Electrocardiographic Clues to Identify Nonresponders to Cardiac Resynchronization Therapy

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Background: The aim of cardiac resynchronization therapy (CRT) is to restore myocardial electromechanical synchrony. Achieving this in patients with chronic severe heart failure due to poor left ventricular (LV) systolic function and cardiac dyssynchrony on optimal medical therapy, is associated with improved clinical performance and outcomes. Up to one-third of patients undergoing CRT do not benefit from implantation. Ensuring LV capture is essential and can be at times difficult to confirm.

Methods: Described herein, are six patients who underwent biventricular pacemaker implantation but failed to experience an improvement in LV systolic function or functional capacity.

Results: In each case, the 12-lead electrocardiogram (ECG) was helpful in unmasking loss of LV capture in patients who were presumed to have biventricular pacing.

Conclusions: Despite the technical wizardry behind CRT and patient system analyzers, the surface ECG should continue to be an invaluable tool for evaluating patients who have undergone CRT.

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BACKGROUND

Cardiac resynchronization therapy (CRT) is indicated for selected patients with symptomatic congestive heart failure on optimal medical therapy, with New York Heart Association (NYHA) functional class III or IV symptoms, an LV ejection fraction of less than or equal to 35%, and a QRS (the deflection on ECG comprising the Q, R, and S waves that corresponds to the depolarization of the right and left ventricles) interval more than 120 milliseconds (ms). The purpose of biventricular pacing is to restore electromechanical synchrony of the heart. For most medically optimized patients with cardiac dyssynchrony and persistently severe clinical heart failure, biventricular pacing promotes reverse remodeling of the left ventricle, enhances clinical performance, and improves prognosis.¹ However, up to one-third of patients with CRT do not experience clinical benefit.² Potential reasons for lack of clinical response to CRT include patient selection, suboptimal lead placement, development of atrial or ventricular tachyarrhythmias, and improper device programing.^{3,4}

Follow-up of patients with CRT typically includes symptomatic assessment, physical examination, and device interrogation and programing, oftentimes aided by real-time echocardiography. Another tool that can greatly influence clinical decision-making is the 12-lead ECG. The algorithm described by Ammann et al. suggests that if the electrocardiographic forces are directed anteriorly (Rs in lead V₁) or to the right (rS in lead I), biventricular pacing is present.⁵ Using this algorithm, we identified several cases that illustrate the importance of the 12-lead ECG and some of the limitations of single-lead ECG in patients with biventricular pacing systems.

CASE 1

N.M. is a 74-year-old lady who sought a second opinion at our facility after failing to experience clinical improvement following biventricular pacemaker implantation at another hospital. The patient's 12-lead ECG during pacing displayed a left bundle branch block (LBBB) pattern in lead V₁ and Rs in lead I, consistent with right ventricular (RV)

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Figure 1. (A) This 12-lead ECG displays a LBBB pattern and inferior axis consistent with pacing from the RVOT (case 1). ECG = electrocardiogram, LBBB = left bundle branch block, RVOT = right ventricular outflow tract. (B) Posterior–anterior chest roentogram with the coronary sinus lead in the pulmonary artery (arrow). The right atrial lead is in the right atrial appendage, and the right ventricular lead is positioned in the RVOT (case 1). (C) Lateral chest roentogram with the coronary sinus lead (arrow) in the pulmonary artery (case 1).

pacing (Fig. 1A).⁶ The inferior axis suggested activation from the RV outflow tract. Failure to capture the left ventricle was suspected, and a chest x-ray (Figs. 1B and C) demonstrated that the coronary sinus lead was in the right pulmonary artery.

Coronary sinus lead dislodgement accounts for 2–9% of failed CRT therapy.^{7–9} RV pacing results in LBBB configuration on surface electrocardiography, a distinctly different configuration than with

most biventricular pacing. The presence of a LBBB pattern should prompt chest radiography to confirm the position of the LV lead.

CASE 2

M.G. is an 85-year-old lady with ischemic cardiomyopathy and LBBB who underwent dual chamber implantable cardioverter defibrillator

(ICD) implantation in 2000 for inducible ventricular tachycardia. The RV lead was placed in the RV apex. At the time of elective replacement in February 2005, an ECG showed a LBBB with a QRS duration of 186 milliseconds (ms), and a PR interval (measured from the beginning of the P wave to the beginning of the QRS complex and reflects the time the electrical impulse takes to travel from the sinus node to the ventricles) of 178 ms. The left ventricular ejection fraction (LVEF) was 30% and there was 2+ mitral regurgitation. At the time of replacement of the pulse generator, a coronary sinus lead was placed in the posterior lateral vein. Following upgrade, the patient had persistent NYHA functional class III symptoms with a Living with Heart Failure score of 67. Although the Medtronic programmer used during device interrogation indicated 99% ventricular pacing with RV and LV output programmed for adequate capture, the 12-lead ECG demonstrated a LBBB pattern similar to the patient's intrinsic QRS complexes with pseudofusion beats and no ECG evidence of LV capture (Fig. 2A). The paced and sensed AV intervals of the device were shortened from 200 and 180 ms to 100 and 70 ms, respectively. The RV and LV outputs were unchanged. The resultant 12-lead ECG was consistent with biventricular (BIV) pacing (Fig. 2B). The patient felt subjectively improved immediately. Subsequently, the LVEF improved to 40% and the Living with Heart Failure score was reduced to 58.

