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Usefulness of the 12-lead electrocardiogram in the follow-up of patients with cardiac resynchronization devices. Part II

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Abstract

The interval from the pacemaker stimulus to the onset of the earliest paced QRS complex (latency) may be prolonged during left ventricular (LV) pacing. Marked latency is more common with LV than right ventricular (RV) pacing because of indirect stimulation through a coronary vein and higher incidence of LV pathology including scars. During simultaneous biventricular (BiV) pacing a prolonged latency interval may give rise to an ECG dominated by the pattern of RV pacing with a left bundle branch block configuration and commonly a QS complex in lead V1. With marked latency programming the V-V interval (LV before RV) often restore the dominant R wave in lead V1 representing the visible contribution of the LV to overall myocardial depolarization.

When faced with a negative QRS complex in lead V1 during simultaneous BiV pacing especially in setting of a relatively short PR interval, the most likely diagnosis is ventricular fusion with the intrinsic rhythm. Fusion may cause misinterpretation of the ECG because narrowing of the paced QRS complex simulates appropriate BiV capture. The diagnosis of fusion depends on temporary reprogramming a very short atrio-ventricular delay or an asynchronous BiV pacing mode.

Sequential programming of various interventricular (V-V) delays may bring out a diagnostic dominant QRS complex in lead V1 that was previously negative with simultaneous LV and RV apical pacing even in the absence of an obvious latency problem. The emergence of a dominant R wave by V-V programming strongly indicates that the LV lead captures the LV from the posterior or the posterolateral coronary vein and therefore rules out pacing from the middle or anterior coronary vein.

In some cardiac resynchronization systems LV pacing is achieved with the tip electrode of the LV lead as the cathode and the proximal electrode of the bipolar RV as the anode. This arrangement creates a common anode for both RV and LV pacing. RV anodal capture can occur at a high LV output during BiV pacing when it may cause slight ECG changes. During LV only pacing (RV channel turned off) RV anodal pacing may also occur in a more obvious form so that the ECG looks precisely like that during BiV pacing. RV anodal stimulation may complicate threshold testing and ECG interpretation and should not be misinterpreted as pacemaker malfunction. Programming the V-V interval (LV before RV) in the setting of RV anodal stimulation cancels the V-V timing to zero. (Cardiol J 2011; 18, 6: 610–624)

Key words: left ventricular pacing, cardiac resynchronization, biventricular pacing, ventricular fusion, electrocardiography, heart failure, anodal capture, first-degree atrioventricular block, left ventricular latency

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Latency

The interval from the pacemaker stimulus to the onset of the earliest paced QRS complex is called latency. An isoelectric onset of the QRS complex in one or only a few leads can mimic latency [1, 2]. Consequently the demonstration of latency requires a 12-lead ECG taken at fast speed for diagnosis. During right ventricular (RV) pacing this interval normally measures < 40 ms. A prolonged latency interval represents first-degree pacemaker exit block. At physiologic rates pronounced latency is uncommon during RV pacing but may be more prevalent during left ventricular (LV) pacing from epicardial cardiac veins [1, 2]. Possible explanations for longer latency intervals during LV pacing are the longer distance of the electrode to the subendocardial His-Purkinje system (similar to epicardial ventricular tachycardia), interposed venous tissue and epicardial fat, prolonged refractoriness, slow impulse propagation in diseased myocardium, and antiarrhythmic drug effect. Potential myocardial substrates for latent conduction include scarring, ischemic myocardium, nonischemic cardiomyopathy, and hyperkalemia. Prolonged LV latency delays LV depolarization during simultaneous biventricular (BiV) pacing producing an ECG pattern dominated by the pattern of RV pacing with left bundle branch block (LBBB) configuration (Figs. 1–3) [1, 2]. The conventional surface ECG cannot differentiate failure of excitation from delayed propagation in the myocardium around the electrode (Fig. 4).

The deleterious effects of LV latency can be treated with V-V programming by advancing LV stimulation ahead of RV stimulation [1]. Four of our 5 patients with prolonged latency and a paced LBBB pattern and a QS complex in lead V1 during simultaneous BiV pacing. RV depolarization pre-empts LV depolarization. However all 4 patients developed a dominant R wave in lead V1 after advancing LV stimulation (Figs. 3, 4) [2]. In the rare case, with refractory heart failure and lack of improvement at the maximum delay between LV and RV, turning off RV stimulation may provide improved hemodynamics. When programming the V-V interval, it is imperative to rule anodal RV pacing which nullifies the V-V interval to zero [3].

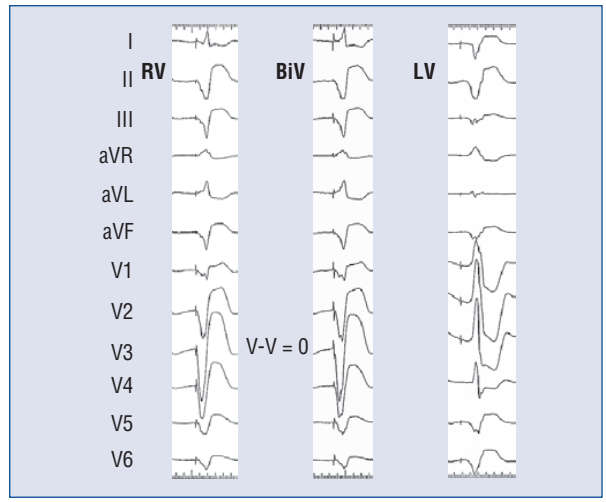

Figure 1. Impact of prolonged left ventricular (LV) latency interval on the ECG. The latency interval during LV pacing is shown in Figure 2. The figure compares QRS morphology in 12-lead ECGs during monochamber right ventricular (RV) pacing, monochamber LV pacing and biventricular (BiV) pacing in the VVI mode at 80 ppm. The patient was in atrial fibrillation with complete atrio-ventricular (AV) block. During BiV pacing there is a left bundle branch pattern that is quite similar to that seen with RV apical pacing. The presence of complete AV block rules out fusion with the spontaneous QRS complex block and cannot be the cause of an absent dominant R wave in lead V1 during BiV pacing. RV and LV voltage outputs were at twice the threshold value. Note the typical pattern of monochamber LV pacing producing a tall R wave in lead V1. (Reproduced with permission from: [2]).

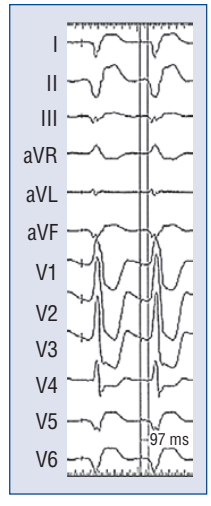

Figure 2. Prolonged left ventricular (LV) latency interval. Same patient and setting of LV output as in Figure 1. During LV pacing the stimulus to QRS latency interval measures 97 ms. (Reproduced with permission from: [2]).

