Clinical update

Cardiac resynchronization therapy: state of the art 2013

Cheuk-Man Yu[1]* and David L. Hayes[2]

[1]Division of Cardiology, Department of Medicine and Therapeutics, Prince of Wales Hospital & Institute of Vascular Medicine, The Chinese University of Hong Kong, Shatin, N.T., Hong Kong; and [2]Division of Cardiology, Mayo Clinic, Rochester, NY, USA

Cardiac resynchronization therapy (CRT) is currently an established device therapy for heart failure (HF) patients. Cumulated knowledge on the pathophysiological mechanisms, implantation techniques, advancement of device-based technologies, and clinical trial experience has impacted on this evolving therapy significantly in the last few years. This article will address the updated CRT guideline and potentially new indications of CRT such as patients with New York Heart Association Class I, normal QRS duration, and non-HF patients with pacing indications. Furthermore, important but unresolved issues will also be discussed which include the impact of QRS morphology and QRS duration on CRT response, new approaches for placement of left ventricular (LV) lead, multisite LV pacing, and the role of HF disease monitoring program.

Keywords   Cardiac resynchronization therapy

Introduction

With the adoption of guidelines for cardiac resynchronization therapy (CRT) for heart failure (HF) patients since early of the millennium, a plethora of research in the field continues which has addressed many important aspects of the therapy. As a result of the research work, the mechanisms that mediated the benefits of CRT are revealed (*Figure 1*). Furthermore, some researchers have contributed to the core knowledge of updated guidelines, while others have provided practical information on how to improve the quality and treatment efficacy for patients receiving CRT, or quest for evolving or new treatment indications by the use of CRT. The current article has summarized these issues based on key research discoveries or results in the last few years (*Table 1*).

Updated cardiac resynchronization therapy guidelines

The European Society of Cardiology (ESC) published a focused update of device guidelines for patients with HF based on findings from more recent clinical trials.[1] For patients with New York Heart Association (NYHA) Class III/IV HF, the updated guidelines specify that left ventricular (LV) dilatation is no longer a requirement, Class IV patients should be ambulatory, and patients should have a reasonable expectation of survival for at least >6 months with good functional status. For cardiac resynchronization therapy-defibrillator (CRT-D) implantation, patients should have a reasonable expectation of survival for 1 year. The document also notes that outcomes are best for patients with a typical left bundle branch block (LBBB) and there is a similar level of evidence for both cardiac resynchronization therapy-pacemaker and CRT-D.

With additional findings from MADIT-CRT and REVERSE (see below), both of which demonstrated reduced HF morbidity, a new recommendation was made for patients with NYHA functional Class II HF. In Class II patients with left ventricular ejection fraction (LVEF) < 35% and QRS width ≥150 ms, CRT, specified as preferentially CRT-D, is a Class I A indication. It is worth to mention that for all the three key studies involved less severe HF symptoms (MADIT-CRT, REVERSE, and RAFT), patients with a QRS duration between 120 and 150 ms did not benefit from CRT-D. This might not be attributable to the milder symptoms *per se* as a recent meta-analysis also did not confirm the benefit of CRT in this sub-population.[2]

Recommendations for patients with chronic atrial fibrillation were further defined in the update. For patients with functional Class III/IV HF, QRS ≥ 130 ms and LVEF < 35%, the indication remains Class IIA. However, a distinction is made that if the patient is pacemaker dependent following atrioventricular (AV) nodal ablation, the level of evidence is 'B' and if the patient requires pacing because of a slow ventricular rate resulting in frequent pacing, the level of evidence is 'C'.

---

* Corresponding author. Tel: +852 2632 3127; Fax: +852 2645 1699, E-mail: cmyu@cuhk.edu.hk
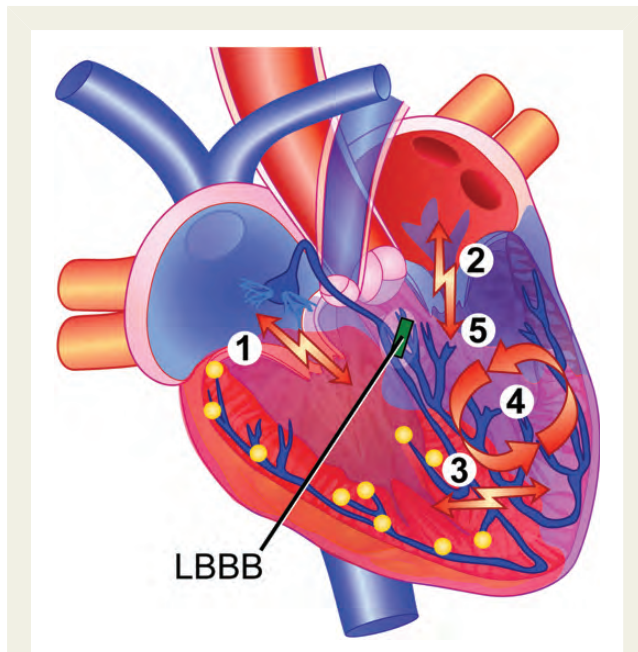
Figure 1 Mechanisms of deterioration of cardiac function in heart failure patients with prolongation of QRS complex (especially in the form of left bundle branch block) resulting in electromechanical delay. Electrical disturbances induce mechanical dyssynchrony at different levels: atrioventricular dyssynchrony (1, 2), interventricular dyssynchrony (3), intraventricular dyssynchrony (4), as well as mitral regurgitation (5). As a result of these abnormalities, there is ineffective contraction with rocking motion of the left ventricle during systole, elevation of filling pressure, left ventricular pressure, and overload overload, as well as decreased cardiac output. Cardiac resynchronization therapy improves and reverses these abnormalities result in left ventricular reverse remodelling and reduction of mitral regurgitation.

Table 1   Cardiac resynchronization therapy: main issues to be addressed

Pre-implantation
Current indication
- QRS duration : >150 ms responses better
- QRS pattern: LBBB responses better

Future indication
- NYHA Class I
- Narrow QRS with co-existing systolic dyssynchrony
- Non-HF patients with Bradycardia pacing indications

At implantation
LV lead
- Location: Free wall or not?
- Role of imaging guided implantation: is it superior?
- Multisite LV pacing: 2 vs. 1 LV lead

Post-implant follow-up
Remote monitoring and device-based disease management
- Reduce clinic visit
- Detect device-related problems
- Shorter hospitalization length
- Improves clinical outcome

For those patients with HF and a Class I indication for a permanent pacemaker as established by earlier guidelines,[3] the indication was elevated to IA for Class III/IV patients with LVEF ≤ 35% and QRS ≥ 120 ms. For patients with the same functional class and LVEF but QRS ≤ 120 ms, CRT was designated a Class II A indication and Class IIB for NYHA functional Class II patients.

