

FOCUS ISSUE: CARDIAC RESYNCHRONIZATION THERAPY

Cardiac Resynchronization Therapy

Part 2—Issues During and After Device Implantation and Unresolved Questions

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Encouraged by the clinical success of cardiac resynchronization therapy (CRT), the implantation rate has increased exponentially, although several limitations and unresolved issues of CRT have been identified. This review concerns issues that are encountered during implantation of CRT devices, including the role of electroanatomical mapping, whether CRT implantation should be accompanied by simultaneous atrioventricular nodal ablation in patients with atrial fibrillation, procedural complications, and when to consider surgical left ventricular lead positioning. Furthermore, (echocardiographic) CRT optimization and assessment of CRT benefits after implantation are highlighted. Also, controversial issues such as the potential value of CRT in patients with mild heart failure or narrow QRS complex are addressed. Finally, open questions concerning when to combine CRT with implantable cardioverter-defibrillator therapy and the cost-effectiveness of CRT are discussed. (J Am Coll Cardiol 2005;46:2168–82) © 2005 by the American College of Cardiology Foundation

Encouraged by the clinical success of cardiac resynchronization therapy (CRT), the implantation rate of CRT devices has increased exponentially. However, some limitations and unresolved issues of CRT have been identified. Pre-implantation selection of patients who will respond to CRT is still difficult. An extensive review on the issues before implantation of a CRT device, mainly focusing on the issue of identification of responders, is provided in part 1 of this review (1). In the current manuscript, issues during implantation are discussed, including the role of electroanatomical mapping during implantation to identify the site of latest activation, whether CRT implantation should be accompanied by simultaneous atrioventricular (AV) nodal ablation in patients with atrial fibrillation (AF), procedural complications, and when to consider surgical left ventricular

(LV) lead positioning. In addition, issues after CRT implantation are discussed, including (echocardiographic) CRT optimization and assessment of CRT benefits. Finally, many issues are still unclear in CRT, including the potential value in mild heart failure or in patients with narrow QRS complexes, when CRT should be accompanied by an ICD, and cost-effectiveness of the therapy; these issues are also addressed.

ISSUES DURING CRT IMPLANTATION

Role of electroanatomical mapping in CRT. In normal individuals, electrical activation of both ventricles is preceded by depolarization of the His-Purkinje system resulting in rapid activation of both ventricles with only a short

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Abbreviations and Acronyms

AF	= atrial fibrillation
AV	= atrioventricular
COMPANION	= Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure
CRT	= cardiac resynchronization therapy
ICD	= implantable cardioverter-defibrillator
LBBB	= left bundle branch block
LV	= left ventricle/ventricular
LVEF	= left ventricular ejection fraction
MR	= mitral regurgitation
MUSTIC	= Multisite Simulation in Cardiomyopathies trial
NYHA	= New York Heart Association
PET	= positron emission tomography
QALY	= quality adjusted life year
RV	= right ventricle/ventricular
TDI	= tissue Doppler imaging
VV	= interventricular

delay in activation between the earliest and the latest activated segments (2). In patients with left bundle branch block (LBBB), the total activation of the LV is prolonged with delayed activation and contraction of the lateral wall. However, even in the presence of LBBB, endocardial activation may be prolonged only minimally (2). In these patients, LBBB morphology could primarily be caused by delayed intramural activation (3). Consequently, it was demonstrated that although QRS duration showed a continuous distribution, there was binary distribution of trans-septal activation times supporting the concept of two different forms of LV activation in the presence of LBBB on the electrocardiogram (ECG). The first entity is characterized by a relatively short trans-septal time (<20 ms) indicating intact His-Purkinje activation, whereas the second entity is characterized by a longer trans-septal activation time (>40 ms) indicating “cell-to-cell” activation from right ventricle (RV) to LV (3). Both mechanisms of delayed LV activation may result in an intraventricular mechanical delay of the LV, which can be analyzed in detail with tissue Doppler imaging (TDI) and electroanatomical mapping. The use of electromechanical mapping to assess intraventricular and intramural dyssynchrony has been reported (3). Of interest, three-dimensional mapping studies revealed the presence of long lines of block or slow conduction in heart failure with LBBB (Fig. 1) (2–4). The location and length of these lines of conduction block were highly variable, with delayed activation of different parts of the lateral wall of the LV. Moreover, the location of these lines of block was not fixed and could change, suggesting that they were (at least in part) functionally determined rather than related to areas of scar tissue. By comparing uni- and bipolar recordings, the conduction delay within these lines of block could be located in the subendocardium or could be intramural in origin (3). The exact nature of the intramural conduction delay is not entirely clear. As a consequence of the presence of long lines

of conduction block, a “U” shaped activation pattern was often observed in patients with LBBB. The activation wave front turns around the LV apex and inferior wall in order to activate the lateral wall. Furthermore, as the activation sequence behind the line of block developed from the apical to the basal part of the lateral wall, the basal part is activated last. It has been hypothesized (3) that absence of these lines of block may preclude CRT benefit (Fig. 2). One of the proposed mechanisms underlying response to CRT in patients with heart failure and LBBB is pre-excitation of the most delayed LV segment, thereby reducing LV dyssynchrony and restoring coordinated contraction. It is reasonable to postulate that, in order to correct electrical dyssynchrony, LV pacing sites should be located lateral to the lines of conduction block (Fig. 1). Positioning of the pacing lead on the “wrong” site of the line of block may even result in an increase of dyssynchrony (the activation wave front has to complete a full U-turn in that case). Furthermore, because the basal part of the LV is activated last, it is tempting to speculate that the LV pacing lead should be positioned near the most basal segments. Currently, however, no studies are available to substantiate this hypothesis.

LV lead positioning: transvenous or surgical? Left ventricular lead placement is usually performed by a transvenous approach using the tributaries of the coronary sinus. Intubation of the coronary sinus with a dedicated guiding catheter facilitates LV lead implantation by providing support for advancing the pacing leads and allowing exchange of the angiography catheter and different pacing leads in difficult cases. Optimal projection for identifying the ostium is the left anterior oblique projection, but the right anterior oblique view may aid in defining the angulation of side-branch take-offs. A “conventional” stylet-guided pacing lead or an “over-the-wire” approach may be used. For the latter, a guidewire is first advanced into the desired branch then followed by the lead that has a central lumen. The “over-the-wire” technique is preferred for small tortuous veins, whereas conventional leads may provide superior stability in large veins with a relatively straight course; fixation is usually passive (anchors or pre-shaped curves). The feasibility of transvenous lead positioning is determined by anatomical and technical factors including venous anatomy, accessibility of the vein, pacing threshold, lead stability, and absence of phrenic nerve stimulation. With state-of-the-art lead technology, the ability to access specific coronary veins is not usually problematic. Venous anatomy can be evaluated during the procedure by retrograde venography but is also possible with non-invasive imaging using multislice computed tomography (5). The precise incidence of suitable veins for CRT is not known and may differ between patients with ischemic and non-ischemic cardiomyopathy. Still, Meisel et al. (6) have shown that 55% of patients have suitable posterior veins, whereas 99% have posterior or left marginal veins. Implant failures are more often due to enlargement of the right atrium and the accompanying distortion of the coronary sinus ostium leading to inability

