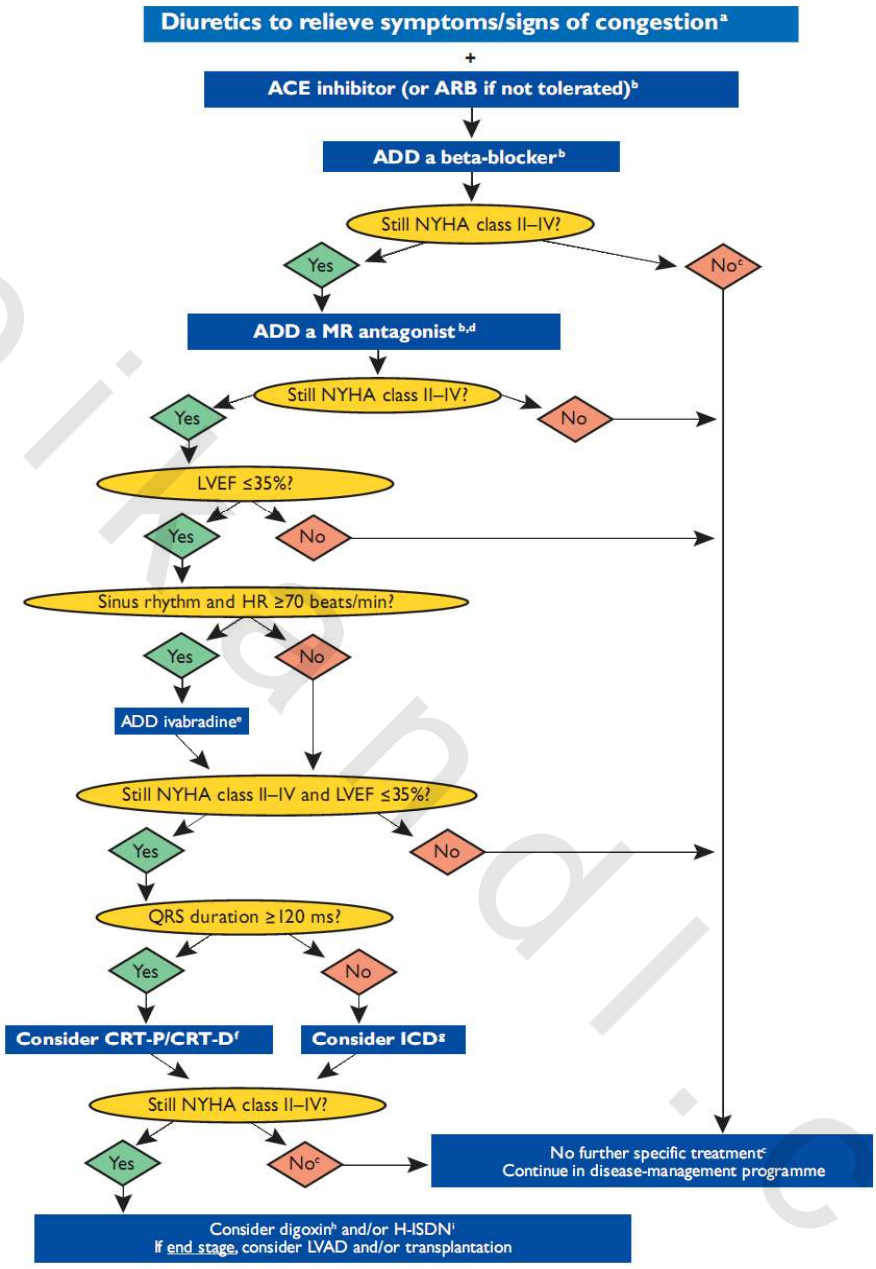
I. Definitions and epidemiology of heart failure

HF is defined, clinically, as a syndrome in which patients have typical symptoms (e.g. breathlessness, ankle swelling, and fatigue) and signs (e.g. elevated jugular venous pressure, pulmonary crackles, and displaced apex beat) resulting from an abnormality of cardiac structure or function.[23] Heart failure is the final stage of virtually all cardiac diseases and represents a major public health problem for Western countries.[23–25] The prevalence of HF has risen to epidemic levels in both North America and Europe.[26] It is estimated there are approximately 5,300,000 adults with HF in the United States with 660,000 new cases diagnosed every year. These cases have been increasing steadily over the past 20 years. [27,28] Due to the aging population and the improvement of acute cardiac care, the burden of HF is expected to grow further, with one projection showing an increase in prevalence of HF of 31% and 17%, in males and females, respectively by the year 2020.[29] The number of hospitalizations has also risen with 1,084,000 hospital discharges (a 171% increase as compared to 1979) were recorded in 2005 in the United States.[26] Similar data have been obtained in Europe with a prevalence of 0.4– 2% of the general European population, which shows acute HF as the main cause of hospitalization in patients >65 years of age.[30,31] The overall economic cost of HF is expected to reach US$34.8 billion in 2008 [26] with HF causing 2–3% of the total healthcare expenditure in European countries Mortality rates have significantly decreased over the last 10 years.[32-35] New drugs and cardiac resynchronization therapy (CRT) have further reduced annual mortality to rates of approximately 8–10%.[16,36–37] However, the prognosis for patients with HF remains worse in an in-hospital mortality rate of 4–9%, with postdischarge 6-month mortality and rehospitalization rates of 9%–15% and 30–45%. One-year and 5-year mortality rates remain at 20–30% and about 50% respectively.[32–35]

II. Medical management of chronic heart failure; General considerations

Medical treatment of HF is based on the combination of different agents administered with the aim of improving prognosis mainly through neurohormonal inhibition) and/or relieving symptoms. Combination of an angiotensin converting enzyme inhibitor (ACEi) and a beta-blocker constitute the



ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CRT-D = cardiac resynchronization therapy defibrillator; CRT-P = cardiac resynchronization therapy pacemaker; H-ISDN = hydralazine and isosorbide dinitrate; HR = heart rate; ICD = implantable cardioverter-defibrillator; LBBB = left bundle branch block; LVAD = left ventricular assist device; LVEF = left ventricular ejection fraction; MR antagonist = mineralocorticoid receptor antagonist; NYHA = New York Heart Association.

[a] Diuretics may be used as needed to relieve the signs and symptoms of congestion (see Section 7.5) but they have not been shown to reduce hospitalization or death.

[b] Should be titrated to evidence-based dose or maximum tolerated dose below the evidence-based dose.

[c] Asymptomatic patients with an LVEF ≤35% and a history of myocardial infarction should be considered for an ICD.

[d] If mineralocorticoid receptor antagonist not tolerated, an ARB may be added to an ACE inhibitor as an alternative.

[e] European Medicines Agency has approved ivabradine for use in patients with a heart rate ≥75 b.p.m. May also be considered in patients with a contraindication to a beta-blocker or beta-blocker intolerance.

[f] See Section 9.2 for details—indication differs according to heart rhythm, NYHA class, QRS duration, QRS morphology and LVEF.

[g] Not indicated in NYHA class IV.

[h] Digoxin may be used earlier to control the ventricular rate in patients with atrial fibrillation—usually in conjunction with a beta-blocker.

[i] The combination of hydralazine and isosorbide dinitrate may also be considered earlier in patients unable to tolerate an ACE inhibitor or an ARB.

Figure 1.1: Treatment options for patients with chronic symptomatic systolic heart failure (NYHA functional class II–IV).[23]

background therapy for virtually all HF patients, the addition of agents, such as angiotensin receptor blockers (ARBs), aldosterone antagonists, hydralazine, and isosorbide dinitrate, may provide, additional survival benefits.[23-25] As a rule, only agents with proven efficacy in large randomized controlled trials are recommended for clinical practice, and these agents should be administered at the doses shown to be effective in controlled trials.[23-25] Failure to reach the target dose may translate into lower clinical benefits or no benefits at all. To be effective, medical therapy of HF with neurohormonal antagonists has to be optimal with regard to drug choice, as well as include up-titration to the recommended dose. Other agents are critical in the management of HF not for prognosis but rather for their effect on symptoms. Diuretics are of crucial importance in the control of the volume status and for improving symptoms due to fluid retention and congestion, while digoxin has a little value to ameliorates the clinical status and reduces the need for hospitalization due to HF especially in patients with concomitant atrial fibrillation (AF).[23-25] Figure 1.1 shows a simple stepwise flowchart to treat chronic systolic heart failure.[23]

III. From medical treatment to devices; the role of dyssynchrony in heart failure outcomes

Current medical treatment has allowed an impressive improvement in the natural history of HF caused by LV systolic dysfunction. However, the quality of life and prognosis of patients with HF remains poor. Despite the benefits obtained with rennin angiotensin aldosterone system (RAAS) inhibitors and beta-blockers, the neurohormonal model of HF has not worked out as expected when other agents, acting on seemingly important mechanisms, have been tested.[38]

The current model of multicenter randomized controlled trials (e.g. large trials targeting the widest study group as possible, with a single new treatment added on top of a more-and-more complex pharmacologic therapy, and with no knowledge of the main pathogenetic mechanisms acting in that single patient) seems to have reached its limits. Thus, the poor prognosis and quality of life of HF patients, the failure of the neurohormonal model with the new agents tested, and the failure of recent multicenter trials targeting a noncharacterized HF population have paved the way to device therapy, namely, CRT. This treatment, differently from neurohormonal antagonists, acts on a specific well characterized mechanical defect leading to LV remodeling and HF. The selection of patients based on a simple criterion (e.g. QRS duration) and its direct correction through a device, (e.g. without some of the limitations of medical treatment (pharmacokinetics variability, need of compliance, etc)) may explain the success

of this treatment, which is, actually, the most beneficial treatment recently shown for patients with HF. The presence of a QRS duration >120 ms on the surface electrocardiogram (ECG) is an index of mechanical dyssynchrony.[39] Although this association is not absolute, it is estimated that approximately 70% of patients with left-sided conduction delay have evidence of mechanical dyssynchrony.[40] The delay in LV electrical activation causing prolonged QRS duration has an important pathophysiological significance because it is associated to an abnormal and mechanically disadvantageous pattern of LV contraction with an impairment of LV pump performance and increased severity of mitral regurgitation.[41] These changes are consistent with the prognostic significance of QRS prolongation as well as with the beneficial effects of CRT on symptoms and prognosis of the HF patients with LV conduction delay.

CRT is device able to perform atrial-synchronized biventricular pacing. It was first successfully implanted by Cazeau in 1994, in a 54-year-old man with NYHA Class IV HF and QRS duration of 200 ms.[42] The clinical status of the patient dramatically improved in the first 6 weeks postimplantation. Following this initial experience, the effects of CRT have been extensively investigated in many observational studies and several randomized controlled trials in patients with HF and LV systolic dysfunction.[43] Inclusion criteria in major clinical trials of CRT were NYHA Class III–IV, sinus rhythm (SR), QRS duration ≥120 ms and LVEF ≤35%.[44,45] Table 1.1 summarizes the current indications for CRT according to the latest european guidelines.[46]

IV. Epidemiology and prognosis of dyssynchrony

A prolongation of the QRS complex, defined as a duration ≥120 ms, has been shown in 14–47% of patients with HF, with proportions close to 30% in most studies.[7,47-49] Intraventricular conduction delay with LBBB morphology is five-fold to seven-fold more frequent than right RBBB.[7] QRS prolongation is directly correlated with LV end-diastolic and end-systolic volumes and hence

ications for CRT in patients in sinus thm

ications for CRT in patients with manent atrial fibrillation

In contrast, it is not related to other factors, such as etiology of HF or concomitant medication. Longitudinal studies have also shown a progressive prolongation of QRS duration during long-term follow-up in HF patients.[56] QRS prolongation has been identified as an independent predictor of poor prognosis in various HF populations.[7] Its potential role was first proposed in the early 1960s.[57] Further studies have shown that QRS prolongation is associated with a higher risk of all-cause death and sudden cardiac death.[7,47-49] Iuliano et al. retrospectively analyzed data from 669 patients with HF secondary to ischemic and nonischemic cardiomyopathy subdivided into two groups according to QRS duration.[47] Over the course of a median follow-up of 45 months, 129 deaths (34%) and 143 deaths (49.3%) occurred in patients with QRS <120 ms and in patients with QRS ≥120 ms, respectively. Sudden death occurred in 17.4% of patients with QRS <120 ms as compared to 24.8% in patients with QRS ≥120. The role of QRS prolongation was additive to that of LVEF.[47] A recent subgroup analysis from the Val-HeFT trial confirmed the prognostic impact of QRS widening, indicating a gradual increase in mortality rate with increasing duration of QRS, with a 1.8% mortality rate in patients with a QRS<120 ms, 8% in patients with a QRS duration of 120–159 ms, and 17% in patients with a QRS duration ≥160 ms during a median observation period of 25.8 ± 5 months.[58] Prolonged QRS duration has been shown to be related to prognosis with a two-fold increase in mortality in patients with a prolonged QRS admitted for acutely decompensated HF.[59]

V. Normal electrical and mechanical activation sequence of the heart

a. Normal electrical activation.

The normal activation wavefront starts in the sinus node (SN), with the electrical impulse propagating to the atria and then to the atrioventricular node (AVN). The impulse exits from the AVN and is spread rapidly into the LV and right ventricle (RV) through the His bundle, its branches and the network of Purkinje fibers. The His bundle and bundle branches are electrically insulated from surrounding muscle as they course toward the ventricular apex.[60] The insulation breaks down within the peripheral networks of Purkinje fibers, enabling direct impulse transmission to the working myocardium at the Purkinje–myocyte junctions. As a consequence of their disposition, activation and contraction of the ventricles proceed in a predominantly apex-to-base direction. This sequence of excitation and contraction is thought to increase ventricular pumping efficiency.[61] Although even in the normal heart there can be variability in the activation sequence, the total duration of this activation is less than 80 ms.

This short duration, which is a reflection of the rapid conduction within the Purkinje fibers, facilitates synchronous activation of the heart.

The LV myocardial wall is first activated at the endocardial level in a central area of the interventricular septum and in an area of the anterior free wall near the anterior papillary muscle and extending toward the apex.[62] Endocardial activation of the RV starts 5–10 ms after the beginning of LV activation in the vicinity of the anterior papillary muscle.[62] From these exits of the Purkinje system, the LV and RV activation sequence travels from apex to base with small timing differences in activation between the septum and LV free wall.[63] The activation patterns of the LV and RV are near mirror images with the latest activated regions of the RV along the lateral wall and the basal area near the atrioventricular (AV) sulcus, while that of the LV occurring in the posterolateral/basal area. The intramural conduction from the endo-to-epicardium is less well-understood and is considered to spread in a centrifugal manner.[62]

Interestingly, the earliest ventricular epicardial activation site does not coincide with the first endocardial site to be activated. The first epicardial breakthrough occurs in the area pretrabecularis of the right ventricle 20–25 ms after the onset of ventricular endocardial activation.[62] Once, the ventricular activation breaks through epicardially, its subsequent spread occurs in a radial fashion toward the apical and basal regions.[62]

b. Normal mechanical activation: The importance of a normal atrio-ventricular and ventricular activation sequence

The electrical activation of the heart determines the mechanical activation via excitation-contraction coupling. This process is mediated at the intracellular level by the entry into the cell of Ca2+ through L-type Ca2+ channels, which, in turn, triggers the release of a large amount of Ca2+ from the sarcoplasmic reticulum (by the mechanism known as Ca2+-induced Ca2+ release), which, in turn, facilitates the interaction between actin and myosin filaments leading to contraction.[64,65] The delay between depolarization and the onset of myocardial contraction (electromechanical delay), which is approximately 30 ms,[66] is mainly determined by the delay between intracellular Ca2+ increase and the development of force. Due to this tight coupling, the electrical activation of the heart is closely followed by mechanical contraction at atrial level and, after a delay required for impulse conduction through the AVN, at the ventricular level. Because of this sequence of events, atrial contraction

precedes ventricular contraction responsible for approximately 10–40% to the ventricular filling in a normal heart.[67]

The relative contribution of atrial contraction to ventricular filling is affected by several variables inclusive of age, and heart rate, and is inconsistent among individuals. An optimal atrio-ventricular (AV) interval optimizes the booster pump function of the atria and consequently optimizes the volume and function of the ventricles, helps atrioventricular valve closure and prevents diastolic regurgitation.[60] The importance of an optimal AV delay becomes evident in pathologic situations. If the electrical activation and the subsequent contraction of the atria occurs too early as in a prolonged PR interval (first degree AV block) or in dual chamber pacing with a long AV interval the mitral valve closes early thereby limiting ventricular diastolic filling time and also promotes diastolic mitral regurgitation. If the atrial contraction occurs too late, for example, in patients with dual chamber pacing and short AV intervals, the atrial contraction can get overtly truncated by the next ventricular systole resulting in impaired ventricular filling. In a normal heart, the synchronous electrical activation of the ventricles is followed by an equally closely timed contraction. In order for the ventricles to function efficiently as pumping chambers, there needs to be a close coordination between the two ventricles and between the walls of the same ventricle (i.e. interventricular and intraventricular synchrony). This electromechanical activation sequence is disrupted due to variety of circumstances, such as extrasystoles and ventricular pacing,[68,69] and most importantly due to conduction system defects accompanying remodeling in the failing heart.[70]