American guidelines have not been updated since 2008[4] but some FDA labelling changes have occurred (see below).

Future or new indications for cardiac resynchronization therapy

Cardiac resynchronization therapy in NYHA functional Class I heart failure

As noted in the 'guidelines' section, MADIT-CRT[5] and REVERSE[6] have added significantly to our knowledge regarding CRT outcomes in patients with less severe clinical symptoms. Both studies demonstrated reduced HF morbidity with CRT and it should be noted that the patient population in both was largely Class II patients. Class I patients accounted for 18% of the

REVERSE population and 15% of the MADIT-CRT population. No definite outcome advantages in Class I patients were appreciated in these trials.

In both trials, improvement was seen primarily in patients with QRS ≥150 ms. (The mean QRS width was 150 ms in ischemic patients and 157 ms in non-ischemic patients in REVERSE and 156 ms in MADIT-CRT.[7])

A subsequent *post hoc* analysis of MADIT-CRT compared patients with LBBB to patients with a non-LBBB QRS morphology.[8] This study demonstrated that NYHA Class I patients with an ischemic aetiology and NYHA Class II patients, regardless of aetiology, and LVEF ≤30% had significant benefit from CRT-D (53% risk reduction in HF event or death compared with implantable cardioverter defibrillator (ICD) only) whereas no evidence of clinical benefit was seen in patients with a non-LBBB QRS morphology.

As a result of this analysis,[8] the FDA issued a labelling change that would apply to specific CRT-D devices approved for use in patients with LBBB and QRS ≥130 ms, LVEF ≤30% (instead of <35%) and mild (NYHA Class II) ischemic or non-ischemic HF or asymptomatic (NYHA Class I) ischemic HF.[9]

Heart failure with narrow QRS and co-existing systolic dyssynchrony

The concept of considering CRT for patients with narrow QRS complex (defined as QRS duration <120 ms) was originated from the observation that systolic dyssynchrony is present in patients with narrow QRS complex with a prevalence of up to 50% when assessed by echocardiography.[10] This stimulated the conduction of single center studies which showed improvement of systolic function, functional status, and LV reverse remodelling

in patients with narrow QRS complex and coexisting systolic dys-synchrony.[11,12] However, in the RETHINQ study which had a ran-domized, controlled and multicenter design of 172 patients did not confirm the beneficial role of CRT in such population.[13] This study was criticized by the use of technically difficult primary endpoint of maximal VO$_2$, the use of dyssynchrony parameters of low specifi-city, and issues related to training and use of echocardiographic equipment leading to the question about the accuracy of dyssyn-chrony measurement.[14]

The Echocardiography Guided Cardiac Resynchronization Therapy trial in patients with narrow QRS and ventricular dys-synchrony (ECHO-CRT) study is underway to examine whether dyssynchrony-guided CRT-D will improve cardiovascular outcome in this population (http://clinicaltrials.gov/show/NCT00683696).

It is important to note that based on available data, current guidelines do not consider patients with narrow QRS complex for CRT.

Non-heart failure patients with bradycardia pacing indications

In patients with pacing indications due to bradycardia, it has well been reported that there is an increased risk of developing HF over time.[15] Such risk presents in patients with both preserved and impaired systolic function.[15,16] In conventional approach, the ventricular lead is placed to the right ventricular apex. It has been described subsequently that right ventricular apical (RVA) pacing may induce systolic dyssynchrony as a result of pacing-induced LBBB,[17] which exerts deleterious effect on LV func-tion and remodelling.[18] In order to reduce the risk of HF in the pacing population, new modalities of pacing therapy have been sug-gested which include the use of specific pacing algorithm to minim-ize the amount of right ventricular pacing[19] and the use of alternative ventricular pacing site other than RVA pacing. While the former is applicable to patients with sinus node dysfunction, the latter is particularly important for patients with advanced atrio-ventricular block that rely on frequent ventricular pacing. Apart from right ventricular septal and outflow track pacing, the use of biventricular pacing is a potential alternative. Early experience of using biventricular pacing in bradycardia patients was conducted to patients with persistent atrial fibrillation who received atrioven-tricular node ablation and permanent pacing. In the PAVE study, 184 patients with a mean EF of 46 ± 16% were randomized into RVA and biventricular pacing showed a superiority of biventricular pacing on preventing the reduction in EF and 6 min hall-walk dis-tance after 6 months.[20] In the recently published Ablate and Pace in Atrial Fibrillation (APAF) study, 186 patients with perman-ent atrial fibrillation who underwent AV nodal ablation were ran-domized to receive CRT or RVA pacing. During a mean follow-up of 20 months, CRT resulted in a significantly lower primary composite endpoint of death from HF, hospitalization due to HF, or worsening HF (11 vs. 26%, $P = 0.005$).[21] The bene-ficial effects of CRT were consistent in patients who had EF ≤35%, NYHA Class ≥III, and QRS width ≥120 and in those who did not.

The PACE study was the first randomized, controlled, multicenter trial of patients with normal systolic function (mean EF of 61.9 ± 6.7%), receiving pacing for bradycardia indications which showed

that biventricular pacing compared with RVA pacing could prevent adverse LV remodelling and reduction in EF at 12 and 24 months.[22,23] However, the remodelling effects of conventional pacing vs. CRT in patients without HF are of yet unknown signifi-cance and that it is unclear at present whether the more difficult implant procedure and potentially higher complication rate asso-ciated with the biventricular device is justified. Currently, the BIOPACE study is ongoing which will examine whether biventricu-lar pacing is superior to RVA pacing in reducing the primary end-points of survival, quality of life, and a 6 min hall walk distance at 24 months.[24]

QRS morphology and duration: patients with non-left bundle branch block and QRS <150ms