This case demonstrates that fusion and pseudofusion complexes may be interpreted as paced complexes by the programmer. A fusion beat is recognized electrocardiographically as a pacemaker spike with a partial change in the QRS complex configuration. A pseudofusion beat is recognized as a pacemaker spike with no change in the QRS complex configuration. Pacemaker spikes may be counted by the pulse generator with assumed capture of the ventricle. The 12-lead ECG helped determine if functional loss of capture has occurred. In this case, only after programming shorter AV intervals, was biventricular pacing established.

CASE 3

B.R. is a 61-year-old female with a nonischemic dilated cardiomyopathy, LBBB, an LVEF of 20% and a QRS duration of 155 ms. A CRT-ICD was implanted, in September 2006, with an anterior

coronary sinus lead position. The patient continued to have NYHA functional class III symptoms. At follow-up, the Medtronic programmer, using an intracardiac signal, suggested LV capture at 2 volts (V) at 1.4 ms with BIV pacing configuration. However, the 12-lead ECG did not fulfill Ammann's criteria for biventricular capture (Fig. 3A). When the LV lead output was increased to 2.5 V at 1.6 ms, electromechanical capture of the left ventricle was subtly appreciated by a difference in the paced QRS morphology only in lead I with an S wave (Fig. 3B). When the rhythm strip from the first ECG (Fig. 3A) was reviewed, a change in QRS morphology was noted. The first four beats did not fulfill Ammann's criteria for biventricular pacing. However, the remaining beats were similar to lead II in the subsequent ECG (Fig. 3B). Only intermittent capture occurred during what was thought to be biventricular pacing.

This case demonstrates the need for multiple ECG leads to confirm LV capture. In this case, only a single lead showed a difference in QRS morphology between biventricular pacing and RV pacing, likely due to the close proximity between the anterior coronary sinus and the RV.

CASE 4

H.L. is a 66-year-old female with nonischemic dilated cardiomyopathy who received CRT-P in July 2002 for NYHA class III heart failure. The LVEF was 25% and the QRS duration was 168 ms. At follow-up, ventricular thresholds were determined during biventricular pacing from tip to ring by a standard Medtronic programmer using an intracardiac signal. As the LV output was reduced from 2.5 to 2.0 V, a change in the intracardiac signal morphology occurred (Fig. 4A) suggesting that the LV threshold was 2.5 V. However, a 12-lead ECG performed later at a different rate showed continued evidence of biventricular pacing (and LV capture) at 2.5 and 2.0 V (Fig. 4B). The correct threshold was 1.5 V that was associated with a change in the QRS morphology in leads I and V₁ resulting in RV pacing only.

This case illustrates the potential for the programming mistakes when a single intracardiac lead is used to determine LV and RV capture. In patients with a single ventricular lead pacing system, the RV lead threshold is traditionally determined by a change in programmer electrogram morphology and a pause in the electrical activity. In patients

Figure 2. (A) The 12-lead ECG with a sensed AV delay of 180 ms and a paced AV delay of 200 ms. Pseudofusion beats are labeled (case 2). AV = atrioventricular and ms = milliseconds. (B) The 12-lead ECG after shortening the sensed AV delay to 70 ms and the paced AV delay to 100 ms. The 12-lead ECG now fulfills Ammann's criteria for biventricular pacing. The RV and LV outputs remain unchanged (case 2).

with biventricular devices, reliance on a change in a single electrogram by the programmer may result in inappropriate threshold determinations and inaccurate programming. This case supports Barold's assertion that single-lead analysis of pacemaker function may be misleading.⁶

CASE 5

B.H. is a 74-year-old lady who underwent CRT-ICD implantation in July 2006 for ischemic cardiomyopathy, an LVEF of 25%, and a QRS duration of 157 ms. AV optimization was performed

Figure 3. (A) The 12-lead ECG with the LV output programed at 2 V at 1.4 ms does not meet criteria for LV capture (case 3). V = volts, LV = left ventricular. (B) The 12-lead ECG with the LV output reprogramed at 2.5 V at 1.6 ms is subtly different. Note that the only significant change in QRS morphology occurred in lead I (case 3).

and a paced AV delay of 200 ms was recommended based on echocardiographic parameters. However, a 12-lead ECG on the same day did not meet criteria for LV capture (Fig. 5A). The paced AV delay was shortened to 150 ms and biventricular pacing was confirmed. In retrospect, the determination of biventricular capture during AV optimization was based on single-lead ECG (lead II) used for

gating purposes during the device optimization (Fig. 5B).