VI. Pathophysiology of heart failure

a. Neurohormonal, structural and molecular changes

Heart failure (HF) is a systemic disease that typically starts with a cardiac insult but is rapidly accompanied by the activation of multiple cascades triggered to offset reduced pump function. The latter includes neurohormonal stimulation, loading changes, and complex chamber structural, cellular, and molecular remodeling.[44,45] neurohormonal stimulation occurs at both the systemic and local myocardial level, and myocardial responses can be induced by hormone receptor interactions, or mechanical loading.[71] Catecholamines play a major role in stimulating the heart to contract more vigorously, working though cAMPPKA pathways. However, when sustained, they result in abnormal calcium handling and activation of stress kinases that worsening cell survival.[72]

Myocytes are certainly not the only cell types involved, and vascular insufficiency, fibroblast activation and generation of interstitial fibrosis, matrix remodeling proteins (metalloproteinase) activation, and other factors all contribute to the HF phenotype.[44]

A key functional consequence of this chronic maladaptive remodeling is that both rest and reserve functions of the heart become compromised. This is manifest by blunted responses to neurohormonal stimulation (i.e. sympathetic stimulation), loading, and increases in heart rate. Many factors contribute to this behavior, including down-regulation of G-coupled receptor pathways, abnormal calcium cycling[73,74], activation of multiple stress response signaling pathways [75,76], depressed energetic, and sarcomere changes.[77] Calcium cycling into and out of the sarcoplasmic reticulum is blunted, reducing Ca2+ available for systolic activation while delaying its re-uptake to prolong relaxation. Activation of many stress kinases, phosphatases, and associated transcription factors alter everything from contractile function and calcium handling to growth remodeling and cell survival. Bio-energetics is also abnormal, with the heart rendered inefficient and its relative use of glucose versus free fatty acids also altered. Lastly, myofilament proteins are altered also in the failure state, involving changes in the type of myosin, posttranslational modifications of regulatory and structural proteins such as troponin I and titin.[44,78]

On this backdrop of overall cardiac failure, a quarter or more of HF patients develop electrical conduction delays resulting in marked discoordinate contraction. Such dyssynchrony reduces chamber function and efficiency even in normal hearts, and its superimposition in HF worsens an already compromised state. Furthermore, the effects of dyssynchrony may not simply be additive but reflect a complex interaction with the HF substrate to generate a particular form of heart failure. As such, dyssynchrony and, correspondingly, resynchronization can influence molecular and cellular signaling in unique ways and understanding how and what is being achieved is increasingly important as cardiac resynchronization (CRT) has taken hold as a clinical therapy for groups of heart failure patients.[79]

b. Pathophysiological changes in the conduction system of the failing heart

Studies in experimental congestive heart failure in animals have shown that ventricular failure is accompanied by atrial remodeling consisting of extensive interstitial fibrosis accompanied by cell loss, degenerative changes, and

Optimized from

hypertrophy. These studies have shown that the myofibril bundles are packed less tightly than in control animals and are separated by thick layers of fibrous tissue along with increased intercellular connective tissue deposition.[80] The connective tissue is composed of increased numbers of fibroblasts, large amounts of collagen, ground substance, and occasionally fat cells.[80] Although histological changes are similar in both atria, they are more extensive in the left atrium (LA), promoting the potential induction of atrial fibrillation. This remodeling itself may impact the inter-atrial and intra-atrial conduction, which may significantly affect ventricular preload and consequently the cardiac output. Ventricular remodeling in heart failure is a progressive process that encompasses degenerative and maladaptive changes occurring at tissue, cellular, and subcellular level which includes myocyte hypertrophy, necrosis, increased apoptosis, inflammation, and fibrosis. The remodeling process affects also the ventricular conduction system. Heart failure causes remodeling of important K+ and Ca2+ currents in cardiac Purkinje cells, which decreases the repolarization reserve with potential implications regarding ventricular arrhythmogenesis.[81] Heart failure is associated with marked ventricular conduction abnormalities that can be at least in part explained by disturbances of gap junction organization. The most consistently observed is the down-regulation of Connexin-43 in patients with end-stage heart failure due to idiopathic dilated cardiomyopathy or ischemic heart disease.[82] Down-regulation of Connexin-43 is accompanied by significant reduction in intercellular coupling and conduction velocity in association with an enhancement of transmural dispersion of action potential duration.[83] Animal studies have confirmed this reduction of Connexin-43 protein expression associated with a redistribution of Connexin-43 from the intercalated disk region to lateral cell borders.[83] The changes in Connexin-43 expression in the failing myocardium contribute to both intraventricular conduction disturbances and arrhythmia substrate formation.

c. Ventricular activation sequence in the failing heart

The structural and functional changes accompanying heart failure can have a significant impact on impulse generation and propagation. Despite, changes in the conduction pattern, the extent of asynchrony can be significantly affected by the alteration of myocardial characteristics. The resulting myocardial conduction is not only slower but more variable depending on the underlying myopathy. The slow conduction through the myocardial wall is often unpredictable, with the presence of scar, fibrosis, and ischemia adding to the complexity of the conduction pattern. The normal ventricular activation sequence has three important components, which include the initial trans-septal

conduction, LV and RV endocardial activation followed by the transmural conduction to the epicardial surface.[84]

To understand the variability in activation sequence among different patients, it is important to first understand some of the basic terminologies derived from electroanatomic mapping: (i) Earliest LV breakthrough site, which is defined as the location from which the propagation wavefront first breaks through to spread to the rest of the LV; (ii) Transeptal activation time, which is the time difference from the onset of the QRS complex on the surface ECG to the earliest LV breakthrough site. The latter point is recognized as the largest rapid deflection of the bipolar electrogram crossing the baseline; and (iii) Transmural activation time, is the time taken from the last activated site to the end of the QRS complex. Regions of slow conduction are defined by the presence of low voltage (<0.5 mV) or fragmented signals (>50 ms).

d. Conduction defects in the failing heart; Left bundle branch block

The most frequent intraventricular conduction abnormality that occurs in approximately 25–30% of patients with heart failure is left bundle branch block (LBBB).[48,54,85] By inducing regional delays in electrical activation it leads to dyssynchronous mechanical activity having a detrimental effect on overall LV function, which ultimately translates into negative impact on prognosis in heart failure patients.[54,85]

Ventricular activation pattern in LBBB has been evaluated in animal studies[86,87] (by direct interruption of the proximal left bundle branch) or in studies in humans using noninvasive electrocardiographic imaging that maps epicardial ventricular activation,[88] or using intraoperative epicardial,[89] or catheter-based endocardial mapping.[90,91] More recently, Auricchio et al. using catheter-based high-resolution three-dimensional endocardial mapping offered more detailed assessment of the sequence of ventricular activation in patients (figure 1.2) with heart failure who have LBBB pattern on the surface ECG.

LBBB can occur in patients with dilated cardiomyopathy of ischemic or nonischemic etiology and is a heterogeneous entity.[70,92–96] It can result from conduction delay located at several anatomic levels in the conduction system from the distal His bundle to the left bundle branch and further distally to the arborization of the left bundle branch system. Different degrees of conduction delays in the right bundle branch system and in the diseased myocardium outside

the conduction system can be also associated, which increases the complexity of this heterogeneous entity.[70,92,94] Because the conduction defect in a LBBB may be mixed and involve other parts of the ventricular His–Purkinje system, the pattern of ventricular activation is variable and unpredictable.[70,88] Also, the variance of the centrifugal conduction from the endocardium to epicardium, due to altered conductive properties of the different myocardial layers may partly explain this variability.[70]

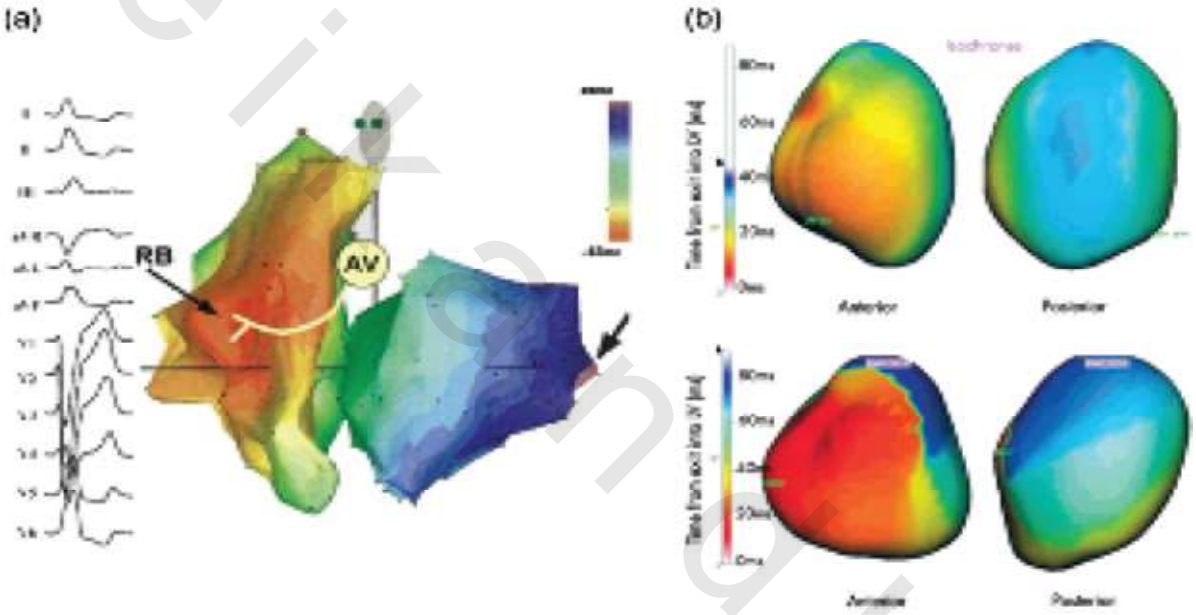


Figure 1.2: (a) Color-coded electroanatomic isochronal maps of right ventricular and left ventricular activation in a heart failure patient with left bundle branch block, generated via contact mapping. The activation sequence is color-coded with red depicting the region with earliest activation and bluish-purple depicting the region of the heart with most delayed activation. Adapted from Peichl et al.[96]) (b) Isochronal maps comparing left ventricular activation on the anterior and posterior endocardial surfaces in (a) a patient with idiopathic dilated cardiomyopathy (DCM) without a slow conduction zone, where there is homogeneous activation and (b) in a patient with DCM and a slow conduction zone. In this subject, the activation wavefront arcs around the zone of slow conduction (see arrows) and reaches the region of latest activation. Times are referenced from exit of the activation wavefront into the left ventricle with earliest activation shown in red and latest in blue-white, as depicted by the reference scale. (Adapted from Lambiase et al.[97])

e. LV breakthrough

The LV endocardial breakthrough sites can be variable in their location and number. Although, most often the earliest portion of the LV to be activated is along the apical septum, it may occur in the septobasal or midseptal region or anterior in a minority of the patients.[70] In the majority of cases LV breakthrough is located at a single site but some patients can have two sites of early activation.[92] Although in a majority of patients with heart failure and LBBB, the myopathic process prolongs the transseptal conduction time, in approximately one-third of patients the transseptal conduction time may be normal. The site of LV breakthrough is dictated by the conductive pattern within the heart-the midseptal or apicoseptal breakthrough sites are often due to the slow cell-to-cell transseptal conduction, while patients with septobasal or anterior breakthrough sites have faster transseptal conduction likely via septal branches of the His–Purkinje system.[70] In patients with nonischemic cardiomyopathy, the prolongation of the LV activation is more homogeneous in comparison to coronary artery disease. In patients with coronary artery disease, despite a classic LBBB on ECG, there may be early septal activation due to preserved conduction down the anterior or posterior fascicle. Additionally, the presence of scar can significantly alter the activation process.

f. LV activation wavefront

Auricchio and colleagues demonstrated that the activation wavefront spreads from the initial LV breakthrough site both superiorly and inferiorly. In most patients the activation cannot cross directly from the anterior to the lateral wall and instead travels inferiorly around the apex and across the inferior wall in a "U-shaped" pattern, reaches the anterolateral wall of the LV, and then propagates toward the basal posterior or posterolateral wall near the mitral valve annulus, which is the last LV segment to be depolarized. This "U-shaped" activation pattern is thought to be generated by a functional line of block that is oriented from the base toward the apex of the LV. The turning point of the U-shaped activation front is located in the vicinity of the LV apex.[70] The LV endocardial activation time in patients with heart failure and LBBB is on average significantly longer than in subjects with normal hearts.[92] That a proportion of the heart failure patients with LBBB may also have normal or near-normal LV endocardial activation times is noteworthy.[92] It is possible that that in this subgroup of patients the LBBB morphology is consequent to a prolonged intramural activation time, accompanying the myopathic process. Simplistically, the endocardial activation time comprises about 75% of the surface QRS complex, while the rest of the activation delay is a consequence of mid-

myocardial or epicardial activation (intramural) delay. However, there does appear to be a relationship between QRS duration, transseptal activation, and the pattern of LV activation. Patients with LBBB and a longer QRS duration (>150 ms) generally demonstrate prolonged (>40 ms) transseptal time, have a midseptal or septoapical LV breakthrough, with a more closely situated (more anterior) functional line of block as opposed to patients with LBBB but with a shorter QRS duration. LBBB with a narrower QRS duration is usually characterized by a shorter transseptal time (<20 ms), an anterior or septobasal LV breakthrough, and a more distantly situated line of functional block, on the lateral wall.[70]

g. Conduction defects in the failing heart; Right bundle branch block

Although right bundle branch block (RBBB) may be commonly observed in the community, its prevalence is greater in subjects of older age, male sex, prior myocardial infarction, and chronic lung disease.[98] Although, in subjects without overt heart disease, RBBB does not appear to have significant impact on cardiovascular mortality,[99,100] in patients with coexistent cardiac disease (especially in acute coronary syndromes), the presence of RBBB and the degree of intraventricular conduction delay are associated with worse prognosis including increased all-cause mortality.[98,101] Approximately 10% of patients with heart failure who present as candidates for CRT have RBBB.[15] Experimental models have shown that cardiac dyssynchrony in failing hearts with RBBB is less than what is seen in the clinical situation. A pure RBBB is associated with less dyssynchrony between lateral and septal walls. It is important to note that these models do not account for scar, comorbidities, pulmonary hypertension, and the concomitant involvement of left-sided fascicles. The right bundle is fairly superficial and prone to injury secondary to right-sided pathologies or catheter manipulation. Consequently, right bundle branch block can result from interruption or delay in the conduction at any level of the right sided intraventricular conduction system inclusive of the right bundle branch or its arborization.

VII. Cardiac resynchronization therapy and electromechanical consequences

Cardiac resynchronization therapy by using LV or biventricular pacing and altering the sequence of electrical activation in patients with heart failure and intraventricular conduction abnormalities improves LV efficiency and overall hemodynamic function.[102] Although the way in which CRT improves the

synchrony of contraction has been well-studied, little information is available on the relationship between changes in electrical synchrony and the resulting changes in the contractile or mechanical synchrony with CRT. Although biventricular pacing has been shown to be beneficial, several studies have shown that acute hemodynamic effects of LV pacing are comparable to biventricular (BiV) pacing.[103-105] An important point to consider is that electrical synchrony does not necessarily imply mechanical synchrony because of the spatiotemporal heterogeneity of the relationship between electrical excitation and mechanical contraction in patients with heart failure. The variable response to CRT is determined by the inconsistent activation patterns between patients and the consequent variance in the electromechanical relationship. Even within the same patient, for the same LV and RV pacing lead positions, a wide range of isovolumic contraction times can exist from varying the atrio-ventricular and interventricular timing.[105]

The LV and RV lead location during the delivery of biventricular pacing is vital.[106] Defining an optimal lead position is still unclear and the choice between an optimal anatomical position, targeting either the segment with maximal mechanical dyssynchrony[107] or a region with maximal electrical delay is still up for debate. There is evidence to suggest that maximal electrical separation between the right and left ventricular leads and positioning the LV lead as far out into the electrical activation sequence may have a beneficial impact on clinical outcomes.[106] Modulating the AV delay, over and above this, has a significant impact on the depolarization wavefront and consequently on the extent of RV and LV pre-excitation, and ventricular contractility. Also, noteworthy is that changes in the AV delay can influence the location and size of the line-of-conduction block.

a. Electromechanical effect of biventricular pacing

Biventricular pacing is based on the premise that modifications in the pattern of electrical activation of both ventricles can lead to an increase in intraventricular as well as interventricular synchrony and ultimately to an improvement in the hemodynamic efficiency of the failing heart.[107]

Although there is significant interpatient variability, ventricular activation during simultaneous biventricular pacing with a short AV delay follows a general pattern that can be summarized as follows. The spatial disposition of the pacing leads allows generation of two ventricular activation wavefronts, which are initiated at the LV and RV pacing sites and move in

opposite directions toward each other. If pacing is delivered with a sufficiently short AV delay, the left and right ventricular wavefronts generated by pacing merge, even before the intrinsic activation generated in the atria could reach the ventricles via the AVN. The RV activation wavefront breaks into the LV after a 50–60 ms delay. The RV is depolarized entirely or almost entirely by the wave front generated by the RV lead. The initially dyssynchronous LV (because of LBBB or other preexistent intraventricular conduction abnormality) is now activated from two sites: one is situated in the interventricular septum where it breaks through at the wavefront initiated by the RV lead, and the other one is situated on the epicardial surface of the lateral LV wall where the LV lead is located. Both endocardial and epicardial mapping have demonstrated that LV activation wavefronts have to circumvent functional lines of block with variable disposition (anterior, lateral, inferior) resembling the lines of block that occur during native rhythm in heart failure patients with LBBB.[70]

It is important to note that the resulting activation pattern can be influenced by several variables, including (i) AV and interventricular (VV) pacing intervals (ii) presence of scar, (iii) local pathologies, (v) variable lead positions, and (v) variable intramural delay. The AV interval significantly influences the pattern of activation not only during LV pacing alone but also during biventricular pacing. If atrio-biventricular pacing is delivered with very long AV interval in a heart failure patient with LBBB, the depolarization initiated in the atria descends via the AVN and right bundle branch and propagates from the RV to the LV. With intermediate AV delays, ventricular depolarization occurs with different degrees of fusion between the wavefronts generated by the right bundle branch (intrinsic conduction) and by the RV and LV leads. At short AV delays, ventricular depolarization can be due exclusively to the two activation wavefronts generated by LV and RV pacing leads leading to ventricular resynchronization.[103,104]

There is considerable data to suggest that adjusting and optimizing the AV interval can result in hemodynamic benefits,[102,108–112] however, there is a paucity of information on the impact of this optimization on the electrical activation pattern. The highest improvement in systolic function is achieved with short AV interval that allows complete capture of the ventricles by the two pacing induced activation wavefronts. The exact value of this AV delay that improves synchrony is variable because it is patient-specific.[102]

Another factor that influences ventricular activation during biventricular pacing is the interventricular (VV) timing. The modern CRT

devices have the possibility of programming the VV pacing interval, allowing LV–RV simultaneous or sequential pacing with different degrees of LV or RV pre-excitation. These adjustments, together with AV interval adjustments can produce a multitude of patterns of ventricular depolarization by offering, in patients with LBBB and intact AV conduction, a certain degree of control over the three fronts of activation originating from the right bundle branch, the RV, and the LV pacing leads. Although in most patients simultaneous RV–LV pacing produces good hemodynamic results, pre-exciting the LV before RV pacing seem to further optimize synchrony and increase LV systolic function. Perego et al. demonstrated an increase in LV dP/dt with sequential LV–RV biventricular pacing as compared to simultaneous biventricular pacing. The highest LV dP/dt was achieved when LV was stimulated before by 25±21 ms.[113] The clinical significance of this hemodynamic benefit remains to be proven.

