Review Article

Cardiac Resynchronization Therapy: A Review of Pathophysiology and Clinical Applications

Skevos Sideris[1], Konstantinos Trachanas[1], Iosif Kelesidis[2], Konstantinos Gatzoulis[3], Petros Arsenos[3], Dimitris Tousoulis[3], Ioannis Kallikazaros[1]

[1]State Cardiology Division, Hippokration General Hospital, Athens, Greece; [2]Cardiology-Electrophysiology Division, Hospital of University of Pennsylvania, Philadelphia, USA; [3]First Department of Cardiology, National University of Athens, Hippokration General Hospital, Athens, Greece

Key words: **Heart failure, left bundle branch block (LBBB), cardiac dyssynchronization, responders.**

Manuscript received: April 17, 2015; *Accepted:* June 16, 2015.

Address: Skevos Sideris

State Cardiology Division Hippokration Hospital 114 Vasilissis Sofias Ave. 115 28 Athens, Greece
skevos1@otenet.gr

Cardiac resynchronization therapy (CRT) is a fundamental device-based, non-pharmacological approach that has been shown to improve morbidity and mortality in selected patients with chronic heart failure (HF). CRT confers a mortality benefit, reduces HF hospitalizations, and improves functional outcome in this population, but not all patients consistently demonstrate a positive CRT response. The reported non-responder rate ranges between 20% and 40%, depending on the response criteria used.[1] The present article reviews the pathophysiology of CRT and discusses areas of controversy.

Electrophysiological and molecular mechanisms

Pathophysiology of the dyssynchronous heart

During normal sinus rhythm in healthy hearts without conduction abnormalities, the electrical activation is relatively synchronous (activation of the ventricles occurring within 70 ms), because the impulse is conducted through a rapid and specialized conduction system. The earliest activation occurs in the left ventricular (LV) septal endocardium and the latest in the epicardium of the LV lateral wall.[2] This conduction pattern can be disrupted by a diseased conducting branch or iatrogenically when a ventricle is electrically stimulated at a single site. Cardiac dyssynchrony is complex and multifactorial. Prolongation of the atrioventricular (AV) interval delays systolic contraction, which might then encroach on early diastolic filling.[3] A delay in LV contraction can cause diastolic mitral regurgitation, loss of ventricular preload and a reduction in LV contractility, due to the loss of the Starling mechanism. Additionally both inter- and intraventricular conduction delays lead to asynchronous contraction of LV wall regions (ventricular dyssynchrony). In this case, the time required for activation of the entire ventricular muscle, as expressed by QRS duration, is significantly prolonged. Consequently, cardiac efficiency may be impaired, poorly coordinated papillary muscle function may cause or aggravate functional systolic mitral regurgitation, and stroke volume and systolic blood pressure may be reduced. Impaired performance can promote adverse LV remodeling.[4,5] In light of the considerable mechanical differences between regions, it is not surprising that during asynchronous activation myocardial blood flow,[6-10] oxygen consumption,[11] and glucose uptake also differ between these regions.[6] Myocardial

blood flow and oxygen consumption are 30% higher in late-activated than in early-activated regions.[5,8,9] In agreement with the aforementioned thoughts, asynchronous ventricles require more oxygen to generate the same amount of mechanical work, i.e. they have a lower efficiency.

Regional molecular changes in dyssynchronous heart failure

According to a study by Chakir et al,[12] the lateral wall of dyssynchronous, failing left ventricles exhibited an increase in p38 MAPK and Ca^{++}-calmodulin kinase II activation and increased tumor necrosis factor-α expression, which were both reversed by CRT. Additionally, dyssynchronous heart failure (DsHF) is characterized by regional heterogeneities in cellular and tissue electrophysiological properties. The hallmark of cells and tissues isolated from failing hearts, independent of the etiology, is action potential prolongation,[13-16] which is most prominent in cells isolated from the late-activated lateral LV wall.[17] Prolongation of the action potential duration and slowed conduction velocity are common results of channel abnormalities that are observed in DsHF, and may lead to ventricular arrhythmias.[13-15] CRT significantly shortens the action potential in lateral myocytes, reduces LV regional heterogeneity in action potential duration, and decreases the risk of fatal ventricular arrhythmias.[18-21] Although some concerns have been raised that epicardial stimulation used by standard CRT may be proarrhythmic,[22] in practice CRT seems to be antiarrhythmic.[23] Myocyte calcium handling is also abnormal in DsHF. Sarcomere shortening in the dyssynchronous failing heart declines, contraction and relaxation kinetics are slowed, and both are coupled to reductions in whole-cell calcium transient amplitude and delayed dynamics.[24-27] Specific repolarizing potassium currents (the inward rectifier K+ current [*I*K1], transient outward K+ current [*I*to], and delayed rectifier K+ current [*I*K]) decline in DsHF,[16] concordant with a decline in protein expression for the corresponding channel proteins (Kir 2.1, Kv4.3 and KChIP2, and KvLQT1, respectively). CRT partially reverses changes in *I*K1, *I*K (but not *I*to), and their related proteins. CRT also reverses the increased late sodium current (*I*Na-L) observed in DsHF. CRT-responsive patients display an enhanced cardiac responsiveness to sympathetic stimulation.[28,29] Acutely, CRT blunts efferent sympathetic tone, which is often elevated in patients with HF,[30] and chronically CRT results in upregulation of β1-adrenergic receptor gene expression in responsive patients.[31] Antiapoptotic effects of resynchronization have been observed in canine[11] and pig models.[32] HF is often considered to be a disease involving energy starvation.[33,34] Mitochondrial basal oxygen consumption is increased in canine DsHF,[35] but is accompanied by a decline in ATPase activity.[36] CRT increases the mitochondrial respiratory control ratio, an index of ATP synthetic capacity to levels similar to those in healthy controls.[34]