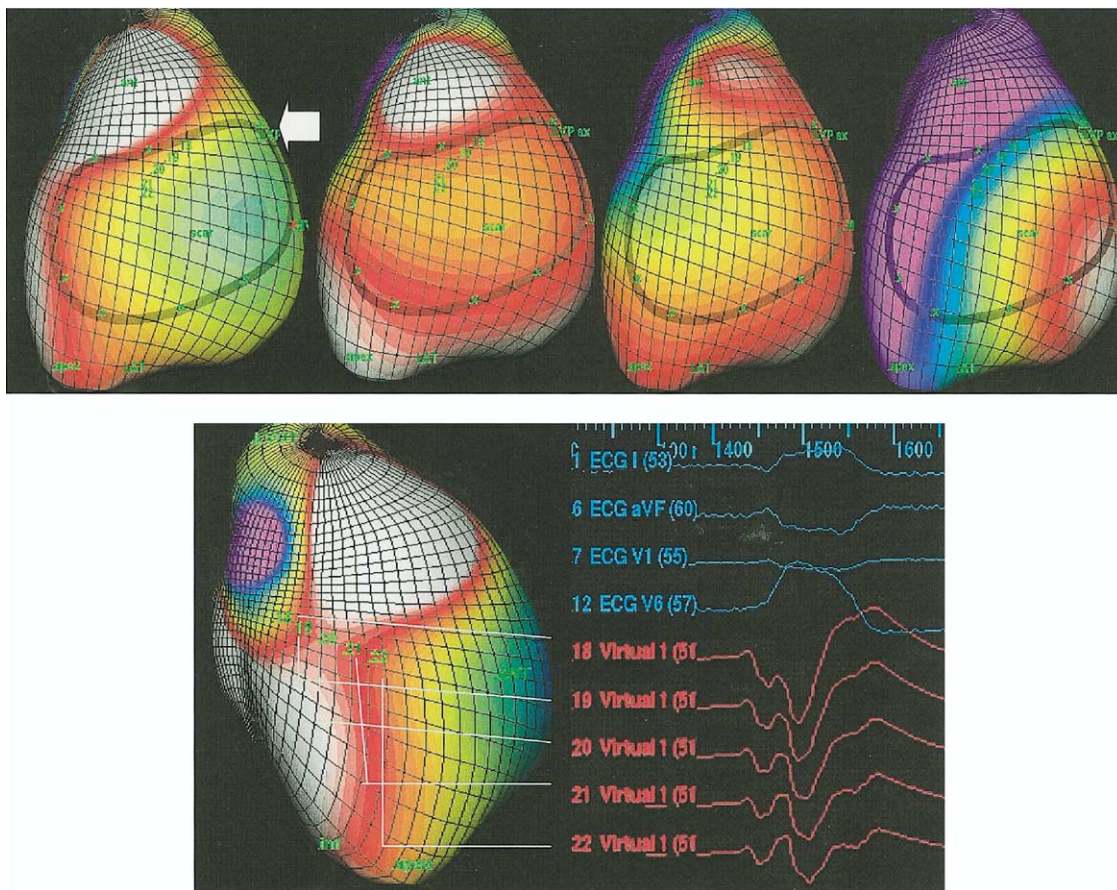


Figure 1. (Top) Ventricular activation sequence using three-dimensional noncontact mapping (EnSite 3000, Endocardial Solutions, Minneapolis, Minnesota) in a patient with dilated (non-ischemic) cardiomyopathy (left ventricular [LV] ejection fraction [EF] 30%, New York Heart Association [NYHA] functional class III) with a QRS duration of 154 ms who responded to cardiac resynchronization therapy (CRT). The propagation wavefront splits when encountering a conduction block located at the LV anterior wall, resulting in delayed activation of the lateral wall. **(Bottom)** The virtual electrograms over the line of block are displayed. Note the fragmented or double potential electrograms. The LV lead was positioned at the basal lateral region of LV (white arrow, top). One year after CRT, the LVEF was 42%, and the patient was in NYHA functional class I. LAT = lateral.

to cannulate the ostium (up to 4%) or insufficient support by the guiding catheter (6). A steerable electrophysiology catheter can be used inside the guiding catheter to facilitate coronary sinus intubation. A myocardial pacing threshold <2 V is acceptable, but phrenic nerve stimulation should be absent even at high output. Overall, implant success rates $>90\%$ can be achieved in experienced centers.

The main procedural complications include lead dislodgement, coronary sinus dissection, and phrenic nerve stimulation. Lead dislodgement occurred in 6% of the patients in the Cardiac Resynchronization-Heart Failure (CARE-HF) trial, in 4% in the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) trial, and in 12% in the Multisite Simulation in Cardiomyopathies (MUSTIC) trial (7–9). Coronary sinus dissection has been reported in about 0.4% to 4% of patients (10); healing is usually uncomplicated, and vessel perforation is uncommon. In most instances, LV lead implantation can safely be performed several weeks after a dissection.

Phrenic nerve stimulation has been noted chronically in 1.6% to 12% of patients (11) and should therefore be assessed during the implant procedure. Still, phrenic nerve

stimulation may occur de novo during follow-up due to changes in body position. Adjustment of pacing output or using other pacing configurations can often resolve this situation, but occasionally lead repositioning is required.

Although lead positioning is limited by anatomical and technical factors, the aim is to resynchronize the LV. With current echocardiographic techniques, including TDI and tissue synchronization imaging, it is possible to precisely locate (before device implantation) the site of latest activation. In general, the site of latest activation is located in the posterolateral region. In a relatively early study, investigators demonstrated that benefit from CRT was significantly greater when the lateral wall was paced as compared to the anterior wall (12); TDI was not used to assess the site of latest activation in this study. A later study confirmed with TDI that the site of latest activation was located in the inferior or posterolateral regions in 75% of patients undergoing CRT (13).

Integration of TDI to assess the site of latest activation and visualization of venous anatomy will allow determination of the feasibility of a transvenous approach. When the site of latest activation is not in the region of suitable veins,

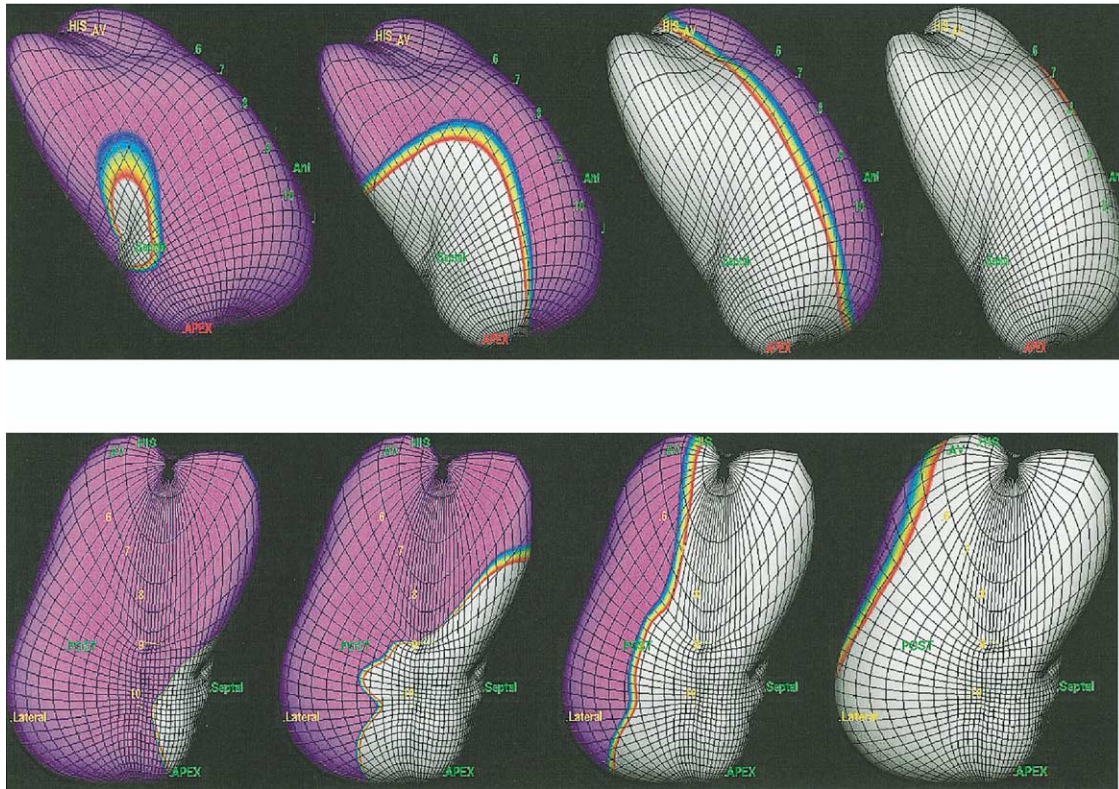


Figure 2. (Top) Ventricular activation sequence (right anterior oblique view [Ant]) using three-dimensional noncontact mapping (EnSite 3000, Endocardial Solutions) in a patient with ischemic cardiomyopathy (left ventricular [LV] ejection fraction [EF] 35%, New York Heart Association functional class III) with a QRS duration of 148 ms who did not respond to cardiac resynchronization therapy (CRT). **(Bottom)** Ventricular activation sequence (posterior view [POST]). There was no line of block or acute change in propagation direction of the depolarization wavefront detected by the mapping system. Of note, there were differences in the electrocardiogram (ECG) pattern between this patient and the patient displayed in Figure 1, indicating that the surface ECG fails to predict the activation sequences in these patients. The prolonged LV activation time in this patient may be due to the relatively slow conduction velocity in the myocardium. The LV lead was positioned in the posterolateral vein. One year after CRT, the LVEF was 34% and the clinical status of the patient unchanged.