Another factor that has an impact on electromechanical activation is lead position. The optimal lead positions are those that offer the greatest reduction in total activation time by producing two activation wavefronts that start from opposite positions.[60] Given that in LBBB the last LV wall to be activated during sinus rhythm is the basal posterolateral wall, placing the pacing lead in the vicinity of this area should theoretically produce maximum benefit in terms of electrical synchrony. This is not always possible with transvenous lead placement because of constraints imposed by the coronary venous anatomy, which is highly variable.[114] Response to pacing from the RV and LV site is often unpredictable, due to the pacing site-dependent changes in the line of functional block. Overall, electromechanical synchrony is dependent on the lead location, local pathology, as well as local activation and responsiveness. Minimal variation in lead positioning and/or orientation may have a large impact on the ventricular activation pattern. This highlights the fact that the variability in clinical response to CRT is driven by the heterogeneity of the LV substrate and their electrical response.

Lambiase and colleagues[97] demonstrated using noncontact endocardial mapping that electrical activation in patients with heart failure and ventricular conduction delays depends on LV lead placement. They identified areas of slow conduction within the LV, present mainly in patients with ischemic cardiomyopathy (ICM) probably related to the underlying process of myocardial hibernation or fibrosis. When the LV lead was found to be positioned in such an area, the electrograms at the pacing site were of low amplitude and the conduction velocity was on average 27% of that in free wall regions with normal amplitude electrograms.[97] Depolarization generated by an LV lead situated in a

slow conduction zone was delayed an average of 70 ms while leaving the area. In order to achieve simultaneous activation of the LV with biventricular pacing in such patients, the LV had to be paced 30–40 ms before RV to allow time for depolarization to leave the slow conduction zone. Endocardial pacing outside regions of slow conduction using a roving catheter decreased LV activation time and significantly increased LV systolic performance as assessed by cardiac output and dP/dtmax, and was accompanied by a reduction in QRS width. There was no significant relationship noted in this study between the degree of decrease in LV activation time and the reduction in QRS width. The phenomenon was also identified in sinus rhythm when depolarization circumvented the areas of slow conduction, which only depolarized in the final phases of ventricular activation. This pattern of activation however did not occur in patients with nonischemic cardiomyopathy who had a more homogenous LV activation.(97)

The impact of the RV pacing site on the activation sequence or fusion of the depolarization wavefront is underestimated. Recent work has demonstrated that by changing the RV pacing site, the electrical distance from the LV lead can be varied and also the dyssynchrony patterns of the LV can be altered.(67) This is again patient specific and affected by the intrinsic conduction, as well as the myopathy, which may influence local cell-to-cell conduction and recruitment of the native conduction system. Adjusting the AV interval, as alluded to above enables a variable extent of the activation wavefront originating from each of the pacing leads and intrinsic conduction.(115)

VIII. Left ventricular dyssynchrony

a. Mechanics of dyssynchrony

Electrical activation of the heart normally occurs in a rapid and coordinated manner as electrical impulses conduct through the His–Purkinje system to activate both ventricles within approximately 50–80 ms. Excitation propagates from endocardium to epicardium and apex to base allowing for coordinated and efficient contraction as all walls simultaneously help to develop pressure. This also provides for appropriate temporal activation of papillary muscles to optimize mitral valve function and prevent regurgitation. In heart failure, electrical impulse propagation can be diffusely impaired by abnormal His-Purkinje activation and slowed intramyocardial conduction.(116) More marked regional delays (as from conduction block) cause regional delay in contraction and thus dyssynchrony. LBBB and right ventricular (RV) pacing results in a phase delay in regional stiffening in the lateral wall, and are the most common

mechanisms for LV dyssynchrony. The septal region is activated first via the intact right bundle (or RV pacing) followed by delayed activation of the lateral LV free wall as excitation occurs through relatively slow intramyocardial conduction. The forces from early septal contraction do not translate into a rise in chamber pressure. Rather, these forces are largely converted into prestretch of the still-quiescent lateral wall. This results not only in the observed delay in intracavitary pressure rise (dP/dtmax) but also increased lateral wall stress. Conversely, late-systolic activation of the lateral free wall generates forces that are dissipated in part by stretching the early relaxing septal region, reducing net cardiac output. Furthermore, delayed papillary muscle activation results in suboptimal stiffening of the mitral valve apparatus, causing mitral regurgitation.[116]

This most common pattern of mechanical dyssynchrony is demonstrated in Figure 1.3a. Tagged magnetic resonance imaging was used to assess regional strain in a canine model of dyssynchronous heart failure (LBB ablation with 3 weeks of atrial tachypacing).[117] Strain is plotted as a function of LV region. In early systole (dashed line), the septum contracts whereas the lateral wall stretches (positive strain). In late systole (solid line), this biphasic pattern is reversed as the lateral wall now contracts and the septum stretches. Conceptually, left ventricular dyssynchrony may be portrayed as two time-varying elastance curves representing regional activation of myocardium, one phase delayed relative to the other (Figure 1.3b).

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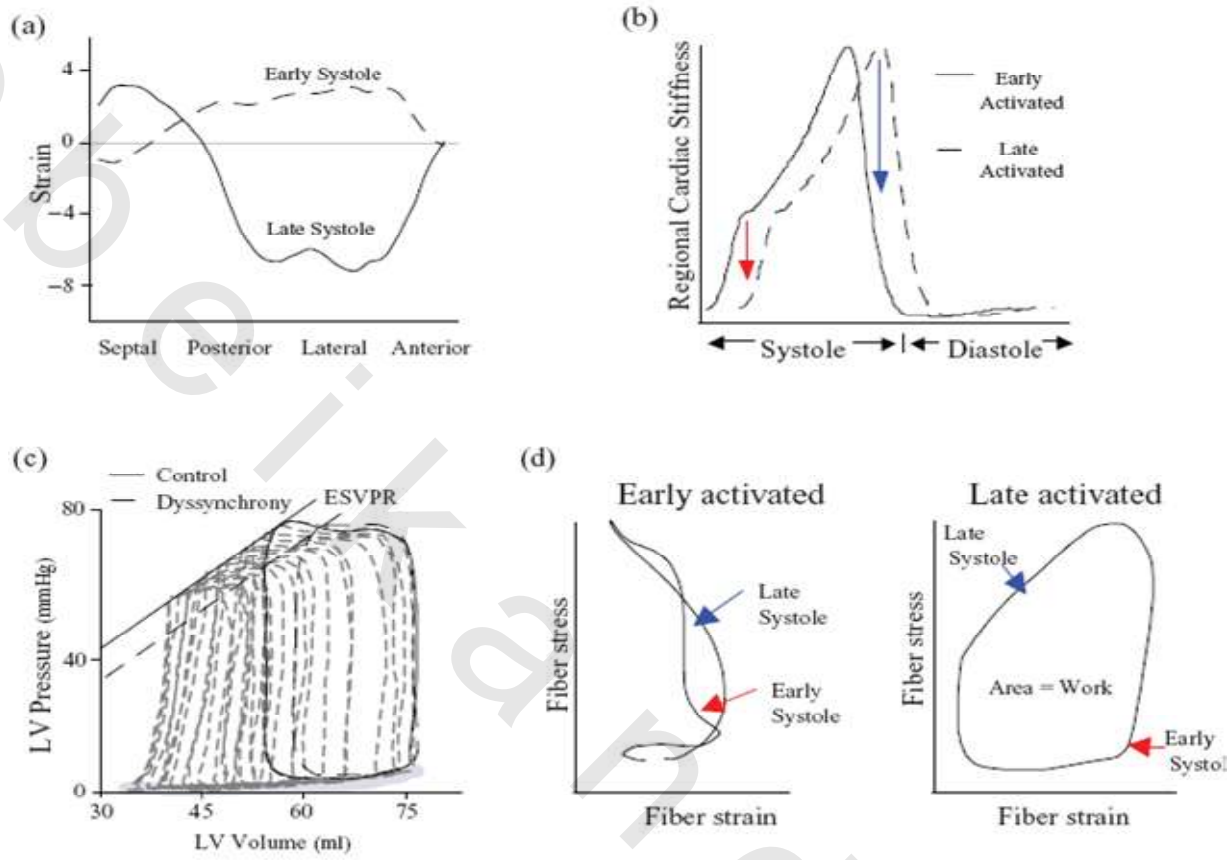

Figure 1.3: (a) Cardiac dyssynchrony is revealed in circumferential strain (relative shortening) at different regions across a short-axis section of the mid-LV. Data for early (dashed) and late (solid) systole are shown, and reveal septal and lateral regions are out-of-phase with each other. [117] (b) Model of generating dyssynchrony based on a time-delay of ventricular activation (stiffening) between early versus late-stimulated myocardium. Vertical distance between the curves would mean one wall pushing on the other, and the arrows highlight two times early contraction and late systole where this disparity is greatest and discoordinate motion most manifest. [117] (c) Pressure–volume loops showing effect of LV dyssynchrony on end-systolic pressure–volume relation (ESPVR) and resting cardiac cycle (loop). The ESPVR shifts rightward, end-systolic volume increases, and stroke volume and work decline. [124] (d) Stress-strain loops from early activated versus late-activated regions in a dyssynchronous heart. Whereas these regions would normally appear the same, with dyssynchrony, the early-activated region first contracts at a low load, and then it is stretched and generates a figure-8 shaped loop with little area (reduced work). In contrast, the late contracting lateral wall operates at higher preload and stress, requiring greater work. This correlates with disparate blood flow, energy consumption, and stress molecular signaling in the two regions.[129]

The vertical difference between the curves indicates disparities in wall stiffening due to the phase delay, and is marked in early systole (i.e. during isovolumic contraction) reducing the peak rate of pressure development (dP/dtmax), and even greater in late systole-early diastole. The latter is typically when echo-Doppler measures of dyssynchrony are observed. Such mechanical dyssynchrony has been documented in humans using magnetic resonance imaging,[118,119] contrast echocardiography,[120] tissue-Doppler imaging,[121,122] gated myocardial perfusion scintigraphy,[123] and other methods.[79] Although most dyssynchrony is due to delay in lateral wall excitation, the converse (right-sided delay) certainly exists, and is most typically coupled to a right-bundle block. This produces less-effective dyssynchrony to the chamber overall, highlighting the fact that the heart is not perfectly symmetric and that both the size of the delay-activated region and its location are important factors to determining its net impact.[117]

b. Effect of dyssynchrony on global function and efficiency

One of the important consequences of ventricular dyssynchrony is that chamber pump function becomes inefficient. Work performed on one side of the heart is wasted by its stretching of the alternative side both in early and later systole. The result is a decline in net cardiac output despite similar energy requirements for the contraction. The global effect is displayed in Figure 1.3c by sets of pressure–volume loops, first reported by the laboratory of Little and colleagues in the mid 1980s.[124] The slope of the end-systolic pressure–volume relationship shifts to the right, indicating a decline in net systolic function due to dyssynchrony. Stroke volume (loop width) and stroke work (loop area) declines as well, without a fall in end-diastolic volume. End-systolic wall stress, however is increased as the end-systolic volume rises Pre-ejection dP/dtmax declines by approximately 20%, stroke work falls by 10–15%, and the time constant of relaxation is increased by approximately 10–15%.[125-128] Chamber efficiency also declines. Using a canine model of ventricular dyssynchrony induced with RV pacing, Prinzen and colleagues [129] assessed regional myocardial strain and work by tagged MRI imaging. With RA pacing, regional work was fairly homogeneous, whereas with RV pacing, there were marked differences in local work with the lateral wall being increased by 125% and early activated septum reciprocally decreased.

Local stress-strain plots illustrate these findings (Figure 1.3d). In the early-activated region, workload (loop area) is low coupled to a figure-8-shaped loop due to early low load shortening and subsequent stretch. It is much greater

in the late contracting lateral wall which operates at higher initial stretch and contracts against higher stress. These regional differences in work correlate with regional blood flow and metabolic demands.[130-132] Owen and colleagues compared myocardial oxygen consumption (MVO2) during RA versus RV pacing in the dog heart, by invasively measuring coronary blood flow and coronary sinus O2 saturation. Despite a striking decline in LV stroke work and external work associated with RV pacing, MVO2 consumption remained the same indicating a marked decrease in LV efficiency (work/MVO2 consumption).[126] Other investigators have shown similar findings.[133,134]

c. Biochemical consequences of dyssynchrony

Regional disparities of wall stress in the dyssynchronous failing heart further impacts the expression and activity of various proteins beyond that observed with heart failure alone. In the first study to test for such effects, Spragg et al.[135] contrasted regional molecular changes in hearts with HF induced by tachypacing with dyssynchrony (RV pacing) or without (atrial pacing). In dyssynchronous HF, calcium-handling proteins including SR Ca2+-ATPase and phospholamban were down-regulated (20–30%) in the lateral endocardium versus other territories. The former actively transfers Ca2+ from the cytosol into the sarcoplasmic reticulum, while the latter is a key coregulator of this uptake process. Another protein examined was the extracellular response kinase (ERK1/2), a mitogen-activated protein (MAP) kinase that was highly activated in the lateral endocardium versus other regions. ERK1/2 is associated with stress stimulation pathways involving cell survival and differentiation. Lastly, the investigators showed marked down-regulation of the gap-junction protein connexin-43. Connexin-43 allows for rapid, coordinated, cell-to-cell depolarization. None of these regional changes in the lateral endocardium were not observed in failing myocardium without dyssynchrony. In another investigation by the same laboratory, Chakir et al.[136] further revealed differential activation of stress response proteins such as tumor necrosis factor-alpha, Ca2+-calmodulin dependent kinase II, and p38 MAP kinase. Interestingly, in a model of dyssynchrony (LBBB) without cardiac failure, these changes were not observed indicating that dyssynchrony interacts specifically with underlying heart failure to trigger these abnormalities.[137]

IX. Assessment of left ventricular dyssynchrony

a. Electrical dyssynchrony

1. *Surface ECG:*

The widely used marker to indicate LV dyssynchrony has been the surface ECG. The rational for that, is that the electrical delayed stimulation may lead to a mechanical delay of the respective LV areas. In LBBB the lateral free wall is activated later than the interventricular septum and thus leads to a delayed contraction of LV free wall.[138] This surrogate marker represented by LBBB is one of the criteria indicating implantation of CRT. It is shown that LBBB leads to impaired pump function which can be improved by CRT.[54,139,140] LBBB is also a predictor of sudden cardiac death in dilated cardiomyopathy (DCM).[141] In 29 patients Alonso et al showed that reducing the QRS duration by CRT correlated to a positive clinical response suggesting a hemodynamic improvement associated with narrowing of QRS indicating reduction of the mechanical dyssynchrony of LV contraction. The study concluded even that the optimal placement for hemodynamic LV improvement of the right and LV leads would be those sites that could induce the greatest shortening of QRS duration.[96] However, still there is no evidence for prediction of clinical response based on baseline QRS width or by the reduction of the QRS width effected by CRT in the individual patient.