QRS morphology

Large clinical trials were conducted with HF patients with wide QRS complexes irrespective of QRS morphology. From a mechan-ical perspective, patients with a complete LBBB will have a more severe form of LV electrical delay leading to significant electro-mechanical coupling delay. On the other hand, patients with right bundle branch block (RBBB) might have minimal electrical or electromechanical delay in the LV unless left fascicular hemi-block is present.[25] In addition, patients with intraventricular delay (IVCD) or incomplete BBB which typically have a QRS duration between 120 and 150 ms will have less severe intraventricular dys-synchrony than those with complete LBBB.[26] Nonetheless, a study that employed electroanatomical mapping to determine the pattern of electrical conduction showed that electrical delay is not uncommon in patients with RBBB, which supports the use of CRT in such patient group.[27] In a large, single center CRT registry that included 636 patients (LBBB in 412, RBBB in 62, and paced QRS in 162 patients), it was shown that patients with LBBB had a significantly higher prevalence of symptomatic and echocardio-graphic response as well as lower transplantation-free mortality than those with RBBB.[28] In an analysis of pooled data from the MIRACLE and CONTAK-CD trials that had consisted of 61 patients with RBBB (34 patients received CRT and 27 controls), there was no objective evidence of improvement in symptoms, 6 min hall-walk distance or quality of life score at 6 months.[29] Similarly, in the CRT population with NYHA class II symptoms, pre-defined subgroup analysis from both MADIT-CRT and RAFT trials revealed that primary endpoint of HF event-free survival was only significantly reduced in patients with LBBB, but not in those with RBBB or IVCD.[8,30] Although current guidelines only based on QRS duration as the selection criteria for CRT, more effort should be attempted to identify those patients with non-LBBB morphology in whom sig-nificant dyssynchrony is present.

QRS duration

Optimal QRS duration for CRT candidates remains somewhat controversial. Although some of the earliest clinical trials required QRS duration of ≥150 ms, the evidence base primarily consists of Class III to ambulatory class IV patients with QRS duration of

>120 to 130 ms. While it seems reasonable to continue the more inclusive QRS duration of ≥120 ms for patients that are more ill, i.e. Class III to ambulatory Class IV, outcomes from REVERSE, MADIT-CRT, and RAFT support more restrictive selection for Class II patients based on the observation that CRT only benefit patients with QRS duration ≥150 ms, but not those <150 ms.[5,30] Although guidelines may appropriately allow a more generous range for QRS criteria, based on these more recent trials the clinician can be more optimistic about achieving a response to CRT in those patients with QRS ≥ 150 ms. Based on the MADIT-CRT sub-study showing that CRT response was seen primarily in patients with LBBB, requiring a longer QRS duration (≥150 ms) definitely seems reasonable in those patients for whom CRT is considered when a non-LBBB morphology is present.[8]

The most recently published 'ESC Guidelines For The Diagnosis And Treatment Of Acute And Chronic Heart Failure 2012'[31] based on MADIT-CRT, REVERSE, and RAFT trials recommend that for patients with milder symptoms, CRT is recommended only in those with either a QRS duration ≥150 ms or ≥130 ms plus an LBBB pattern.

Furthermore, in a recent meta-analysis that included 6501 patients with mild to severe HF patients based on current guideline (4437 with QRS ≥150 ms and 2064 with QRS <150 ms), CRT significantly decreased the primary endpoint of death or hospitalization for HF in patients with QRS ≥150 ms (HR = 0.58, 95% CI: 0.50–0.68; $P < 0.00001$), but not in patients with QRS <150 ms (HR = 0.95, 95% CI: 0.83–1.10; $P = 0.51$).[2] In fact, lack of endpoint benefit was consistently observed in both NYHA class III/IV and NYHA class II patients.[2]

Given the limited clinical trial data available in Class I patients, questions remain as to when CRT should be offered. Although this should be better defined by ongoing studies such as BioPace, it is reasonable to apply the ≥150 ms QRS duration in such patients until more data are available.

Left ventricular lead-related issues

Left ventricular lead location

Although the overall responder rate has seen some improvement since the early use of CRT, it is still suboptimal. One issue that has been shown to contribute to a lack of response to CRT is inadequate LV lead location. In one study that assessed reasons for lack of CRT response, suboptimal LV lead position was implicated in 21% of patients.[32] Controversy persists with anterior positioning of the LV lead having been shown to be a predictor of non-response in one study[33] although in a sub-study from MADIT-CRT only apical but not anterior positioning predicted a lower response to CRT.[34]

General wisdom continues to be that in patients with a non-ischemic aetiology, a lateral LV lead position is a reasonable position for many patients and in those with ischemic aetiology knowledge of LV viability and contraction patterns helps optimize LV lead position.

There has long been interest in LV endocardial pacing as a method theoretically advantageous to coronary sinus epicardial lead positioning for CRT.[35] Initial concerns were raised related to the potential for thromboembolic events in patients with hardware placed in the systemic circulation. However, the experience is growing with LV endocardial stimulation via multiple approaches. The majority of the experience with LV endocardial lead positioning has been done by transseptal approach.[36,37] Apical lead positioning has also been accomplished.[38]

Four trials are registered at www.clinicaltrials.gov which are assessing the feasibility and potential advantages of LV endocardial pacing. One study aims to assess acute hemodynamics of LV endocardial pacing [Endocardial Pacing in On-table Non-responders in Cardiac Resynchronization Therapy] and two trials study chronic LV endocardial lead systems [Randomized Comparison of Endocardial Versus Epicardial—From the Coronary Sinus—Left Ventricular Pacing for Resynchronization in Heart Failure (EPI-ENDO) and ALternate Site Cardiac ReSYNChronization (ALSYNC) Study]. The final trial is assessing leadless stimulation to achieve CRT [Wireless Stimulation Endocardially for Cardiac Resynchronization Therapy (WiSE-CRT)]. Feasibility of ultrasonic leadless or wireless stimulation of the LV has been demonstrated and could potentially change the landscape of CRT and pacing in general.[39] The technology is still in its infancy and probably somewhat distant from commercialization.