Definition of left bundle branch block

In normal conduction, activation begins within the LV and right ventricular (RV) endocardium. In complete left bundle branch block (LBBB), activation only begins in the right ventricle and must proceed through the septum for 40-50 ms before reaching the LV endocardium. It then requires another 50 ms for reentry into the LV Purkinje network and to propagate to the endocardium of the posterolateral wall, and then another 50 ms to activate the posterolateral wall.[37] This produces a total QRS duration of ≥140 ms.[38] Any increase in septal or posterolateral wall thickness or LV endocardial surface area further increases QRS duration. The key LBBB QRS morphology feature is the mid-QRS notching that occurs at 50 and 90 ms, with slurring in between. The first notch represents the time when the electrical depolarization wavefront reaches the endocardium of the LV (after proceeding through the septum). The second notch occurs when the depolarization wavefront begins to reach the epicardium of the posterolateral wall. These notches are best seen in leads I, aVL, V_1, V_2, V_5, and V_6. Conventional criteria for LBBB that are used clinically include a QRS duration ≥120 ms, QS or rS in lead V_1, and a monophasic R wave with no Q waves in leads V_6 and I.[39] The American Heart Association, American College of Cardiology Foundation, and Heart Rhythm Society recommendations go beyond this to include a "broad notched or slurred R wave in leads I, aVL, V_5 and V_6, and an occasional RS pattern in V_5 and V_6 attributed to displaced transition of the QRS complex".[40] In the presence of QRS prolongation due to right bundle branch block (RBBB) or left ventricular hypertrophy (LVH), the LV endocardium is activated normally via the rapidly conducting Purkinje system.[41] The major randomized clinical trials[42,43] that led to the widespread adoption of CRT used a prolonged QRS duration ≥120 ms, but did not select patients on the basis of QRS morpholo-

gy, which can usually determine the cause of the prolonged ventricular depolarization. Approximately one third of these patients did not have LBBB. On top of that, one-third of patients diagnosed with LBBB by conventional electrocardiographic criteria may not have true complete LBBB, but are likely to have a combination of LV hypertrophy and left anterior fascicular block. Additionally, a pooled analysis of smaller trials found no significant improvement in the LV ejection fraction or maximal oxygen consumption in patients with RBBB.[44]

The importance of left bundle branch block

Approximately one third of patients with HF present with conduction disturbances that result in a QRS >120 ms. Most commonly (in approximately 25% of HF patients), this is exhibited as an LBBB pattern.[45] This percentage is significantly higher than the estimated 1.5% prevalence of LBBB in the general patient population.[46] LBBB appears to be irreversible despite pharmacological treatment, but can be mitigated by CRT in patients with moderate to severe HF and deteriorated LV systolic function. The anatomical basis behind this concept relates to the model of the helical ventricular myocardial band described by Torrent-Guasp,[47] whereby the heart is formed by a wrap around the left and right ventricle (the wrap is called the basal loop and is composed of transverse fibers) and an internal helix composed of oblique fibers called the descending and ascending fibers of the apical loop as it forms a vortex at the ventricular apex. The sequential contraction of these fibers fully explains the normal motions of narrowing, shortening, lengthening, widening, twisting and uncoiling.[48] In a dilated, failing heart, the stretched helical fibers develop a more transverse orientation, which closely resembles the angulation of the circumferential fibers of the basal loop.[49] In a failing heart with LBBB, an asynchronous beat will cause a bulging of the septum because of the asynchronous contraction of LV wall regions. Resynchronization geometrically restores the midline septum position to counteract tethering and offset MR, but does not reestablish physiological septal twisting or longitudinal strain.[50]

Pathophysiology and indications of CRT

CRT is predominantly employed to resynchronize ventricles. Conceptually, resynchronization can be achieved by creating more than one wavefront of activation. The most common approach is to use biventricular pacing to create two activation wavefronts, preferably originating from opposite walls, in order to create a more synchronous activation. Because of the tight excitation–contraction coupling in the heart, the more synchronous activation is expected to and indeed does create a more synchronous and more coordinated contraction. A similar, and sometimes better, effect can be achieved when using LV pacing at an AV-delay that allows fusion of the wavefront originating from the RBB and from the LV pacing site.[51] While biventricular pacing clearly resynchronizes asynchronous hearts, it may worsen the synchrony and sequence of activation in hearts without conduction block.[52] De Boeck et al demonstrated that CRT does not change the total amount of systolic deformation, but redistributes shortening from the LV lateral wall to the septum and decreases systolic stretch, mainly in the septum.[53] In desynchronized ventricles, systolic shortening is highly polarized between the interventricular septum and the LV free wall, with the LV free wall demonstrating a greater amount of local shortening during systole. Furthermore, the twisting action of the LV disappears in rhythm interruption from wide QRS or LBBB.[54] CRT homogenizes the distribution of systolic shortening ("recoordination") by strongly increasing shortening in the septal segments and slightly decreasing shortening in lateral and posterior LV wall segments.[40] Further improvement in pump function is possibly mediated by reduction of mitral regurgitation[55] and prolongation of diastolic filling time. These beneficial effects occur almost immediately after the start of resynchronization,[38,41] but also translate to long-term effects such as reverse remodeling, as well as better clinical outcomes, including better survival.[56] Ventricular pacing returns the septum to a midline location to create a shortened, rigid central curtain with movement of the papillary muscles to a normal position, but does not restore the natural septal twisting motion.[57,58] CRT restores the compromised energy metabolism.[59,60] The improved cardiac efficiency achieved by CRT is unlikely to be due to alterations in intrinsic myocyte function. Rather, most of the net effect is observed at the chamber level because of the more coordinated contraction in different regions of the LV wall. Based on current criteria,[61] only a small proportion of patients with HF (perhaps 5-10%) are indicated for CRT, but this is still a large number of patients. The indications for CRT, according to the current ESC guidelines, are as follows:[62]

Patients in sinus rhythm

1. LBBB with QRS duration >150 ms. CRT is recommended in chronic HF patients and LVEF≤35% who remain in NYHA functional class II, III and ambulatory IV despite adequate medical treatment (IA).
2. LBBB with QRS duration 120-150 ms. CRT is recommended in chronic HF patients with LVEF≤35% who remain in NYHA functional class II, III and ambulatory IV despite adequate medical treatment (IB).
3. Non-LBBB with QRS duration >150 ms. CRT should be considered in chronic HF patients and LVEF≤35% who remain in NYHA functional class II, III and ambulatory IV despite adequate medical treatment. (IIaB).
4. Non-LBBB with QRS duration 120-150 ms. CRT may be considered in chronic HF patients and LVEF≤35% who remain in NYHA functional class II, III and ambulatory IV despite adequate medical treatment (IIbB).
5. CRT *is not recommended* in chronic HF patients with QRS duration <120 ms (IIIB).

