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Cardiac resynchronisation therapy in patients with chronic heart failure

Gautam G Lalani, Ulrika Birgersdotter-Green

University of California, San Diego, California, USA

Correspondence to
Dr Ulrika Birgersdotter-Green, University of California, San Diego, 9300 Campus Point Drive, #7411, San Diego, CA 92037, USA;
ubgreen@ucsd.edu

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ABSTRACT

Cardiac resynchronisation therapy (CRT) is common treatment for congestive heart failure (HF) with decreased LV function and wide QRS complex. Its foundations are set in the understanding of the pathophysiology of ventricular dyssynchrony. Over the last several decades, CRT has evolved through changes in implantation techniques, device and lead design, imaging modalities and our growing clinical experience. This review article will discuss the vast clinical experience that has led to current guidelines recommendations for CRT in patients with mild-to-severe HF. In addition, the article will also discuss recent evidence of benefits of CRT in patients beyond the guidelines. The article will also address the issue of non-responders, optimisation of CRT, postimplant evaluation and remote monitoring.

INTRODUCTION

Cardiac resynchronisation therapy (CRT) has been revolutionary in the treatment of patients with congestive heart failure (CHF) and depressed LVEF. There is substantial evidence to support the use of biventricular patients with New York Heart Association (NYHA) classes II–IV HF and dyssynchrony.[1–6] There have now been many randomised, clinical trials that have consistently demonstrated improvements in quality of life, functional status and improvement in cardiac function and structure in this patient population.[1 3 6]

In most patients with CHF, dyssynchrony manifests with a QRS duration >120 ms, commonly presenting as a left bundle branch block (LBBB). In these cases, LV depolarisation is markedly delayed, which leads to shortened filling time and abnormal septal motion with increase in LV end-systolic diameter and decreased LVEF.[7 8] Over time, this dyssynchrony has further deleterious effects on LV structure and function.

The first case series on the benefits of biventricular pacing started in 1993,[9] placing one lead in the RV and the other on the LV free wall, epicardially. By the late 1990s, a total transvenous approach was described,[10 11] leading the way to the current era of CRT implantation.

CLINICAL STUDIES OF CRT

Moderate-to-severe HF

The overall safety and efficacy of CRT was first addressed in the early 2000s by applying this pacing method to patients with moderate-to-severe HF in the Pacing Therapies in Congestive Heart Failure [12] and the Multisite Stimulation in Cardiomyopathy [13] studies. Both studies showed benefits of CRT in patients with NYHA class III/IV HF with increase in quality of life, walking distance and peak VO_2, paving the way for further prospective secondary prevention trials.

The Multicenter InSynch Randomized Clinical Evaluation (MIRACLE) study was the first prospective, randomised, double-blinded CRT trial[1] in patients with NYHA class III/IV HF, LV dysfunction (EF ≤35%) and QRS >130 ms. Patients randomised to CRT showed improvement in 6 min walk, NYHA functional class, peak VO_2 and LVEF. Furthermore, there was also decrease in HF hospitalisation.

This study was further expanded to MIRACLE Implantable Cardioversion Defibrillation (ICD), with the first addition of CRT to internal cardioverter-defibrillator (CRT-D).[14] Patients underwent CRT-D implantation and were randomised to CRT on or off. Patients with CRT-D showed similar improvements to MIRACLE.

In the Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure trial, CRT-P (pacing only) and CRT-D were compared with optimal medical therapy alone.[2] In patients with NYHA class III/IV HF, LVEF ≤35% and QRS ≥120 ms, both CRT arms showed significant reduction in the primary composite endpoint of all-cause mortality and all-cause hospitalisation.

Lastly, the Cardiac Resynchronization in Heart Failure trial compared CRT-P with medical therapy alone.[3] In this study, patients enrolled had NYHA class III/IV HF, LVEF ≤35% and either QRS ≥150 ms or 120–149 ms with echocardiography evidence of dyssynchrony. At a mean of 29 months, patients with CRT-P showed a reduction in all-cause mortality and unplanned hospitalisations for cardiovascular events. Additionally, patients had improvements in LVEF and reverse remodelling.