During echocardiogram-guided AV optimization in our laboratory, paced and sensed AV delays are programed to optimize LV filling and output parameters. AV optimization is often performed using single-lead ECG gating during echo evaluations. It is critical to confirm LV capture at the time of

Figure 4. (A) During a routine threshold check, the Medtronic programmer intracardiac electrogram demonstrates a new morphology at 2 V (case 4). (B) The surface ECG performed later at a different rate remains unchanged at 2.0 V compared to that obtained at 2.5 V (only leads I and V₁ are shown). Loss of LV capture is confirmed at 1.5 V with the development of a LBBB pattern in lead V₁ (case 4).

Figure 5. (A) The clinic surface ECG (case 5). (B) Depiction of the single-lead ECG utilized for gating purposes during the echocardiogram-guided device optimization. Use of lead II for gating is suspected (case 5).

AV optimization because reliance on a single-lead ECG is error prone. We recommend confirmation of biventricular pacing with a 12-lead ECG after AV optimization. If a frontal plane single-lead system is used for gating purposes, lead I may be the most useful lead to substantiate biventricular pacing.

CASE 6

R.S. is a 64-year-old human with heart failure due to idiopathic dilated cardiomyopathy, an LVEF of 20%, LBBB and a 6-minute walk distance of 493 m. A CRT device was implanted with the coronary sinus lead positioned in the posterior vein. On follow-up, initial ECG did not suggest LV capture (Fig. 6A). When the RV and the LV outputs were programed to 2.5 V, ventricular capture was confirmed by the 12-lead ECG. Figure 6B demonstrates LV capture with LV only pacing with a ventricular output of 2.5 V. RV only capture at 2.5 V is also demonstrated in the first nine complexes of Figure 6C and is typical of RV only pacing. However, during the second half of Figure 6C, the addition of LV pacing (at 2.5 V) changes the ECG morphology. Both RV and LV captures occur but the last four complexes in Figure 6C do not satisfy criteria for LV capture using Ammann's algorithm.

The case demonstrates that Ammann's algorithm, to determine loss of LV, is not always accurate. Sometimes individual programing of the RV and LV leads guided by the 12-lead ECG is the surest way to confirm adequate output from both leads.

DISCUSSION

These cases present just a few of the challenges that clinicians face when caring for patients with biventricular pacing systems. Because CRT is interrupted in a substantial number of recipients,¹⁰ it is important to recognize various reasons for lack of clinical response to CRT, including loss of LV capture. Our case vignettes illustrate several key points: single-lead determination of LV capture is fallible, lack of LV capture may be relatively common yet under recognized, and the surface ECG remains an indispensable tool even after a patient had undergone CRT implantation.

It should be emphasized that loss of LV capture fails to provide the electromechanical cardiac resynchronization initially sought at device implantation. The implications of inaccurate single-

lead analysis regarding LV capture, whether from the patient system analyzer or during echocardiography-guided device optimization for instance, potentially leave the device recipient sub-optimally treated and should be avoided when possible. It should also be noted that, depending on the lead, it may be difficult to confirm LV pacing with the home monitoring devices, which often rely on a single ECG lead.

Until a more sophisticated patient system analyzer is developed that enables multilead electrogram display, we advocate the routine use of surface electrocardiography for device programing in patients with CRT and native LBBB. Of course, one should ensure that the ECG leads, particularly V_1 , are placed in the correct position. Placement of lead V_1 in the 2nd or 3rd intercostal space rather than the 4th can yield a predominantly negative QRS complex in lead V_1 .¹¹ The study protocol used by Ammann et al. was highly specific (93%) and sensitive (94%) for identifying those patients who lost LV capture, but there are limitations to applying Ammann's algorithm to all patients who have biventricular pacing systems. The electrocardiograms (ECGs) of only 54 patients had RV pacing from the RV apex. The algorithm was less accurate at correctly identifying patients with true biventricular pacing (5 out of 54 patients) when the coronary sinus lead was positioned in the posterior or left marginal vein compared to the middle cardiac vein or diagonal branches of the anterior interventricular vein (90% vs. 100% accuracy, respectively).⁵ This limitation likely applies to case 6 (R.S.).

Although newer pacing devices can be programed to automatically detect ventricular capture,^{12,13} the surface ECG should continue to be an invaluable instrument for evaluating patients who have undergone CRT. New studies should test Ammann's algorithm in those patients with underlying right bundle branch block (RBBB) or nonspecific interventricular conduction delay and alternate RV pacing sites. Larger studies could help validate Ammann's algorithm and identify other diagnostic criteria for loss of LV capture irrespective of various clinical factors. Some investigators, for instance, have compared the native with the paced QRS duration and axis to corroborate changes in the pacing mode.¹¹ There may also be acute and chronic ECG changes after biventricular pacing related to LV remodeling or reverse remodeling.¹⁴ So despite the technical wizardry behind CRT and patient system analyzers, there remains a great deal

Figure 6. (A) The ECG with output programmed at 2.5 V lacks features of LV capture (case 6). (B) LV only pacing with LV output at 2.5 V. The presence of a RBBB pattern in lead V₁ is consistent with LV capture (case 6). RBBB = right bundle branch block (C) RV only pacing with RV output at 2.5 V during the first nine complexes, followed by biventricular pacing (case 6).

of basic but highly pertinent information one can glean from the not-so-fancy but clinically proven surface ECG.

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