Patients with permanent atrial fibrillation

1A. Patients with HF, wide QRS and reduced LVEF. CRT should be considered in chronic HF patients with intrinsic QRS≥120 ms and LVEF≤35% who remain in NYHA functional class III and ambulatory IV despite adequate medical treatment, provided that biventricular pacing as close to 100% as possible can be achieved (IIaB).

1B. AV junction ablation should be *added* in case of incomplete biventricular pacing (IIaB).

2. Patients with uncontrolled heart rate who are candidates for AV junction ablation. CRT should be considered in patients with reduced LVEF who are candidates for AV junction ablation for rate control (IIaB).

Patients with conventional pacemaker indications

1. Upgrade from conventional pacemaker or implantable cardioverter defibrillator (ICD). CRT is indicated in HF patients with LVEF <35% and a high percentage of ventricular pacing who remain in NYHA class III and ambulatory IV despite adequate medical treatment.[63] (IB).
2. *De novo* cardiac resynchronization therapy. CRT should be considered in HF patients with reduced EF and an expected high percentage of ventricular pacing in order to decrease the risk of worsening HF (IIaB).

Additionally, in a systematic review of 5 randomized clinical trials involving >4000 patients with asymptomatic or mildly symptomatic HF (NYHA functional class I/II), reduced EF, and wide QRS complex (RAFT, MADIT-CRT, REVERSE, MIRACLE ICD II, CONTAK CD), CRT was associated with a 19% reduction in mortality and a 32% reduction in HF events or hospitalization in comparison with ICD therapy alone. Further, CRT was associated with a significant improvement in LV dimensions, volume, and LVEF.[64]

How much resynchronization?

The term "Cardiac Resynchronization Therapy" for biventricular pacing assumes that restoration of synchrony between left and right ventricles and/or between the walls of the LV is the mechanism of benefit. However, it is far from clear whether the beneficial effects of CRT are the result of the inter/intraventricular resynchronization or of the shortening of the long intrinsic AV interval, very commonly present in these patients—or indeed a varying combination of the two.[65] A prolonged AV interval allows pre-systolic mitral and tricuspid regurgitation to take place, which means that the net forward flow across those valves is smaller than it might otherwise be, and causes fusion of the E and A waves, reducing left ventricular filling time and thus cardiac output.[66-68] A wide QRS prolongs isovolumic contraction time (IVCT) and isovolumic relaxation time (IVRT) by impairing the rate of rise and fall of pressure in the ventricle.[69] Long IVCT and IVRT prolong the potential for mitral regurgitation to occur while blood is not being ejected forward. CRT can both shorten AV delay and reduce any ventricular dyssynchrony.[70,71] Until recently, the importance of the biventricular-pacing percentage and the need to maximize it had never been emphasized. The first study stressing this point was published in 2006,[72] using an arbitrary cut-off rate of biventricular pacing of 85% of the pacing time needed to define CRT as effective in patients with atrial fibrillation. In the following years, Koplan et al,[73] in a large retrospective analysis of more than 1800 patients, found that the greatest magnitude of reduction in heart failure hospitalization and all-cause mortality was observed with a biventricu-

lar pacing cutoff of 92%. This striking evidence was confirmed and even amplified by the work of Hayes et al.[74] The novel finding was that the greatest magnitude of reduction in mortality was observed with a biventricular pacing cutoff more than 98%. Biventricular capture was the single most important variable predicting improvement after CRT, reducing heart failure hospitalizations and, most importantly, increasing survival. Atrial fibrillation patients with a biventricular pacing percentage more than 98.5% presented a survival rate equivalent to that of their counterparts in normal sinus rhythm. Theoretically (and even more practically), CRT requires the biventricular pacing percentage to be as close to 100% as possible. Effective delivery of continuous CRT may be hindered by the presence of native ventricular conduction, due to long AV delay programming, atrial tachycardia or atrial fibrillation.