Mild HF

Prior studies that enrolled a number of NYHA class II HF patients suggested the benefits of CRT in patients with mild HF with evidence of reverse remodelling.[14] However, the benefits of CRT in this population were closely examined in MIRACLE ICD II,[15] which demonstrated LV reverse remodelling in NYHA class II HF patients with QRS ≥130 ms and LVEF ≤35%.

The Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) trial[4] and Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT)[6] trial validated the benefits of CRT in this group. The REVERSE trial enrolled patients with NYHA class I/II HF, QRS ≥120 ms and LVEF ≤40%. All patients underwent CRT-D implantation and were randomised to CRT-on or CRT-off. Patient with CRT-on had improved LVEF and decrease in HF events. MADIT-CRT is the

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largest trial with patients with mild HF. Enrolled patients had NYHA class I/II HF, with QRS duration ≥130 ms and LVEF ≤30%. This study demonstrated the benefits of CRT-D over ICD therapy with a significant reduction in non-fatal HF events in the CRT-D group.

The Resynchronization/Defibrillation for Ambulatory Heart Failure (RAFT) study also had a large NYHA class II cohort.[5] Patients with NYHA class II/III HF with QRS ≥120 ms and LVEF ≤30% who were randomised to CRT-D instead of ICD had an improvement in overall mortality and decrease in HF events.

The majority of patients in MIRACLE ICD II, REVERSE, MADIT-CRT and RAFT were NYHA class II HF subjects (91%). These results provide compelling evidence in support of CRT in mild HF.

Furthermore, subsequent analysis of the CRT trials suggests the greatest benefit in[16] patients with LBBB versus right bundle branch block or other non-LBBB conduction abnormalities. However, non-LBBB patients still gain significant benefits with resynchronisation therapy.[17]

CURRENT GUIDELINES

Based on the results of these large, randomised trials of CRT, many patients with mild-to-severe HF with reduced function and ventricular conduction abnormalities are candidates for resynchronisation therapy. The most current European Society of Cardiology (ESC) guidelines and American College of Cardiology Foundation (ACCF)/American Heart Association (AHA)/Heart Rhythm Society (HRS) guidelines for CRT are listed in table 1.

RESYNCHRONISATION THERAPY IN SPECIFIC PATIENT POPULATIONS

Atrial fibrillation

The incidence of atrial fibrillation (AF) in HF can be as high as 50%.[18] The irregularity in the ventricular intervals can impede the effective delivery of CRT. Similarly, rapid AF may also hinder the benefits of biventricular pacing.

Most of the initial large studies of CRT excluded patients with atrial arrhythmias. However, there are a few small studies that suggest the benefits of CRT in AF and HF.[19 20] However, these benefits require a high rate of biventricular pacing.

When adequate CRT cannot be achieved due to difficult to control AF, atrioventricular (AV) node ablation should be considered (figure 1). In the Left Ventricular-based Cardiac Stimulation Post AV Nodal Ablation Evaluation study,[21] patients who underwent AV node ablation for poorly controlled, rapid AF were randomised to RV versus CRT pacing. Patients with CRT demonstrated improvement in HF symptoms, exercise duration and preservation of LVEF.