2. *Electrophysiological mapping:*

An additional method to elucidate the intraventricular activation pattern in HF patients eligible for CRT is electroanatomical activation mapping. In 26 patients Peichl et al. showed that the surface ECG is of limited value to describe the complex conduction disturbance of the LV.[93] They found differences in electroanatomical LV activation between ischemic cardiomyopathy and DCM with similar QRS morphology on the surface ECG. Also Yu et al. showed that endocardial electrical LV activation sequences was variable among 7 HF patients with LBBB.[142] Lambiase et al. showed hemodynamic improvements in 10 HF patients by CRT in terms of increased cardiac output and dP/dt(max) when the LV was paced by placing the pacing lead away from areas with demonstrated slow conduction.[143] They concluded that clinical non response may reflect LV lead placement in regions with slow conduction which can be avoided by pacing in more normally activated LV regions.

b. Mechanical dyssynchrony

1. *3D-tagged magnetic resonance imaging (MRI):*

Asynchronous contraction of LV was demonstrated in patients with DCM with intraventricular conduction delay by Curry et al. who used MRI.[144] MRI is a time consuming method and can so far not be employed in patients with implanted pacemakers.

2. ***Scintigraphic blood pool and phase image analysis**:*

By using gated equilibrium radionuclide angiography and Fourier phase analyses Fauchier et al. demonstrated in 103 patients with DCM that QRS duration was related to both interventricular and intraventricular dyssynchrony.[145] Further, intraventricular dyssynchrony was an independent predictor of cardiac event (cardiac death, worsening of HF and heart transplantation) in DCM and the prognosis was related to intraventricular rather than to interventricular dyssynchrony. Another radionuclide angioscintigraphy study by Toussaint JF et al. in 21 patients showed that resynchronization by CRT between LV apex and base which persisted up to 12 months was also associated with a persisting improvement in LV systolic function.[146] The same group showed in 34 patients that basal dyssynchrony and early resynchronization demonstrated by radionuclide angioscintigraphy might predict long-term evolution of ventricular function after CRT in patients with very broad QRS (179 ± 18).[147] Kerwin et al. used gated blood pool scintigraphy in 13 patients to demonstrate asynchronous contraction of LV and to show the resynchronizing effect of CRT.[148] DCM with intraventricular conduction delay was also associated with significant interventricular dyssynchrony. Improvements in interventricular synchrony during CRT correlated with acute improvements in LV ejection fraction. One limitation of the scintigraphic methods is the relatively poor time resolution of 30 frame/sec.

3. **Echocardiographic methods:**

Echocardiography is an essential method to diagnose HF and is also used to evaluate the effect of treatment to improve cardiac performance. The echocardiographic measurement of LV fractional shortening by M-mode and EF measured from two-dimensional images by using Simpsons method in accordance with the recommendations of the American Society of Echocardiography Committee, are widely used parameters for cardiac evaluation.[149] An additional method is the use of the Doppler principle to measure and quantify blood flow velocity. The method is based on the fact that the frequency of reflected ultrasound from a moving target towards the

transducer is higher than the transmitted frequency. When the reflecting target is moving away from the transducer, the frequency is lower than the original transmitted ultrasound frequency. The Doppler signals from the moving red blood cells have low amplitude and high velocity, and the echocardiographic methods used are continuous wave Doppler, pulsed Doppler and color flow imaging. A recently developed ultrasonographic method is tissue velocity imaging (TVI). This method uses frequency shifts of ultrasound waves to calculate myocardial tissue velocity at lower velocities, but higher intensity compared to blood flow velocity measurement. TVI can be used to measure movements of cardiac structures and to assess regional LV contractility, which has been shown in both animal experiments and human studies.[150,151] The TVI method is used in a wide range of cardiac diseases to characterize systolic ejection velocities. Recent research showed the usefulness of TVI for assessing the severity of LV and interventricular dyssynchrony in patients with HF receiving CRT because of the excellent time resolution which can be achieved by TVI providing frame rates of 100 frames per second (fps) or more, i.e. a time resolution of 10 ms. Another assessment of regional LV function is the calculation of the myocardial velocity gradient or strain rate imaging, reflecting deformation and thereby a more direct measurement of contraction and relaxation using data set from color-coded TVI.[152-154] Post-processing the color coded TVI (c-TVI) data set can as well be used to evaluate the time related contraction pattern of the LV, which is less angle dependent than strain itself. Major interest of the regional time aspect of LV contraction measured by TVI has increased because of the promising results of CRT in HF patients.

i. M-Mode: Using the septal-to-posterior wall motion delay in M-mode recordings from the parasternal short axis view Pitzalis et al. demonstrated in 20 patients that a septal-to-posterior wall motion delay of > 130 ms and QRS duration > 150 ms predicted response to CRT in terms of > 15 % reduction of left ventricular end-systolic volume index in 79% of the patients. The authors demonstrated the prediction of reverse remodelling by septal-to-posterior wall motion delay (SPWMD) to be more precise than the QRS duration (accuracy 85% vs. 65%).[155] The same group demonstrated using this method in 60 patients that ischemic cardiomyopathy, changes in the QRS duration after implantation, and SPWMD significantly correlated with progression toward HF (defined as a worsening clinical condition leading to a sustained increase in conventional therapies, hospitalization, cardiac transplantation, and death). A long SPWMD remained significantly associated with a reduced risk of HF progression. An improvement in LVEF was observed in 79% of the patients with a baseline SPWMD of > 130 ms and in 9% of those with an SPWMD of <130 ms ($p < 0.0001$).[156] The septal-to-posterior wall motion delay in M-mode recordings

can also be examined in the parastrenal long axis view and a decrease of the posterior delay during CRT can be shown. (figure 1.4)

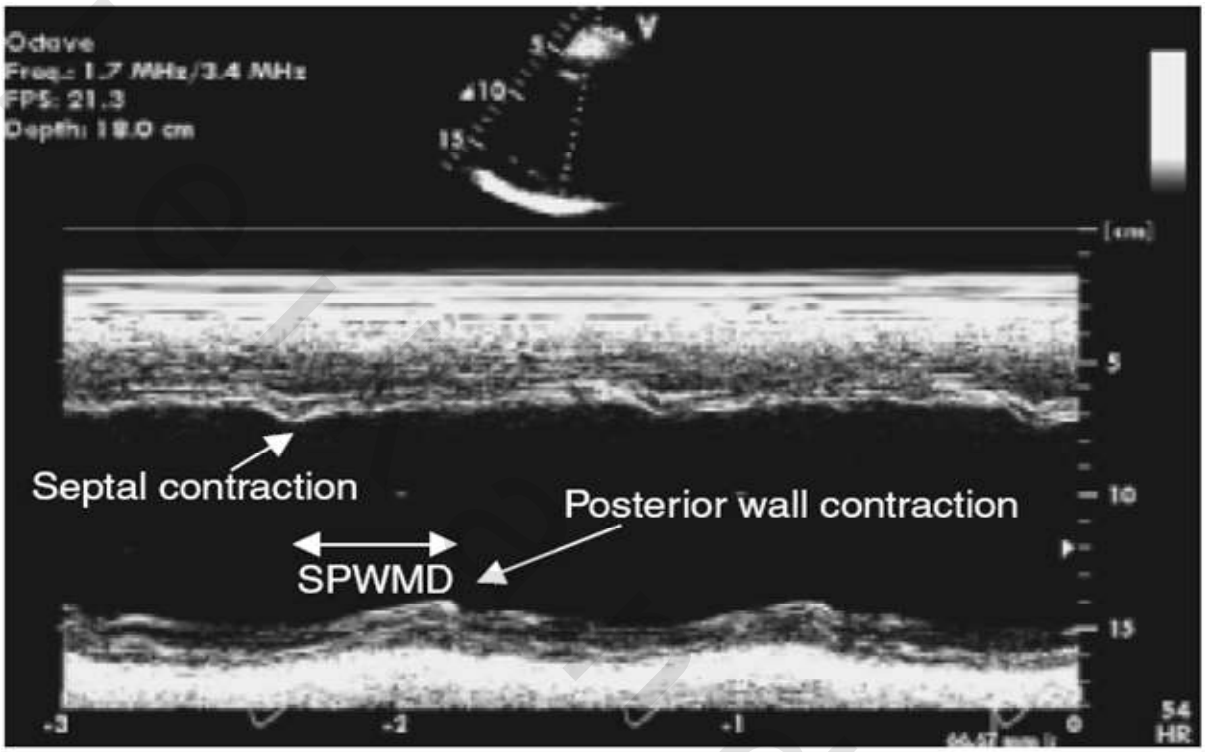

Fig. 1.4. M-mode imaging demonstrating septal to posterior wall mechanical delay (SPWMD).

ii. Doppler echocardiography: The measurement of interventricular electromechanical delay using pulsed Doppler imaging was examined by Rouleau et al in 35 patients with DCM.[157] A QRS width of more than 150 ms was correlated with a delayed aortic flow compared to the pulmonary flow as well as a delayed mitral annulus systolic wave compared to tricuspid annulus systolic wave. The authors concluded that QRS of more than 150 ms is a good marker of interventricular mechanical dyssynchrony. Various echocardiographic parameters of ventricular dyssynchrony were examined by Bordachar et al. in 41 patients undergoing CRT. Changes in interventricular dyssynchrony, defined as the difference between the aortic and pulmonary pre-ejection delays and determined as the time from the onset of the QRS complex to the beginning of each respective systolic ejection by pulsed wave Doppler imaging were not correlated with changes in cardiac output, whereas several TVI modalities could confirm high correlation with hemodynamic changes.[158] The use of pulsed tissue velocity Doppler imaging by Ansalone et al in 21 non ischemic patients receiving CRT demonstrated a reduction of asynchronous contraction of LV basal segments. After CRT, LV performance improved significantly in patients with

better LV resynchronization evaluated by TVI, whereas the QRS narrowing was not predictive of this functional improvement.[159]

The effect of inflow based AV optimization adopted from use in DDD pacing[108] showed in CRT responders, that changes in preload only partly could explain the improved LV performance in terms of pulse pressure. The authors emphasize the importance of LV resynchronization for improved LV performance.[160] Functional mitral regurgitation is reduced by CRT in patients with HF and LBBB shown in 24 patients by Breithardt et al, explained by a more coordinated LV contraction and due to the increased closing force (left ventricular systolic pressure rise).[161]

iii. Contrast echocardiography: A new echocardiographic method based on contrast variability imaging was used in 10 patients by Kawaguchi et al. to quantify dyssynchrony and magnitude of resynchronization achieved by CRT.[120] The method showed that lateral wall motion occurred earlier during CRT and that both spatial and temporal dyssynchrony in the LV contraction declined with LV pacing and CRT correlated with increasing ejection fraction.

iv. Borderline detection: A semiautomatic border detection method based on the fact that each region of the ventricular endocardial wall undergoes a periodic cycle of inward and outward displacement was performed in 34 patients by Breithardt et al. The authors showed a septallateral resynchronization during CRT by using this echocardiographic phase analysis of radial endocardial wall motion predicting an acute hemodynamic response (dp/dt).[162]

v. Three dimensional echocardiography: Three dimensional (3D) echocardiography has been used by Kim et al. to document hemodynamic improvement by CRT and additionally to identify LV segments with dyssynchrony.[163] The latter 3D echocardiographic method uses semi-automated contour analysis by a fast-rotating second harmonic transducer and was used in 16 patients by Krenning et al. to demonstrate a reduction of the LV contraction delay during CRT. The authors claim that this new 3D echocardiographic method might also be used to select the optimal pacing site during CRT.[164]

vi. Tissue Color Doppler Velocity Imaging (c-TVI): The excellent time resolution of c-TVI by using a postprocessing procedure is used in several studies to demonstrate the regional time aspect of LV contraction. In addition to the high time resolution another main advantage of c-TVI method is the possibility of comparing the contraction pattern of different LV regions simultaneously from

the recording (figure 1.5). Synchronicity of LV contraction pattern in the structurally normal heart is demonstrated and compared to HF patients with bundle brunch block showing a significant dyssynchrony within the LV in the HF patients.[165,166] Comparing surface ECG with the mechanical contraction pattern in HF patients showed that neither QRS duration nor QRS pattern predicts the mechanical dyssynchrony. Even HF patients with normal QRS width can have significant LV asynchronous contraction.[167,168] The reduction of post systolic LV contraction was demonstrated during CRT by Sogaard et al. and is assumed to be an indirect marker of LV resynchronization.[169] Based on data from 25 patients receiving CRT the same group did also show by tissue Doppler imaging that occurrence of postsystolic contraction prior to CRT may predicts improved systolic performance and reversed LV remodelling during CRT whereas QRS duration failed to predict resynchronization efficacy.[170] Using c-TVI has shown resynchronization during CRT, both as measurement of regional contraction timed to the QRS complex by Yu et al. and measured as an absolute resynchronization of the contraction of LV septum and the lateral free wall by Schuster et al. and by Bax et al.[171-173] One study by Bax et al in 25 patients showed a possible predictive value of c-TVI dyssynchrony prior to implantation which points in the same direction as Yu et al in 30 patients.[174]

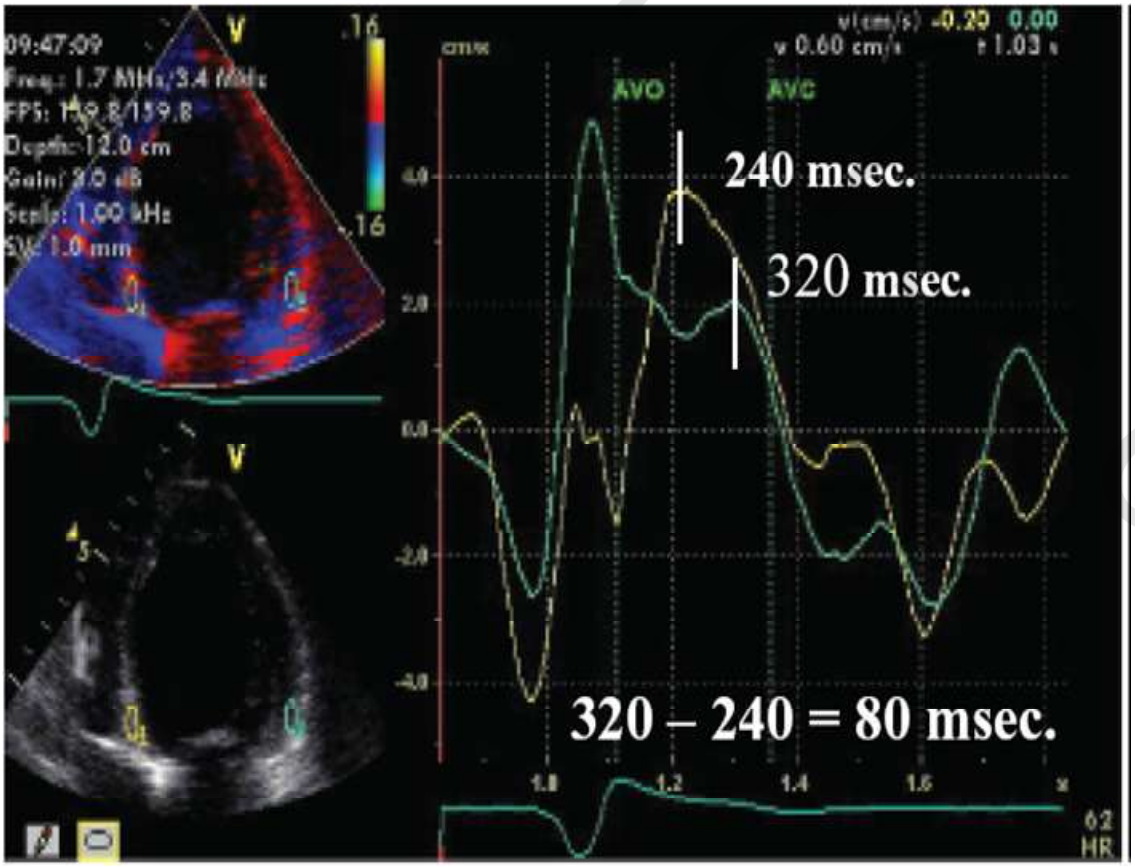

Figure 1.5: Color-coded Tissue Doppler Imaging. Areas of interest can be selected simultaneously during off line processing. Myocardial velocities are displayed simultaneously allowing for precise calculation of mechanical delay (here between the basal septum and the basal lateral wall).

vii. Speckle Tracking, Strain and strain rate imaging: The measurement of LV segment shortening or lengthening (strain) is also used to demonstrate resynchronization during CRT, but the more angle dependency of strain compared to TVI allows only the measurement of relative resynchronization because of the fact that the different regions have to be examined in separate recordings (figure 1.6). However a resynchronization effect by CRT is shown using the strain method by Breithardt et al.[175]

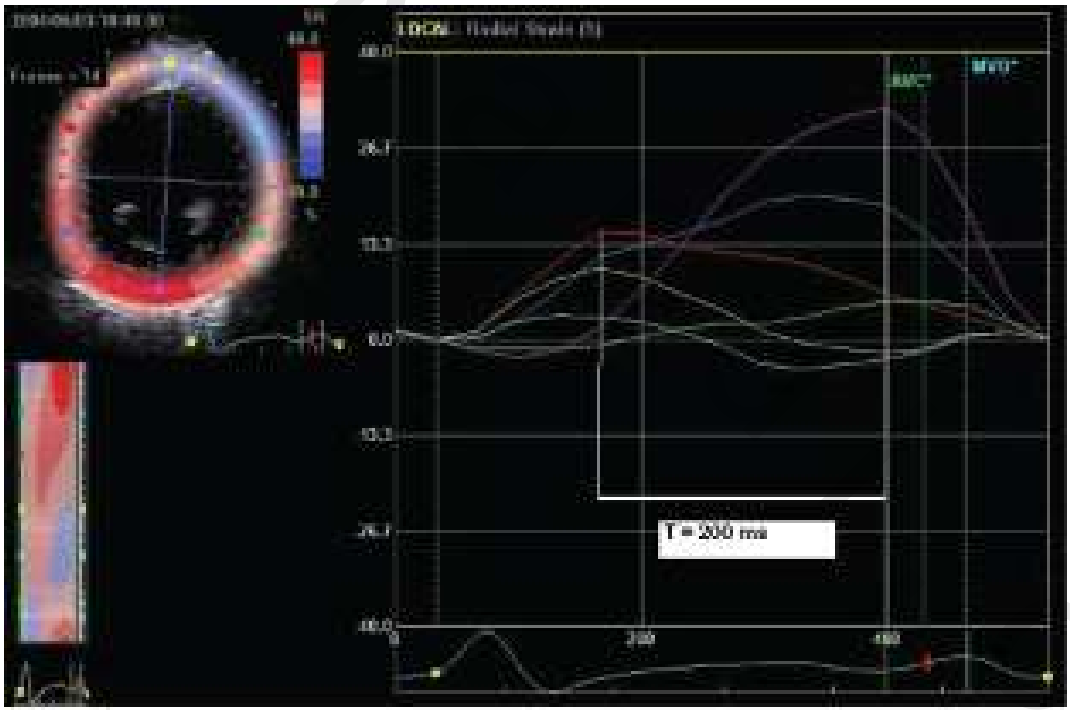

Figure 1.6: Speckle Tracking Imaging. Regional radial strain is displayed over time. The timing in the areas of normal contraction [anteroseptum (red), anterior wall (yellow) and lateral wall (light blue)] may be compared to the timing in the delayed contracting segments [here the inferoseptum (dark blue), inferior wall (purple) and posterolateral wall (green)]. A difference of greater than 130 msec consistent with significant LV dyssynchrony.