Multisite left ventricular pacing

Currently only one LV lead is implanted to achieve resynchronization of the ventricle(s). However, in HF patients with enlarged LV and ventricular conduction delay, true multisite pacing with a second LV lead placed in a location distant from the first one may further abbreviate LV conduction time and hence further reduce mechanical dyssynchrony. The potential superiority of placing two LV leads than a single LV lead was suggested by a study compared with a historical cohort of conventional CRT implantation[40] and another small randomized study that compared the two pacing strategies in patients with atrial fibrillation.[41] These two studies observed a greater improvement of EF for patients implanted with two LV leads.[40,41] There are two ongoing randomized, single-center clinical trials that examined the role of dual-site LV leads when compared with a single LV lead. The Dual Site Left Ventricular Pacing (DIVA) study will enrol 50 patients with the primary endpoint of change in LVESV at 6 months, and the 'Triple-Site Versus Standard Cardiac Resynchronization Therapy' (TRUST CRT) study that will enrol 100 patients with the primary objective of evaluating the 6-month's combined endpoint of alive status, freedom from hospitalization for HF or heart transplantation, change in EF, and functional capacity.[42]

Imaging guided placement of left ventricular lead

With the advancement of comprehensive cardiac imaging, studies have been conducted to explore the role of imaging to guide placement of the ventricular leads, especially the LV lead. Although pre-implant cardiac magnetic resonance imaging (cMRI) is still uncommon in most practices, studies have shown the potential benefit of pre-implant cMRI to determine optimal LV lead position in ischemic cardiomyopathy, in particular the scar burden and distribution.[43–46] Also, placing the LV lead in the posterolateral wall with a transmural scar tissue as evident by cMRI will substantially reduce the response to CRT.[47] Whether the LV lead shall be

placed in the segment exhibited most severe mechanical delay remains controversial.[48–50] The TARGET trial is the first randomized study that compared echocardiographic-guided implantation of the LV lead at the most delayed segment of the free wall vs. conventional approach showed that the former strategy would result in greater extent of LV reverse remodelling and volumetric responders as well as lower HF hospitalization, although there is no difference in all-cause mortality. Of note, all these studies were single center in design.[51] Practical issues remain to be resolved for imaging-guided approach, such as where to place the LV lead if the latest contraction occurs at the segment with low strain. Furthermore, even the segment with most severe mechanical delay is being mapped, whether there is a sizable coronary vein for placement of LV lead is another practical limitation, unless epicardial or endocardial approaches are being considered.

Non-responders of cardiac resynchronization therapy

About one-third of patients currently do not respond to CRT clinically based on the current guideline, and more than 40% do not show LV reverse remodelling response. However, some patients might potentially be responders if managed properly.[32] Figure 2 suggested the algorithm of managing CRT non-responders.

3 month post-implant lack of subjective clinical improvement

Do 12 lead ECG and assess QRS morphology and compare to post-implant morphology
Is there evidence of biventricular pacing?[1]

Assess % biventricular pacing with goal to be as close to 100% as possible
If % is unacceptable what is explanation for low %, i.e. inhibition by intrinsic rhythm, failure to capture, atrial and/or ventricular arrhythmias?[2]

Assess patient co-morbidities, i.e. worsening anemia, renal dysfunction, etc.
If significant change in co-morbidities → Are they reversible?

Assess Chest X-ray and compare with post-implant images
Is lead position stable and acceptable?[3]

Reassess medical regimen for heart failure
Is the patient compliant?

Repeat 2D echocardiogram to assess LVEF and LVESV and ventricular dimensions and compare with pre-implant echocardiogram

If 6 minute hall walk had been done prior to implant, repeat and compare distance achieved

Consider treadmill exercise test
Is biventricular pacing maintained during exercise?
↓
AV and VV interval optimization by echocardiography
↓
Reassess in another 1 to 3 months with careful attention to:

Subjective evidence of improvement
% biventricular pacing
Δ LVEF, LVEDD, LVESV
Level of activity based on sensor-indicated data
↓
If lack of response persists and % biventricular pacing is ≥ 95% consider benefit of LV lead repositioning and/or addition of a 2nd LV lead; prior to procedure, reassessment of LV dyssynchrony by echocardiographic techniques may be helpful

---

[1] If biventricular pacing is not present, what is the cause, i.e. lead dislodgement, high thresholds, inhibition by intrinsic rhythm, or AV delay is not long enough etc? Based on etiology, steps should be taken to restore biventricular pacing. At this stage also assess for anodal stimulation.
[2] If % biventricular pacing is clearly unacceptable, appropriate steps should be taken if appropriate, i.e. suppress intrinsic rhythm pharmacologically or in the case of atrial fibrillation with AV nodal ablation. If ventricular arrhythmias the reason for a low % of biventricular pacing, consider pharmacologic suppression or ablation of ventricular foci.
[3] If lead has dislodged, consider lead revision. If micro-dislodgement, consider reprogramming to select a pair of electrode and vector that maintains biventricular pacing. If lead position unchanged but suboptimal, consider lead revision after subsequent assessment and recommendations in this algorithm completed.

Figure 2 Clinical approach to cardiac resynchronization therapy non-responder.

Although echocardiographic assessment of dyssynchrony has been shown to predict CRT response in studies preformed in experienced center, it was unable to be replicated in multicenter trials.

This complex issue has been discussed elsewhere recently.[52] However, dyssynchrony assessment remains helpful in illustrating the mechanisms of CRT benefit, potentially in assisting patient
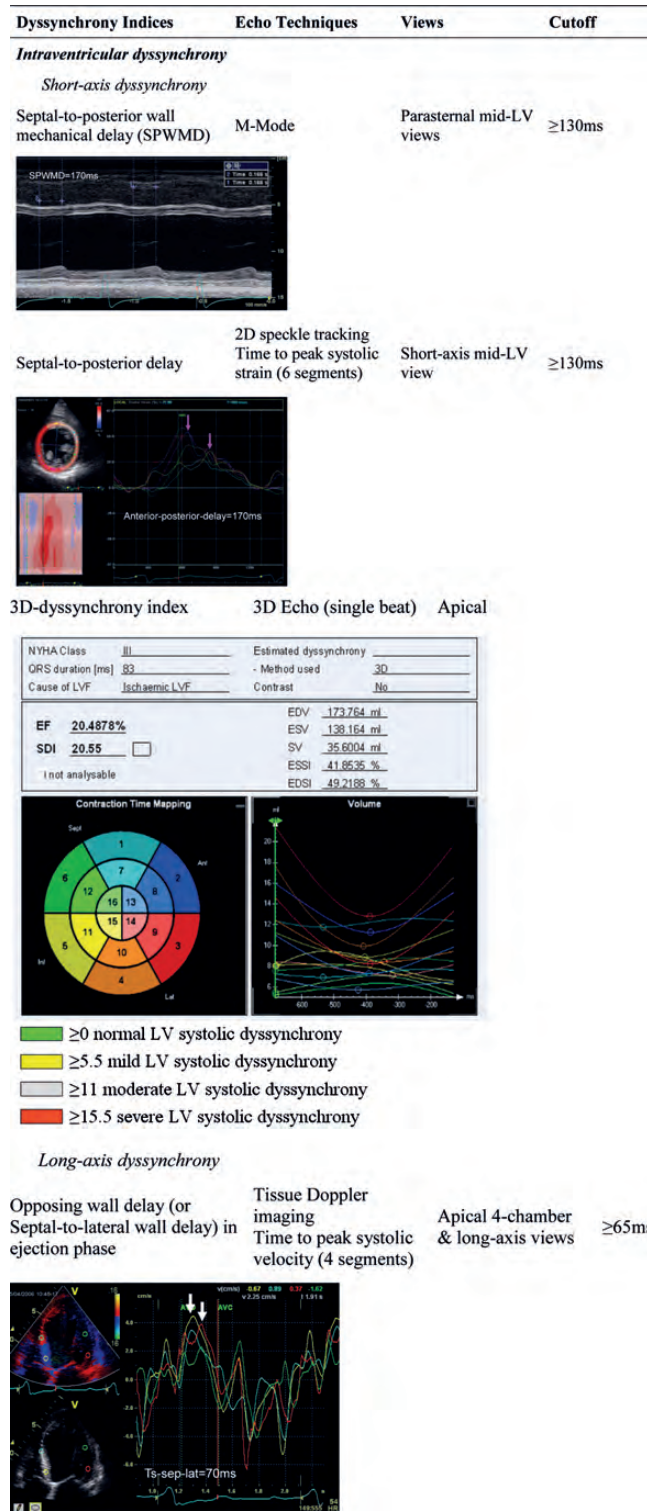