Table 1 Major society guidelines for cardiac resynchronisation therapy

2013 ESC guidelines	2012 ACCF/AHA/HRS guidelines
Class I	
1. CRT is recommended for patients who have LVEF ≤35%, sinus rhythm, LBBB with a QRS duration ≥150 ms and NYHA class II, III or ambulatory IV symptoms on medical therapy 2. CRT is recommended for patients who have LVEF ≤35%, sinus rhythm, LBBB with a QRS duration 120–149 ms and NYHA class II, III or ambulatory IV symptoms on medical therapy	1. CRT is indicated for patients who have LVEF ≤35%, sinus rhythm, LBBB with a QRS duration ≥150 ms and NYHA class II, III or ambulatory IV symptoms on medical therapy
Class IIa	
1. CRT should be considered for patients who have LVEF ≤35%, sinus rhythm, a non-LBBB pattern with a QRS duration ≥150 ms and NYHA class II, III or ambulatory IV on medical therapy	1. CRT can be useful for patients who have LVEF ≤35%, sinus rhythm, LBBB with a QRS duration 120–149 ms and NYHA class II, III or ambulatory IV symptoms on medical therapy 2. CRT can be useful for patients who have LVEF ≤35%, sinus rhythm, a non-LBBB pattern with a QRS duration ≥150 ms and NYHA class III/ambulatory IV symptoms on medical therapy 3. CRT can be useful in patients with AF and LVEF ≤35% on medical therapy if (a) the patient requires ventricular pacing or otherwise meets CRT criteria and (b) AV nodal ablation or pharmacological rate control will allow near 100% ventricular pacing 4. CRT can be useful for patients on medical therapy who have LVEF ≤35% and are undergoing new or replacement device placement with anticipated requirements for significant (>40%) ventricular pacing
Class IIb	
1. CRT may be considered for patients who have LVEF ≤35%, sinus rhythm, a non-LBBB with a QRS duration 120–149 ms and NYHA class II, III or ambulatory class IV symptoms on medical therapy	1. CRT may be considered for patients who have LVEF ≤30%, ischaemic heart failure, sinus rhythm, LBBB with a QRS duration ≥150 ms and NYHA class I symptoms on medical therapy 2. CRT may be considered for patients who have LVEF ≤35%, sinus rhythm, a non-LBBB with a QRS duration 120–149 ms and NYHA class III/ambulatory class IV symptoms on medical therapy 3. CRT may be considered for patients who have LVEF ≤35%, sinus rhythm, a non-LBBB with a QRS duration ≥150 ms and NYHA class II symptoms on medical therapy
Class III	
1. CRT is not recommended for patients with HF and QRS duration <120 ms	1. CRT is not recommended for patients with NYHA class I or II symptoms and non-LBBB pattern with QRS duration ≤150 ms 2. CRT is not indicated for patients whose expected survival with good functional capacity is <1 year

ACCF, American College of Cardiology Foundation; AF, atrial fibrillation; AHA, American Heart Association; AV, atrioventricular; CRT, cardiac resynchronisation therapy; ESC, European Society of Cardiology; HF, heart failure; HRS, Heart Rhythm Society; LBBB, left bundle branch block; NYHA, New York Heart Association.