Effect of stimulus amplitude and pacing rate

An increase in the pacing rate may prolong the abnormal stimulus to QRS interval during RV and LV stimulation while a prolonged latency interval may shorten by slowing the pacing rate [1]. An increase in stimulus amplitude may shorten the stimulus-QRS interval and a decrease accentuates the latency interval [1]. In this respect, some investigators have shown that increasing the LV stimulus

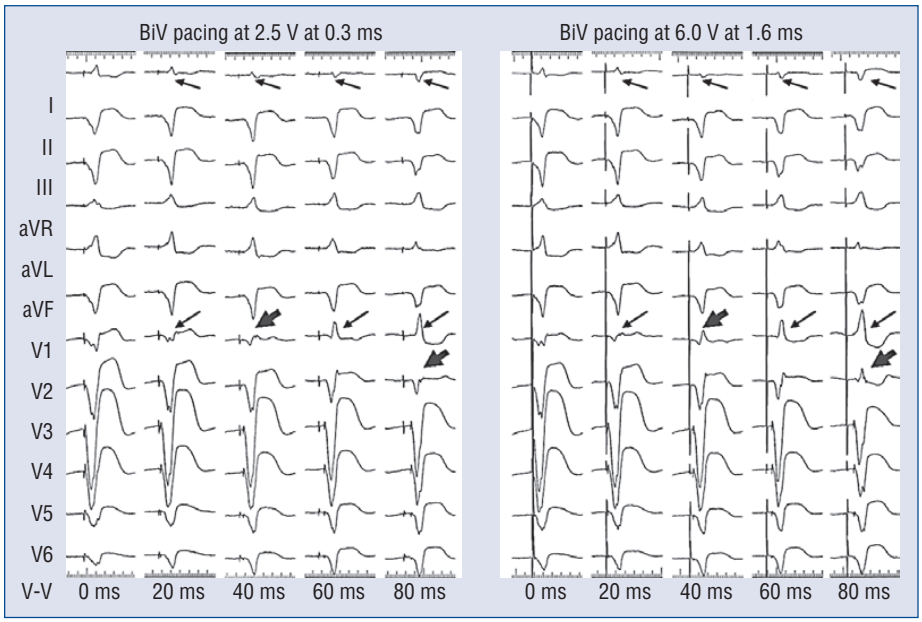

Figure 3. Impact of progressive left ventricular (LV) pre-excitation during biventricular (BiV) pacing (80 bpm at 2.5 V at 0.3 ms on the left (× 3 threshold value) and 80 ppm maximum output 6 V at 1.6 ms pulse duration on the right) on QRS morphology in a patient with an increased LV latency interval. The ECG shows a left bundle branch block pattern during simultaneous BiV pacing (V-V = 0). On the left programming of incremental left to right ventricular (V-V) delays (LV pre-excitation = 20, 40, 60, and 80 ms) brings out a dominant R wave in lead V1 and may guide the selection of a V-V interval to produce balanced left and right paced ventricular fusion from the 2 pacing sites. On the right with the same V-V intervals as on the left side, but at maximum output (6 V at 1.6 ms), the sequential ECG changes resemble those on the left but differences can be seen by comparing the QRS complexes labeled with thick arrows on the left and on the right tracings. (Reproduced with permission from: [2]).

output decreases interventricular conduction time and commonly produces a change in the QRS configuration [4, 5]. Investigations with temporary unipolar LV pacing (anode in the inferior vena cava) have shown that patients with an LV scar or infarction near the pacing site may exhibit a change in paced QRS configuration, a decreased latency interval, shorter QRS duration and conduction time to the RV when the LV output is increased (Fig. 3) [4]. These changes were independent of RV anodal stimulation. Increasing the LV output strength probably works by enlarging the area of myocardial capture beyond a site of conduction block creating a larger virtual electrode. In patients with implanted implanted cardiac resynchronization therapy (CRT) devices (unipolar LV lead and anode in the RV proximal electrode), increasing the LV output may also reduce the paced QRS duration, the conduction time from LV to RV and may alter QRS configuration by a combination of RV anodal pacing and a larger virtual electrode effect [4]. A larger virtual electrode may be of particular importance during pacing of diseased myocardium but may be complicated by phrenic stimulation, rapid battery depletion and RV anodal capture. Bipolar LV leads are needed to show the true impact of increasing the LV output because they are not associated with RV anodal capture.

Programming the interventricular interval

Prolonged LV latency intervals or any condition delaying LV activation can result in a suboptimal hemodynamic CRT response that is potentially correctable by advancing LV stimulation (before RV stimulation) via a programmable interventricular (V-V) delay (Figs. 3–5). The hemodynamic consequences depend on the difference (delta latency) between right and left sided latency intervals during BiV pacing rather than absolute values.

RV anodal stimulation during BiV pacing interferes with a programmed V-V delay (often programmed with the LV preceding the RV) aimed at optimizing CRT because RV anodal capture causes simultaneous RV and LV activation (the V-V interval becomes zero) [3]. In patients with a BiV system using the RV apex, the true configuration of