Lead placement and pacing considerations

CRT is administered using a pacemaker, called a CRT-P, or an ICD with bradycardia pacing capabilities, called a CRT-D. The Dual Chamber and VVI Implantable (DAVID) trial[75] and a subanalysis of the Multicenter Automatic Defibrillator Trial II (MADIT II)[76] have provided strong evidence for the negative effects of RV pacing in patients with reduced baseline LVEF. RV pacing greater than 40-50% is associated with adverse clinical outcomes.[77] The purpose of RV non-apical pacing is to take advantage of the specialized conduction system and thereby reduce ventricular dyssynchrony. Three main anatomical sites have been evaluated: the RV outflow tract (RVOT), the intraventricular septum (IVS), and the His bundle. Overall, evidence from several studies suggests that dyssynchrony is reduced and that LVEF is improved with RVOT,[78] IVS,[79] and His bundle[80] pacing, although negative results have also been reported.[81] There are several pacemaker algorithms that permit prolonged AV intervals, all potentially capable of reducing RV pacing, and they can be divided into two large groups: (1) algorithms that periodically prolong the AV interval to search for, and if present, allow intrinsic AV conduction (AV hysteresis); and (2) algorithms that operate in a primary atrial pacing mode, with mode switch to secondary mode ventricular pacing (DDD) in case of significant loss of AV conduction.[82,83] Non-response to CRT remains a significant problem in up to 30% of patients. One issue that has been shown to contribute to a lack of response to CRT is inadequate LV lead location. Current strategies involve the placement of leads "anatomically", rather than using more patient-specific physiological approaches, and the site of LV lead placement remains controversial, with the final position of the LV pacing lead dictated by the cardiac venous system anatomy, the performance and stability of the pacing lead, and the absence of phrenic nerve stimulation. General wisdom continues to be that in patients with non-ischemic heart failure, a lateral LV lead position is reasonable, while in those with ischemic etiology, knowledge of LV viability and contraction patterns helps optimize LV lead position. In an effort to improve CRT response, alternative methods of CRT delivery, including LV endocardial and epicardial multisite pacing (MSP), have been developed.[84,85] There has long been interest in LV endocardial pacing as a method theoretically advantageous to coronary sinus epicardial lead positioning for CRT.[86] Initial concerns were raised in relation to the potential for thromboembolic events in patients with hardware placed in the systemic circulation. The majority of the experience with LV endocardial lead positioning has involved the transseptal approach.[87] Apical lead positioning has also been accomplished.[88] The concept of MSP using multiple leads is based on the hypothesis that pacing at multiple points within the ventricles will improve cardiac resynchronization. Two different pacing modalities have been proposed using multiple leads: the first using two RV leads and one LV lead; the second using one RV lead and two LV leads inserted in the two separate tributaries of the coronary sinus. A non-contact mapping study of the underlying myocardial substrate in patients receiving CRT[89] showed that the majority of patients with a non-ischemic heart failure etiology or functional block responded to conventional single-site CRT, whereas those with myocardial scar or the absence of functional block often required MSP to achieve a CRT response. Studies[90,91] have shown that bifocal RV and LV pacing were superior to biventricular pacing in acutely improving mechanical dyssynchrony. The advantage of this concept is that implantation of two RV leads may be technically easier than two LV leads; however, this pacing configuration has yet to be evaluated chronically in a prospective randomized trial. The feasibility of chronic implantation of two leads into the coronary sinus has been demonstrated, with a success rate of 85-95% and encouraging mid-term follow-up results.[92,93] MSP with multiple pacing leads (dual-vein LV pacing) could be a

potential solution for patients who do not respond to conventional CRT. Although attractive from a pathophysiological view, dual-vein MSP to achieve CRT is hindered by several clinical and technical issues.[94-96] The alternative approach to delivering MSP, rather than via multiple leads, is using a multipolar lead capable of stimulating multiple LV stimulation sites. Quadripolar leads to pace the LV can now deliver resynchronization therapy, with the first report of human use in 2010.[97] Implant success rates have been above 95% and mid-term data confirm that quadripolar leads offer good stability with satisfactory dislodgement rates (≤3%) and stable performance in terms of pacing threshold.[98-100]

Predictors of responsiveness

Imaging modalities

Correction of LV dyssynchrony is thought to be the main therapeutic effect of CRT. Several imaging techniques have been used to quantify mechanical dyssynchrony and predict the CRT response: these imaging techniques include M-mode echocardiography, tissue Doppler imaging, strain imaging, 3-dimensional echocardiography, magnetic resonance imaging (MRI), and nuclear cardiology. In addition to the technical difficulty and increased cost associated with the use of these imaging techniques, the accuracy of such modalities in predicting CRT is questionable. The PROSPECT study demonstrated that the 12 different echocardiographic dyssynchrony markers that were tested were unable to distinguish responders from non-responders to a degree that might influence clinical decision making.[101-103] Nuclear imaging with single photon emission computed tomography and MRI are other modalities that have been used in the assessment of LV mechanical dyssynchrony.[104] An additional advantage of both techniques is their ability to assess the presence and location of LV transmural scar, which may influence LV lead positioning. Large-scale clinical trials are needed to evaluate the role of such modalities in predicting the long-term response to CRT.[105-107]

The role of the ECG

A prolonged QRS duration (≥120 ms) measured on the standard 12-lead ECG is the most commonly used parameter in clinical practice to identify eligible candidates for CRT.[108] The RethinQ study showed no benefit in 172 patients with QRS duration <130 ms and mechanical dyssynchrony randomized to CRT-D against the control group. Furthermore, at six months there was no difference in peak VO_2, 6-minute walk test, LV reverse remodeling, or quality of life score between the treatment and control groups.[109-111] The presence of typical LBBB morphology is a strong predictor of response compared with RBBB morphology and nonspecific intraventricular conduction delay (IVCD).[112] Unlike LBBB, ventricular activation is not largely affected in RBBB. Therefore, from the theoretical perspective, CRT is not expected to be effective in this subgroup of patients.[113] A meta-analysis of 5356 patients included in the major CRT trials (COMPANION, CARE-HF, MADIT-CRT, and RAFT) showed no benefit from CRT in patients with RBBB (RR: 0.91; 95% CI: 0.69-1.20; p=0.49) or nonspecific IVCD (RR: 1.19; 95% CI: 0.87–1.63; p=0.28).[114]

Conclusion

CRT confers a mortality benefit, reduces HF hospitalizations, and improves functional outcome in the HF population, but not all patients consistently demonstrate a positive CRT response. Non-response to CRT remains a significant problem in up to 30% of patients, despite the multiple mechanisms that have been proposed to explain the regional changes in a dyssynchronous ventricle. MSP has been used to improve the CRT response. The ECG remains the strongest predictor of clinical response compared with other imaging modalities. Large-scale clinical trials are needed to evaluate the best modality for predicting the long-term response to CRT.