surgical LV lead positioning may be considered, using limited left-lateral thoracotomy with direct epicardial lead placement (14). There is no data from large trials on surgical LV lead placement. Mair et al. (15) compared 16 patients undergoing surgical lead placement with 63 patients undergoing transvenous lead placement; the authors reported a lower incidence of procedural-related events with the surgical approach. Koos et al. (14) evaluated 81 patients undergoing CRT, with 25 having a surgical approach for LV lead positioning. A lower incidence of re-interventions was observed after surgical LV lead positioning; however, hospitalization was longer, and clinical benefit was smaller (lesser LV reverse remodeling, less increase in LV ejection fraction [EF] and peak O_2) as compared to transvenous lead positioning. With surgery, the LV leads were more often positioned anteriorly (44% vs. 4.5% with the transvenous approach), and this position may not be ideal for LV resynchronization. More data on surgical LV lead implantation are needed.

CRT in chronic AF. Chronic AF occurs frequently in patients with end-stage heart failure. The prevalence of AF has been reported to increase in parallel to the severity of heart failure, with 10% to 15% of patients in New York

Heart Association (NYHA) functional class II to III and up to 50% of patients in NYHA class IV having AF (16). Considering the high prevalence of AF in patients with severe heart failure, it is noteworthy that all major trials reported on patients with sinus rhythm, which may not be an adequate reflection of the heart failure population. If CRT is considered in patients with chronic AF, it is essential that rapid intrinsic AV nodal conduction does not inhibit resynchronization therapy. This is at times accomplished by performing an AV nodal ablation. At present, no controlled, randomized studies are available to support this hypothesis.

The limited available evidence suggests a beneficial effect of CRT in patients with chronic AF. Initial studies have focused on the acute effect of CRT on hemodynamic parameters in patients with AF. Several single-center studies with relatively small numbers of patients have been reported (17,18) and demonstrated acute hemodynamic improvement in patients with chronic AF receiving CRT. The available evidence on the long-term effects of CRT in patients with heart failure and chronic AF is also scarce. As illustrated in Table 1, the effects of CRT (with follow-up between 3 and 14 months) were evaluated in a total of 124

Table 1. CRT in Randomized Clinical Trials

Trials	Design	Patients (n)	End Points		Results Summary
			Primary	Secondary	
PATH-CHF (1)	Crossover	41	6MWT Peak VO ₂	NYHA functional class QOL Hospitalizations	Improvement in 6MWT NYHA functional class QOL Less hospitalizations
MUSTIC-SR (2)	Crossover	58	6MWT	NYHA functional class QOL Peak VO ₂ LV volumes MR Hospitalizations Total mortality	Improvement in 6MWT NYHA functional class QOL Peak VO ₂ LV volumes MR Less hospitalizations
MIRACLE (3)	Parallel arms	453	6MWT NYHA functional class QOL	Peak VO ₂ LVEF LVEDD MR Clinical composite response	Improvement in 6MWT NYHA functional class QOL LVEF LVEDD MR
MIRACLE-ICD (4)	Parallel arms	555	6MWT NYHA functional class QOL	Peak VO ₂ LVEF LV volumes MR Clinical composite response	Improvement in NYHA functional class QOL
COMPANION (5)	Parallel arms	1,520	All-cause mortality or hospitalization	All-cause mortality and cardiac morbidity	Reduced all-cause mortality/ hospitalization
CARE-HF (6)	Open label, randomized	814	All-cause mortality	NYHA functional class QOL LVEF LVESV Hospitalization for heart failure	Reduced mortality/morbidity Improvement in NYHA functional class QOL LVEF LVESV
PATH-CHF II (7)	Crossover (no pacing vs. LV pacing)	86	6MWT Peak VO ₂	NYHA functional class QOL	Improvement in 6MWT QOL Peak VO ₂
CONTAK-CD (8)	Crossover, parallel controlled	490	6MWT NYHA functional class QOL	LVEF LV volumes Composite of mortality, hospitalizations, VT/VF	Improvement in 6MWT NYHA functional class QOL LVEF LV volumes

CARE-HF = Cardiac Resynchronization-Heart Failure; CONTAK-CD = CONTAK-Cardiac Defibrillator; COMPANION = Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure; CRT = cardiac resynchronization therapy; LV = left ventricular; LVEDD = left ventricular end-diastolic dimension; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; MIRACLE = Multicenter InSync Randomized Clinical Evaluation; MIRACLE-ICD = MIRACLE Implantable Cardioverter Defibrillator trial; MR = mitral regurgitation; MUSTIC = Multisite Simulation in Cardiomyopathies; NYHA = New York Heart Association; PATH-CHF = Pacing Therapies in Congestive Heart Failure trial; QOL = quality-of-life score; VF = ventricular fibrillation; VO₂ = volume of oxygen; VT = ventricular tachycardia; 6-MWT = 6-min walk test.

patients with AF, ranging from 15 to 59 patients per study. In the majority of these four studies, however, an improvement in NYHA functional class, 6-min walking distance, and quality-of-life score was shown, associated with improvement in LVEF. In single-center studies, improvement in additional echocardiographic parameters has been shown (19).

Two studies reported on the comparison of benefit from CRT in patients with AF as compared to patients with sinus rhythm (20,21), and demonstrated comparable benefit of CRT in both groups. On an individual basis, however, the clinical response rate was significantly higher in the patients

with sinus rhythm as compared to AF (Fig. 3) (21). This difference may be (partially) due to the relatively low response rate in the patients with AF who did not undergo AV nodal ablation, as compared to those who underwent ablation (54% vs. 71%) (21).

To date, only one prospective, randomized, and controlled trial designed to assess the efficacy of CRT in AF patients with severe heart failure has been published (22). In the MUSTIC AF trial (22,23), 59 patients with end-stage heart failure and permanent AF, LVEF <35%, and wide (RV-paced) QRS complex were randomized for two periods

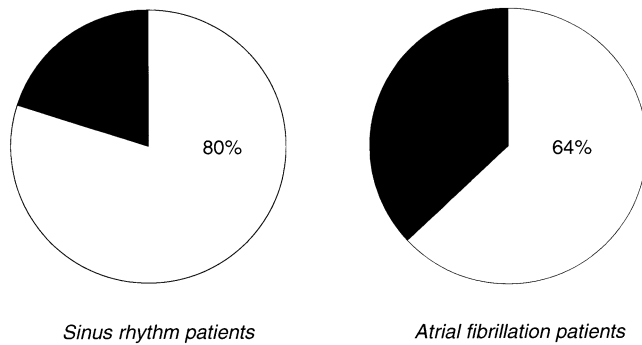


Figure 3. The incidence of responders to cardiac resynchronization therapy in patients with sinus rhythm (**left**) is higher than in patients with atrial fibrillation (**right**) (data based on reference 21). **Black** = non-responders; **white** = responders.

of three months (conventional RV pacing or CRT). In patients with effective therapy (i.e., CRT for $\geq 85\%$ of time), a significant improvement was observed in NYHA functional class, 6-min walking distance, and quality-of-life score. In addition, LV reverse remodeling was observed with a reduction in hospitalization rate for heart failure. Linde et al. (23) subsequently demonstrated that benefit of CRT was sustained at 12 months.