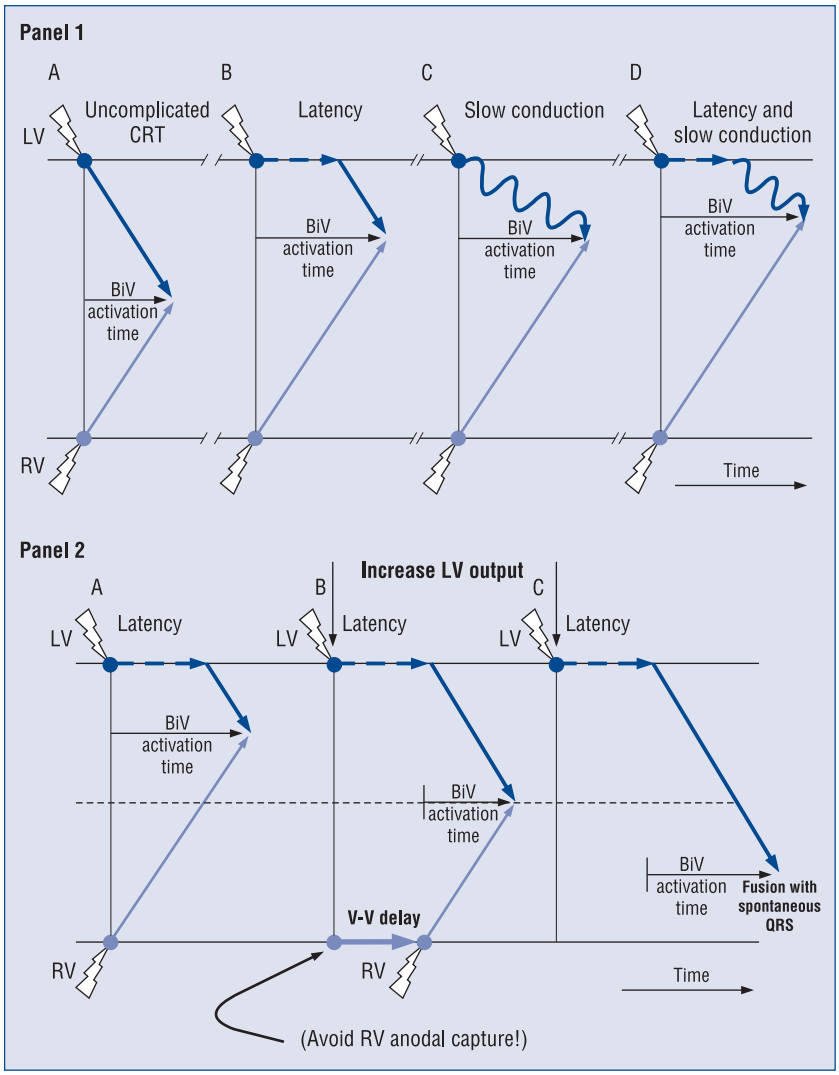

Figure 4. Diagrammatic representation of the significance of left ventricular (LV) latency and slow conduction during simultaneous biventricular (BiV) pacing. **Panel 1A.** During uncomplicated cardiac resynchronization therapy (CRT) undisturbed impulse propagation from both pacing sites produces balanced fusion of right ventricular (RV) and LV wavefronts. **Panel 1B.** In the presence of a prolonged LV latency interval (dashed black arrow) LV activation occurs late and the RV wavefront depolarizes more myocardium causing a longer BiV activation time. **Panel 1C.** Slow conduction in the proximity to the LV pacing site (due to scar tissue or myocardial fibrosis) produces a similar effect as in Panel 1B. **Panel 1D.** Coexistence of a long LV latency interval and slow conduction in the proximity to the LV pacing site may coexist in some patients. Major portions of the LV are then depolarized by the RV wavefront with minimal contribution from LV pacing and further prolongation of the BiV activation time. **Panel 2.** Compensatory programming for LV latency. **Panel 2A.** Simultaneous activation of both ventricles (on the left) results in late LV activation and more myocardium depolarized by the RV wavefront. **Panel 2B.** V-V programming permits LV pre-excitation to compensate for the prolonged LV latency interval. Both ventricles are activated synchronously resulting in a shorter BiV activation time. **Panel 2C.** Pacing the LV only may result in some degree of fusion with native conduction on the right side depending on the programmed atrio-ventricular delay. This approach may yield satisfactory hemodynamic results in patients with a markedly prolonged LV latency interval. (Modified with permission from: Barold SS, Ilercil A, Herweg B. Programmability of the interventricular interval during cardiac resynchronization therapy. In: Barold SS, Ritter P eds. Devices for cardiac resynchronization. Technologic and clinical aspects. Springer, New York, NY 2008: 237–251).

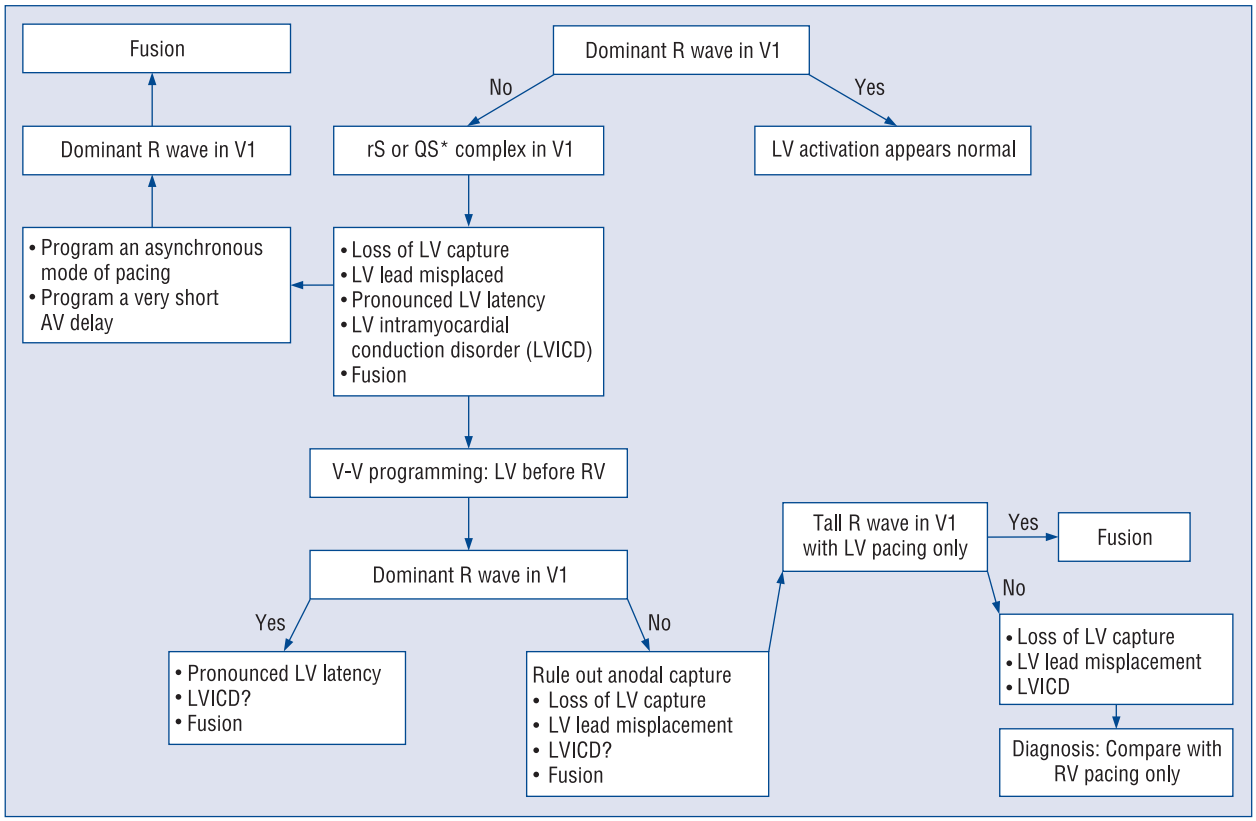

Figure 5. Algorithm to evaluate the configuration of the paced ECG in lead V1 during simultaneous biventricular pacing. Ventricular fusion with the intrinsic rhythm is the great ECG imitator and appears at several levels. A misplaced left ventricular (LV) lead means location in the anterior or the middle cardiac vein; LVICD — LV intramyocardial conduction delay. Little is known about this entity and precisely where it fits in the algorithm. It should always be a diagnosis of exclusion. A QS complex (barring fusion with the intrinsic rhythm) is not diagnostic of any problem but cause for concern (*) as it often represents an unfavorable situation with right ventricular (RV) preponderance when LV activation is delayed (or absent) and being overshadowed by RV activation. Note that fusion appears at many sites in this algorithm to emphasize the ubiquity of fusion in cardiac resynchronization therapy. The operator can evaluate the presence or absence of fusion by using only the first step of the protocol. For more precise LV lead location another algorithm can be consulted (Ploux S, Bordachar P, Deplagne A et al. Electrocardiogram-based algorithm to predict the left ventricular lead position in recipients of cardiac resynchronization systems. Pacing Clin Electrophysiol, 2009; 32 (suppl. 1): S2–S7).

lead V1 can be easily evaluated during BiV VVI pacing at a rate faster than the spontaneous rate. Serial ECGs at various V-V intervals may allow the emergence of a previously masked dominant R wave in lead V1. When programming the V-V interval, it is important to appreciate that the relationship between the presence and/or amplitude of the paced R wave in lead V1 has not yet been correlated with the best mechanical or hemodynamic response in individual patients though the data of Sweeney et al. [6] suggests that a large increment in the R wave (compared to baseline) in lead V1 favors a positive response to CRT.