References

1. Daubert JC, Saxon L, Adamson PB, et al. 2012 EHRA/HRS expert consensus statement on cardiac resynchronization therapy in heart failure: implant and follow-up recommendations and management. Europace. 2012; 14: 1236-1286.
2. Durrer D, van Dam RT, Freud GE, Janse MJ, Meijler FL, Arzbaecher RC. Total excitation of the isolated human heart. Circulation. 1970; 41: 899-912.
3. Barold SS, Ilercil A, Herweg B. Echocardiographic optimization of the atrioventricular and interventricular intervals during cardiac resynchronization. Europace. 2008; 10 Suppl 3: iii88-95.
4. Burkhoff D, Oikawa RY, Sagawa K. Influence of pacing site on canine left ventricular contraction. Am J Physiol. 1986; 251: H428-435.
5. Park RC, Little WC, O'Rourke RA. Effect of alteration of

left ventricular activation sequence on the left ventricular end-systolic pressure-volume relation in closed-chest dogs. Circ Res. 1985; 57: 706-717.
6. Delhaas T, Arts T, Prinzen FW, Reneman RS. Regional fibre stress-fibre strain area as estimate of regional oxygen demand in the canine heart. J Physiol. 1994; 477 (Pt 3): 481-496.
7. Nowak B, Sinha AM, Schaefer WM, et al. Cardiac resynchronization therapy homogenizes myocardial glucose metabolism and perfusion in dilated cardiomyopathy and left bundle branch block. J Am Coll Cardiol. 2003; 41: 1523-1528.
8. Prinzen FW, Augustijn CH, Arts T, Allessie MA, Reneman RS. Redistribution of myocardial fiber strain and blood flow by asynchronous activation. Am J Physiol. 1990; 259: H300-308.
9. Van Oosterhout MFM, Arts T, Bassingthwaighte JB, Reneman RS, Prinzen FW. Relation between local myocardial growth and blood flow during chronic ventricular pacing. Cardiovasc Res. 2002; 53: 831-840.
10. Vernooy K, Verbeek XA, Peschar M, et al. Left bundle branch block induces ventricular remodelling and functional septal hypoperfusion. Eur Heart J. 2005; 26: 91-98.
11. Lindner O, Vogt J, Kammeier A, et al. Effect of cardiac resynchronization therapy on global and regional oxygen consumption and myocardial blood flow in patients with non-ischaemic and ischaemic cardiomyopathy. Eur Heart J. 2005; 26: 70-76.
12. Chakir K, Daya SK, Tunin RS, et al. Reversal of global apoptosis and regional stress kinase activation by cardiac resynchronization. Circulation. 2008; 117: 1369-1377.
13. Akar FG, Rosenbaum DS. Transmural electrophysiological heterogeneities underlying arrhythmogenesis in heart failure. Circ Res. 2003; 93: 638-645.
14. Beuckelmann DJ, Näbauer M, Erdmann E. Alterations of K+ currents in isolated human ventricular myocytes from patients with terminal heart failure. Circ Res. 1993; 73: 379-385.
15. Tsuji Y, Zicha S, Qi XY, Kodama I, Nattel S. Potassium channel subunit remodeling in rabbits exposed to long-term bradycardia or tachycardia: discrete arrhythmogenic consequences related to differential delayed-rectifier changes. Circulation. 2006; 113: 345-355.
16. Nattel S, Maguy A, Le Bouter S, Yeh YH. Arrhythmogenic ion-channel remodeling in the heart: heart failure, myocardial infarction, and atrial fibrillation. Physiol Rev. 2007; 87: 425-456.
17. Aiba T, Hesketh GG, Barth AS, et al. Electrophysiological consequences of dyssynchronous heart failure and its restoration by resynchronization therapy. Circulation. 2009; 119: 1220-1230.
18. Higgins SL, Yong P, Sheck D, et al. Biventricular pacing diminishes the need for implantable cardioverter defibrillator therapy. Ventak CHF Investigators. J Am Coll Cardiol. 2000; 36: 824-827.
19. Cleland JG, Daubert JC, Erdmann E, et al. Longer-term effects of cardiac resynchronization therapy on mortality in heart failure [the CArdiac REsynchronization-Heart Failure (CARE-HF) trial extension phase]. Eur Heart J. 2006; 27: 1928-1932.
20. Di Biase L, Gasparini M, Lunati M, et al; InSync/InSync ICD Italian Registry Investigators. Antiarrhythmic effect of reverse ventricular remodeling induced by cardiac resynchronization therapy: the InSync ICD (Implantable Cardioverter-Defibrillator) Italian Registry. J Am Coll Cardiol. 2008; 52: 1442-1449.
21. Markowitz SM, Lewen JM, Wiggenhorn CJ, et al. Relationship of reverse anatomical remodeling and ventricular arrhythmias after cardiac resynchronization. J Cardiovasc Electrophysiol. 2009; 20: 293-298.
22. Fish JM, Brugada J, Antzelevitch C. Potential proarrhythmic effects of biventricular pacing. J Am Coll Cardiol. 2005; 46: 2340-2347.
23. Kutyifa V, Zareba W, McNitt S, et al. Left ventricular lead location and the risk of ventricular arrhythmias in the MADIT-CRT trial. Eur Heart J. 2013; 34: 184-190.
24. Chakir K, Daya SK, Aiba T, et al. Mechanisms of enhanced beta-adrenergic reserve from cardiac resynchronization therapy. Circulation. 2009; 119: 1231-1240.
25. Nishijima Y, Sridhar A, Viatchenko-Karpinski S, et al. Chronic cardiac resynchronization therapy and reverse ventricular remodeling in a model of nonischemic cardiomyopathy. Life Sci. 2007; 81: 1152-1159.
26. Chakir K, Depry C, Dimaano VL, et al. Galphas-biased beta2-adrenergic receptor signaling from restoring synchronous contraction in the failing heart. Sci Transl Med. 2011; 3: 100ra88.
27. Sachse FB, Torres NS, Savio-Galimberti E, et al. Subcellular structures and function of myocytes impaired during heart failure are restored by cardiac resynchronization therapy. Circ Res. 2012; 110: 588-597.
28. Najem B, Unger P, Preumont N, et al. Sympathetic control after cardiac resynchronization therapy: responders versus nonresponders. Am J Physiol Heart Circ Physiol. 2006; 291: H2647-2652.
29. Cha YM, Chareonthaitawee P, Dong YX, et al. Cardiac sympathetic reserve and response to cardiac resynchronization therapy. Circ Heart Fail. 2011; 4: 339-344.
30. Hamdan MH, Zagrodzky JD, Joglar JA, et al. Biventricular pacing decreases sympathetic activity compared with right ventricular pacing in patients with depressed ejection fraction. Circulation. 2000; 102: 1027-1032.
31. Vanderheyden M, Mullens W, Delrue L, et al. Endomyocardial upregulation of beta1 adrenoreceptor gene expression and myocardial contractile reserve following cardiac resynchronization therapy. J Card Fail. 2008; 14: 172-178.
32. Klug D, Boule S, Wissocque L, et al. Right ventricular pacing with mechanical dyssynchrony causes apoptosis interruptus and calcium mishandling. Can J Cardiol. 2013; 29: 510-518.
33. Neubauer S. The failing heart—an engine out of fuel. N Engl J Med. 2007; 356: 1140-1151.
34. Gupta A, Akki A, Wang Y, et al. Creatine kinase-mediated improvement of function in failing mouse hearts provides causal evidence the failing heart is energy starved. J Clin Invest. 2012; 122: 291-302.
35. Agnetti G, Kaludercic N, Kane LA, et al. Modulation of mitochondrial proteome and improved mitochondrial function by biventricular pacing of dyssynchronous failing hearts. Circ Cardiovasc Genet. 2010; 3: 78-87.
36. Wang SB, Foster DB, Rucker J, O'Rourke B, Kass DA, Van Eyk JE. Redox regulation of mitochondrial ATP synthase: implications for cardiac resynchronization therapy. Circ Res. 2011; 109: 750-757.
37. Grant RP, Dodge HT. Mechanisms of QRS complex prolongation in man; left ventricular conduction disturbances. Am J Med. 1956; 20: 834-852.
38. Selvester RHS, Solomon JC. Computer simulation of ventricular depolarization, QRS duration and quantification of wall thickness. In: Willems JL, Van Bemmel JH, Zywietz C, eds. Computer ECG Analysis: Toward Standardization. Am-