From the limited data (Table 1), it appears that CRT is effective in patients with chronic AF, although larger studies are needed to confirm the findings. An important issue remains whether CRT in chronic AF patients should be accompanied with AV nodal ablation, and, although anecdotal data support this concept, more substantial data are needed. A theoretical argument against AV nodal ablation is the hypothesis that CRT results in reverse LV remodeling, with reduction of mitral regurgitation (MR), and that sinus rhythm may be restored spontaneously over time during CRT. However, no solid data exist on the incidence of spontaneous restoration of sinus rhythm in AF patients undergoing CRT.

ISSUES AFTER CRT IMPLANTATION

Optimization of AV and interventricular (VV) delays in CRT. Optimization of pacemaker settings may further enhance benefit from CRT. Both AV and VV delay can be optimized with contemporary CRT devices. The aim of AV delay optimization is to avoid LV systolic contraction taking place after suboptimal LV filling. In an early study (24) in 15 patients with heart failure and severely depressed LV function who underwent dual-chamber (atrial synchronized RV) pacing, AV delay optimization substantially increased cardiac output. The AV delay was optimized using Doppler echocardiography, and benefit was validated by invasive measurements including cardiac output. An optimal AV delay was programmed when the end of the “Doppler A-wave” (corresponding to left atrial contraction) occurred just before the onset of aortic systolic Doppler flow. This echocardiography-guided AV optimization appeared crucial in some heart failure patients who exhibited an increase in

cardiac output by 50%. Unfortunately, the LV systolic activation sequence remained delayed and heterogeneous because pacing was performed via the RV apex, not using the highly differentiated Purkinje tissue. Cardiac resynchronization therapy now allows stimulation of both ventricles simultaneously, which reduces the aortic pre-ejection time interval (25,26) making re-optimization of the timing between the end of the “Doppler A-wave” and the onset of the aortic systolic flow necessary (Fig. 4). Auricchio et al. (27) have shown that quality of LV filling determined optimal LV ejection. The authors studied 27 patients and evaluated the acute effect of different AV delays on maximum LV pressure derivative and aortic pulse pressure, and demonstrated individual AV optimization yielded optimal improvements in hemodynamic measurements. These observations indicate that the AV delay needs to be evaluated on a patient basis instead using generalized settings. Still, evidence is needed on the beneficial effect of AV delay optimization during long-term follow-up.

The recent generation of CRT devices also allows for optimization of VV delay (28–31). Sogaard et al. (29) were the first to demonstrate additional benefit of sequential ventricular pacing over simultaneous CRT. The authors demonstrated an immediate reduction in LV dyssynchrony (assessed by tissue tracking) after onset of CRT (with simultaneous RV and LV pacing), resulting in an increased LVEF (from $22 \pm 6\%$ to $30 \pm 5\%$, $p < 0.01$). Optimization of VV delay induced a further reduction in LV dyssynchrony with an additional increase in LVEF (to $34 \pm 6\%$, $p < 0.01$). Other investigators (30) demonstrated a significant reduction in MR after CRT with simultaneous ventricular pacing, with a further reduction after VV optimization (Fig. 5). Thus, the benefit of sequential CRT with an individually optimized VV delay is related to an increased diastolic filling time with a reduction in LV dyssynchrony, leading to a better systolic performance with more synchronous motion of the mitral leaflets, thereby reducing MR.

Recent observations suggest that the optimal sequence of ventricular pacing varies substantially between patients. Porciani et al. (31) demonstrated that 50% of patients showed most benefit from LV pre-activation, whereas the other 50% had most benefit from RV pre-activation, illustrating the need for a patient-tailored approach to optimize pacemaker settings. The definition of an optimal VV delay has not yet been fully characterized and could reflect the VV interval that yields a maximal reduction in LV dyssynchrony and/or a maximal increase in LV systolic function. In daily practice, echocardiographic assessment of cardiac output using the LV outflow (aortic velocity-time integral) at different VV intervals may be the preferred approach to assess optimal VV settings. It should be emphasized, however, that long-term benefit of sequential over simultaneous ventricular pacing has not yet been demonstrated. In addition, the sequence of AV and VV optimization (i.e., which first and which second) is also not yet clear.

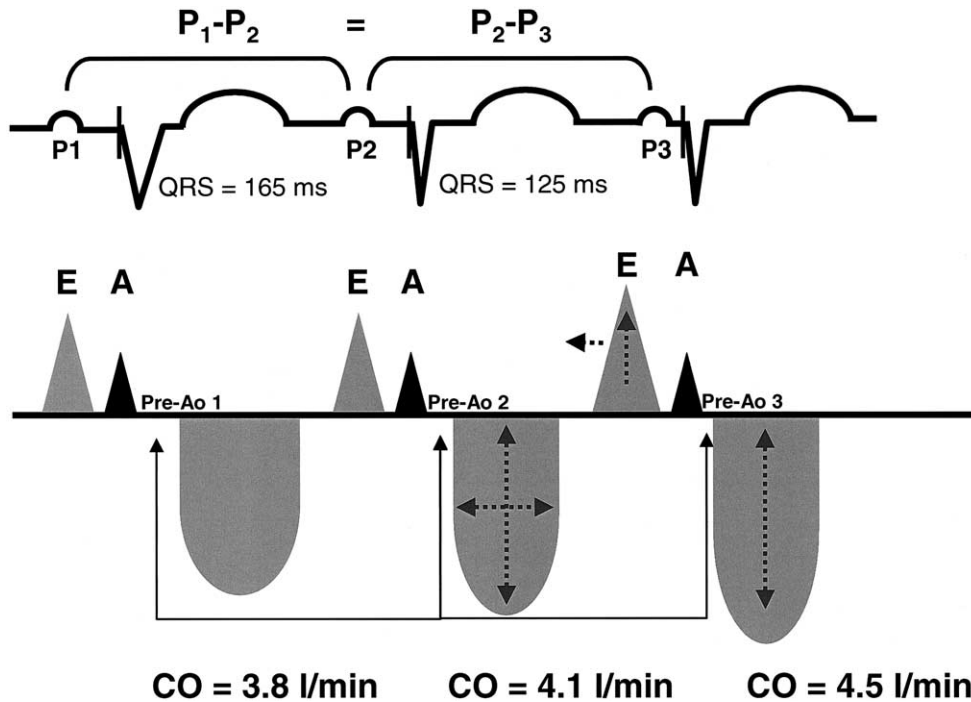


Figure 4. Consequences of optimization of atrioventricular (AV) delay during biventricular pacing at stable heart rate. The QRS complex resulting from P1 is wide due to apical right ventricular pacing (165 ms). The aortic pre-ejection time interval (Pre-Ao1) is long; the aortic systolic phase is also long due to the wide QRS complex. The second QRS complex resulting from P2 is narrowed due to biventricular pacing leading to a shorter aortic pre-ejection time interval (Pre-Ao2) compared with Pre-Ao1. Consequently, time duration of the aortic systolic phase is reduced, and the E-wave corresponding to P3 occurs earlier (compared to P1 and P2) with a greater amplitude, indicating a better LV filling phase. Pre-Ao3 is even shorter than Pre-Ao2 due to the addition of an AV delay optimization during P3, resulting in a greater cardiac output (CO) during P3 compared with the one obtained during P2, in which biventricular pacing was delivered without AV delay optimization.