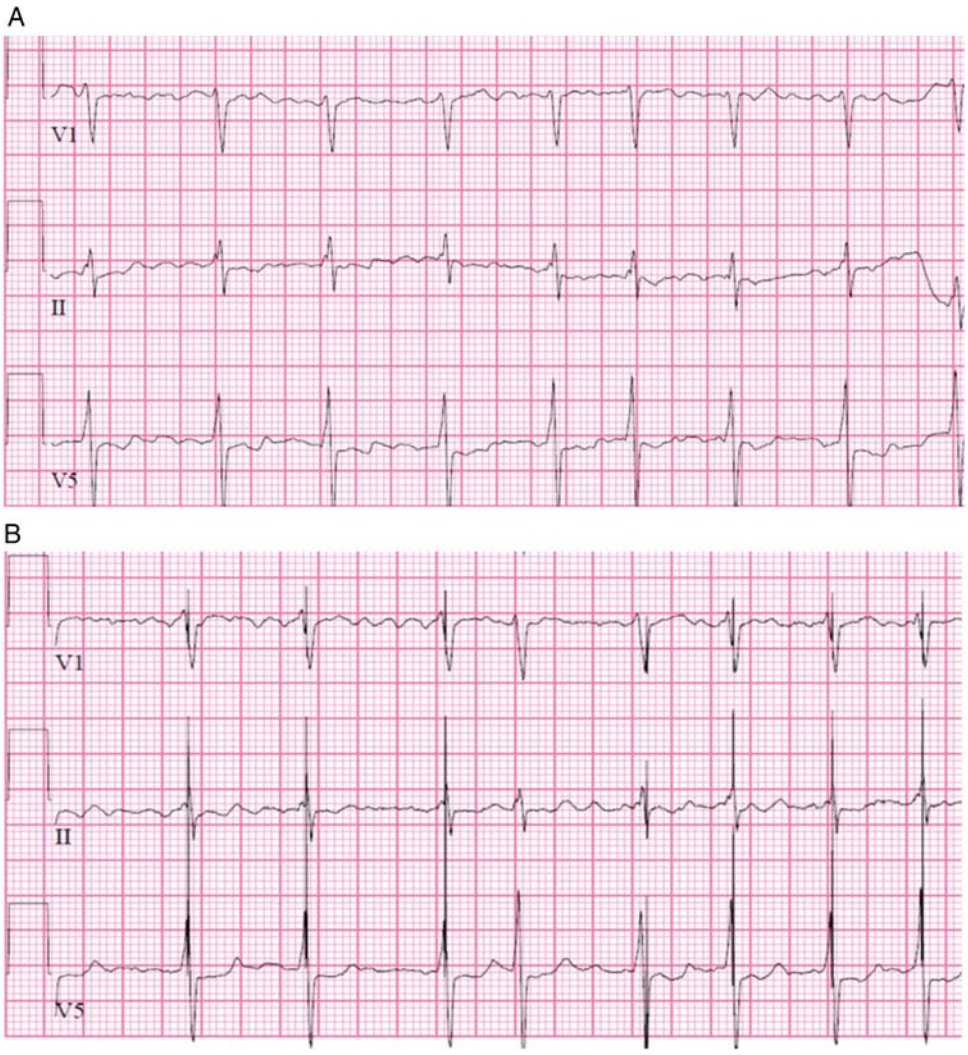

Figure 1 A 65-year-old man with history of non-ischaemic cardiomyopathy and permanent atrial fibrillation (A) who despite medical therapy remained with depressed LVEF (21%) and rapid ventricular rates. The patient underwent cardiac resynchronisation plus defibrillator therapy implantation with subsequent atrioventricular node ablation to control heart rate and provide ventricular synchronous pacing (B). LVEF improved to 55% at 10 months.

Therefore, current ESC[22] and ACCF/AHA/HRS[16] guidelines recommend the consideration of CRT in patients with AF with LVEF ≤35% who require frequent ventricular pacing or otherwise meet CRT criteria. Aggressive pharmacological control or AV node ablation should be considered to achieve close to 100% biventricular pacing. Alternatively, patients who had reduced LVEF and will undergo AV node ablation for uncontrolled, rapid AF are also candidates for CRT (ESC class IIa recommendation).

Pacemaker candidates with reduced EF (35–50%)

Similar to LBBB, RV pacing contributes to ventricular dyssynchrony. Furthermore, chronic RV pacing has been shown to have deleterious effects on LV function compared with biventricular pacing.[23] This is a major concern in patients with reduced LVEF who present with high-grade AV blocks, which would require frequent ventricular pacing.

The Biventricular Pacing for Atrioventricular Block and Systolic Dysfunction trial[24] studied patients with NYHA class I–III HF and LVEF ≤50% with AV block, which would require frequent pacing (>40%). Patients with EF 36–49% were randomised to CRT-P versus RV-only pacing. Patients with RV-only pacing had more HF events and worsened LV function, as measured by a greater increase in LV end-systolic volume.