sterdam, The Netherlands: North Holland; 1986: pp 221-272.
39. Wagner GS. Marriott's Practical Electrocardiograpy. Philadelphia, Pennsylvania: Lippincott Williams & Wilkins, 2008.
40. Surawicz B, Childers R, Deal BJ, et al. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part III: intraventricular conduction disturbances: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society. Endorsed by the International Society for Computerized Electrocardiology. J Am Coll Cardiol. 2009; 53: 976-981.
41. Strauss DG, Selvester RH. The QRS complex—a biomarker that "images" the heart: QRS scores to quantify myocardial scar in the presence of normal and abnormal ventricular conduction. J Electrocardiol. 2009; 42: 85-96.
42. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med. 2004; 350: 2140-2150.
43. Cleland JG, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med. 2005; 352: 1539-1549.
44. 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.
45. Baldasseroni S, Opasich C, Gorini M, et al. Left bundle-branch block is associated with increased 1-year sudden and total mortality rate in 5517 outpatients with congestive heart failure: a report from the Italian network on congestive heart failure. Am Heart J. 2002; 143: 398-405.
46. Eriksson P, Hansson PO, Eriksson H, Dellborg M. Bundle-branch block in a general male population: the study of men born 1913. Circulation. 1998; 98: 2494-2500.
47. Torrent-Guasp F, Ballester M, Buckberg GD, et al. Spatial orientation of the ventricular muscle band: physiologic contribution and surgical implications. J Thorac Cardiovasc Surg. 2001; 122: 389-392.
48. Buckberg G, Hoffman JI, Mahajan A, Saleh S, Coghlan C. Cardiac mechanics revisited: the relationship of cardiac architecture to ventricular function. Circulation. 2008; 118: 2571-2587.
49. Buckberg G. Ventricular structure and surgical history. Heart Fail Rev. 2004; 9: 255-268.
50. Sade LE, Demir O, Atar I, Müderrisoglu H, Ozin B. Effect of mechanical dyssynchrony and cardiac resynchronization therapy on left ventricular rotational mechanics. Am J Cardiol. 2008; 101: 1163-1169.
51. Verbeek XA, Auricchio A, Yu Y, et al. Tailoring cardiac resynchronization therapy using interventricular asynchrony. Validation of a simple model. Am J Physiol Heart Circ Physiol. 2006; 290: H968-977.
52. Auricchio A, Stellbrink C, Block M, et al. Effect of pacing chamber and atrioventricular delay on acute systolic function of paced patients with congestive heart failure. The Pacing Therapies for Congestive Heart Failure Study Group. The Guidant Congestive Heart Failure Research Group. Circulation. 1999; 99: 2993-3001.
53. De Boeck BW, Teske AJ, Meine M, et al. Septal rebound stretch reflects the functional substrate to cardiac resynchronization therapy and predicts volumetric and neurohormonal response. Eur J Heart Fail. 2009; 11: 863-871.
54. Saleh S, Liakopoulos OJ, Buckberg GD. The septal motor of biventricular function. Eur J Cardiothorac Surg. 2006; 29 Suppl 1: S126-138.
55. Breithardt OA, Sinha AM, Schwammenthal E, et al. Acute effects of cardiac resynchronization therapy on functional mitral regurgitation in advanced systolic heart failure. J Am Coll Cardiol. 2003; 41: 765-770.
56. Brokalaki H, Patelarou E, Giakoumidakis K, et al. Translation and validation of the Greek "Minnesota Living with Heart Failure" questionnaire. Hellenic J Cardiol. 2015; 56: 10-19.
57. Suga H, Hayashi T, Suehiro S, Hisano R, Shirahata M, Ninomiya I. Equal oxygen consumption rates of isovolumic and ejecting contractions with equal systolic pressure-volume areas in canine left ventricle. Circ Res. 1981; 49: 1082-1091.
58. Suga H, Igarashi Y, Yamada O, Goto Y. Mechanical efficiency of the left ventricle as a function of preload, afterload, and contractility. Heart Vessels. 1985; 1: 3-8.
59. De Sousa E, Veksler V, Minajeva A, et al. Subcellular creatine kinase alterations. Implications in heart failure. Circ Res. 1999; 85: 68-76.
60. Hasenfuss G, Holubarsch C, Heiss HW, et al. Myocardial energetics in patients with dilated cardiomyopathy. Influence of nitroprusside and enoximone. Circulation. 1989; 80: 51-64.
61. Dickstein K, Vardas PE, Auricchio A, et al. 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 J Heart Fail. 2010; 12: 1143-1153.
62. Brignole M, Auricchio A, Baron-Esquivias G, et al. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). Eur Heart J. 2013; 34: 2281-2329.
63. Sideris S, Poulidakis E, Aggeli C, et al. Upgrading pacemaker to cardiac resynchronization therapy: an option for patients with chronic right ventricular pacing and heart failure. Hellenic J Cardiol. 2014; 55: 17-23.
64. Adabag S, Roukoz H, Anand IS, Moss AJ. Cardiac resynchronization therapy in patients with minimal heart failure: a systematic review and meta-analysis. J Am Coll Cardiol. 2011; 58: 935-941.
65. Salo RW, Auricchio A. Topic review: mechanisms of benefit in pacing of patients in heart failure. Herzschrittmachertherapie und Elektrophysiologie 2003; 10: 16-22.
66. Rutishauser W, Wirz P, Gander M, Lüthy E. Atriogenic diastolic reflux in patients with atrioventricular block. Circulation. 1966; 34: 807-817.
67. Rokey R, Murphy DJ Jr, Nielsen AP, Abinader EG, Huhta JC, Quinones MA. Detection of diastolic atrioventricular valvular regurgitation by pulsed Doppler echocardiography and its association with complete heart block. Am J Cardiol. 1986; 57: 692-694.
68. Panidis IP, Ross J, Munley B, Nestico P, Mintz GS. Diastolic mitral regurgitation in patients with atrioventricular conduction abnormalities: a common finding by Doppler echocardiography. J Am Coll Cardiol. 1986; 7: 768-774.
69. Xiao HB, Lee CH, Gibson DG. Effect of left bundle branch