What benefit can be measured acutely and chronically after CRT? The effects of CRT can be divided into acute and chronic effects (Table 2). Studies in the acute setting have demonstrated that CRT abruptly enhances LV systolic function. In both experimental and clinical studies, this is manifest by a modest (6 mm Hg) rise in systolic pressure (27,32), increase in stroke volume (10% to 30%) (32), reduction in the LV end-systolic volume and, thus, LV end-systolic stress, and a more rapid rise of LV pressure (dp/dt_{max} between 15% to 35%) (27,32,33). There is also improved cardiac work at similar or lower oxygen consumption (34) so that chamber energetic efficiency is improved. Many of these changes can be observed within a single beat upon activating CRT, and are sustained in

the short-term studies until CRT is abruptly terminated where they are rapidly reversed. The impact of CRT on diastolic function remains somewhat less clear. Acute studies have rarely shown significant effects on relaxation time constant, and there is no demonstrable effect on chamber stiffness (32).

Chronic CRT triggers similar changes in a number of hemodynamic parameters, but also results in reversal of LV dilation. Echocardiographic studies have shown ~10% declines in LV end-systolic and end-diastolic volumes, associated with an increase in LVEF (35-37).

Effect of CRT on MR. A significant reduction in MR has also been reported after CRT. Some patients exhibit immediate reduction in MR, whereas other patients show im-

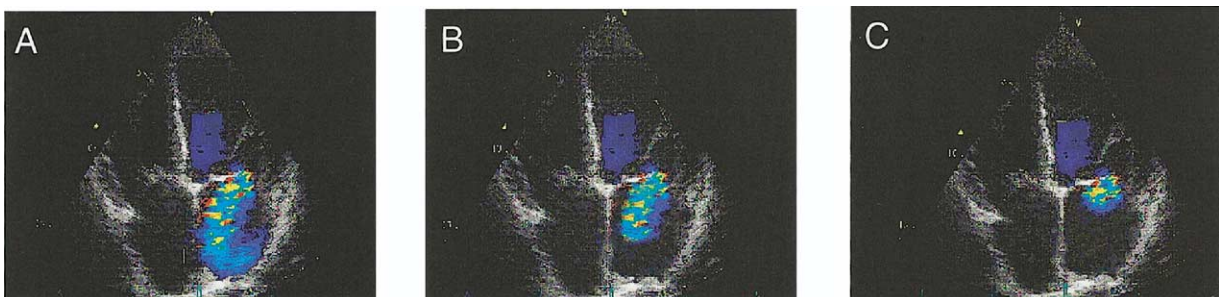


Figure 5. Changes in mitral regurgitation according to different pacing modes. (A) Spontaneous sinus rhythm showing severe mitral regurgitation. (B) Simultaneous biventricular pacing, showing significant reduction in mitral regurgitation. (C) Further reduction of mitral regurgitation after biventricular pacing with optimized interventricular delay (left ventricular pre-activation of 20 ms).

Table 2. Early and Late Effects After CRT

Acute Changes	Chronic Changes
↑ Systolic pressure	↑ Systolic pressure
↑ Stroke volume	↓ End-systolic volume
↓ End-systolic volume	↓ End-diastolic volume
↑ Cardiac energetic efficiency	↑ Ejection fraction
↑ Arterial pulse pressure	↑ Arterial pulse pressure
↑ dP/dt _{max}	↑ dP/dt _{max}
↓ or ↔ Relaxation time	↔ Relaxation time
↔ Diastolic compliance	Reverse remodeling

CRT = cardiac resynchronization therapy; dP/dt_{max} = change in left ventricular pressure over time.

provement only late after CRT. This is related to the underlying pathophysiology of MR in end-stage heart failure. The LV dilation results in systolic retraction of the papillary muscles towards the apex, which inhibits complete leaflet coaptation in particular in the presence of a simultaneous decrease in the systolic closing force (38). In addition, wall motion abnormalities in the inferior/posterior regions can result in papillary muscle dysfunction with subsequent MR (39); LV dyssynchrony does also contribute to MR (40). A prolonged AV interval delays the onset of LV contraction and predisposes to incomplete mitral valve closure with the occurrence of pre-systolic (diastolic) MR (41). The resulting LV volume overload contributes further to the progressive deterioration in LV function, which in turn again increases MR (42). The pre-systolic component of MR can be effectively eliminated by pacing with a short (optimized) AV delay, while the CRT-related immediate reduction in the degree of systolic MR is associated with an acute hemodynamic improvement. Breithardt et al. (43) studied patients during brief re-programming of a CRT device and quantified the changes in the extent of MR with echocardiography by the proximal isovelocity surface area method. The changes in MR severity were compared to the changes in LV systolic function (LV peak positive rate of pressure rise, LV +dP/dt_{max}), measured noninvasively by Doppler echocardiography. A linear correlation between the effective regurgitant orifice area and LV +dP/dt_{max} was observed, and it was concluded that an improved transmitral pressure gradient (the closing force on the mitral leaflet) reduces MR severity by earlier and more effective mitral leaflet closure. An example of an acute reduction in MR after onset of CRT is demonstrated in Figure 6. Kanzaki et al. (44) confirmed these findings and added data on the role of papillary muscle resynchronization during CRT. The authors studied the deformation sequence of the papillary muscles by strain rate imaging and reported a direct relationship between the interpapillary muscle activation time delay and the improvement in the degree of MR by CRT. Thus, the immediate reduction in MR severity can be attributed to an improved coordination of ventricular contraction, including resynchronized papillary muscle activation, which results in improved systolic function and reduced mitral leaflet tethering forces. This effect can be observed in patients with ischemic and non-ischemic car-

diomyopathy (36). Effective CRT immediately reduced the transmitral regurgitant volume at rest by about 30% to 40% on average (35,43,44). A further 10% to 20% improvement can be observed after some months of CRT and is probably related to the LV reverse remodeling (35).

Effect of CRT on quantitative blood flow and metabolism. Various studies have evaluated the effect of CRT on myocardial perfusion and metabolism. In order to assess small differences in a quantitative manner, positron emission tomography (PET) was used. In mild heart failure, LV efficiency of forward work is reduced, whereas RV oxidative metabolism is increased (probably due to an increased pressure load) (45). Resting perfusion may be normal, but the perfusion reserve is typically reduced. With more severe heart failure, LV oxidative metabolism becomes also compromised (46). In addition to the effects of heart failure per se, commonly coexisting LBBB leads to striking regional heterogeneity in perfusion and oxidative metabolism. In particular, perfusion and metabolism are reduced in the VV septum and increased in the lateral wall. The various PET studies that have evaluated the effect of CRT on myocardial blood flow and metabolism are summarized in Table 3. It should be noted that the total number of patients (n = 99) studied with PET is still limited, and the number of patients per study is also small (ranging from 6 to 14) (47–55). The available evidence indicates that CRT does not increase resting myocardial blood flow (Table 3, Fig. 7). The evidence on flow reserve is minimal. Knaapen et al. (54) studied 14 patients with PET and O15-labeled water and demonstrated a significant increase in flow reserve after CRT; conversely, Sundell et al. (50) also studied 10 patients with PET and O15-labeled water and demonstrated no change in flow reserve. Clearly, more information is needed on this topic.

Myocardial glucose utilization was evaluated in two studies, demonstrating that glucose uptake in the VV septum increased significantly after CRT (47,53).

In addition, three studies evaluated LV oxidative metabolism using PET and C11 acetate before and after CRT (48,50,51). These studies uniformly demonstrated no change in global LV oxidative metabolism, although an improvement in systolic LV function was demonstrated. The studies were also consistent in demonstrating increased myocardial efficiency, indicating improved oxygen cost of forward work by CRT (Table 3, Fig. 8). These studies confirm the earlier work by Nelson et al. (34) who demonstrated in an invasive setting that CRT improved systolic function with a reduction in energy cost. The PET studies also showed that oxidative metabolism became more homogenous throughout the LV. Similar to glucose utilization, CRT appears to enhance oxidative metabolism in the VV septum with a simultaneous reduction in the lateral wall. This observation suggests a more balanced wall stress and energy requirements during CRT.