Long-term ECG changes

The paced QRS duration does not vary over time as long as the LV pacing lead does not move from its initial site [7]. Yet, surface ECGs should be performed periodically because the LV lead may become displaced into a collateral branch of the coronary sinus. The underlying spontaneous ECG should be exposed periodically to confirm the continuing presence of a LBBB type of intraventricular conduction abnormality. In this respect, turning off the pacemaker could potentially improve LV function and heart failure in the rare patients who

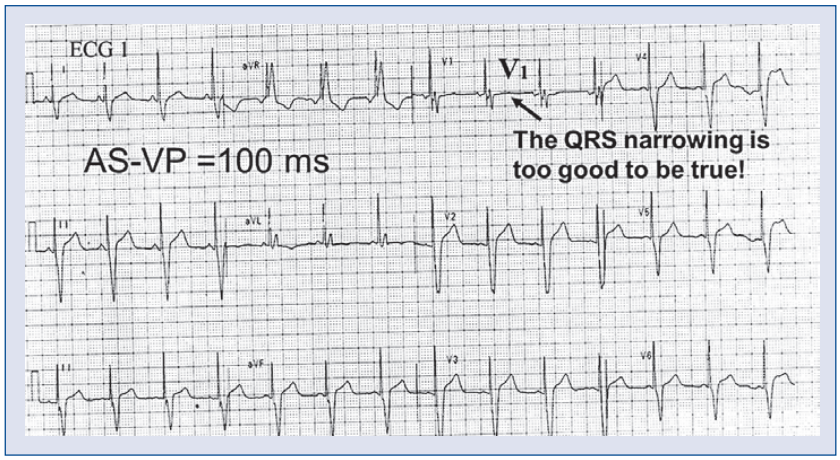

Figure 6. 12-lead ECGs during biventricular (BiV) pacing showing ventricular fusion with the conducted spontaneous QRS complex. There is narrowing of the paced QRS complex (well seen in V1). This ECG was the initial recording taken upon arrival of the patient to the follow-up center. AV delay = 100 ms. The marked narrowing of the QRS complex in lead V1 strongly suggests ventricular fusion with the intrinsic QRS complex rather than QRS narrowing from satisfactory BiV pacing without fusion with the intrinsic rhythm. (Reproduced with permission from: Barold SS, Herweg B, Giudici M. Electrocardiographic follow-up of biventricular pacemakers. Ann Noninvasive Electrocardiol, 2005; 10: 231–255).

have lost or reduced their intraventricular conduction delay or block through electrical ventricular remodeling [8]. In other words, a spontaneous narrow QRS is better than BiV pacing.

Ventricular fusion beats with native conduction

In patients with sinus rhythm and a relatively short PR interval, ventricular fusion (defined as involving spontaneous conduction) with competing native conduction during BiV pacing may cause misinterpretation of the ECG, and is a common pitfall in device follow-up (Figs. 5–7). The investigation of substantial QRS shortening mandates exclusion of ventricular fusion (for diagnosis) with the spontaneous QRS complex rather than attributing the pattern to near-perfect electrical ventricular resynchronization. The presence of ventricular fusion should be evaluated by observing the paced QRS morphology during progressive shortening of the atrial sensing-ventricular pacing (AS-VP) interval in the VDD mode or the atrial pacing-ventricular pacing (AP-VP) interval in the DDD mode. Alternatively BiV pacing in the VVI mode at a rate faster than the spontaneous rate can also be used to evaluate the presence of fusion. A dissimilar QRS pattern confirms the diagnosis of fusion in the DDD(R) mode.

There is evidence that the acute effect of intrinsic conduction over the right bundle branch (causing fusion) improves hemodynamics. The data were obtained in patients who are candidates for CRT according to standard indication by comparing LV pacing (BiV activation with LV monochamber pacing) with BiV pacing activation [9, 10].

Vatasescu et al. [11] performed contact electro-anatomical mapping of ventricular activation during sinus rhythm in 15 patients with echocardiographically optimized CRT. Fusion with the intrinsic rhythm during pacing was defined by LV septal activation produced at least partially by intrinsic depolarization when compared with LV activation map during sinus rhythm. Patients were considered responders to CRT if they had ≥ 10% reduction in LV end-systolic volume after 6 months. BiV pacing (using the RV apex) revealed fusion with intrinsic depolarization in 8 of 15 patients. The native PR interval was shorter in patients with fusion BiV/RV apical pacing (164 ± 24 *vs* 234 ± 55 ms, p = 0.006). In patients with fusion, the 6 months responder rate was significantly higher (100% *vs* 28.5%, p = 0.007) as was the degree of LV end-systolic volume reduction.

Ventricular fusion. Clinically beneficial or harmful?

The traditional practice of avoiding fusion was based on presumed variability of atrio-ventricular (AV) conduction and the lack of data about the chronic effect of fusion. In 2006 a major review of implantable cardioverter-defibrillator (ICD) troubleshooting stated that "that any parameter that permits fusion will adversely affect CRT" [12]. The

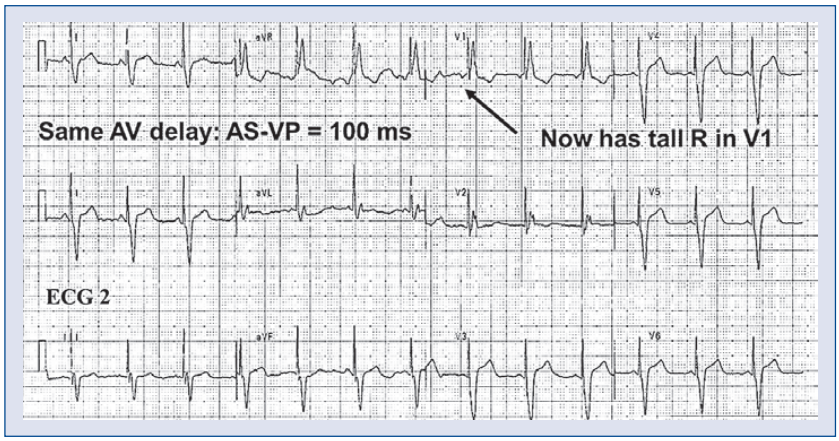

Figure 7. Dynamic QRS changes in lead V1 during biventricular pacing. Same patient as in Figure 6. The ECG taken 15 min later (same parameters and AV delay) when the patient was more relaxed shows no evidence of obvious ventricular fusion with the spontaneous conducted QRS complex. The tracings illustrate the dynamic nature of AV conduction (emotion, catecholamines etc.) and the importance of appropriate programming of the AV delay to prevent ventricular fusion with the spontaneous conducted QRS complex if the absence of fusion is clinically desirable. (Reproduced with permission from: Barold SS, Herweg B, Giudici M. Electrocardiographic follow-up of biventricular pacemakers. Ann Noninvasive Electrocardiol, 2005; 10: 231–255).

same statement in 2008 appeared in a major textbook on pacing and defibrillation [13]. The pendulum is presently swinging in the opposite direction. Fusion allows for RV activation via the right bundle branch and is associated with rapid and organized RV contraction. At present, it's best to optimize the AV delay regardless of fusion. At this juncture it's worth starting with right bundle branch fusion in patients with a normal or short PR interval in an attempt to provide the best resting hemodynamics. A suboptimal CRT response with fusion and without an obvious cause deserves reprogramming the AV delay so as to avoid all forms of ventricular fusion because fusion may sometimes be associated with a suboptimal CRT response.

