200 ms), right atrial triggered LV pacing produced a hemodynamic response superior to that of optimized sequential biventricular pacing and was equivalent to that of simultaneous biventricular

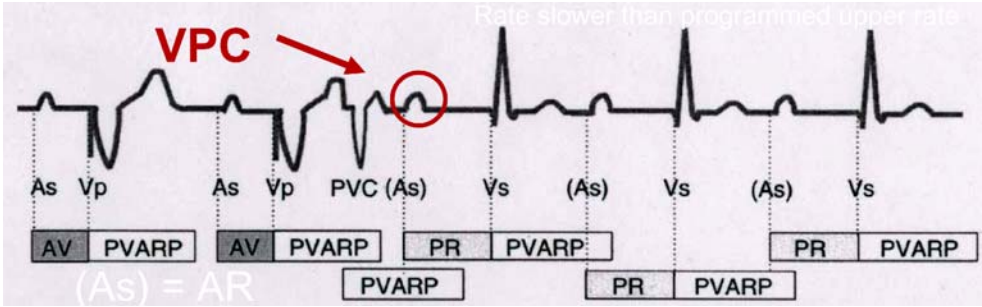

Fig. 11 Diagrammatic representation of loss of ventricular synchronization induced by a ventricular premature complex (*PVC*). The sinus P wave following the PVC falls in the PVARP initiated by the PVC. This P wave is not tracked but it conducts to the ventricle giving rise to a QRS complex that is sensed by the pacemaker. The timing cycles are altered so that the sinus P waves now fall within the PVARP initiated by sensing the spontaneous QRS complex. Note that desynchronization or locking of the P waves within the PVARP occurs at a heart rate slower than the programmed upper rate. *As* = atrial sensed event, (*As*) = atrial sensed event within the pacemaker atrial refractory period, *Vs* = ventricular sensed event, *AV* = atrioventricular delay, *PVARP* = postventricular atrial refractory period, *PR* = PR interval