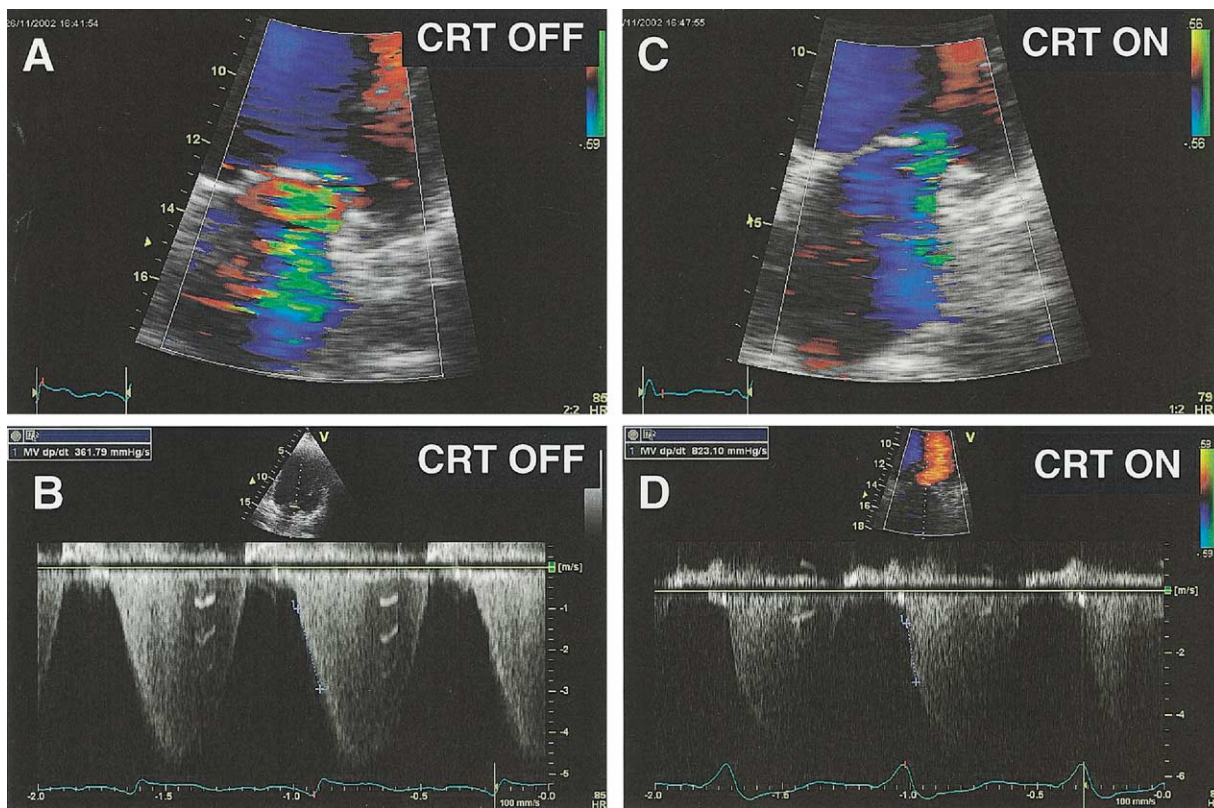


Figure 6. Immediate effect of cardiac resynchronization therapy (CRT) on the severity of mitral regurgitation. Color-coded Doppler echocardiography shows moderate mitral regurgitation during no pacing (CRT OFF, A) and the estimated left ventricular (LV) peak +dP/dt is 361 mm Hg/s (CRT OFF, B). During CRT, the mitral regurgitant jet is smaller, corresponding to mild mitral regurgitation (CRT ON, C). The simultaneously acquired LV peak +dP/dt by continuous-wave Doppler echocardiography has improved significantly to 823 mm Hg/s (CRT ON, D).

UNRESOLVED ISSUES IN CRT

CRT in NYHA class II heart failure. It has been hypothesized that patients with mild heart failure (i.e., NYHA functional class II) may also benefit from CRT, not so much as a therapy for heart failure, but rather to prevent development of heart failure. Thus far, one double-blind, parallel-controlled study focused on the effects of CRT in patients with NYHA functional class II heart failure and a classic indication for an implantable cardioverter-defibrillator (ICD) (56). These patients did not improve (but also did not worsen) in quality-of-life score and exercise tolerance, but significant reverse LV remodeling was observed. Another CRT study suggested improvement in clinical parameters in NYHA functional class II heart failure patients (57). To further substantiate these findings, controlled studies are needed. The REsynchronization reVERsEs Remodeling in Systolic left vEntricular dysfunction (REVERSE) trial is an ongoing prospective, randomized, double-blind parallel study, designed to assess whether CRT combined with optimized medical therapy can attenuate progression of heart failure over at least 12 months, as compared to optimized medical treatment alone. Approximately 500 patients with either asymptomatic LV dysfunction or mild (NYHA functional class II) heart failure, QRS duration ≥ 120 ms, LVEF $\leq 40\%$, and LV end-diastolic diameter ≥ 55 mm will be included and followed-up for five

years. The primary end point is the clinical composite end point, with LV end-systolic volume index as the first-order secondary end point.

CRT in narrow QRS complex. The value of CRT in heart failure patients with narrow QRS complex has not been resolved. Assuming that LV dyssynchrony is the main determinant of response to CRT, these patients need to be screened with advanced echocardiographic techniques (58). Two studies evaluated the incidence of LV dyssynchrony in patients with narrow QRS complex (59,60). Yu et al. (59) evaluated 67 patients with narrow QRS complex (≤ 120 ms, average 99 ± 11 ms) and heart failure with TDI and demonstrated LV dyssynchrony in 43% of patients. An example of a patient with LV dyssynchrony is presented in Figure 9. Bleeker et al. (60) showed a somewhat lower incidence (27%) of LV dyssynchrony (Fig. 10), which may have been related to patient characteristics or to a slightly different analysis of data and definition of LV dyssynchrony. Thus far, two small studies have shown actual benefit from CRT in patients with severe heart failure, depressed LVEF, and narrow QRS complex with LV dyssynchrony on echocardiography (61,62). In a study of 14 patients with QRS duration ≤ 120 ms, an improvement in NYHA functional class, 6-min walking distance and LVEF, with reverse LV remodeling were noted after six months of CRT (61). Moreover, it was demonstrated that the magnitude of

Table 3. Summary of the Available Studies Using PET to Assess Effect of CRT on Myocardial Blood Flow and Metabolism

Study	Study Population	Measured PET Parameters (Radionuclides)	Main Findings: CRT ON Versus OFF
Neri et al. (47)	8 100% DCM LVEF 27 ± 12%	Resting MBF (N13 ammonia) Glucose uptake (F18 deoxyglucose)	No effect on MBF Septal glucose uptake increased
Ukkonen et al. (48)	8 25% DCM LVEF 26 ± 9%	MVO ₂ rest (C11 acetate)	LV and RV global MVO ₂ unchanged Myocardial efficiency improved Septal to lateral wall ratio of MVO ₂ increased
Nielsen et al. (49)	14 36% DCM LVEF 21 ± 5%	Resting MBF (N13 ammonia)	No effect on global and regional MBF
Sundell et al. (50)	10 100% DCM LVEF 32 ± 8%	MBF at rest/during adenosine (O15 water) MVO ₂ at rest/during dobutamine (C11 acetate)	No effect on global and regional MBF No effect on global and regional flow reserve LV global MVO ₂ unchanged Myocardial efficiency improved Stress (dobutamine) MVO ₂ enhanced
Braunschweig et al. (51)	6 50% DCM LVEF 22 ± 9%	MBF at rest/during dobutamine (C11 acetate) MVO ₂ at rest/during dobutamine (C11 acetate)	No effect on resting MBF/flow reserve No effect on resting MVO ₂ Stress (dobutamine) MVO ₂ enhanced
Nowak et al. (52)	14 100% DCM LVEF 23 ± 13%	Resting MBF (O15 water)	No effect on global and regional MBF
Nowak et al. (53)	15 100% DCM LVEF 22 ± 12%	Glucose uptake (F18 deoxyglucose)	Septal glucose uptake increased
Knaapen et al. (54)	14 57% DCM LVEF 25 ± 7%	MBF at rest/during adenosine (O15 water)	No effect on global MBF but regional MBF became more homogeneous Global hyperemic MBF increased Global flow reserve increased
Knuuti et al. (55)	10 100% DCM LVEF 32 ± 8%	RV MVO ₂ at rest/during dobutamine (O15 water)	No effect on resting MVO ₂ in RV Stress MVO ₂ enhanced in RV Subjects with high MVO ₂ in RV were functionally non-responders