Influence of first-degree AV block

In an early and relatively small study (based on the MIRACLE trial), Reynolds et al. [14] found no correlation of the PR interval with CRT outcome. In a later larger study (based on the MIRACLE trial), Pires et al. [15] found that the absence of first-degree AV block was associated with a better response to CRT ($p = 0.005$). Tedrow et al. [16] 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, $p = 0.0650$). Two large studies have shown that a prolonged baseline PR interval is associated with an unfavorable CRT outcome [17, 18], so that only study [14] involving relatively few patients failed to show the predictive value of a long PR interval. Analysis of the CARE-HF data revealed that PR shortening in the first 3 months is associated with a favorable CRT outcome [17]. Enhanced hemodynamic response in patients with normal AV conduction may have occurred by concealed resynchronization or fusion from the right bundle branch with the impulse initiated by the LV electrode together with the avoidance of RV apical stimulation. Alternatively the influence of a long PR interval might be explained by more severe myocardial disease before CRT initiation.

Mechanism of altered CRT response in first-degree AV block

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 (sinus P wave falling continually in the postventricular atrial period) especially in devices without appropriate restorative algorithms [19]. Enhanced hemodynamic response in patients with normal AV conduction by concealed resynchroniza-

tion or fusion as suggested by Kurzidim et al. [10]. These workers studied 22 heart failure 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 BiV 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 BiV pacing and was equivalent to that of simultaneous BiV 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 ms *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 BiV pacing in patients with a long PR interval supports their hypothesis.

Electrocardiography during exercise

Exercise testing in CRT patients is now technically less difficult with the advent of wireless telemetry. Exercise testing is helpful in the overall evaluation of CRT particularly in patients with a suboptimal CRT response where no obvious cause is found at rest [20, 21].

The assessment of effective BiV capture should include exercise testing. There are many reasons why BiV capture may fail during exercise: loss of atrial sensing (with preservation of BiV capture), frequent premature ventricular complexes, atrial tachyarrhythmias, and spontaneous AV conduction that is faster than the programmed AV delay (Fig. 8). The development of spontaneous AV conduction indicates that the upper rate and/or the AV delay should be reprogrammed to ensure consistent BiV capture with effort. Changes of the QRS complex during exercise may suggest loss of capture in one ventricle but as the PR interval shortens on exercise, the emergence of the spontaneous QRS complex may complicate interpretation of the ECG because of fusion (ventricular activation from 3 sites).

Exercise testing is important in patients with permanent atrial fibrillation who have not undergone ablation of the AV junction to determine the status of spontaneous AV conduction to verify the constancy of BiV capture. In such patients, adequate BiV capture at rest should not be considered a marker of satisfactory BiV capture because improvement of spontaneous AV conduction on exercise may generate a relatively fast spontaneous ventricular rate capable of inhibiting BiV pacing.

With regard to the programmed upper rate, Maass et al. [21] reported that at moderate exercise, defined as 25% of the maximal exercise tolerance that is comparable to daily life exercise. CRT non-responders (defined as a decrease in LV end--systolic volume < 10% after 6 months) more frequently went above the upper rate of the device (13 [22%] *vs* 2 [3%], $p < 0.0001$), most of whom were patients in permanent atrial fibrillation. One must avoid „break-through" ventricular sensing within a patient's exercise zone.

Anodal stimulation in biventricular pacemakers

Although anodal capture may occur with high output traditional bipolar RV pacing, this phenomenon is almost always indiscernible electrocardiographically. Some BiV pacing systems utilize a unipolar lead for LV pacing: LV pacing is achieved with the tip electrode of the LV lead as the cathode and the proximal electrode of the bipolar RV as the anode. This arrangement creates a common anode for both RV and LV pacing (Fig. 9). RV anodal capture can occur at a high LV output during lone LV pacing and also during BiV pacing [3, 23, 24].

Anodal capture involving the proximal electrode of the bipolar RV lead can occur with BiV pacemakers with separately programmable ventricular outputs. During monochamber LV pacing at a relatively high output (with the RV output programmed off), RV anodal capture produces a paced QRS complex identical to that registered with BiV pacing (Figs. 10, 11). With the proper electrode arrangement as described above this form of anodal stimulation can occur in almost 80% of systems programmed to a high LV output. The threshold for RV anodal pacing is almost always above the LV pacing threshold. This means that during LV testing, and gradual reduction of the LV output anodal