Figure 3 Commonly used systolic dyssynchrony indices and their reported cutoff values. (*A*) Intraventricular dyssynchrony, short-axis dyssynchrony. (*B*) Intraventricular dyssynchrony, long-axis dyssynchrony. (*C*) Interventricular dyssynchrony.
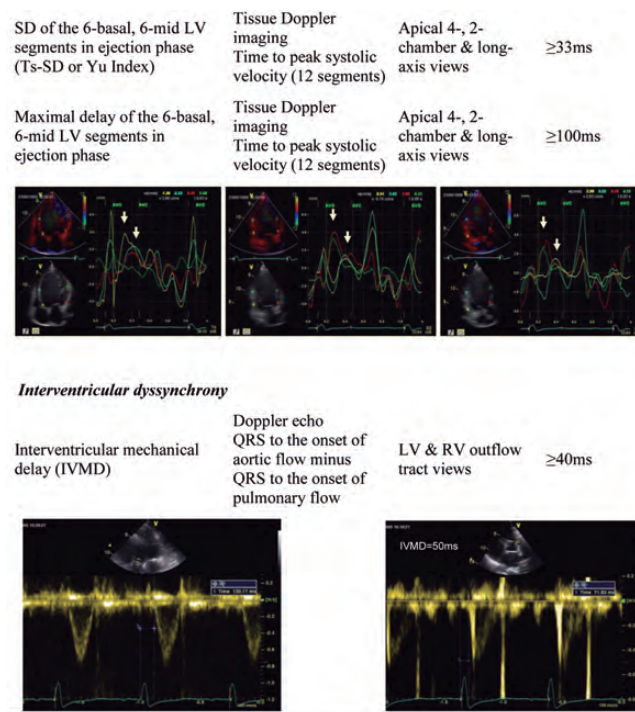
Figure 3 Continued.

selection in those who have a narrow QRS complex with mechanical dyssynchrony, as well as guiding the placement of LV lead. *Figure 3* summarizes the commonly used parameters of dyssynchrony assessment and their cut-off values.

Remote monitoring and device-based disease management

Remote monitoring (RM) has been widely embraced in the USA and Europe. In the USA, there are now over 800 000 patients actively monitored by the RM network. There are many potential benefits of remote patient monitoring beyond the obvious convenience and security of being able to download detailed stored information of an event. Although RM is not limited to CRT, the subject of this review, the growing body of literature regarding RM for all implantable cardiac devices is germane given overlap of devices and overlap of data collected that currently is or could be remotely transmitted.

When RM was introduced, and to some extent this persists, there was concern that patients and caregivers would not be satisfied with RM because they would lose the advantage of a face-to-face visit. Multiple studies have shown that both patients and caregivers are satisfied with RM both in terms of its ease of use and remaining connected to the follow-up center.[53] In some situations, specifically following an advisory or recall, patients have expressed a preference for RM in terms of psychological well-being, feeling as though there is a better chance of diagnosing a problem should it occur.

Advantages of RM for pacemakers, ICDs, and CRT devices have been demonstrated in randomized clinical trials. In the CONNECT trial,[54] resource utilization was shown to be lower with RM with the observed rate of total clinic visits per patient year was 3.92 in the RM group as opposed to 6.27 for the group monitored in-office. Remote monitoring also has the potential to detect clinical abnormalities that would potentially be detected later or missed by less frequent in-office visits in the absence of regular RM data assessment. In the TRUST trial ($n =$ 1333), RM detected ICD system related problems earlier, detected by RM at a median of 1 day vs. 5 days for the control (non-RM) group.[55] Overall, the study detected 20 device-related problems that required surgical revision and 15 of these were detected by RM and only 5 in their control group.[55] In the PREFER trial[56] which assessed pacemakers only, the mean time to the diagnosis of the first clinical event that required clinical action occurred at 5.7 months in the RM arm of the study and at 7.7 months in the control group. Perhaps as a result of earlier detection of clinical problems, resulting hospitalizations may be shorter in patients enrolled in a RM system. In the CONNECT trial which evaluated 1997 patients with ICDs and CRT-D devices, the RM arm of the trial had significantly shorter hospitalization length of stays than those patient's followed in the clinic ($P = 0.002$).[54] There is trial data to support more rapid clinical decision making as a result of RM. In the CONNECT trial,[54] the time from a clinically significant event to making a clinical decision in the RM arm was significantly shorter than in the 'in-office' arm ($P < 0.001$), and the median time in the RM arm was 4.6 days vs. 22 days in the in-office arm.