X. Acute effects of cardiac resynchronization therapy; mechanics and energetic

The chamber mechanical and hemodynamic effects of cardiac resynchronization therapy (CRT) occur rapidly-essentially within a beat. This is depicted by the time tracings from a patient with HF and a LBBB (Figure 1.7.a), which shows abrupt increases in dP/dtmax and aortic pulse pressure when pacing is turned on. The pressure–volume loop (Figure 1.7.b) shows a corresponding increase in stroke volume and decline in end-systolic stress, with little change in end diastolic volume or pressure. Improved chamber contraction is accompanied by enhanced efficiency.(176) Figure 1.3.c shows the change in MVO2 (per beat) induced by dobutamine infusion versus CRT; the latter increased dP/dtmax similar to the drug, but with a fall in O2 consumption versus a rise with the former. The finding of negligible energetic cost despite improved systolic function from CRT has been supported by other studies, and is a particularly unique feature of CRT among current HF therapies.(177,178) Pharmacologic treatments that enhance systolic function acutely (without lowering afterload as the mechanism) have been associated with chronic increases in mortality. CRT is different, and the enhancement of energetics may play a key role. CRT also enhances the functional reserve response associated with increasing heart rate. This behavior, known as the force–frequency relation, is related to enhanced calcium cycling coupled to beat frequency.

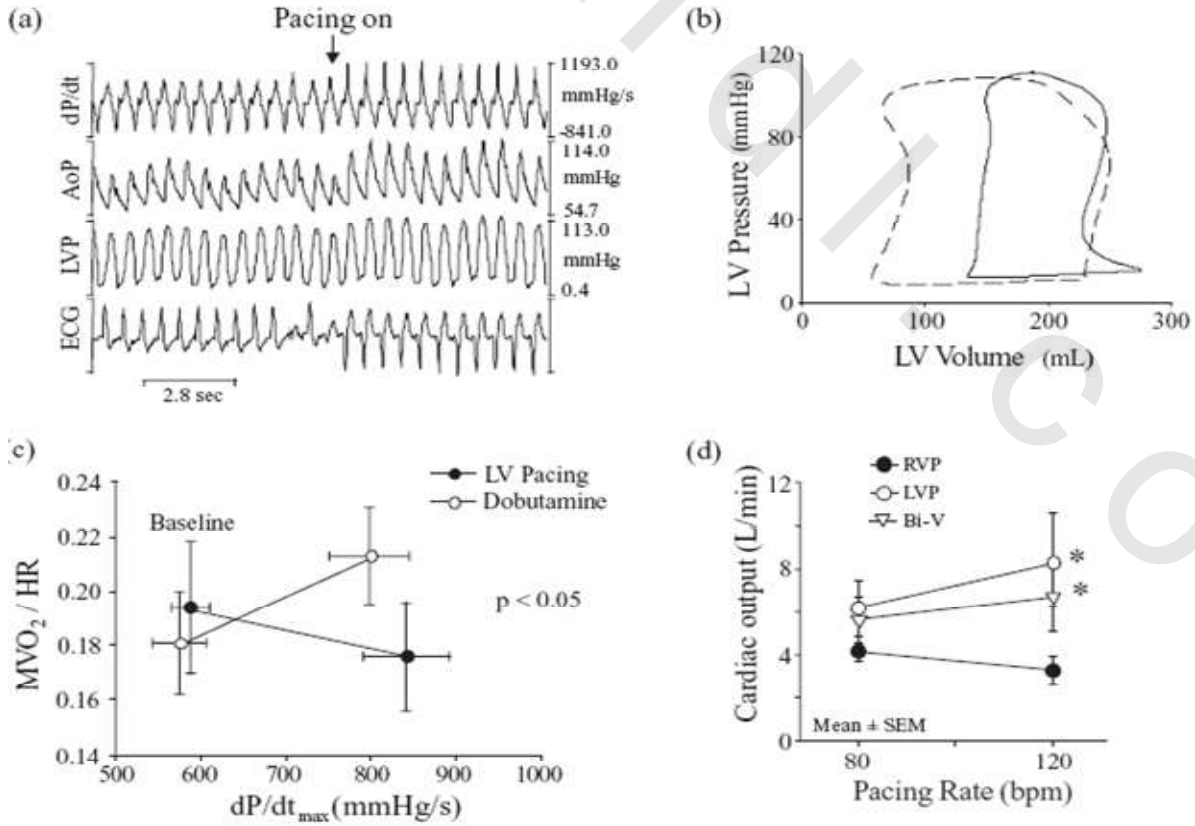

Figure 1.7: (a) Acute hemodynamic effects of CRT in a patient, assessed by peak rate of pressure rise (dP/dtmax), aortic pressure (AoP) pulse–indicating enhanced cardiac output), and LV pressure (LVP). Changes occur abruptly upon initiating CRT (note change in QRS morphology). (b) Pressure–volume loops showing the acute effect of CRT (dashed line) compared with baseline dyssynchronous contraction (solid line). Resynchronization induces a left shift of the entire loop, with increased stroke volume and reduced end diastolic filling pressures. (From Kass et al.[183]) (c) CRT improves LV energetics. Data shows comparison to intravenous dobutamine. Both interventions raised dP/dtmax over baseline, but dobutamine increased myocardial oxygen consumption (MV02), whereas CRT reduced it.) From Nelson et al.[176]) (d) CRT enhances cardiac output more at faster heart rates. Patients with atrial fibrillation and complete AV block received RV, LV, or BiV pacing. Output was lowest with RV pacing (LBBB-type dyssynchrony) and improved by either LV only or BiV pacing. These disparities became enhanced at the faster pacing rate, and shown due to improved diastolic filling with CRT. (From Hay et al.[186])

As shown in Figure 1.7.d, the augmentation of cardiac function with LV only or biventricular (BiV) pacing compared to RV pacing (the latter modeling LBBB) is greater at faster heart rates. This was subsequently explored in more detail by Vollmann et al.[179] and has been further investigated in several studies.[180-186]

XI. Chronic effects of cardiac resynchronization

a. Reverse chamber remodeling

Chronic CRT induces further changes in LV remodeling.[187–190] Here, the focus has been on chamber end-systolic and end-diastolic volumes that decline in most studies by an average of 10% over a 6-month period. As first indicated by Yu et al.[191] this reduction of heart volumes is not an acute effect of CRT, as it persisted even if pacing was temporarily suspended, whereas the rise in dP/dtmax associated with resynchronization acutely declined. Reduction of end-systolic volume has been used as a surrogate for mortality in heart failure patients receiving CRT[192], and marker of response, whereas acute hemodynamic changes have not generally predicted long-term response to therapy.[193]

b. Altered gene expression

As noted, excitation–contraction coupling and calcium handling is impaired in heart failure, and contributes to blunting of the force frequency response. CRT was shown to acutely enhance function at faster rates, and chronically, this appears to be coupled to improved gene expression of key Ca2+ handling proteins. Mullens et al.[180] obtained endomyocardial biopsies from the left interventricular apical septum and contrasted gene expression of calcium-handling proteins at the time of CRT implant to results at the 4-months follow-up. Significant up-regulation in sarcoplasmic reticular ATPase (SERCA2α), phospholamban (PLB), and the β1- adrenergic receptor gene expression was found after chronic CRT, with the SERCA2α/PLB ratio rising. The latter is thought associated with improving calcium uptake into the SR and thus the force–frequency response. There was also a trend toward increased sodium calcium exchange gene expression, which has also been associated with an improved FFR.[193] The authors found that these chronic gene expression changes were accompanied by an increase in the FFR. In another study of CRT effects on gene expression, Iyengar et al. [194] obtained endomyocardial biopsies from the RV septum in 10 patients with nonischemic cardiomyopathy and NYHA Class III–IV symptoms undergoing CRT implantation and repeated this after 6 months of CRT. The investigators found CRT increased the expression of α–myosin heavy chain (MHC) with a trend toward decreasing β–MHC, an isoform switch that is the reversal of that observed in heart failure (fetal gene recapitulation pattern).[195] The investigators also found a rise in phospholamban and trend toward increased SERCA2α–expression. Most recently, Vanderheyden et al.[181] reported similar changes in gene expression, but further suggested they occurred only in clinical "responders" to the therapy, and not those who were not. CRT reverses localized molecular remodeling and enhances global cell-survival signaling to more comprehensively explore the impact of CRT on molecular and cellular remodeling; one must obtain more than the tiny pieces of tissue extracted from endomyocardial biopsies. To approach this, their laboratory developed a canine model combining HF with dyssynchrony and CRT. In this model, dogs first undergo LBB ablation, followed by 3 weeks of atrial tachypacing to develop dyssynchronous HF. They are then randomized to an additional 3 weeks of atrial tachypacing (dyssynchronous HF) or biventricular tachypacing (CRT), both at the same rapid rate. Using this model, Chakir et al.[136] again found regional amplification of stress kinase expression and activation (e.g. MAP kinase and calcium-calmodulin dependant kinase II) in the late activated lateral wall of HF animals. Both proteins are linked to maladaptive changes in heart failure, contributing to fibrosis and myocyte dysfunction as well as arrhythmia.[196,197] In addition, the cytokine tumor necrosis factor-α (TNF-α) was markedly increased in the lateral wall. Up regulation of TNF-α itself induces dilated

cardiomyopathy.[198] In the resynchronized (CRT) failing dogs, however, these regional increases were reduced to re-achieve more homogeneous activation and expression. Although little human data on such kinases have been obtained, D'Ascia et al.[199] have reported similar suppression of TNF-α in LV biopsies from a small group of patients studied before and after receiving CRT. An even more intriguing finding was global improvement in cell survival signaling associated with CRT. Myocyte apoptosis increased in DHF, confirmed by TUNEL staining, caspase-3 activity (a key pro-apoptotic enzyme) and other assays. This was also showing reduced TUNEL positive myocytes in LV myocardial biopsies of patients having received chronic CRT.[199] Unlike stress kinase signaling, however, the decline in apoptosis was global. These findings were further related to global normalization of activated (phosphorylated) Akt kinase, an important regulator of cell survival pathways, with CRT. This was further coupled to the phosphorylation of pro-apoptotic molecule (BAD), inactivating the protein by its dissociation from Bcl-2 to suppress apoptosis.[199]

XII. Optimizing CRT

Several parameters determine the efficacy of CRT, including timing intervals between atrial-ventricular and right–left ventricular stimulation, the location of the left ventricular lead, and whether one stimulates both ventricles or only stimulates the LV. The last issue attracted attention early on, when it was found that LV only pacing could enhance systolic function as well if not slightly better than Bi-V modes.[182-184] Both modes similarly enhanced LV function as reflected in parameters such as dP/dtmax, stroke work, and cardiac output[183], yet the former does not typically shorten the QRS duration nor generate electrical synchrony.[184,185] This was also revealed in studies in which there was no possibility of a fusion complex as patients had complete AV blockade[186], leading to the conclusion that mechanical synchrony was more important to achieve CRT effects.[102,119,120,127,184] Biventricular stimulation may better impact diastolic relaxation and early filling.[186]

AV timing delay influences both the interaction of atrial systole on cardiac preload and mitral valve function, as well as determines if sufficient pre-excitation has been achieved for BiV stimulation. Although many studies have examined how this delay can be optimized[112,200], clinical findings Indicate that it has only minor impact in most patients and that a standard delay of near 120 ms is generally effective.[183,102] The RV–LV delay similarly has been shown to be a parameter that can influence CRT efficacy in some subjects, with LV advanced being the usually preferred mode. However, the phase delay is short ($\leq$20 ms in

most patients) and simultaneous stimulation results in similar effects on average.[186] Furthermore, optimization of these delays has been always performed in subjects at rest, and it remains unclear if these values remain "optimal" under stress. One factor that clearly makes a difference is where the LV lead is placed. This was first reported by Butter[201] in patients, and more comprehensively by Helm et al.[127] in a canine model of dyssynchronous heart failure. For the latter, dogs with dilated HF and a LBBB were subjected to CRT where the LV pacing site was randomly varied across the entire LV wall by means of a multielectrode epicardial sock. Three-dimensional maps of global functional response were generated where the percent change in a given parameter was color coded and placed on the map where the LV pacing lead was located. The optimal pacing site certainly depends on the specifics of the conduction delay, and although most patients have late lateral-wall activation, this can vary, and some extent of right-sided blockade is common. Interestingly, dyssynchrony generated from a pure right bundle branch is significantly less than that associated with left bundle branch block[117], and the corresponding impact of CRT is less. Furthermore, one achieved the same benefit using a right heart pacing lead alone as from a traditional biventricular activation mode.

XIII. Clinical response to cardiac resynchronization

For appropriately selected patients, resynchronization therapy improves exercise capacity and reduces symptoms. The most commonly reported measures of functional capacity include 6-minute walk distance (a measure of the ability to perform activities of daily living[202]), peak oxygen consumption during a cardiopulmonary stress test (MVO2 max), and quality of life (usually assessed using the Minnesota Living with Heart Failure Questionnaire). [203] Diminished 6-minute walk distance [204] and diminished MVO2 max[205] are both strong indicators of poor prognosis in advanced heart failure. The results of the major randomized clinical trials reporting outcomes for these variables are summarized in Figures 1.8 & 1.9.

In such trials as MUSTIC[13], PATH-CHF[206], MIRACLE[14], CONTAK CD[207], MIRACLE ICD[208], and PATH-CHF II[209], resynchronization therapy consistently improved functional capacity and reduced heart failure symptoms. Specifically, resynchronization was associated with a 1–23% improvement in 6-minute walk distance, a 7–10% increase in MVO2max, and an 11–31% improvement in quality of life scores. The MUSTIC trial was designed as a blinded crossover trial comparing active and inactive pacing. After the end of the crossover period, when patients were asked which phase they preferred, an

overwhelming majority (85%) chose the period of active pacing.[13] In the MIRACLE trial, total exercise time during treadmill testing improved by more than 1 minute in patients receiving resynchronization therapy compared with those getting inactive pacing; this represents a 13% improvement over baseline.[207] Reflecting the overall impact of these changes, the data consistently show that resynchronization therapy results in a one NYHA functional class improvement in symptoms, corresponding (on average) to a change from moderate heart failure symptoms to mild heart failure symptoms. Thus, in the MIRACLE trial 52% of patients improved by one functional class whereas a much smaller number improved by two functional classes (16%) and the remainder failed to respond to therapy.[207] It is, however, extremely important to interpret these results in the context of the 38% response rate in the placebo arm of the trial.