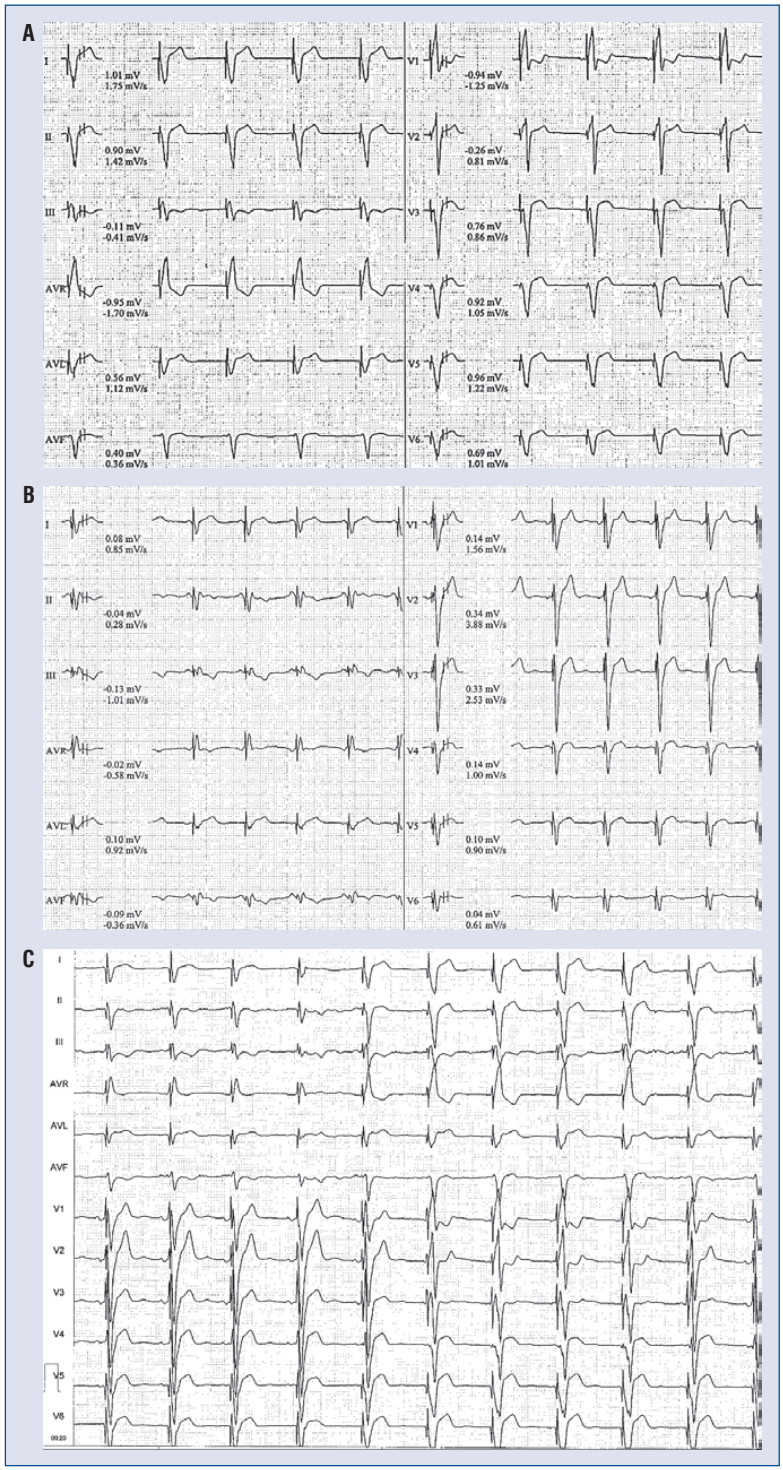

Figure 8. Changes in the paced QRS complex during exercise in a patient with a biventricular (BiV) system (right ventricular [RV] lead at the apex) and sinus rhythm. **A.** At rest (rate = 60 ppm) the tracing is typical for BiV pacing because of the axis lies the right superior quadrant and there is a dominant R wave in lead V1. **B.** During exercise (rate = 78 ppm) lead V1 assumes a left bundle branch block (LBBB) configuration and there is a slight shift in the frontal plane axis. The differential diagnosis is between left ventricular (LV) pacing + RV pacing + ventricular fusion with the intrinsic rhythm or RV pacing + ventricular fusion with the intrinsic rhythm (and failure of LV pacing). The LBBB pattern is not suggestive of pure RV pacing (no LV) because the QRS morphology is indicative of fusion with the intrinsic rhythm on the basis of QRS narrowing. **C.** In the resting period, the ECG abruptly returns to its original configuration but the transition reveals a single beat with a configuration different from those seen on the left and on the right of the tracing, a finding highly suggestive of fusion. (Courtesy of Carsten Israel MD).

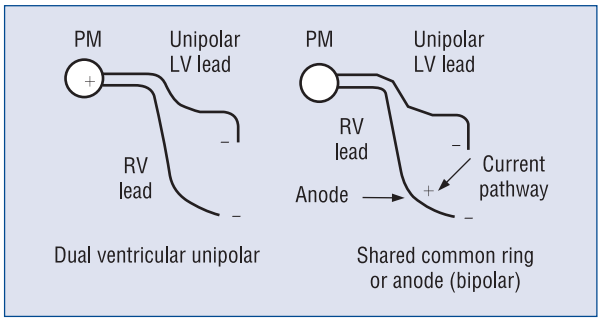

Figure 9. Diagrammatic representation of pacing arrangements with a unipolar left ventricular (LV) lead. **Left.** True unipolar LV pacing with the anode on the pacemaker (PM) can utilized for both right ventricular (RV) pacing and LV pacing. RV anodal capture cannot occur. **Right.** Pacing arrangement with a unipolar LV lead and bipolar RV lead an arrangement capable of causing RV anodal capture. LV pacing utilizes the LV tip (cathode) and the ring electrode of a bipolar RV lead (anode) creating a common or ring electrode for both RV and LV pacing. This is sometimes called pseudo-bipolar LV pacing. True bipolar LV pacing (not shown) utilizes bipolar leads for both LV and RV pacing. RV anodal capture cannot occur with dedicated bipolar LV pacing. However RV anodal capture may occur in bipolar systems with programmable lead polarity when only one pole of the LV lead is active.

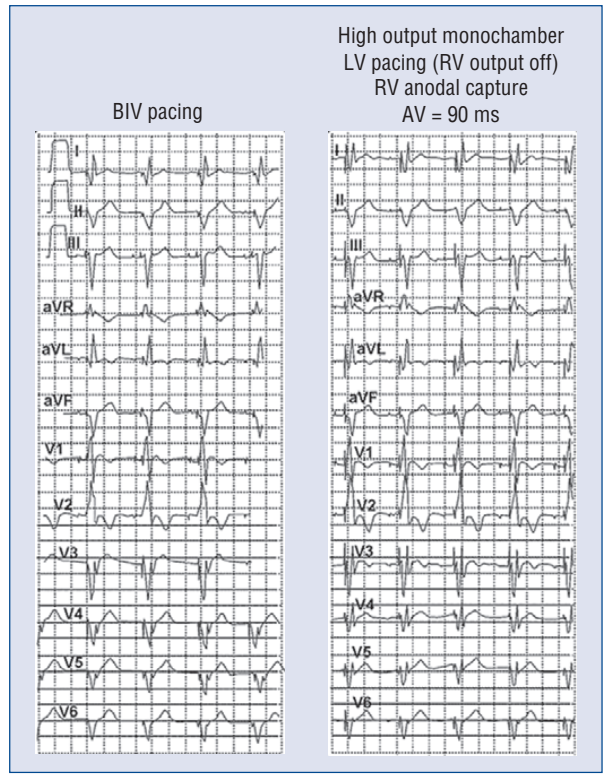

Figure 10. Right ventricular (RV) anodal capture. The ECGs during biventricular (BiV) pacing is identical to the one during monochamber left ventricular (LV) pacing. This occurs at a high output from the LV channel if the LV tip is the cathode and the ring electrode on the bipolar RV lead is the anode. Anodal stimulation causes effective BiV pacing when the RV channel is programmed off. (Reproduced with permission from: Barold SS, Stroobandt RX, Sinnaeve AF. Cardiac pacemakers and resynchronization step by step. An illustrated guide. Wiley-Blackwell, Hobocken NJ 2010: 331).

capture will disappear before LV pacing is lost. Theoretically this type of anodal capture could prevent electrocardiographic documentation of pure LV pacing if the LV pacing threshold is higher than that of RV anodal stimulation. Such anodal stimulation may complicate LV threshold testing and should not be misinterpreted as pacemaker malfunction. Furthermore if loss of anodal capture is misinterpreted as loss of capture, it may lead to an inappropriately high LV output above the anodal threshold precluding the programming of an effective V-V interval.

A high current density (from two sources) at the common anode during BiV pacing may cause anodal capture manifested as a paced QRS complex with a somewhat different configuration from that derived from standard BiV pacing (Fig. 12). RV anodal capture can be recognized on the ECG during BiV pacing but in only about 40% of cases where the phenomenon is documented during LV monochamber pacing (Fig. 12). Thus anodal stimulation is present but concealed. When apparent in the ECG, it has been called "triple stimulation" with one LV electrode and two RV electrodes. The electrocardiographic manifestations during BiV pacing are usually slight, minimal or even subtle.

Lead polarity is now programmable in some devices with bipolar RV and bipolar LV leads. This function is known as electronic repositioning and is useful in dealing with high LV thresholds and phrenic nerve stimulation. In 228 patients Champagne et al. [24] used the LV tip to RV ring configuration in 39% of patients and LV ring to RV ring in 14% of patients for long-term pacing. Both these combination predispose to RV anodal stimulation which can therefore occur in bipolar LV leads when programmed to the unipolar mode with a common RV anode.