Analyses of large numbers of patients enrolled in RM are providing useful data from large-scale registries offering an insight into real-world outcomes. For example, data from LATITUDE and CARELINK RM networks have demonstrated long-term survival benefits of RM as well as insights into clinical management of patients with implanted cardiac devices.[57] A recent study of 377 patients with CRT-D devices capable of daily transmission of their diagnostic data evaluated an automated algorithm for dynamically predicting cardiovascular events. This algorithm and potentially others that incorporate additional physiological parameters data for which transmitted RM data are sparse have the potential to improve quality of life and reduce morbidity and mortality.[58]

Conclusion

With cumulated knowledge and clinical trial experience in the last decade, the management of HF patients by CRT is rapidly evolving. Apart from updates in treatment guideline, a large number of current trials are ongoing to address unresolved issues of CRT. These concerted efforts will shape the future of HF device therapy leading to a boarder spectrum of patient selection, a high implantation success rate as well as better treatment response.

Funding

Conflict of interest: none declared.

References

1. Dickstein K, Vardas PE, Auricchio A, Daubert JC, Linde C, McMurray J, Ponikowski P, Priori SG, Sutton R, Van Veldhuisen DJ, Vahanian A, Auricchio A, Bax J, Ceconi C, Dean V, Filippatos G, Funck-Brentano C, Hobbs R, Kearney P, McDonagh T, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Vardas P, Widimsky P, Tendera M, Anker SD, Blanc JJ, Gasparini M, Hoes AW, Israel CW, Kalarus Z, Merkely B, Swedberg K, Camm AJ. 2010 Focused Update of ESC Guidelines on device therapy in heart failure: an update of the 2008 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure and the 2007 ESC guidelines for cardiac and resynchronization therapy. Developed with the special contribution of the Heart Failure Association and the European Heart Rhythm Association. *Eur Heart J* 2010;**31**:2677–2687.
2. Stavrakis S, Lazzara R, Thadani U. The benefit of cardiac resynchronization therapy and QRS duration: a meta-analysis. *J Cardiovasc Electrophysiol* 2012;**23**: 163–168.
3. Vardas PE, Auricchio A, Blanc JJ, Daubert JC, Drexler H, Ector H, Gasparini M, Linde C, Morgado FB, Oto A, Sutton R, Trusz-Gluza M. Guidelines for cardiac pacing and cardiac resynchronization therapy. The Task Force for Cardiac Pacing and Cardiac Resynchronization Therapy of the European Society of Cardiology. Developed in collaboration with the European Heart Rhythm Association. *Europace* 2007;**9**:959–998.
4. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA III, Freedman RA, Gettes LS, Gillinov AM, Gregoratos G, Hammill SC, Hayes DL, Hlatky MA, Newby LK, Page RL, Schoenfeld MH, Silka MJ, Stevenson LW, Sweeney MO, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Buller CE, Creager MA, Ettinger SM, Faxon DP, Halperin JL, Hiratzka LF, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura RA, Ornato JP, Page RL, Riegel B, Tarkington LG, Yancy CW. ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2008;**51**:e1-62.
5. Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, Estes NA III, Foster E, Greenberg H, Higgins SL, Pfeffer MA, Solomon SD, Wilber D, Zareba W. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med* 2009;**361**:1329–1338.
6. Linde C, Abraham WT, Gold MR, St John SM, Ghio S, Daubert C. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. *J Am Coll Cardiol* 2008;**52**:1834–1843.
7. Daubert C, Gold MR, Abraham WT, Ghio S, Hassager C, Goode G, Szili-Torok T, Linde C. Prevention of disease progression by cardiac resynchronization therapy in patients with asymptomatic or mildly symptomatic left ventricular dysfunction: insights from the European cohort of the REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction) trial. *J Am Coll Cardiol* 2009;**54**:1837–1846.
8. Zareba W, Klein H, Cygankiewicz I, Hall WJ, McNitt S, Brown M, Cannom D, Daubert JP, Eldar M, Gold MR, Goldberger JJ, Goldenberg I, Lichstein E, Pitschner H, Rashtian M, Solomon S, Viskin S, Wang P, Moss AJ. Effectiveness of Cardiac Resynchronization Therapy by QRS Morphology in the Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT). *Circulation* 2011;**123**:1061–1072.
9. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm226123. htm.XX, 2011.
10. Yu CM, Lin H, Zhang Q, Sanderson JE. High prevalence of left ventricular systolic and diastolic asynchrony in patients with congestive heart failure and normal QRS duration. *Heart* 2003;**89**:54–60.
11. Bleeker GB, Holman ER, Steendijk P, Boersma E, van der Wall EE, Schalij MJ, Bax JJ. Cardiac resynchronization therapy in patients with a narrow QRS complex. *J Am Coll Cardiol* 2006;**48**:2243–2250.
12. Yu CM, Chan YS, Zhang Q, Yip GW, Chan CK, Kum LC, Wu L, Lee AP, Lam YY, Fung JW. Benefits of cardiac resynchronization therapy for heart failure patients with narrow QRS complexes and coexisting systolic asynchrony by echocardiography. *J Am Coll Cardiol* 2006;**48**:2251–2257.
13. Beshai JF, Grimm RA, Nagueh SF, Baker JH, Beau SL, Greenberg SM, Pires LA, Tchou PJ. Cardiac-resynchronization therapy in heart failure with narrow QRS complexes. *N Engl J Med* 2007;**357**:2461–2471.
14. Yu CM, Bax JJ, Gorcsan J III. Critical appraisal of methods to assess mechanical dyssynchrony. *Curr Opin Cardiol* 2009;**24**:18–28.
15. Sweeney MO, Hellkamp AS, Ellenbogen KA, Greenspon AJ, Freedman RA, Lee KL, Lamas GA. Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal baseline QRS duration in a clinical trial of pacemaker therapy for sinus node dysfunction. *Circulation* 2003;**107**: 2932–2937.
16. Wilkoff BL, Cook JR, Epstein AE, Greene HL, Hallstrom AP, Hsia H, Kutalek SP, Sharma A. Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: the Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial. *JAMA* 2002;**288**:3115–3123.
17. Zhang Q, Fang F, Yip GW, Chan JY, Shang Q, Fung JW, Chan AK, Liang YJ, Yu CM. Difference in prevalence and pattern of mechanical dyssynchrony in left bundle branch block occurring in right ventricular apical pacing versus systolic heart failure. *Am Heart J* 2008;**156**:989–995.
18. Tops LF, Suffoletto MS, Bleeker GB, Boersma E, van der Wall EE, Gorcsan J III, Schalij MJ, Bax JJ. Speckle-tracking radial strain reveals left ventricular dyssynchrony in patients with permanent right ventricular pacing. *J Am Coll Cardiol* 2007;**50**:1180–1188.
19. Sweeney MO, Bank AJ, Nsah E, Koullick M, Zeng QC, Hettrick D, Sheldon T, Lamas GA. Minimizing ventricular pacing to reduce atrial fibrillation in sinus-node disease. *N Engl J Med* 2007;**357**:1000–1008.
20. Doshi RN, Daoud EG, Fellows C, Turk K, Duran A, Hamdan MH, Pires LA. Left ventricular-based cardiac stimulation post AV nodal ablation evaluation (the PAVE study). *J Cardiovasc Electrophysiol* 2005;**16**:1160–1165.
21. Ungar A, Del Rosso A, Giada F, Bartoletti A, Furlan R, Quartieri F, Lagi A, Morrione A, Mussi C, Lunati M, De MG, De ST, Marchionni N, Brignole M. Early and late outcome of treated patients referred for syncope to emergency department: the EGSYS 2 follow-up study. *Eur Heart J* 2010;**31**:2021–2026.
22. Yu CM, Chan JY, Zhang Q, Omar R, Yip GW, Hussin A, Fang F, Lam KH, Chan HC, Fung JW. Biventricular pacing in patients with bradycardia and normal ejection fraction. *N Engl J Med* 2009;**361**:2123–2134.
23. Chan JY, Fang F, Zhang Q, Fung JW, Razali O, Azlan H, Lam KH, Chan HC, Yu CM. Biventricular pacing is superior to right ventricular pacing in bradycardia patients with preserved systolic function: 2-year results of the PACE trial. *Eur Heart J* 2011;**32**:2533–2540.
24. Funck RC, Blanc JJ, Mueller HH, Schade-Brittinger C, Bailleul C, Maisch B. Biventricular stimulation to prevent cardiac desynchronization: rationale, design, and endpoints of the 'Biventricular Pacing for Atrioventricular Block