The MUSTIC, PATH-CHF, MIRACLE, CONTAK CD, MIRACLE ICD, and PATH-CHFII trials enrolled patients with: (1) moderate to severely symptomatic congestive heart failure despite optimal medical therapy, (2) severe left ventricular systolic dysfunction (LVEF ≤35%), (3) a wide QRS complex (generally defined as a QRS ≥120–130 ms), and (4) sinus rhythm. As a result, these inclusion criteria have become the conventional indications for resynchronization. As seen in Figure 1.9, the effects in these "conventional indication" trials are far more robust than the effects observed with conventional pharmacologic therapy of heart failure. For instance, improvement in 6-minute walk distance was observed in only 2 of 6 trials of ACE-inhibitors, 3 of 17 trials of beta-blockers, and 1 of 4 trials of digoxin.[210] Trials of both beta-blockers and ACE inhibitors have likewise shown inconsistent results with respect to MVO2max[211,212] and quality of life.[213,214]

In contrast to patients meeting conventional indications for CRT, patients in other groups have not been shown to benefit from resynchronization. In the MUSTIC AF trial [215], resynchronization failed to improve outcomes when used in patients with persistent atrial fibrillation and bradycardia requiring permanent pacing. In the MIRACLE ICD II trial, resynchronization did not improve 6-minute walk distance, MVO2max, or quality of life among patients with mildly symptomatic heart failure at the baseline.[216] The same observations were made for the subgroup of NYHA Class II patients enrolled in CONTAK CD.[207] Finally, the RETHINQ trial demonstrated that CRT did not improve exercise capacity for patients with echocardiographic evidence of intraventricular dyssynchrony but with a narrow QRS.[217]

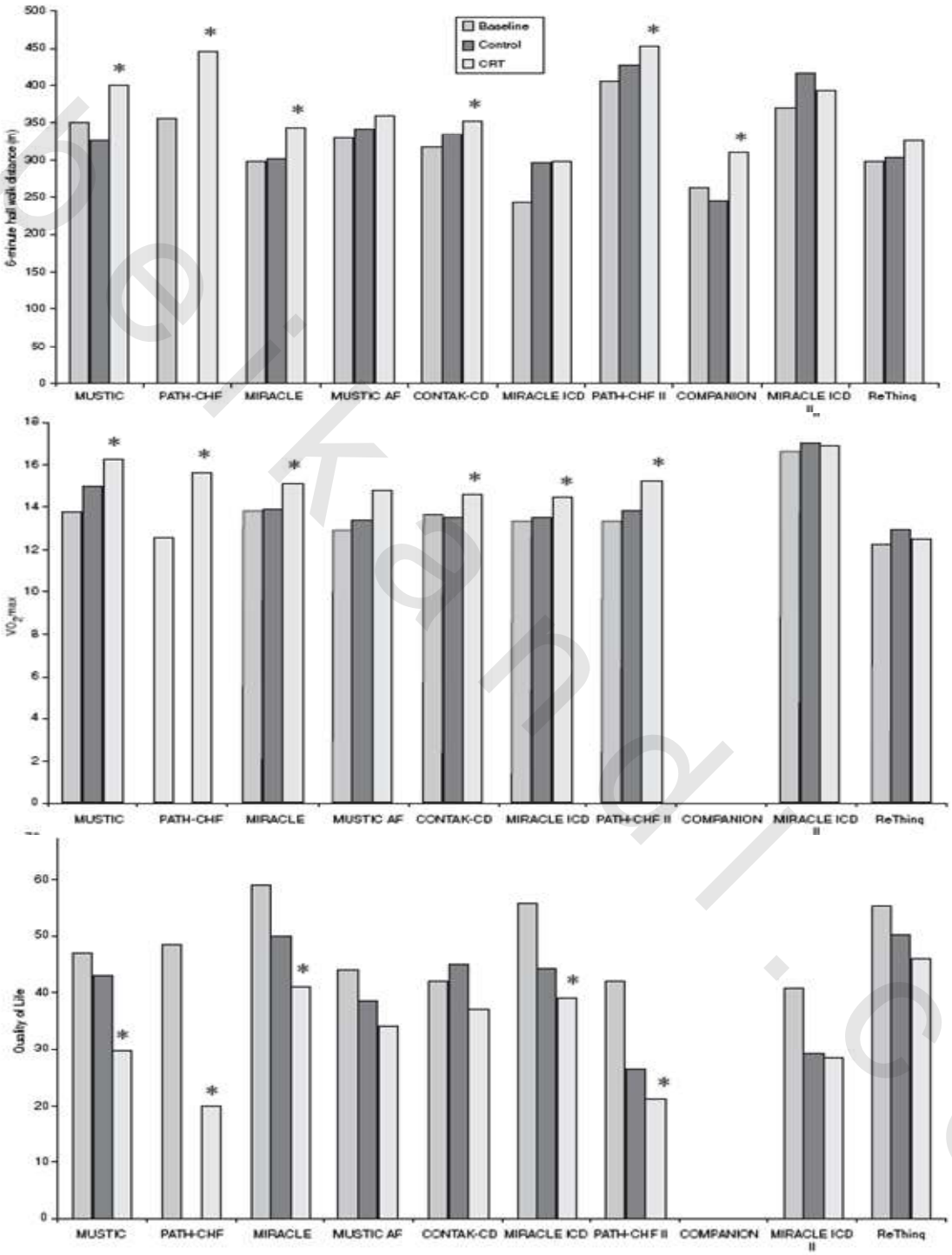

Figure 1.8: Effect of resynchronization therapy on 6-minute walk distance, MVO2 max, and Quality of Life in randomized multicenter trials.

In addition to improving symptoms, randomized clinical trials have also shown that conventionally indicated patients derive objective evidence of beneficial structural changes (often referred to as "reverse remodeling") in

response to CRT. Resynchronization reduces left ventricular end-systolic [16,200,207,218] and end-diastolic volumes [200,207,218] and increases left ventricular ejection fraction.[16,200,207]The improvements in ejection fraction ranged from 2–7 absolute percentage points and are noteworthy given that the baseline ejection fractions in these trials were in the range of 21–25%. The data from trials reporting sufficient information to determine baseline, and treatment versus control ejection fractions. A meta-analysis of randomized clinical trials of cardiac resynchronization therapy found the average absolute improvement in ejection fraction to be 3 percentage points.[43] The remodeling effects of resynchronization therapy are progressive [200,218] and persist for at least 18 months after the initiation of therapy.[16] Resynchronization is also associated with reduced mitral regurgitation [16,200,218] and with improvements in the neurohormonal milieu as evidenced by lower plasma catecholamine levels [219], increased heart rate variability [189], and striking reductions in N-terminal pro-BNP levels (reductions of 454–567 pg/ml at 12–18 months).[219, 220]

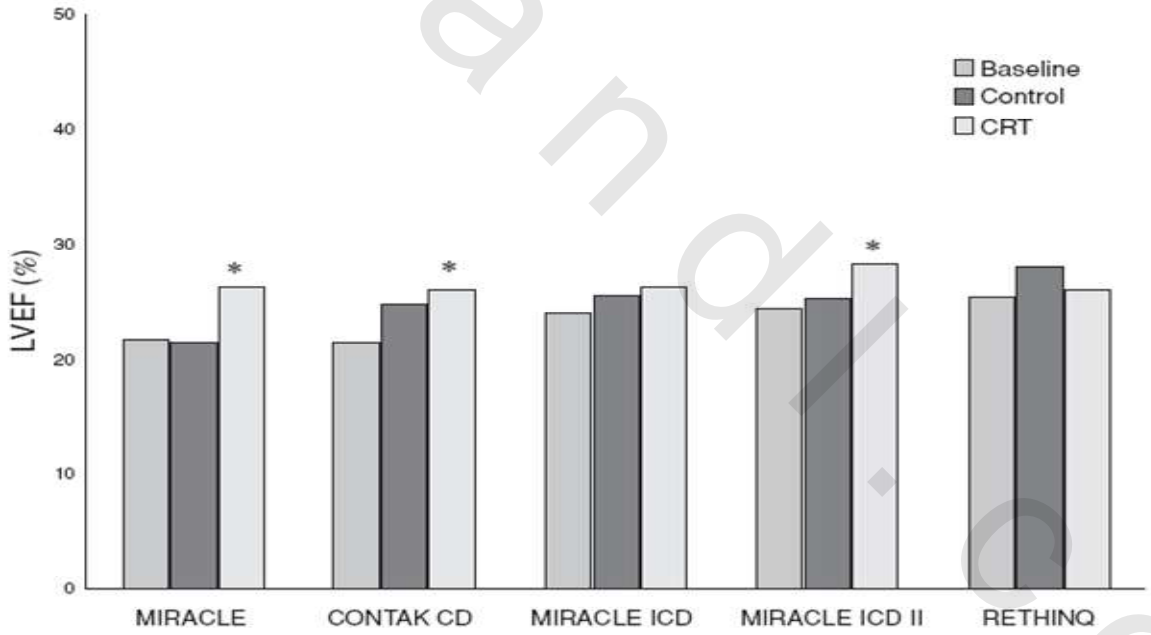

Figure 1.9: Effect of resynchronization therapy on left ventricular ejection fraction. ∗denotes a significant improvement compared to the control.

XIV. Resynchronization and survival

In addition to improving symptoms, cardiac resynchronization therapy is also proven to improve survival in conventionally indicated populations. Although the early randomized clinical trials of CRT were not large enough to include mortality as a primary endpoint, a meta-analysis of the MUSTIC, MIRACLE, MIRACLE ICD, and CONTAK CD trials concluded that

resynchronization therapy, with or without concomitant use of a defibrillator, reduced mortality due to progressive heart failure by 51%.[221] COMPANION was the first trial adequately powered to analyze total mortality as an independent endpoint.[15] In addition to significantly reducing the combined endpoint of hospitalizations and mortality, all-cause mortality was reduced by 24% ($p = 0.06$) in the group receiving CRT-pacemakers and reduced by 36% ($p = 0.003$) in the group receiving CRT-defibrillators. The absolute mortality rate at 1 year was 19% in the medically treated group (a result that serves to highlight the remarkably poor prognosis for patients with advanced heart failure and left bundle branch block), 15% in the pacemaker group, and 12% in the pacemaker–defibrillator group. The survival benefit from resynchronization therapy was confirmed in the CARE-HF trial. In this study, which almost exclusively employed CRT pacemakers (rather than CRT-defibrillators), all-cause mortality was reduced by 36% with resynchronization therapy ($p<0.002$).[16] The absolute mortality rate in the medical-therapy group was 13% at one year as opposed to 10% in the cardiac resynchronization group. Longer-term evaluation of the CARE-HF cohort shows that the mortality benefit increased in magnitude with longer duration follow-up: mortality at 3 years was 35% in the medical group and 24% in the CRT group.[37] Extensive subgroup analysis was performed in both the COMPANION and CARE-HF trials to attempt to identify which patient groups derive the greatest benefit from the therapy, but neither trial identified any significant heterogeneities, according to pre-implant patient characteristics.[15,16]

Although resynchronization has been proven to improve survival compared with standard medical therapy of heart failure, it should be emphasized that there is no evidence that resynchronization therapy improves survival when compared with ICD therapy alone.[43] It is also curious to note that the addition of resynchronization did not reduce ICD therapies for ventricular tachycardia/ventricular fibrillation in either the CONTAK CD or the MIRACLE ICD trials.[207,208] It is possible that these observations may reflect the relatively large proportion of secondary prevention patients enrolled in these trials [222] as well as the relatively short duration of follow-up. The improvements in functional outcome and survival associated with resynchronization therapy have translated into reduced hospitalizations for heart failure patients.[13-16,215] A meta-analysis of the trial data concluded that resynchronization reduced the risk of hospitalization for heart failure exacerbation by approximately one-third.[43] As a result, the therapy is highly cost effective. An analysis using data from COMPANION and CARE-HF calculated that an incremental cost of approximately $10,000 per quality-adjusted year of life is associated with the use of cardiac resynchronization therapy in a conventionally indicated population.[223]

XV. Unresolved questions

The available clinical trials regarding cardiac resynchronization therapy provide a wealth of evidence on which to base practice. Nevertheless, numerous fundamental questions remain unanswered.

a. Minimally symptomatic patients

Among the unresolved questions concerning resynchronization therapy is whether the therapy has any role for patients with severe left ventricular dysfunction but minimally symptomatic or asymptomatic heart failure. Many of these patients are candidates for prophylactic ICD implantation.[224, 225] As noted above, resynchronization therapy results in limited functional improvement for patients who are minimally symptomatic at baseline. In CONTAK CD there was no improvement in 6-minute walk distance, MVO2max, quality of life, or NYHA functional status among the NYHA Class I and Class II patients enrolled in the trial.[207] In MIRACLE ICD II trial, which only enrolled patients in NYHA Class II, there was no improvement in the primary outcome (change in MVO2max), and there was inconsistent improvement in secondary functional endpoints: a marginally significant improvement in NYHA functional class was observed but there was no change in quality of life score or 6-minute walk distance.[216] On the other hand, both the CONTAK CD and MIRACLE ICD II trials showed that resynchronization results in convincing echocardiographic evidence of reverse remodeling in minimally symptomatic patients less than was observed in more highly symptomatic populations.

In both trials, resynchronization led to statistically significant reductions in LV end-systolic and end-diastolic dimensions. The MIRACLE ICD II trial data showed a significant increase in ejection fraction; there was also a corresponding trend toward an increase in LVEF in the minimally symptomatic patients in CONTAK-CD. Therefore, it is conceivable that there may be long-term hemodynamic or survival benefits to resynchronization therapy in minimally symptomatic patients. It may be that these effects were not apparent in earlier trials due to the relatively short duration of follow-up or inadequate sample size.

b. Atrial fibrillation

A second fundamental question concerns the role of resynchronization therapy in patients with persistent atrial fibrillation. Atrial fibrillation (AF) is common in advanced heart failure [226], but patients with persistent atrial fibrillation were excluded from the majority of randomized clinical trials of resynchronization. Three multicenter randomized trials of resynchronization therapy have enrolled patients with persistent atrial fibrillation who required permanent pacing. In the MUSTIC trial, resynchronization therapy did not result in an improvement in the primary endpoint (improvement in 6-minute walk distance).[215] However, when analyzed on an efficacy basis (rather than according to the intention to treat principle), the resynchronization therapy group achieved borderline increases in both 6-minute walk distance and MVO2max.

In the PAVE trial, patients receiving cardiac resynchronization therapy following atrio-ventricular (AV) node ablation experienced a greater improvement in 6-minute walk distance than did patients treated with RV-only pacing.[227] Furthermore, the resynchronized patients avoided the deterioration in left ventricular ejection fraction that was observed in the right ventricular (RV)-paced group. In the OPSITE trial, biventricular pacing was also associated with a modest improvement in symptoms and a greater improvement in LVEF when compared with RV-only pacing following AV node ablation for atrial fibrillation.[228] Thus, these data suggest that resynchronization therapy is a better alternative than conventional RV-only pacing for patients with moderate-to-severely symptomatic heart failure and persistent atrial fibrillation who independently require permanent pacing. The PAVE and OPSITE trials stand out among the published randomized trials of cardiac resynchronization therapy in enrolling patients irrespective of pre-implant ejection fraction. In fact, nearly half of the patients in PAVE had a left ventricular ejection fraction above 45%. Post hoc analysis of PAVE suggests that the majority of the benefit in the trial was confined to the subgroup with a pre-implant ejection fraction of less than 45%. However, the opposite pattern was observed in the OPSITE trial. In that trial, the comparative benefit to biventricular pacing was greatest in those patients with normal baseline left ventricular function. It is possible that these discordant results reflect the play of chance a larger trial is necessary to resolve the issue.

Limited nonrandomized data suggest that even without undergoing AV node ablation, patients with atrial fibrillation may derive a benefit from resynchronization that can be comparable to that experienced by patients with sinus rhythm. However, there is a higher incidence of nonresponders among patients who do not undergo AV node ablation (46%) compared to those who do undergo the procedure (29%).[229] This observation highlights the importance of

achieving adequate rate control (sufficient to permit a high percentage of biventricular pacing) in these patients. Such rate control may be difficult to achieve solely with pharmacologic therapy: in one study, fully 70% of atrial fibrillation patients required AV node ablation in order to achieve adequate (>85%) biventricular pacing.[230] It should be noted that although there are numerous patients with persistent AF converting to sinus rhythm following the institution of CRT, this is a rare event, and there is no reduction in the incidence of new atrial fibrillation in patients receiving resynchronization for conventional indications.[231]

c. Nonresponders

One of the most critical issues in the field of CRT concerns "nonresponders." A substantial minority of patients receiving resynchronization therapy for conventional indications derive little or no benefit, whether defined on the basis of echocardiographic response (typically a reduction in left ventricular end-systolic volume of at least 15%) or symptomatic improvement (typically improvement by at least one NYHA functional class). A closer look at the MIRACLE data is instructive: 52% of patients improved by one functional class and another 16% of patients improved by two or more functional classes. Very few patients experienced a worsening of symptoms with the therapy (2%), but 30% of patients were "nonresponders".[14]

Three potential explanations might explain "nonresponse" (Table 1.2). First is patient selection: Was the device implanted in a patient who never possibly could have responded? Substantial controversy exists regarding the appropriate QRS width cut-off to determine eligibility for resynchronization. As noted above, most resynchronization trials used a QRS duration of greater than 120–130 ms as an enrollment criterion, but this has not been uniform. In the MUSTIC trial, for example, the QRS duration cut-off was 150 ms.[13] Even in the trials with more liberal enrollment criteria, the mean QRS width for patients actually enrolled in the trial tended to be quite long: in the MIRACLE trial the mean QRS width in the group eventually randomized to resynchronization was 167 ms, and it is estimated that only about one-sixth of patients had a baseline QRS duration less than 145 ms.[14] Extrapolation of these results to populations with QRS durations in the 120-130 ms range is thus difficult.

ent Selection	ents without dyssynchrony, including those with BB, QRS <120 msec ents with transmural lateral myocardial infarction

ice Programming	ure to achieve adequate biventricular capture optimal AV interval optimal LV-RV timing
d Placement	ure to place the LV lead in an area leading to quate resynchronization

Table 1.2: Nonresponders to resynchronization therapy: Potential etiologies.