Although anodal capture is generally benign, it is avoided as one recent report described two patients who developed more severe LV dysfunction acutely [23], and another suggested long-term effects on LV function in 3 patients [25]. This issue

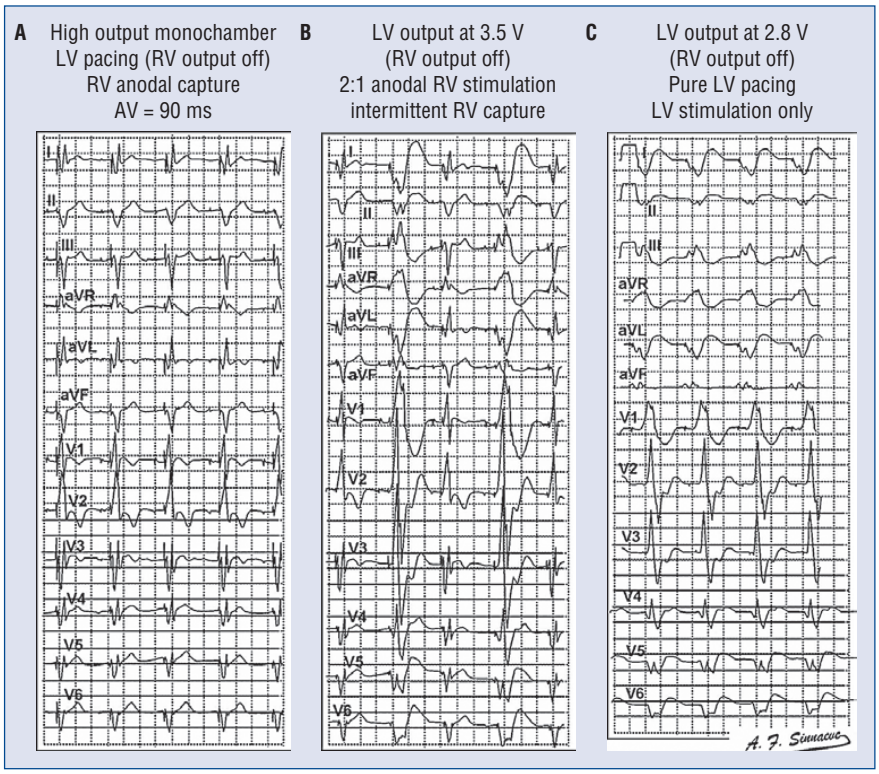

Figure 11. Testing the threshold for anodal stimulation during monochamber left ventricular (LV) pacing when the right ventricular (RV) channel was turned off. **A.** ECG during high LV output shows biventricular pacing. **B.** LV pacing close to the threshold for anodal capture. There is 2:1 anodal capture. **C.** LV pacing below the threshold for anodal stimulation now shows pure LV pacing with a wider QRS complex, the typical right bundle branch block configuration and right axis deviation. (Reproduced with permission from: Barold SS, Stroobandt RX, Sinnaeve AF. Cardiac pacemakers and resynchronization step by step. An illustrated guide. Wiley-Blackwell, Hobocken NJ 2010: 332).

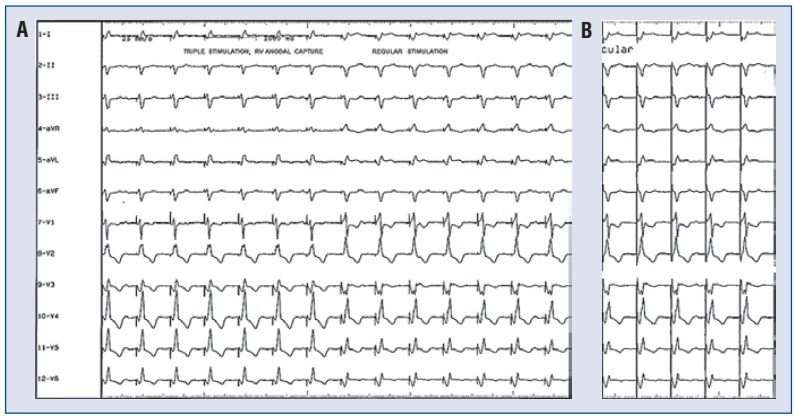

Figure 12. Right ventricular anodal capture. **A.** There is anodal capture causing triple stimulation during biventricular (BiV) pacing (unipolar left ventricular [LV] lead and bipolar right ventricular [RV] lead). The voltage output of the LV channel was gradually decreased (from left to right) so that anodal capture terminated. The transition appears to be in the middle of the recording (where anodal capture subsides) seen where the R waves of both leads V1 and V2 increase their heights. The ECG during anodal capture with pseudo-bipolar LV pacing shows subtle differences compared to pure BiV pacing on the right. **B.** True unipolar pacing (both the LV and RV leads are unipolar). True unipolar BiV pacing cannot cause RV anodal capture so this arrangement yields an ECG identical to that recorded with bipolar RV and pseudo-bipolar LV pacing when anodal capture was eliminated (Courtesy of Michael Glikson MD).

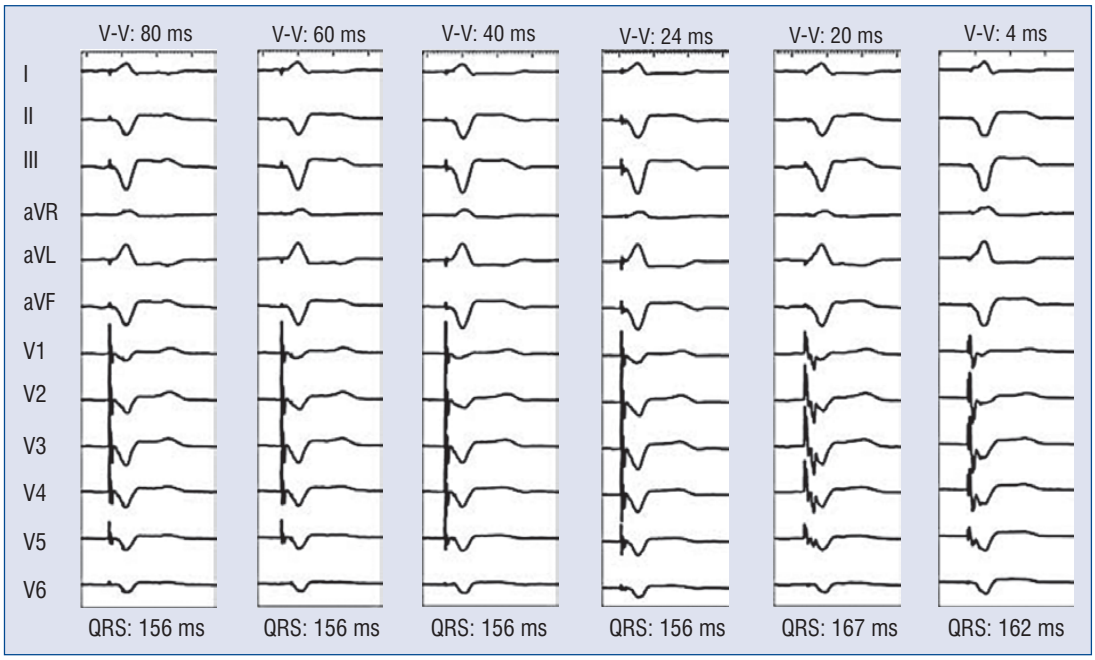

Figure 13. Effect of right ventricular (RV) anodal capture on left ventricular (LV) pre-excitation at various V-V intervals. Sequential biventricular pacing (LV first) with V-V intervals varying from 80 to 4 ms with LV first. The LV pacing configuration is LV tip to RV ring with anodal capture at the RV ring electrode. There is an identical morphology of the QRS complex at V-V intervals of 80, 60, and 40 ms, which then changes after shortening the V-V interval from 24 ms to 20 ms and 4 ms. The QRS complex at V-V intervals of 20 ms and 4 ms is different and shows an initial sharp negative deflection. This is because activity arising from RV anodal stimulation was conducted to the RV tip electrode (cathode) causing triple stimulation (LV cathode + RV anode + RV cathode). In other words, this is possible because of the short distance between RV anode and RV cathode and the timing before the onset of myocardial refractoriness. RV stimuli at V-V intervals > 20 ms appear to be delivered in the RV myocardial refractory period generated from RV anodal stimulation. The QRS changes at a V-V interval of 20 ms (LV and RV are activated simultaneously) do not equal those produced by a V-V interval of 20 ms without RV anodal stimulation. See text for details. (Adapted with permission from: [3]).

should be investigated in a larger number of patients. Thus, if the LV threshold is not too high, appropriate programming of the LV output should eliminate anodal stimulation in most cases.