CRT = cardiac resynchronization therapy; DCM = idiopathic dilated cardiomyopathy; LV = left ventricular; LVEF = left ventricular ejection fraction; MBF = myocardial blood flow; MVO₂ = myocardial oxygen consumption; PET = positron emission tomography; RV = right ventricular.

improvement in clinical parameters after CRT was similar in a comparable group of patients with wide QRS complex. **Should CRT be combined with ICD back-up?** Heart failure has a poor prognosis with a five-year mortality of approximately 50% (63); cardiac mortality is high, and mode of death appears related to severity of heart failure. Patients with severe heart failure die more frequently of worsening

heart failure, and patients with mild-to-moderate heart failure have a higher incidence of sudden death. Still, in absolute numbers, the sudden death rate is high even in patients with NYHA functional class III or IV heart failure (59% and 33% of all deaths, respectively) (63). Improving survival in these patients should focus on treatment of heart failure and prevention of sudden death; CRT has been demonstrated in large trials to improve heart failure symp-

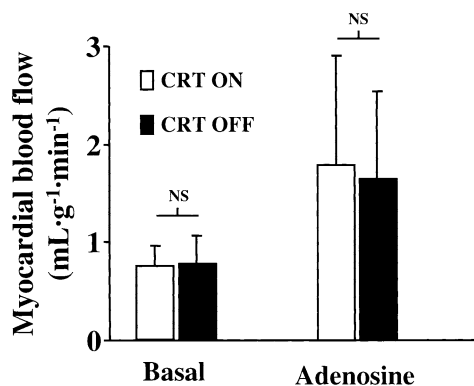


Figure 7. Cardiac resynchronization therapy (CRT) appears to have no effect on basal (resting) blood flow (measured quantitatively by positron emission tomography using O15-labeled water) (left) or blood flow reserve (measured after adenosine vasodilation, right). (Data based on reference 50).

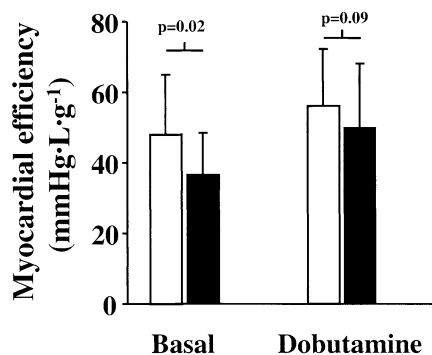


Figure 8. Cardiac resynchronization therapy (CRT) significantly increased basal myocardial efficiency (based on assessment by positron emission tomography using C11 acetate) (left), and a similar trend was observed during dobutamine stress (although not significant, right). (Data based on reference 50). Open bars = CRT on; solid bars = CRT off.

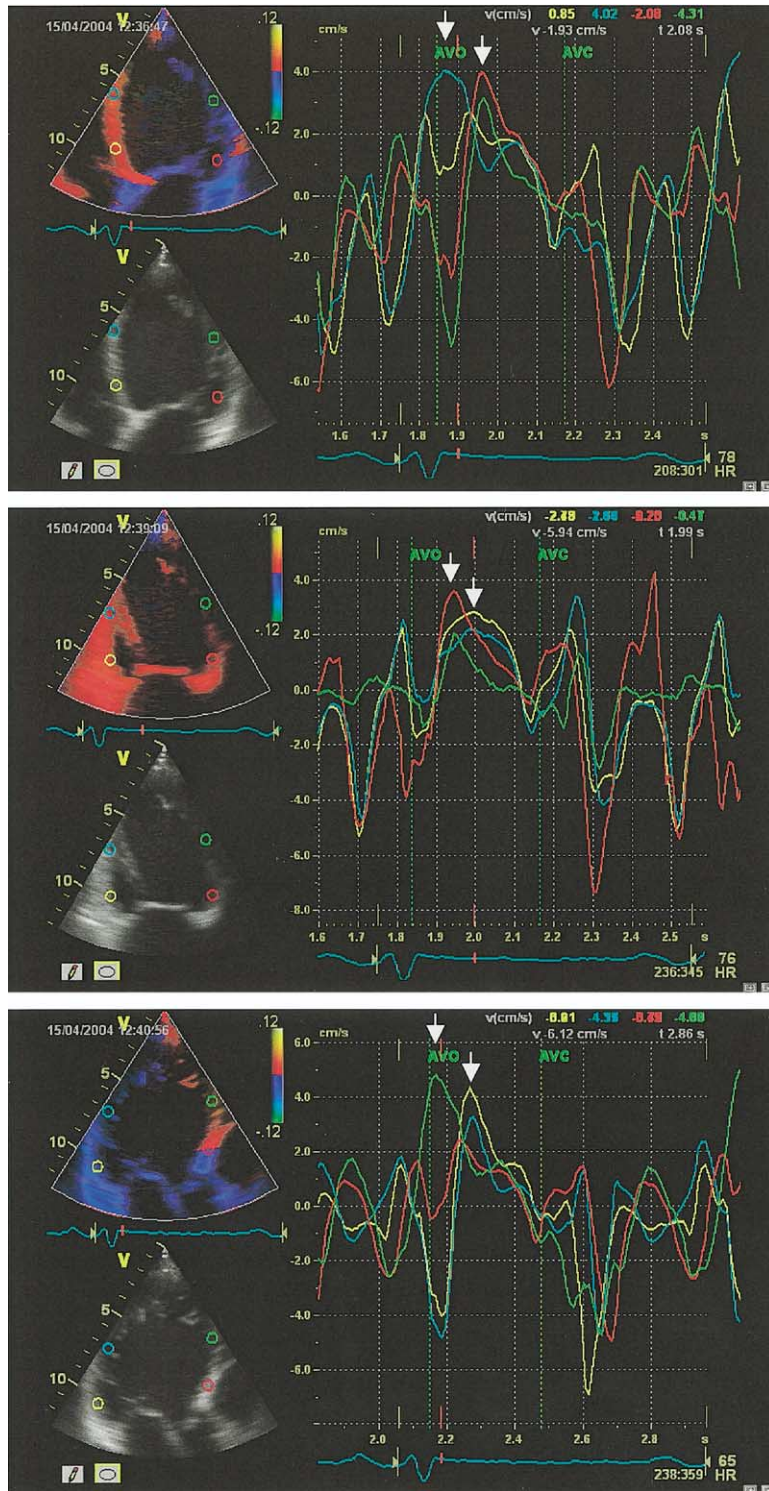


Figure 9. Tissue Doppler imaging in a patient with heart failure and narrow QRS complex, showing left ventricular (LV) dyssynchrony in multiple segments (**top, middle, and bottom panels**) as illustrated by the temporal difference in peak systolic velocity during the ejection phase (**arrows**). (**Top**) Tissue Doppler imaging velocity tracings obtained in the interventricular septum (**yellow and light blue curves**) and lateral wall (**red and green curves**). Earliest activation (peak systolic velocities, **first arrow**) is in the septum, and latest activation in the lateral wall (peak systolic velocities, **second arrow**). Thus, significant LV dyssynchrony is present between the septum and the lateral wall. (**Middle**) Tissue Doppler imaging velocity tracings obtained in the anterior wall (**red and green curves**) and inferior wall (**yellow and light blue curves**). Earliest activation (peak systolic velocities, **first arrow**) is in the anterior wall, and latest activation in the inferior wall (peak systolic velocities, **second arrow**). Thus, significant LV dyssynchrony exists between the anterior and inferior wall. (**Bottom**) Tissue Doppler imaging velocity tracings obtained in the anteroseptal wall (**red and green curves**) and posterior (**yellow and light blue curves**). Earliest activation (peak systolic velocities, **first arrow**) is in the anteroseptal wall, and latest activation in the posterior wall (peak systolic velocities, **second arrow**). Thus, significant LV dyssynchrony is present between the anteroseptal and posterior wall. AVC = aortic valve closure; AVO = aortic valve opening.