The PATH-CHF II investigators prospectively stratified patients according to baseline QRS duration (QRS 120–150 vs. QRS >150 ms) and found that the benefit of resynchronization was confined to the group with a QRS duration >150 ms.[206] There was a nonsignificant tendency toward a similar result in the subgroup analysis of COMPANION.[15] The cohort of patients eligible for CRT in trials based on QRS width alone includes the group of patients with RBBB. In these patients, late activation occurs in the right ventricular free wall and there is no a priori reason to expect them to benefit from left ventricular pacing. Indeed, an analysis of pooled data from the MIRACLE and CONTAK CD trials shows that patients with right bundle branch block derive limited benefit from CRT.[232]

Growing data show that patients without intraventricular dyssynchrony are unlikely to respond to resynchronization therapy, no matter how wide their QRS. [233,234] Two randomized clinical trials have used echocardiographic measurement of dyssynchrony to aid in patient selection for resynchronization therapy. In CARE-HF patients could be enrolled on the basis of QRS duration alone, if the QRS was 150 ms or greater. Patients with a QRS of 120–149 ms were required, in addition, to demonstrate two of three echocardiographic criteria for dyssynchrony:

(1) an aortic pre-ejection delay >140 ms
(2) an interventricular mechanical delay of >40 ms
(3) delayed activation of the posterolateral LV wall by M-mode or tissue Doppler imaging.[235]

Perhaps as a result, subgroup analysis of the CARE-HF data did not show any heterogeneity of response according to pre-implant QRS duration.[16] In the RETHINQ trial, patients with a QRS <130 ms were selected for resynchronization if they had echocardiographic evidence of intraventricular dyssynchrony, predominantly on the basis of tissue Doppler imaging. In this trial, patients with a QRS interval of less than 120 ms experienced no improvement in the primary endpoint (MVO2max), but in the prespecified subgroup of patients

with a QRS interval of 120–129 ms MVO2max increased significantly with resynchronization.[217] It should be acknowledged, however, that the results of the PROSPECT trial raise concern regarding the ability of current echocardiographic techniques to reproducibly measure dyssynchrony and to distinguish clinical responders from nonresponders.[236] Data also exist to suggest that patients with transmural myocardial infarctions of the lateral wall are unlikely to improve with lateral left ventricular pacing.[237] Echocardiographic substudies of the MUSTIC and MIRACLE trials have shown greater reverse remodeling in patients with nonischemic as opposed to ischemic cardiomyopathies.[200,218] It is, however, important to recognize that substudy analysis shows no difference in clinical outcomes between patients with ischemic versus nonischemic heart disease.[15,16,207]

A second potential cause of "nonresponse" is suboptimal programming, not only with respect to programming AV delay [102,108] but also potentially with respect to programming LV–RV timing.[112] In fact, failure to program an optimal AV delay may result in as much as a 10–15% decline in cardiac output.[238] Although many trials have shown acute hemodynamic benefits to AV optimization, limited data exist to show that systematic optimization results in a long-term improvement in clinical outcome.[239,240]

The major randomized clinical trials have used wildly different approaches to programming the AV delay:
(1) in the CONTAK CD trial, a fixed, short AV delay was empirically programmed [206]
(2) in the COMPANION trial, the AV delay was programmed according to a formula taking into account the baseline PR interval and baseline QRS duration [15]
(3) in the MIRACLE [14] and CARE-HF [16] trials, echocardiographic imaging of mitral valve inflow was used to determine an "optimum" AV delay.

In addition to AV optimization, it has been proposed that programming sequential rather than simultaneous LV and RV pacing (often referred to as "VV timing") may further improve ventricular performance.[241] However, in neither of two randomized clinical trials did VV optimization following AV optimization affect the long-term clinical response to resynchronization therapy.[242,243] The effect of other programming choices is unclear. The potential for an improvement in outcome with rate adaptive pacing is particularly interesting. Chronotropic incompetence is common in patients with

advanced heart failure, [244] and may itself reduce functional capacity as well as limit the use of beta blockers.

A third possible cause of "nonresponse" is failure to place the left ventricular lead in an adequate position. Early data showed that the hemodynamic response to resynchronization was greatest for left ventricular leads placed on the midlateral wall of the left ventricle.[245] Bearing this in mind, the actual lead positions achieved in clinical trials are striking. For example, in the CONTAK CD trial, the left ventricular lead was placed on the mid-lateral wall in only 40% of all of the cases. The extent to which precise lead placement affects the response to therapy is controversial. In an animal study, the area yielding 90% of the maximal response to CRT covered only 16% of the left ventricular free wall, but sites yielding 70% of the optimal dP/dtmax covered fully 43% of the free wall.[127] Observational data suggest that the choice of optimum lead position may need to be individualized and that leads should be placed in the region of latest left ventricular activation [246], although this has yet to be proven in a prospective manner.

XVI. Implantation of a CRT device, technical aspects:

a. Anatomy of the coronary sinus

The venous drainage system of the heart runs for the most part parallel to the coronary artery system.[247] The anterior cardiac vein of the left ventricle runs in the anterior interventricular groove and becomes the great cardiac vein as it enters the atrio-ventricular groove. The greater cardiac vein receives a variable number of contributing left marginal (left lateral) and posterior cardiac veins. After the Vieussens valve the greater cardiac vein becomes the coronary sinus (CS) which drains the venous blood into the posterobasal right atrium.[248]

The coronary sinus also receives blood from the middle cardiac vein, which runs in the posterior interventricular groove parallel to the posterior interventricular branch of the right coronary artery. From the right heart chambers, the venous blood reaches the coronary sinus through the small cardiac vein. Although the anterior and middle cardiac veins are virtually always present, there is great variability in the presence and anatomy of the left marginal and posterior cardiac veins.[249] In addition to the Vieussens valve, the Thebesian valve at the ostium of the coronary sinus (Figure 1.10) can serve as an obstacle.[250]

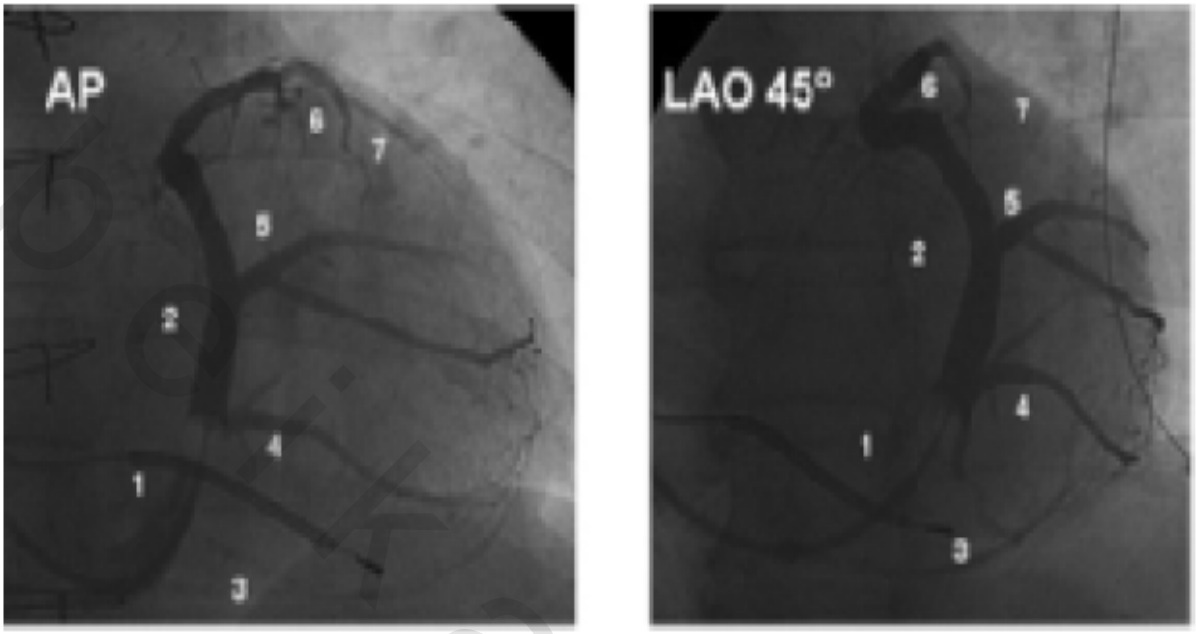

Figure 1.10: The cardiac venous system (Fluoroscopic views in AP and LAO45 degree angulation). An ICD lead is already positioned in the right ventricle. 1: coronary sinus; 2: greater cardiac vein; 3: middle cardiac vein; 4: posterior vein; 5: posterolateral vein; 6: anterior cardiac vein; 7: anterolateral cardiac vein.

b. Implantation techniques

CRT implantation should preferentially be carried out in the catheterization laboratory because it is important to have high-quality fluoroscopy equipment at hand. The patient should be in a fasting state for about 6 hours, and adequate hydration should be maintained with a stable intravenous line, ideally at the side of the planned implantation. This allows the operator to perform a venography in the case of difficult venous access. The patients are usually allowed to take their heart failure medication the same morning. It is not necessary to interrupt oral anticoagulation for CRT implantation, but patients should have their (INR) reduced to about 2.[251] Apart from rare instances, the devices can be implanted using local anesthetics and conscious sedation (e.g. midazolam and fentanyl). This has been proven to be safe and minimizes the risks of general anaesthesia in patients with severely reduced left ventricular function and common comorbidities.[252] Antibiotic prophylaxis reduces the risk for device infection.[253,254] For shock testing in defibrillator implantion, short-acting intravenous anaesthetics (e.g. propofol or etomidate) can be used.

1. Venous access

Left-sided venous access should be preferred because most patients will receive a CRT-defibrillator, and most guiding catheters are designed to be placed from the left side. Right-sided access will create a second right-angle turn at the junction from the subclavian vein to the superior vena cava.[255] In case of an upgrade and pre-existing intravenous leads, an intravenous line should be placed in the ipsilateral arm to visualize the venous system and to prepare oneself for a more complex implantion in the case of venous occlusion.[256]

2. Implantation of the RV and RA leads

The right ventricular lead should be positioned first. Because the majority of patients will display LBBB, this lead will provide back-up pacing in the case of induction of a complete AV block during catheterization of the coronary sinus. Additionally, the movement of the lead body may help to visualize the level of the tricuspid valve, which may assist in localizing the ostium. The proximal portion of the Implantable Cardioverter-Defibrillator (ICD) coil is often located near the coronary sinus os. Some operators prefer to implant the atrial lead at the end because the atrial lead is prone to dislodgement during difficult LV lead placement.[255]

3. Coronary sinus cannulation

One has to bear in mind, that chamber enlargement in the failing heart causes an upward shift of the long axis and a posterior shift of the short axis, which result in a lower and more posterior position of the CS ostium in the right atrium.[255] Although it is virtually always possible to succeed with a postero-anterior (PA) projection of the fluoroscopy, it may initially be helpful to briefly use an RAO 30-degree projection to look for the fat pad in the AV groove. This and possible calcifications of the right coronary artery may serve as anatomic markers for the position of the AV groove and the course of the CS. Cannulation of the CS ostium is best performed in a left anterior oblique (LAO) 30–45 degree projection. In this view, the coronary sinus runs posteriorly toward the spine. It is helpful to review the venous phase of previous coronary angiograms to get an idea of the location of the CS ostium.[255] Although there are numerous shapes of guiding catheters, operators should become acquainted with "their" catheter and not change types too often. If the catheter does not engage directly by probing with the J wire one can give contrast "puffs" to visualize the ostium in the low right atrium. One has to be careful not to use too much contrast with this approach because many patients suffer from some degree of renal failure and are

prone to cardiac decompensation. It is preferred to insert an "inner" sheath through the guiding catheter, thereby creating a telescopic system with gives better reach and allows for better rotational capabilities to locate the ostium. An alternative approach is the use of a deflectable electrophysiology (EP) catheter. Apart from the steerability of the catheter, this approach has the advantage of using intracardiac signals to locate the ostium. This approach is considered the best in difficult cannulations in patients with severe impairment of their renal function. Manufacturers now also offer a steerable guiding catheter with a lumen for guidewire insertion and contrast injection.[255]

4. Coronary sinus venography

Once the CS has been entered, venography should be performed to get an overview of potential target veins (Figure 1.10). Potential obstacles, like Vieussens valve, should be carefully crossed with the guide wire in order to avoid perforation.[257] Contrast injection is then carried out through a single-lumen, balloontip catheter after occlusion of the vessel. In order to avoid coronary sinus dissection, it is advisable to confirm that the balloon is not wedged in a side branch or underneath a valve by injecting a little contrast puff before inflating the balloon. It is helpful to store two venograms, typically in a PA or a RAO 30-degree projection and/or in a LAO 30–45 degree projection. The use of CT angiography to delineate the CS anatomy prior to LV lead implantation has been described.[258] However, given the high radiation exposure (6–13 mSv) and the relative ease to perform a simple venography, this modality should be reserved for patients with difficult anatomies (e.g. adults with certain forms of congenital heart disease). Cardiac magnetic resonance also allows visualization of the cardiac venous system without any additional radiation exposure.[259]

5. Selection of a target vein

The target veins for cardiac resynchronization therapy should be at the left free wall (i.e. the left lateral or posterolateral vein). It has been shown that these positions clearly yield better results than anterior stimulation.[201] Should there be no apparent suitable vein on the venogram, this should be repeated in an occlusive position and with prolonged filming. Frequently, collateral flow then demonstrates large lateral wall drainage through a large middle cardiac vein; alternatively, one can look for anterolateral branches of the anterior cardiac vein. In the PA projection, these veins run at the anterior border of the heart silhouette parallel to the diagonal branches of the coronary artery (Figures 1.10, 1.11).

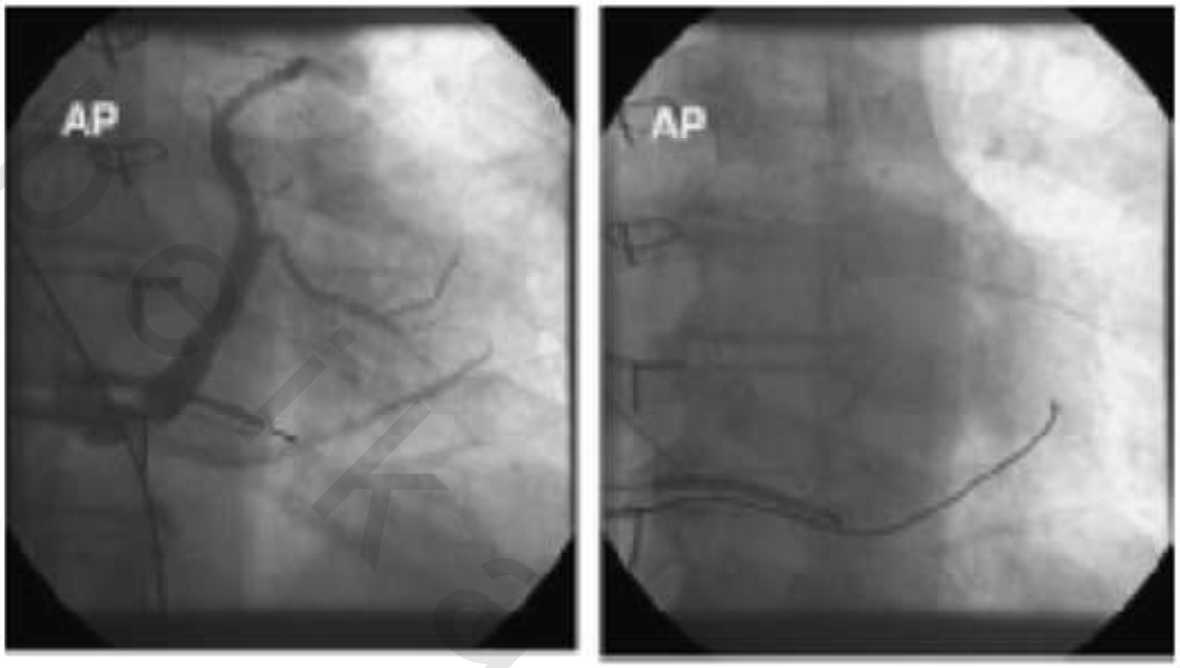

Figure1.11: Fluoroscopy: lateral side branch draining in the middle cardiac vein.

6. LV lead placement

Depending on the anatomy of the target vein, this part of the implantation can be straight forward or develop into a tedious undertaking. Operators should have different shapes and sizes of available LV leads at hand because one size does not fit all veins.[260] Unipolar or bipolar leads in different shapes and sizes, ranging from 4 to 6 French are available. These can be used either stylet-driven or in an over-the-wire technique.[255] The anchoring mechanisms differ from small tines, over preshaped distal curves to helical fixation mechanisms (Figure 1.12). If one targets small branches of a vein, a small, flexible unipolar lead should be chosen. With this lead, one has very few options if this pacing site does not prove to be optimal because it is virtually impossible to position this lead in a greater vein in a wedge position without a high risk for dislodgment. Therefore, it`s better to use bigger preshaped LV leads with more rigid loops at their distal segment because these give the greatest freedom to place the lead at many locations within the venous tree.

Figure 1.12: Different anchoring mechanisms of available LV-pacing leads

The use of bipolar/quadripolar leads can reduce the occurrence of phrenic nerve stimulation and may help to improve LV-pacing thresholds (e.g. by electrical repositioning, Figure 1.13) in selected cases. In case of a medium-sized vein that enters the CS at a wide angle, a preshaped bipolar lead can be readily advanced using a stylet only (figure 1.14).