Based on this evidence, patients with mild HF who require frequent ventricular pacing should be considered for CRT. Further studies should also look at the benefits of CRT in patients with normal LV function and frequent ventricular pacing.

RESPONSE, OPTIMISATION AND EFFICACY OF CRT

Non-responders

Approximately 30% of patients are considered non-responders to CRT. However, there is no consensus on the definition of response to CRT.[25] Most commonly, response is considered as improvement in LV echocardiography parameters or NYHA HF symptom class.

Reason for inadequate response may be due to one or several factors. These include suboptimal LV lead placement, incorrect device programming, poor patient selection and interruption of biventricular pacing. Patient selection should follow current guideline recommendations, which have strong support from large clinical trials.[16 22] Patients with poor response should have a thorough investigation of possible contributing factors.

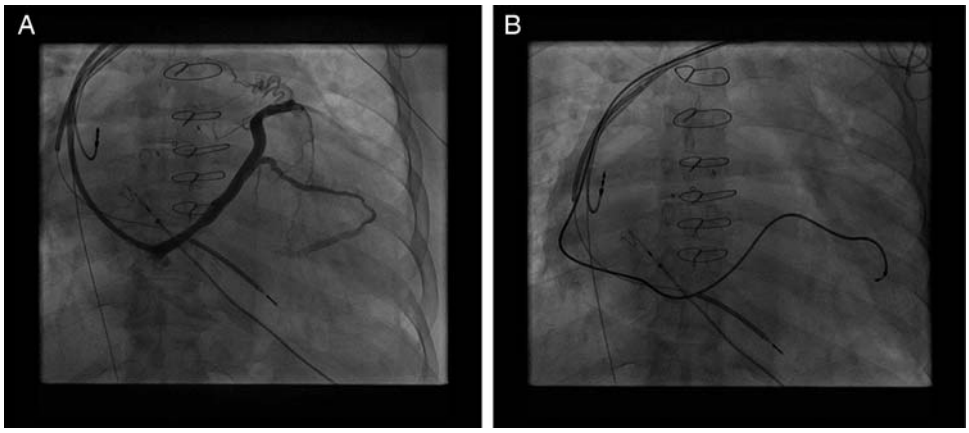

Figure 2 (A) Coronary sinus venogram shows opacification of posterolateral branches. (B) Successful LV lead placement in the mid posterolateral branch.

Utility of cardiac imaging prior to device implant

Echocardiography has been extensively studied to improve the efficacy of CRT. However, in the Predictors of Response to CRT trial,[26] no specific echocardiographic parameter had significant sensitivity or specificity to identify CRT responders. This may be partly due to high variability in echocardiography quality and techniques between cardiac centres. More recently, speckle tracking of strain patterns may help predict the response or non-response to CRT.[27] However, further large prospective studies are needed to confirm these findings.

Additionally, cardiac MRI may also be used to assess ventricular dyssynchrony.[28] This modality can also provide information regarding regions of LV scar, which are less likely to respond to CRT. Again, further large-scale trials are necessary to validate these results.

LV lead placement

Consideration for device optimisation in CRT starts at the time of implant. Based on prior haemodynamic studies, lead placement is targeted to the lateral and posterolateral branches of the coronary sinus (figure 2), while avoiding the apical region. In patients with LBBB and dyssynchrony, the posterolateral LV is most commonly the latest activated site. Several recent studies have looked at the benefits of directed LV lead placement to the latest activated segments. Although both Targeted Left Ventricular Lead Placement to Guide Cardiac Resynchronization Therapy[29] and Speckle Tracking Assisted Resynchronization Therapy for Electrode Region[30] studies suggest improvement in risk of death and HF, the concordance between LV lead position and the latest site of activation was 60% and 30%, respectively. Other anatomic considerations include sites of LV scar and phrenic nerve stimulation.