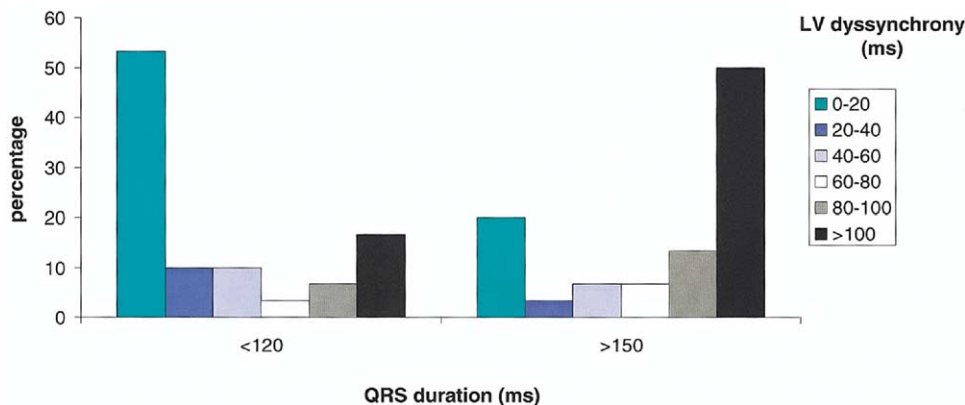


Figure 10. The incidence of left ventricular (LV) dyssynchrony in patients with narrow QRS complex (<120 ms) or wide QRS complex (>150 ms). The LV dyssynchrony is expressed as the extent of dyssynchrony between the septum and lateral wall. Considering LV dyssynchrony >60 ms as significant, the incidence of LV dyssynchrony was 27% in patients with narrow QRS complex as compared to 70% in the patients with wide QRS complex. (Data based on Bleeker et al. [60]).

toms and LV systolic function. The effect was larger than that obtained with optimized medical therapy (7,8,10), and many patients improved from NYHA functional class III or IV to I or II after CRT (7,8,10). Moreover, results from the CARE-HF study demonstrated a reduced two-year mortality rate with CRT as compared to optimized medical therapy (18% vs. 25.1%) (7). Detailed analysis on the mode of death revealed that 47% of deaths in the medical-therapy group could be attributed to worsening heart failure as compared to 40% in the CRT group. Moreover, 32% of deaths in the medical-therapy group were attributed to sudden cardiac death as compared to 35% in the CRT group.

Implantable cardioverter defibrillator therapy is the optimal therapy to prevent sudden death; efficacy of ICD therapy is well established in both secondary and primary prevention trials (64–66). Currently, the Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) trial is the only randomized study evaluating whether CRT with or without ICD back-up would reduce all-cause mortality and hospitalization compared to optimized medical therapy (10). Patients were randomly assigned to optimized medical therapy (20%), CRT therapy (40%), and CRT + ICD back-up (40%). This trial was terminated after inclusion of 1,600 patients (originally projected 2,200 patients with a minimum follow-up of one year). The combined end point of all-cause mortality and hospitalization was 20% lower in both device groups compared to optimized medical therapy. No difference was noted with respect to the combined primary end point between the two device arms, and it was suggested that adding an ICD had no additional positive effects. However, a significant reduction (36%) in the risk of death was found in the CRT + ICD group (from 19% to 11%) compared to standard therapy whereas CRT resulted only in a non-significant risk of death reduction of 20%. Still, the trial was not designed to evaluate the individual benefits from CRT and CRT + ICD, and currently no data are available on this topic.

Considering that patients with mild-to-moderate heart failure die more often from sudden cardiac death, the improvement in NYHA functional class after CRT may be associated with a higher incidence of ventricular arrhythmias, and CRT should always be combined with ICD back-up. On the other hand, preliminary data suggest that the reverse LV remodeling was associated with a reduction in ventricular arrhythmias (that could be secondary to a reduction in wall stress) (67). Also, the inducibility of ventricular arrhythmias was less after CRT (68). Still, these results were obtained in a small number of patients, and studies are needed to provide more insight whether CRT should be combined with ICD back-up.

Economic considerations on CRT. There are two general questions that can be addressed by medical economic analyses: 1) what is the value of a new therapy or technology, and 2) can we afford it?

To facilitate comparisons among alternative medical therapies, one can express incremental health benefits either as additional life years (if the therapy in question increases life expectancy) or as additional quality adjusted life years (QALYs) (if quality of life is an important aspect of either the therapeutic benefit or the underlying disease state being treated). By general consensus, any therapy that can generate an additional life year for \$50,000 or less is judged to be economically attractive, while therapies that generate additional life years for over \$100,000 are judged economically unattractive. As can be easily seen, an expensive therapy such as CRT-ICD can be economically attractive as it produces a proportionally large improvement in health benefits. In most cases, the magnitude of health benefits produced rather than the price of the therapy is the primary determinant of whether the therapy is economically attractive. Thus, economic value analysis should focus much attention on careful definition of what are the incremental health benefits of a particular therapy, along with determining the long-term net cost.

The second economic question, that of affordability, stands apart from the value question. A new therapy may be

very economically attractive (that is, a very efficient way to increase health benefits with extra health care dollars), but still be out of reach for a country or health care system because there are not the extra health care dollars to spend.

Relatively little data exist on the economics of CRT. It is generally appreciated that the devices are expensive, with a typical U.S. cost for a CRT-ICD device around \$30,000. As previously noted, the economic questions that need to be answered about these devices are: what extra health benefits (expressed in terms of QALYs) does CRT produce, and what are its long-term incremental costs, taking into consideration such downstream issues as device replacements, lead and other complications, as well as heart failure hospitalizations and emergency department visits prevented.

On the health benefits side, CRT has been reported to improve functional capacity (quality of life) and survival (7). On the cost side, there are reasonable data that CRT reduces heart failure hospitalizations. In the COMPANION study (10), CRT + ICD and CRT therapy were both associated with a 20% reduction in follow-up hospitalization (representing about \$7,700) relative to medical therapy alone. In the COMPANION trial, CRT + ICD therapy added 0.5 life years during the course of follow-up relative to medical therapy alone. The cost effectiveness ratio for CRT-ICD therapy was \$37,000 per life year saved, which is an economically attractive result.

As discussed in Part 1 of this review (1), better identification of responders to CRT should further improve cost-effectiveness of the therapy.

Conclusions. Cardiac resynchronization therapy has significantly contributed to the treatment of patients with severe heart failure. To further optimize individual benefit from CRT, identification of potential responders is needed. Echocardiography is the technique of choice to identify responders before implantation (1). During implantation, electroanatomical mapping can be used to identify the site of latest activation in order to optimize LV lead positioning. Most patients will have suitable venous anatomy for LV lead positioning; however, in the absence of suitable veins in the target region, minimally invasive surgical implantation should be considered. In patients with AF, AV nodal ablation during pacemaker implantation should be considered, to further optimize response to CRT. Optimization of pacemaker settings after CRT using echocardiography is important; optimization of AV and VV delays has been demonstrated to further improve benefit from CRT.

The response to CRT extends from immediate benefit (improvement of hemodynamic parameters, MR) to long-term benefit (improvement in clinical parameters, systolic LV function, reverse LV remodeling, and further reduction in MR). In addition, PET studies have shown that cardiac efficiency is improved after CRT; blood flow does not improve after CRT.

Several issues in CRT need further study. These include: the benefit from CRT in mild-to-moderate heart failure, the benefit from CRT in patients with narrow QRS

complex, and whether ICD back-up is always needed. More research in these fields is needed. Finally, economic considerations are important, and cost-effectiveness of CRT needs further study.

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