to Prevent Cardiac Desynchronization (BioPace)' study. *Europace* 2006;**8**: 629–635.

25. Haghjoo M, Bagherzadeh A, Farahani MM, Haghighi ZO, Sadr-Ameli MA. Significance of QRS morphology in determining the prevalence of mechanical dyssynchrony in heart failure patients eligible for cardiac resynchronization: particular focus on patients with right bundle branch block with and without coexistent left-sided conduction defects. *Europace* 2008;**10**:566–571.

26. Yu CM, Fung JW, Chan CK, Chan YS, Zhang Q, Lin H, Yip GW, Kum LC, Kong SL, Zhang Y, Sanderson JE. Comparison of efficacy of reverse remodeling and clinical improvement for relatively narrow and wide QRS complexes after cardiac resynchronization therapy for heart failure. *J Cardiovasc Electrophysiol* 2004;**15**: 1058–1065.

27. Fantoni C, Kawabata M, Massaro R, Regoli F, Raffa S, Arora V, Salerno-Uriarte JA, Klein HU, Auricchio A. Right and left ventricular activation sequence in patients with heart failure and right bundle branch block: a detailed analysis using three-dimensional non-fluoroscopic electroanatomic mapping system. *J Cardiovasc Electrophysiol* 2005;**16**:112–119.

28. Adelstein EC, Saba S. Usefulness of baseline electrocardiographic QRS complex pattern to predict response to cardiac resynchronization. *Am J Cardiol* 2009; **103**:238–242.

29. Egoavil CA, Ho RT, Greenspon AJ, Pavri BB. Cardiac resynchronization therapy in patients with right bundle branch block: analysis of pooled data from the MIRACLE and Contak CD trials. *Heart Rhythm* 2005;**2**:611–615.

30. Tang AS, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S, Hohnloser SH, Nichol G, Birnie DH, Sapp JL, Yee R, Healey JS, Rouleau JL. Cardiac-resynchronization therapy for mild-to-moderate heart failure. *N Engl J Med* 2010;**363**:2385–2395.

31. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Sanchez MA, Jaarsma T, Kober L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Ronnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A, Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, McDonagh T, Sechtem U, Bonet LA, Avraamides P, Ben Lamin HA, Brignole M, Coca A, Cowburn P, Dargie H, Elliott P, Flachskampf FA, Guida GF, Hardman S, Iung B, Merkely B, Mueller C, Nanas JN, Nielsen OW, Orn S, Parissis JT, Ponikowski P. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2012;**33**:1787–1847.

32. Mullens W, Grimm RA, Verga T, Dresing T, Starling RC, Wilkoff BL, Tang WH. Insights from a cardiac resynchronization optimization clinic as part of a heart failure disease management program. *J Am Coll Cardiol* 2009;**53**: 765–773.

33. Shanks M, Delgado V, Ng AC, Auger D, Mooyaart EA, Bertini M, Marsan NA, van Bommel RJ, Holman ER, Poldermans D, Schalij MJ, Bax JJ. Clinical and echocardiographic predictors of nonresponse to cardiac resynchronization therapy. *Am Heart J* 2011;**161**:552–557.

34. Singh JP, Klein HU, Huang DT, Reek S, Kuniss M, Quesada A, Barsheshet A, Cannom D, Goldenberg I, McNitt S, Daubert JP, Zareba W, Moss AJ. Left ventricular lead position and clinical outcome in the multicenter automatic defibrillator implantation trial-cardiac resynchronization therapy (MADIT-CRT) trial. *Circulation* 2011;**123**:1159–1166.

35. Bordachar P, Derval N, Ploux S, Garrigue S, Ritter P, Haissaguerre M, Jais P. Left ventricular endocardial stimulation for severe heart failure. *J Am Coll Cardiol* 2010; **56**:747–753.

36. van Gelder BM, Houthuizen P, Bracke FA. Transseptal left ventricular endocardial pacing: preliminary experience from a femoral approach with subclavian pull-through. *Europace* 2011;**13**:1454–1458.

37. Spragg DD, Dong J, Fetics BJ, Helm R, Marine JE, Cheng A, Henrikson CA, Kass DA, Berger RD. Optimal left ventricular endocardial pacing sites for cardiac resynchronization therapy in patients with ischemic cardiomyopathy. *J Am Coll Cardiol* 2010;**56**:774–781.

38. Kassai I, Foldesi C, Szekely A, Szili-Torok T. New method for cardiac resynchronization therapy: transapical endocardial lead implantation for left ventricular free wall pacing. *Europace* 2008;**10**:882–883.