Furthermore, the design of quadripolar LV leads, which significantly increases the number of pacing vectors over the prior generation of bipolar leads (figure 3), allows programming around electroanatomic barriers, such as phrenic nerve stimulation and high thresholds while allowing optimal lead posterolateral placement. The quadripolar lead has shown decreased hospitalisation rates, cost and better survival.[31 32]

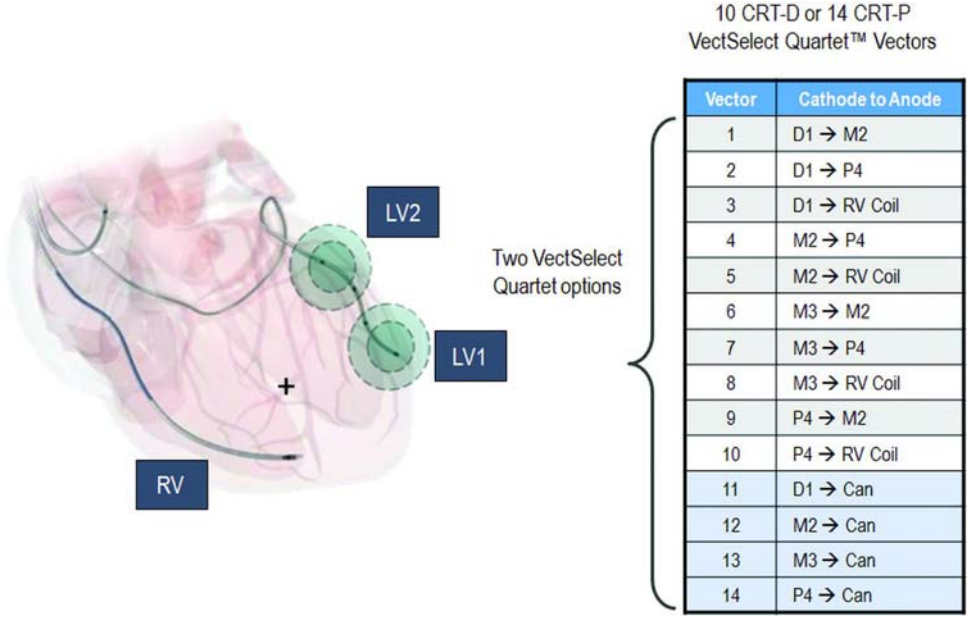

Figure 3 The quadripolar LV lead has four electrodes allowing a significantly larger number of pacing vectors. The Quartet (St. Jude Medical, USA) allows the ability to pace from three ventricular sites and can also incorporate the device generator (cardiac resynchronisation pacing therapy (CRT-P) only). CRT-D, cardiac resynchronisation plus defibrillator.