If the best target vein enters the CS in an acute angle, or if the operator tries to manipulate the lead into a small tributary branch to ensure optimal lead stability, the over-the-wire technique should be chosen. Soft/medium distal strength 0.014 inch guidewires are usually preferred. In the case of very acute angles, the lead might not track across the angle and dislodge the wire. In this situation, one can engage the vein selectively with an inner sheath and try to advance the soft-tipped guiding catheter into the side branch. Should this not be possible, operator can position a heavy weight 0.016 inch guidewire in the most distal position, remove the inner sheath and then advance the lead. Currently, modern lead technology allows one to advance a multipolar 4 French LV-pacing lead through the inner catheter into the subselected vein. In case of very small veins, a unipolar lead may be advantageous to ensure proper placement of the lead.[260]

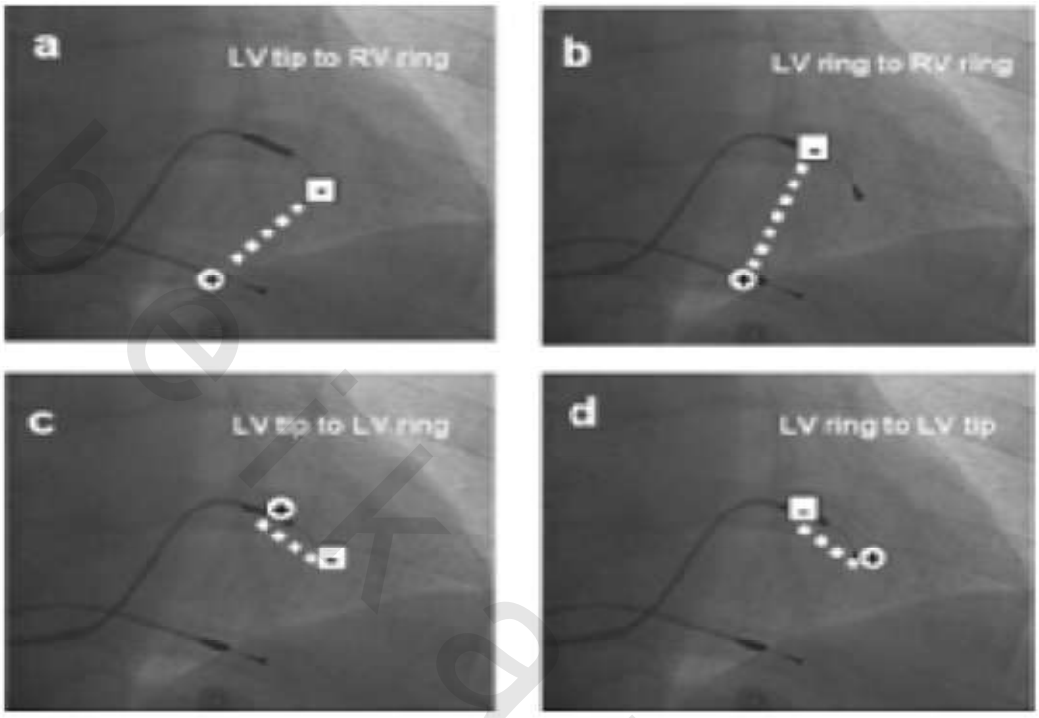

Figure 1.13 Electrical reprogramming to avoid phrenic nerve stimulation. (a) LV tip to RV ring; extended bipolar vector; (b) LV ring to RV ring; extended bipolar pacing vector; (c) LV tip to LV ring; dedicated bipolar pacing vector; (d) LV ring to LV tip.

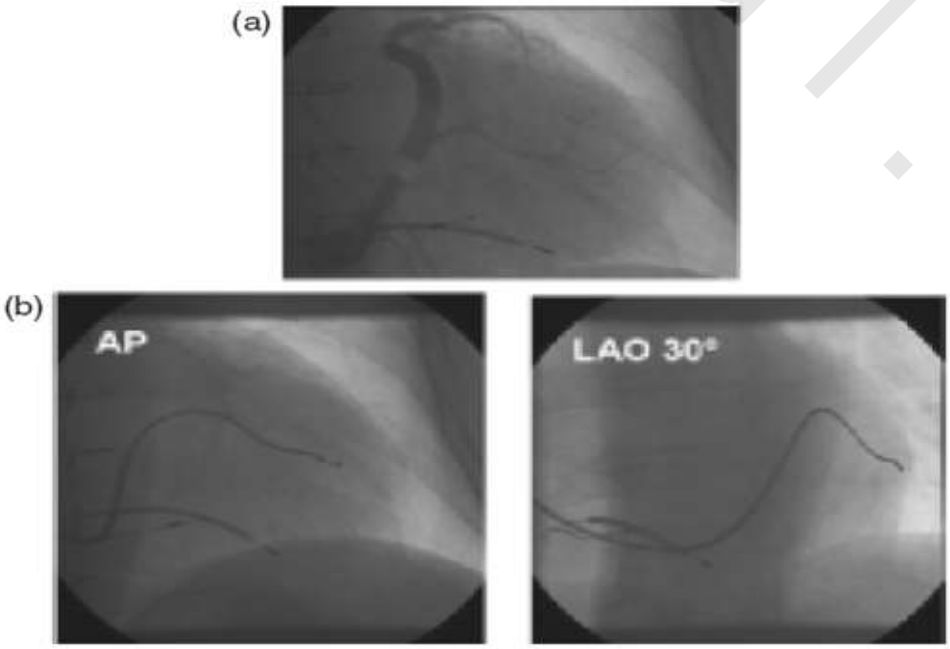

Figure 1.14 (a) Easy access of a lateral vein (Venogram, PA projection); (b) Excellent position of a bipolar lead in a lateral vein. Note the distance between RV- and LV-pacing lead in a LAO 30-degree projection

7. LV lead testing

The ideal pacing site should be a position as far lateral or posterior and as far away from the right ventricular lead as possible. Visual dyssynchrony can be confirmed by fluoroscopy in a LAO projection. Several methods, such as the timing of the LV electrogram relative to the onset of the QRS complex-ideally at late as possible [106], determination of the most delayed site by electroanatomical mapping systems [70], or echocardiographic methods [107,264] have been proposed for determination of the best left ventricular pacing site. During implantation, a negative QRS complex in lead I of the surface ECG indicates a LV lead position on the left lateral wall.[265]

Once one has placed the lead in the desired anatomical and/or electrical position, the lead impedance and pacing threshold should be tested. One may accept higher thresholds (e.g. 3.5V @ 0.5 ms) than usual, if no other promising target veins appear to be readily accessible. Unfortunately, the intimate relation between the left lateral wall and the left phrenic nerve will frequently cause phrenic nerve stimulation resulting in diaphragmatic contraction. Even intermittent diaphragmatic stimulation is unacceptable. Therefore, one should test for phrenic nerve stimulation with 10V @ 0.5 ms during deep inspiration and maximal expiration. Generally, phrenic nerve stimulation mandates repositioning of the lead. In rare cases with a very low LV-pacing threshold and very high threshold for phrenic nerve stimulation, one gets away without repositioning.

If the patient sits or stands after the implantation, the LV pacing threshold frequently rises and the diaphragmatic threshold may fall. Different programming options, like true LV bipolar pacing or change of the unipolar pacing pathway, may then solve the problem through “electrical repositioning.” However, intraoperative avoidance of phrenic nerve stimulation by repositioning of the LV lead is time well spent and will reduce the risk for re-operation later.

8. Removal of the guiding catheter

Once the LV lead is in place, the guiding catheter has to be removed without dislodging the lead. For that purpose numerous slitting tools are

available. During removal of the catheter, a stylet or a stabilizing wire should be kept inside the lead up to the level of the CS. Should the LV lead become dislodged at this step, the LV lead placement has to start from scratch because then the lead usually cannot be maneuvered back into the CS system without the back-up of the guiding catheter. Sheathless LV-pacing lead implantation is possible and has been described to result in a 70% implantation success.[266] This approach does not require one to perform venography. Without the knowledge of the precise anatomic details of the coronary sinus, one may fortuitously implant the lead in a lateral vein, but this may not be the best location. Furthermore, many better implant sites cannot be reached without the support of the guiding catheter.[267]

AIM OF THE WORK

The aim of the present study is to:

1. Assess the different predictors of CRT response in patients with systolic heart failure .

2. Identify the best predictors of CRT response.

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PATIENTS AND METHODS

We initially enrolled 187 consecutive patients with chronic systolic heart failure scheduled for CRT device implantation in Zentralklinik, Bad Berka, Germany from March 2011 to September 2011. Seventeen patients were exluded from analysis after initial enrollment as they were lost to follow-up before the echocardiographic evaluation visit at 6 months postimplantation or had lead dislocation requiring re-implantation (6 patients died from non-cardiac cause, 4 lead dislocations and 7 refused to continue the study), so we included a final total of 170 patients. All patients provided oral and written informed consent to device implantation and agreed to data retrieval and analysis. All patients met the criteria for CRT implantation, including moderate and severe HF (NYHA II, III and ambulatory IV), persistent symptoms despite optimal medical treatment, severely depressed LVEF (≤35%) and QRS duration ≥ 120 msec (or echocardiographic evidence of LV dyssynchrony if QRS duration < 120 msec). Patients were classified as having HF of ischemic or nonischemic etiology based on a history of myocardial infarction or based on objective evidence of coronary artery disease as assessed with coronary angiography.

Exclusion criteria:

1. Patients with previously implanted pacemaker.
2. Patients with recent revascularization (Percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) during the previous 6 months before implantation).
3. Acute coronary syndrome in the previous 3 months before implantation.
4. Failed CRT implantation or lead dislocation in the 1st 6 months after implantation requiring reimplantation.
5. Patients who are lost to follow-up before the echocardiographic evaluation visit at 6 months postimplantation were excluded from statistical analysis.

All patients were subjected to:

1. Pre-implantation assessment:

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- History: Previous hospitalization for heart failure, previous myocardial infarction, family history of dilated cardiomyopathy, medications (doses and compliance) and NYHA functional class.
- Clinical examination: evidence of fluid overload (neck venous congestion, lower limb edema, chest rales).
- 6 min. Walk distance (6MWD).
- ECG: QRS duration, QRS morphology for LBBB or RBBB, PR interval, heart rate and rhythm.
- Echocardiography (using commercially available Philips HD 11) was done by an experienced operator blinded to the clinical status of the patients at baseline and 6 months after implantation to assess:
    - LVEF: Left ventricular ejection fraction was assessed by biplane Simpson equation using apical 4-chamber and 2-chamber views.
    - LVIDd: Left ventricular internal dimension at end diastole by M-mode in parasternal long axis view.
    - LVIDs: Left ventricular internal dimension at end systole by M-mode in parasternal long axis view.
    - LVEDV: Left ventricular end diastolic volume by planimetry in apical 2-chamber & 4-chamber views.
    - LVESV: Left ventricular end systolic volume by planimetry in apical 2&4 chamber views.
    - SPWMD: Septal-posterior wall motion delay; measured by M-mode in parasternal long-axis view.
    - IVD: Interventricular delay defined as the difference between left and right ventricular pre-ejection intervals measured by pulsed wave doppler.
    - LV FT/RR: Left ventricular filling time (LVFT) in relation to cardiac cycle length (RR) as measured by transmitral Doppler expressed as percentage.
    - LVPEI: Left ventricular preejection interval defined as the time interval between the beginning of QRS and beginning of left ventricular ejection by Doppler.

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- Ts-sep-lat: Delay between time to peak systolic velocity in ejection phase at basal septal and basal lateral segments using TVI.
- Degree of mitral regurgitation (MR).
- RV dimensions in apical 4-chamber view.
- RV function using tricuspid annular peak systolic excursion (TAPSE).
- Degree of pulmonary hypertension and tricuspid valve regurgitation.

- Coronary angiography in patients with history of ischemic heart disease, angina pectoris or multiple risk factors for coronary artery disease.

2. Biventricular pacemakers were implanted as described in the current literature. When a conventional indication for an internal cardioverter defibrillator existed, a combined device was implanted. In brief, All pacemaker implantation procedures were performed under local anesthesia. Pacemaker leads were inserted through the right-sided or left-sided cephalic or subclavian veins. The right atrial and ventricular leads were positioned conventionally at the right atrial appendage and the RV apex.

   A coronary sinus venogram was obtained using a balloon catheter, followed by the insertion of the LV pacing lead. An 8F guiding catheter was used to place the LV lead in the coronary sinus. The LV lead position was targeted to the lateral coronary vein; if unavailable, the posterolateral coronary vein, a posterior vein or anterior vein was used. LV lead position was assessed in LAO and RAO views.

   Quick device based optimization was done in most patients within 24 hours after CRT device implantation. One day after implantation, the LV lead position was assessed from a chest x-ray using the postero-anterior and lateral views.

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3. Assessment during and immediately after CRT implantation:

- Whether CRT device optimization is done or not.
- The position of LV lead in left anterior oblique (LAO) and right anterior oblique (RAO) views as shown in figure 2.1.

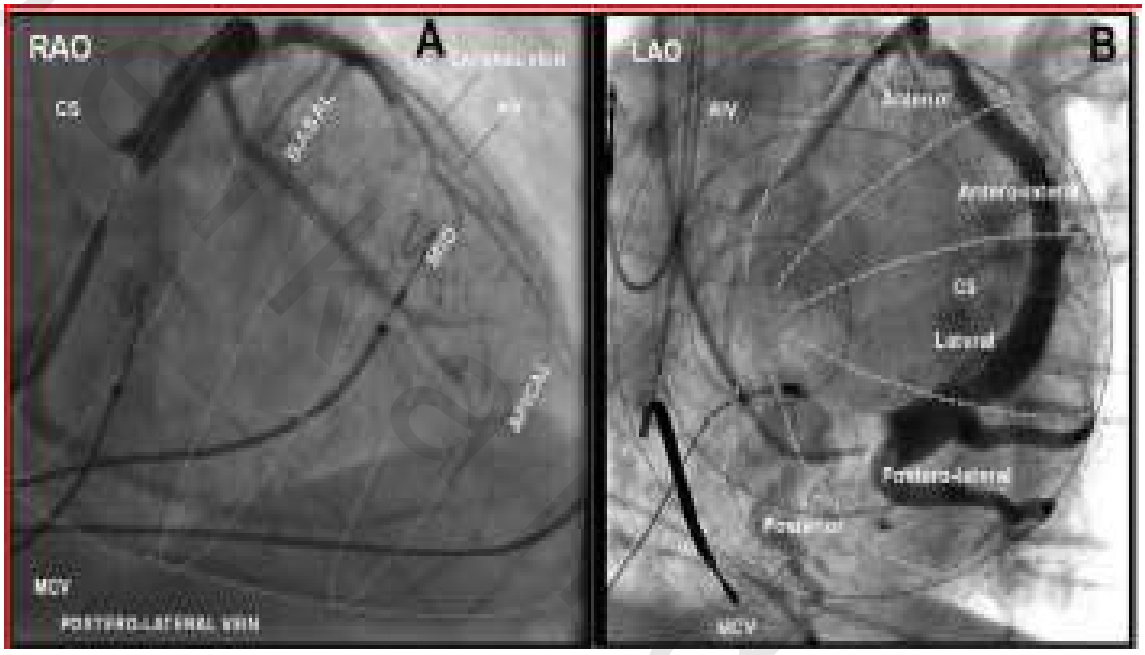

Figure 2.1**:** Angiographic classification of left ventricular lead position. A, Right anterior oblique (RAO) view representative of the long axis of the heart. This view enables segmentation of the heart into basal, midventricular (MID), and apical segments. B, Left anterior oblique (LAO) view used to divide the left ventricular wall along the short axis of the heart into 5 equal parts; anterior, anterolateral, lateral, posterolateral, and posterior.AIV indicates anterior interventricular vein; CS, coronary sinus; and MCV, middle cardiac vein.[268]

4. Assessment of response to CRT:

Patients were followed with regular clinical evaluation, echocardiographic and electrocardiographic assessments, and device interrogation. Follow-up of patients was done at 1, 3, 6 and 12 months after CRT implantation for evidence of CRT response (assessed at the 6th month visit) which is defined as:

- Responders (combined clinical and echocardiographic) :
  - Clinical response: Improvement in NYHA functional class (at least one class) and increase of the 6. min walk distance $\geq$ 10%.

- Echocardiographic response: Reduction in LVESV (at least 15%) and/or improvement in LVEF $\geq$ 10%

- Non-responders: Unchanged or worsening of the clinical or echocardiographic parameters, any hospitalization for unprovoked worsening of heart failure or cardiac mortality due to worsening heart failure during the 1st 6 months after implantation. Hospitatlization for heart failure was considered to be provoked if it was due to new onset arrhythmia, pulmonary embolization, significant infection, surgery or lack of copmliance to medication.

Statistical analysis:

Results for continuous variables are presented as mean & SD and for discrete variables as frequency (percentage). A p value < 0.05 was considered statistically significant and all tests were 2-sided. Differences between baseline and follow-up characteristics in the same patients were investigated by paired *t* tests for continuous variables. Differences between groups were tested by chi-square test for comparison of discrete variables and by analysis of variance for comparison of continuous variables. Univariate odds ratios (OR) and 95% confidence intervals (CIs) were calculated and multivariate stepwise nominal logistic regression analyses were used for identifying variables predictive of response to CRT. In the stepwise procedure all variables significant at univariate analysis were entered. All statistical analyses were performed using SPSS for Windows, version 20 (SPSS Inc, Chicago, IL).

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