block on diastolic function in dilated cardiomyopathy. Br Heart J. 1991; 66: 443-447.
70. Xiao HB, Brecker SJ, Gibson DG. Effects of abnormal activation on the time course of the left ventricular pressure pulse in dilated cardiomyopathy. Br Heart J. 1992; 68: 403-407.
71. Xiao HB, Roy C, Gibson DG. Nature of ventricular activation in patients with dilated cardiomyopathy: evidence for bilateral bundle branch block. Br Heart J. 1994; 72: 167-174.
72. Gasparini M, Auricchio A, Metra M, et al; Multicentre Longitudinal Observational Study (MILOS) Group. Long-term survival in patients undergoing cardiac resynchronization therapy: the importance of performing atrio-ventricular junction ablation in patients with permanent atrial fibrillation. Eur Heart J. 2008; 29: 1644-1652.
73. Koplan BA, Kaplan AJ, Weiner S, Jones PW, Seth M, Christman SA. Heart failure decompensation and all-cause mortality in relation to percent biventricular pacing in patients with heart failure: is a goal of 100% biventricular pacing necessary? J Am Coll Cardiol. 2009; 53: 355-360.
74. Hayes DL, Boehmer JP, Day JD, et al. Cardiac resynchronization therapy and the relationship of percent biventricular pacing to symptoms and survival. Heart Rhythm. 2011; 8: 1469-1475.
75. Wilkoff BL, Cook JR, Epstein AE, et al. 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.
76. Steinberg JS, Fischer A, Wang P, et al. The clinical implications of cumulative right ventricular pacing in the multicenter automatic defibrillator trial II. J Cardiovasc Electrophysiol. 2005; 16: 359-365.
77. Sharma AD, Rizo-Patron C, Hallstrom AP, et al. Percent right ventricular pacing predicts outcomes in the DAVID trial. Heart Rhythm. 2005; 2: 830-834.
78. Leong DP, Mitchell AM, Salna I, et al. Long-term mechanical consequences of permanent right ventricular pacing: effect of pacing site. J Cardiovasc Electrophysiol. 2010; 21: 1120-1126.
79. Cano O, Osca J, Sancho-Tello MJ, et al. Comparison of effectiveness of right ventricular septal pacing versus right ventricular apical pacing. Am J Cardiol. 2010; 105: 1426-1432.
80. Catanzariti D, Maines M, Cemin C, Broso G, Marotta T, Vergara G. Permanent direct his bundle pacing does not induce ventricular dyssynchrony unlike conventional right ventricular apical pacing. An intrapatient acute comparison study. J Interv Card Electrophysiol. 2006; 16: 81-92.
81. Stambler BS, Ellenbogen K, Zhang X, et al. Right ventricular outflow versus apical pacing in pacemaker patients with congestive heart failure and atrial fibrillation. J Cardiovasc Electrophysiol. 2003; 14: 1180-1186.
82. Murakami Y, Tsuboi N, Inden Y, et al. Difference in percentage of ventricular pacing between two algorithms for minimizing ventricular pacing: results of the IDEAL RVP (Identify the Best Algorithm for Reducing Unnecessary Right Ventricular Pacing) study. Europace. 2010; 12: 96-102.
83. Sweeney MO, Ellenbogen KA, Casavant D, et al. Multicenter, prospective, randomized safety and efficacy study of a new atrial-based managed ventricular pacing mode (MVP) in dual chamber ICDs. J Cardiovasc Electrophysiol. 2005; 16: 811-817.
84. Ginks MR, Lambiase PD, Duckett SG, et al. A simultaneous X-Ray/MRI and noncontact mapping study of the acute hemodynamic effect of left ventricular endocardial and epicardial cardiac resynchronization therapy in humans. Circ Heart Fail. 2011; 4: 170-179.
85. Duckett SG, Ginks M, Shetty A, et al. Invasive acute hemodynamic response to guide LV lead implantation predicts chronic remodeling in patients undergoing cardiac resynchronization therapy. J Am Coll Cardiol 2011; 58: 1128-1136.
86. Bordachar P, Derval N, Ploux S, et al. Left ventricular endocardial stimulation for severe heart failure. J Am Coll Cardiol. 2010; 56: 747-753.
87. 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.
88. 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.
89. Ginks MR, Shetty AK, Lambiase PD, et al. Benefits of endocardial and multisite pacing are dependent on the type of left ventricular electric activation pattern and presence of ischemic heart disease: insights from electroanatomic mapping. Circ Arrhythm Electrophysiol. 2012; 5: 889-897.
90. Yoshida K, Seo Y, Yamasaki H, et al. Effect of triangle ventricular pacing on haemodynamics and dyssynchrony in patients with advanced heart failure: a comparison study with conventional bi-ventricular pacing therapy. Eur Heart J. 2007; 28: 2610-2619.
91. Sideris S, Aggeli C, Poulidakis E, et al. Bifocal right ventricular pacing: an alternative way to achieve resynchronization when left ventricular lead insertion is unsuccessful. J Interv Card Electrophysiol. 2012; 35: 85-91.
92. Leclercq C, Gadler F, Kranig W, et al. 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.
93. Lenarczyk R, Kowalski O, Kukulski T, et al. Triple-site biventricular pacing in patients undergoing cardiac resynchronization therapy: a feasibility study. Europace. 2007; 9: 762-767.
94. Spragg DD, Dong J, Fetics BJ, et al. Optimal left ventricular endocardial pacing sites for cardiac resynchronization therapy in patients with ischemic cardiomyopathy. J Am Coll Cardiol. 2010; 56: 774-781.
95. Rogers DP, Lambiase PD, Lowe MD, Chow AW. A randomized double-blind crossover trial of triventricular versus biventricular pacing in heart failure. Eur J Heart Fail. 2012; 14: 495-505.
96. Goldenberg I, Moss AJ, Hall WJ, et al. Predictors of response to cardiac resynchronization therapy in the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT). Circulation. 2011; 124: 1527-1536.
97. Thibault B, Karst E, Ryu K, Paiement P, Farazi TG. Pacing electrode selection in a quadripolar left heart lead determines presence or absence of phrenic nerve stimulation. Europace. 2010; 12: 751-753.
98. Forleo GB, Della Rocca DG, Papavasileiou LP, Molfetta AD, Santini L, Romeo F. Left ventricular pacing with a new quadripolar transvenous lead for CRT: early results of a prospective comparison with conventional implant outcomes. Heart Rhythm. 2011; 8: 31-37.
99. Sperzel J, Dänschel W, Gutleben KJ, et al. First prospective, multi-centre clinical experience with a novel left ventricular