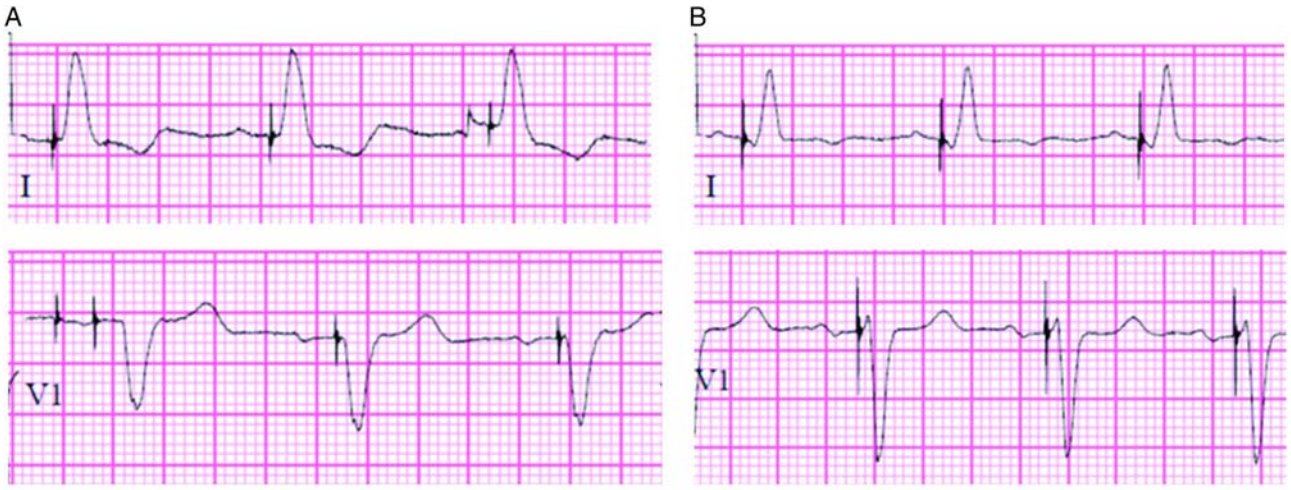

Figure 4 A 62-year-old man with non-ischaemic cardiomyopathy and depressed EF (23%) who underwent cardiac resynchronisation plus defibrillator therapy implantation. Postoperative EKG (A) demonstrates loss of biventricular pacing (due to increased pacing threshold), with predominant initial R-wave in lead I and Q-wave in V1 and wide QRS consistent with RV pacing. After changing pacing vector and output, the patient's ECG showed initial Q-wave in lead I and R-wave in V1 (narrow QRS), consistent with LV contribution to biventricular pacing.

The Triple Resynchronization in Paced Heart Failure Patients study demonstrated the potential benefits of pacing from 2 LV site pacing from the coronary sinus branches in addition to RV pacing.[33] Resynchronisation with pacing from 2 LV sites +RV showed significantly greater improvement in LVEF and decreased in left ventricular end-systolic volume compared with single LV site+RV pacing. However, larger studies are needed to confirm these results.

Device programming

Following implantation, device optimisation can be performed through the programmer. Several parameters should be considered including AV delay and V-V offset. Optimisation of AV delay and V-V offset can be performed during real-time echocardiography or through device-based algorithms. However, these methods have not shown clear improvement in outcomes compared with nominal settings (SmartDelay determined AV optimization Trial[34]).

The ECG is also a powerful tool in the assessment of biventricular pacing. ECG features of adequate LV contribution include initial Q-wave in lead I and R wave in V1 (figure 4).

Effective CRT delivery

Delivery of effective CRT requires a high degree of biventricular pacing. In >36 000 patients with implanted CRT and remote monitoring, survival benefit was greater in patients with >98% biventricular pacing.[35] Several factors may contribute to the interruption of CRT delivery. Most commonly, this is a result of frequent atrial and ventricular ectopy (figure 5) or tachyarrhythmias or loss of ventricular capture. All efforts should be made to minimise CRT interruption including medical or invasive therapies such as antiarrhythmic medications or cardiac ablation.

Furthermore, frequent right atrial (RA) pacing may also have adverse effects on effective resynchronisation therapy.[36] RA pacing results in delayed activation of the left atrium and can effect LV preload. Therefore, intrinsic atrial activation and conduction may be preferred.

Much of the assessment of effective CRT delivery can be performed through device interrogation, which can quantify biventricular pacing and ectopy. However, there are several pitfalls to this method. Newer device generations have attempted to optimise CRT delivery by 'RV-triggered LV-pacing' (figure 5) that paces in the LV in response to sensed event on the RV. Additionally, programmed V-V offset may provide little LV contribution to the initial ventricular activation. Despite incomplete BiV pacing, the interrogation may still show a high pacing percentage. Therefore, these patients should be considered for continuous surface ECG monitoring, which may provide insight into the lack of CRT response.

Remote monitoring

Current device technology allows routine wireless transmission of device information to the provider. The transmission provides basic device information such as device settings, pacing, sensing and thresholds. For example, the percentage of biventricular pacing can be assessed remotely. Additionally, some devices have specific features to assess patient fluid status (OptiVol, Medtronic, USA). Wireless notifications can quickly alert the physicians to major abnormalities in rhythm, therapies delivered, lead integrity and changes in device settings. Table 2 shows a sample of information that can be assessed by remote monitoring.