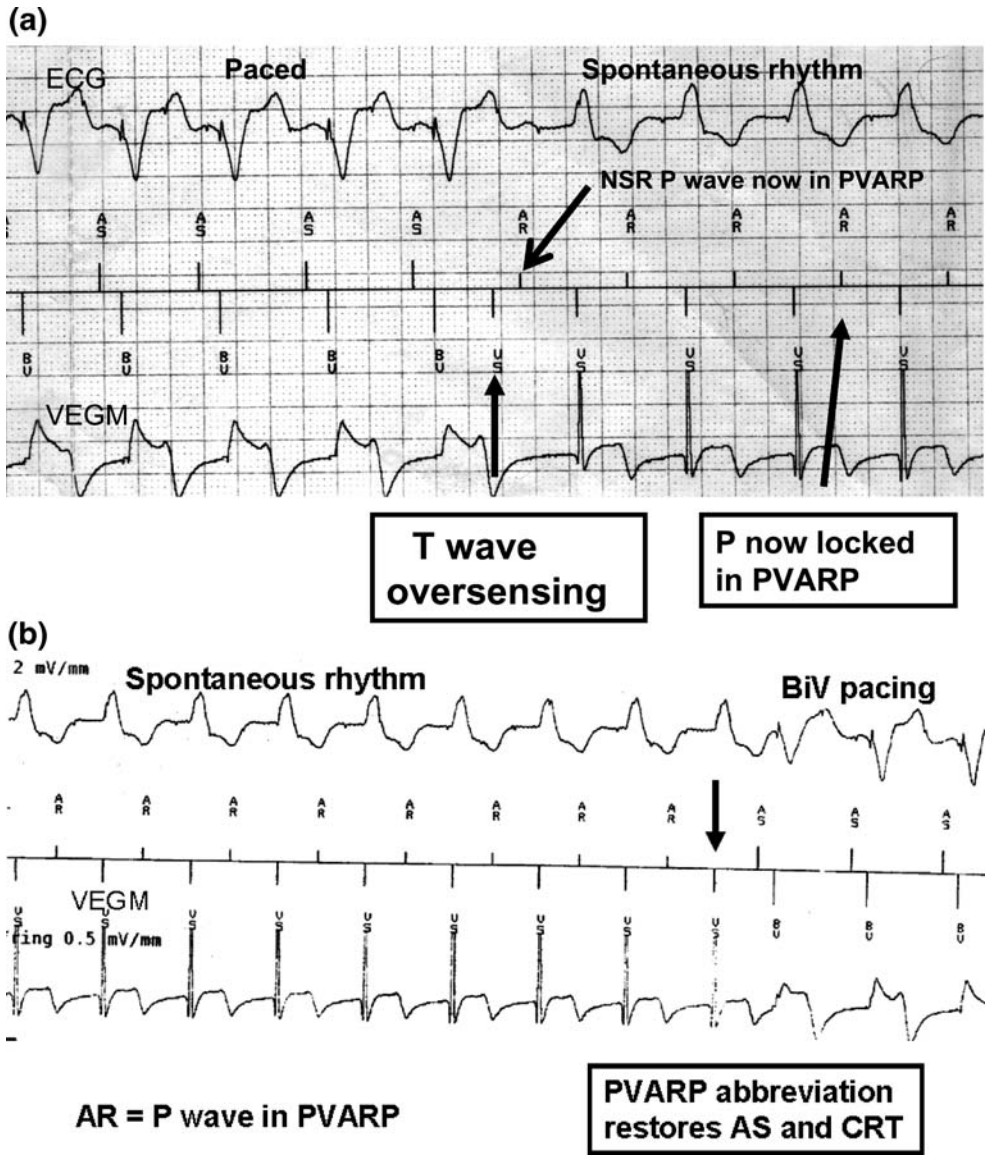

Fig. 12 (**a**) Recordings (ECG on *top*, markers in the *middle* and ventricular electrogram at the *bottom*) from a patient with marked first-degree AV block, *left bundle* branch block and an InSync II Marquis biventricular ICD showing the development of electrical desynchronization induced by T wave oversensing (VS, *arrow*). The sinus rhythm remains undisturbed. VS initiates a new PVARP into which the succeeding P wave is detected as AR but not tracked. AR conducts to the ventricle with a long PR interval thereby perpetuating the desynchronization process with the sinus P waves (locked in the PVARP) continually conducting to the ventricle. *VS* = ventricular sensed event, *AR* = atrial event sensed in the pacemaker atrial refractory period, *PVARP* = postventricular atrial refractory period. (Reproduced with permission from Reference [28]) (**b**). Same patient and format as in Fig. 12(**a**). On the left the pattern of electrical desynchronization is identical to that in Fig. 12(**a**). The ICD restores resynchronization with an algorithm that detects a specific number of AR-VS sequences (interpreted by the device as loss of ventricular synchrony) and then temporarily abbreviates the PVARP (*arrow*). The shorter PVARP permits P wave tracking and restores resynchronization on the right of the recording. *VS* = ventricular sensed event, *AR* = atrial event sensed in the pacemaker atrial refractory period, *PVARP* = post-ventricular atrial refractory period. (Reproduced with permission from Reference [46])

pacing in the remaining (4/10) patients. This was not the case in any patient with a prolonged PR interval or AV-block of any degree. The baseline PR interval of patients showing a superior response with LV pacing was significantly shorter than that of the remaining patients (179 ± 14 vs. 252 ± 64 ms, $P < 0.001$). In this group with normal AV conduction the baseline PR interval was very similar to the optimal AV delay determined for LV pacing (178 ± 13 ms). The effect of the underlying PR interval duration may be explained in terms of "concealed resynchronization." Ventricular activation in patients with a normal PR interval may have resulted from fusion of electrical wave fronts coming from the right bundle branch and the impulse from the LV electrode. Hemodynamic response

may thereby be superior as detrimental effects of RV apical stimulation are avoided. These workers believe that the wider QRS width during biventricular pacing in patients with a long PR interval supports their hypothesis. Similar hemodynamic benefit by producing fusion with right bundle branch activation was demonstrated by van Gelder et al. [51].

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