It is important to understand that in the presence of anodal capture because it is impossible to advance LV activation by V-V interval programming because the effective V-V interval remains at zero (Fig. 13) [3]. The use of true (dedicated) bipolar LV leads eliminates all forms of RV anodal stimulation.

Triggered ventricular pacing

The triggered ventricular pacing mode, available in some devices, is a programmable option that attempts resynchronization by triggering a BiV output immediately when the CRT device senses a spontaneous QRS complex within the programmed AV delay or it senses a pacemaker-defined ventricular premature complex. Because ventricular sensing in modern CRT devices is limited to the RV channel, only rhythms arising from the RV will be sensed relatively early to possibly allow resynchronization by triggered LV pacing. Ectopic rhythms arising remotely from the RV lead will be sensed relatively late and, therefore, the delivered triggered stimuli may occur too late for effective electrical resynchronization. The use of the triggered mode should only be used after demonstrating its efficacy by hemodynamic echo/Doppler techniques [26]. The use of this modality should raise the question as to whether pacing-induced LV depolarization actually occurs and if it does, to what degree.

Repolarization parameters

LV and BiV pacing may increase the QT interval but they rarely cause torsades de pointes. The normal ventricular myocardium is not uniform and exhibits electrical heterogeneity in that it is comprised of three electrophysiologically distinct cell types, epicardial, endocardial, and M (mid-myocardial) cells differing

mainly with respect to repolarization characteristics [27–31]. The hallmark of M cells is their tendency for their action potentials to prolong disproportionately compared to those in the epicardium or endocardium during bradycardia or in the presence of QT prolonging drugs or in response to agents that normally prolong the action potential. Hence, M cells (which have a different ionic basis) are thought to play an important role in delayed ventricular repolarization.

Normally, ventricular activation starts with the endocardium via a subendocardial Purkinje network and spreads across the ventricular wall. Although the epicardium is activated last, it repolarizes first because of its shorter action potential duration, producing a repolarization sequence opposite to activation. Full repolarization of the epicardial action potential coincides with the peak of the T wave and repolarization of the M cells is coincident with the end of the T wave. It follows that the duration of the M cell action potential determines the QT interval, whereas the duration of the epicardial action potential determines the QT peak interval [27–31].

The QT (JT) interval alone is a poor parameter of ventricular depolarization. QT dispersion (the difference between the longest and shortest QT intervals on a 12-lead ECG) has been proposed as a measure of myocardial repolarization heterogeneity but the T_{peak}-T_{end} interval is widely used. The T_{peak}-T_{end} interval on the surface ECG provides an index of total transmural dispersion of repolarization (TDR) or electrical heterogeneity if the measurements are limited to precordial leads [27–31]. However, reliability of this interval may not be feasible owing to the frequent occurrence of a flat, biphasic or bifurcated T wane [31]. A great deal of evidence has accumulated in support of the concept that amplification of TDR rather than QT prolongation underlies the substrate responsible for the creation of re-entry and the development of polymorphic ventricular tachycardia or torsades de pointes, and this also applies to CRT patients. Increased TDR and a prolonged QT interval do not facilitate the emergence of sustained monomorphic VT). It is generally believed that BiV and LV pacing both increase the TDR (more prominently with LV pacing) though some studies have shown a decrease of the TDR with BiV pacing [32, 33]. An increased TDR may be prognostic of arrhythmic risk only under conditions in which a trigger (e.g., early after depolarizations) and enhanced TDR are both present. Little is known about which factors modulate the arrhythmogenic substrate of CRT patients. It is important in CRT patients to avoid situations known to prolong the QT interval.

Torsades de pointes and polymorphic ventricular tachycardia are rare in CRT patients and usually occur in the early period after device implantation [34, 35]. The repolarization abnormalities (QT interval) tend to dissipate after a week and when present they can be attenuated by increasing the pacing rate (e.g., from 60 to 80 ppm) [31]. There was no proarrhythmia in the BELIEVE trial which followed 74 patients with single lead-LV pacing for 1 year [36, 37].

Repolarization parameters should be recorded before starting a class III antiarrhythmic agent so that the data are available for comparison in the future.

Configuration of the P wave

The attention focused on the configuration of the QRS complex during CRT should not completely overshadow scrutiny of the P wave. The diagnosis is important because it is a cause of a potentially correctible suboptimal CRT response. Interatrial conduction delay is characterized by a wide and notched P wave (> 120 ms) traditionally in ECG lead II, associated with a wide terminal negative deflection in lead V1 [38]. The latter is commonly labeled left atrial enlargement though it reflects left atrial conduction disease. Interatrial conduction time is also measured as the activation time from the high right atrium or onset of the P wave to the distal coronary sinus (60–85 ms) [38]. In the presence of interatrial conduction delay with late left atrial activation, left atrial contraction occurs late and even during LV systole. Consequently, the need to program a long AV interval to adjust for delayed left atrial contraction can preclude CRT in heart failure patients because of the emergence of competing spontaneous AV conduction. The incidence of interatrial conduction delay in patients who are candidates for CRT is unknown. When the ECG suggests interatrial conduction delay, it would be wise to look for delayed left atrial activation at the time of pacemaker or CRT implantation by showing that the conduction time from the right atrium to the left atrium is longer than the conduction time from right atrium to the ventricles (onset of the QRS complex) [39]. In the presence of interatrial conduction delay, one should consider placing the atrial lead in the interatrial septum where pacing produces a more simultaneous and more homogeneous activation of both atria and abbreviates total atrial activation time judged by a decrease in P wave duration [40, 41]. In the presence of established pacemaker or CRT with an atrial lead already in the right atrial appendage, restoration of mechanical

left-sided AV synchrony requires simultaneous biatrial pacing performed by the implantation of a second atrial lead either in the proximal coronary sinus or low atrium near the coronary sinus to preempt left atrial systole [42, 43]. Difficult cases of interatrial conduction delay can be managed by AV nodal ablation whereby the AV delay can then be extended with impunity though BIV ICDs may limit the maximum programmable AV delay [44].

Conclusions

The paced 12-lead ECG is an indispensible tool in the assessment of patients with CRT devices. There is no place for single-lead rhythm strips in the evaluation, programming, and troubleshooting of CRT devices. The interpretation of the paced 12-lead ECG requires detailed knowledge of device specifications and familiarity with the multiplicity of clinical situations described in this two-part review. The design of programmers capable of registering a 12 lead ECG would obviate the need of an additional electrocardiograph which is sometimes cumbersome and would encourage the routine recording of the paced 12-lead ECG with each patient encounter. Furthermore the implanted device might one day be able one to transmit a full "surface" ECG. This is already feasible by reconstruction of the ECG using a set of ventricular electrograms [45].

Disclosures

The authors do not report any conflict of interest regarding this work.

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