Remote monitoring can allow providers to promptly address device issues, avoiding unnecessary complications, and has been shown to improve overall survival.[37]

CONCLUSIONS

It has been over 20 years since biventricular pacing was first introduced into patient care. Over the years, there have been significant strides in implantation techniques and optimisation of resynchronisation therapy. CRT has been no less than revolutionary in the treatment of patients with HF with wide QRS complexes, with significant improvements in symptoms and cardiac function and reduction in morbidity and mortality. We should continue to improve the delivery of resynchronisation therapy. Current research and studies are directed at reaching a greater subset of patients who may benefit from biventricular pacing.

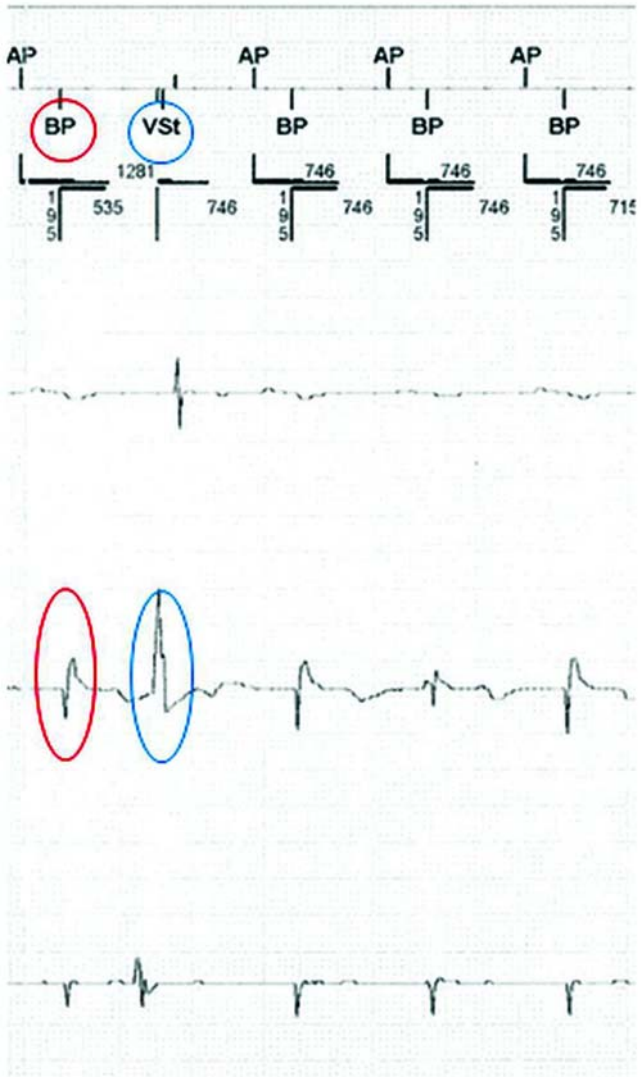

Figure 5 This device interrogation demonstrated frequent premature ventricular complexes (PVC). The PVCs (along with shorter intrinsic atrioventricular conduction) are sensed in the RV and trigger LV pacing (Vst, blue circles), which is not as effective as true BiV pacing (BP, red circles). Shortening the paced interval and suppression of PVCs with medication were effective in increasing cardiac resynchronisation therapy delivery.

Table 2 Remote monitoring information

Device interrogation	Device alerts
Device parameters	AT/AF burden
Capture threshold	Fast ventricular rates
Lead impedance	Therapies delivered
Sensing	Lead impedance out of range
Battery	Low battery
Pacing percentage	Device reset
Arrhythmia episodes	

AF/AF, atrial tachyarrhythmias/atrial fibrillation.

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