39. Lee KL, Tse HF, Echt DS, Lau CP. Temporary leadless pacing in heart failure patients with ultrasound-mediated stimulation energy and effects on the acoustic window. *Heart Rhythm* 2009;**6**:742–748.

40. Lenarczyk R, Kowalski O, Kukulski T, Pruszkowska-Skrzep P, Sokal A, Szulik M, Zielinska J, Kowalczyk J, Pluta S, Sredniawa B, Musialik-Lydka A, Kalarus Z.

41. Leclercq C, Gadler F, Kranig W, Ellery S, Gras D, Lazarus A, Clementy J, Boulogne E, Daubert JC. A randomized comparison of triple-site versus dual-site ventricular stimulation in patients with congestive heart failure. *J Am Coll Cardiol* 2008;**51**:1455–1462.

42. Lenarczyk R, Kowalski O, Sredniawa B, Pruszkowska-Skrzep P, Pluta S, Sokal A, Kukulski T, Stabryla-Deska J, Wozniak A, Kowalczyk J, Zielinska T, Mazurek M, Streb W, Zembala M, Kalarus Z. Triple-site versus standard cardiac resynchronization therapy study (TRUST CRT): clinical rationale, design, and implementation. *J Cardiovasc Electrophysiol* 2009;**20**:658–662.

43. White JA, Yee R, Yuan X, Krahn A, Skanes A, Parker M, Klein G, Drangova M. Delayed enhancement magnetic resonance imaging predicts response to cardiac resynchronization therapy in patients with intraventricular dyssynchrony. *J Am Coll Cardiol* 2006;**48**:1953–1960.

44. Rodriguez LM, Timmermans C, Nabar A, Beatty G, Wellens HJ. Variable patterns of septal activation in patients with left bundle branch block and heart failure. *J Cardiovasc Electrophysiol* 2003;**14**:135–141.

45. Adelstein EC, Saba S. Scar burden by myocardial perfusion imaging predicts echocardiographic response to cardiac resynchronization therapy in ischemic cardiomyopathy. *Am Heart J* 2007;**153**:105–112.

46. Ypenburg C, Roes SD, Bleeker GB, Kaandorp TA, de RA, Schalij MJ, van der Wall EE, Bax JJ. Effect of total scar burden on contrast-enhanced magnetic resonance imaging on response to cardiac resynchronization therapy. *Am J Cardiol* 2007; **99**:657–660.

47. Bleeker GB, Kaandorp TA, Lamb HJ, Boersma E, Steendijk P, de Roos A, van der Wall EE, Schalij MJ, Bax JJ. Effect of posterolateral scar tissue on clinical and echocardiographic improvement after cardiac resynchronization therapy. *Circulation* 2006;**113**:969–976.

48. Murphy RT, Sigurdsson G, Mulamalla S, Agler D, Popovic ZB, Starling RC, Wilkoff BL, Thomas JD, Grimm RA. Tissue synchronization imaging and optimal left ventricular pacing site in cardiac resynchronization therapy. *Am J Cardiol* 2006;**97**:1615–1621.

49. Ypenburg C, van Bommel RJ, Delgado V, Mollema SA, Bleeker GB, Boersma E, Schalij MJ, Bax JJ. Optimal left ventricular lead position predicts reverse remodeling and survival after cardiac resynchronization therapy. *J Am Coll Cardiol* 2008;**52**: 1402–1409.

50. Fung JW, Lam YY, Zhang Q, Yip GW, Chan WW, Chan GC, Chan JY, Yu CM. Effect of left ventricular lead concordance to the delayed contraction segment on echocardiographic and clinical outcomes after cardiac resynchronization therapy. *J Cardiovasc Electrophysiol* 2009;**20**:530–535.

51. Khan FZ, Virdee MS, Palmer CR, Pugh PJ, O'Halloran D, Elsik M, Read PA, Begley D, Fynn SP, Dutka DP. Targeted left ventricular lead placement to guide cardiac resynchronization therapy: the TARGET study: a randomized, controlled trial. *J Am Coll Cardiol* 2012;**59**:1509–1518.

52. Yu CM, Sanderson JE, Gorcsan J III. Echocardiography, dyssynchrony, and the response to cardiac resynchronization therapy. *Eur Heart J* 2010;**31**: 2326–2337.

53. Raatikainen MJ, Uusimaa P, van Ginneken MM, Janssen JP, Linnaluoto M. Remote monitoring of implantable cardioverter defibrillator patients: a safe, time-saving, and cost-effective means for follow-up. *Europace* 2008;**10**:1145–1151.

54. Crossley GH, Boyle A, Vitense H, Chang Y, Mead RH. The CONNECT (Clinical Evaluation of Remote Notification to Reduce Time to Clinical Decision) trial: the value of wireless remote monitoring with automatic clinician alerts. *J Am Coll Cardiol* 2011;**57**:1181–1189.

55. Varma N, Michalski J, Epstein AE, Schweikert R. Automatic remote monitoring of implantable cardioverter-defibrillator lead and generator performance: the Lumos-T Safely RedUceS RouTine Office Device Follow-Up (TRUST) trial. *Circ Arrhythm Electrophysiol* 2010;**3**:428–436.

56. Crossley GH, Chen J, Choucair W, Cohen TJ, Gohn DC, Johnson WB, Kennedy EE, Mongeon LR, Serwer GA, Qiao H, Wilkoff BL. Clinical benefits of remote versus transtelephonic monitoring of implanted pacemakers. *J Am Coll Cardiol* 2009;**54**:2012–2019.

57. Saxon LA, Hayes DL, Gilliam FR, Heidenreich PA, Day J, Seth M, Meyer TE, Jones PW, Boehmer JP. Long-term outcome after ICD and CRT implantation and influence of remote device follow-up: the ALTITUDE survival study. *Circulation* 2010;**122**:2359–2367.

58. Sack S, Wende CM, Nagele H, Katz A, Bauer WR, Barr CS, Malinowski K, Schwacke H, Leyva F, Proff J, Berdyshev S, Paul V. Potential value of automated daily screening of cardiac resynchronization therapy defibrillator diagnostics for prediction of major cardiovascular events: results from Home-CARE (Home Monitoring in Cardiac Resynchronization Therapy) study. *Eur J Heart Fail* 2011; **13**:1019–1027.

Mid-term outcomes of triple-site vs. conventional cardiac resynchronization therapy: a preliminary study. *Int J Cardiol* 2009;**133**:87–94.