quadripolar lead. Europace. 2012; 14: 365-372.
100. Tomassoni G, Baker J, Corbisiero R, et al. Postoperative performance of the Quartet® left ventricular heart lead. J Cardiovasc Electrophysiol. 2013; 24: 449-456.
101. Mele D, Pasanisi G, Capasso F, et al. Left intraventricular myocardial deformation dyssynchrony identifies responders to cardiac resynchronization therapy in patients with heart failure. Eur Heart J. 2006; 27: 1070-1078.
102. Pitzalis MV, Iacoviello M, Romito R, et al. Cardiac resynchronization therapy tailored by echocardiographic evaluation of ventricular asynchrony. J Am Coll Cardiol. 2002; 40: 1615-1622.
103. Chung ES, Leon AR, Tavazzi L, et al. Results of the Predictors of Response to CRT (PROSPECT) trial. Circulation. 2008; 117: 2608-2616.
104. Papadopoulos CH, Kyriakides ZS, Maniotis C, Dymarkowski S, Bogaert J. Noninvasive cardiovascular imaging as a guide to cardiac resynchronization therapy. Hellenic J Cardiol. 2015; 56: 72-84.
105. Chen J, Garcia EV, Folks RD, et al. Onset of left ventricular mechanical contraction as determined by phase analysis of ECG-gated myocardial perfusion SPECT imaging: development of a diagnostic tool for assessment of cardiac mechanical dyssynchrony. J Nucl Cardiol. 2005; 12: 687-695.
106. Bilchick KC, Dimaano V, Wu KC, et al. Cardiac magnetic resonance assessment of dyssynchrony and myocardial scar predicts function class improvement following cardiac resynchronization therapy. JACC Cardiovasc Imaging. 2008; 1: 561-568.
107. 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.
108. Dickstein K, Vardas PE, Auricchio A, et al. 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. Europace. 2010; 12: 1526-1536.
109. Bleeker GB, Holman ER, Steendijk P, et al. Cardiac resynchronization therapy in patients with a narrow QRS complex. J Am Coll Cardiol. 2006; 48: 2243-2250.
110. Yu CM, Chan YS, Zhang Q, et al. 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.
111. Beshai JF, Grimm RA, Nagueh SF, et al. Cardiac-resynchronization therapy in heart failure with narrow QRS complexes. N Engl J Med. 2007; 357: 2461-2471.
112. Zareba W, Klein H, Cygankiewicz I, et al. 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.
113. Kaszala K, Ellenbogen KA. When right may not be right: right bundle-branch block and response to cardiac resynchronization therapy. Circulation. 2010; 122: 1999-2001.
114. Sipahi I, Chou JC, Hyden M, Rowland DY, Simon DI, Fang JC. Effect of QRS morphology on clinical event reduction with cardiac resynchronization therapy: meta-analysis of randomized controlled trials. Am Heart J. 2012; 163: 260-7.e3.