Cardiac Resynchronization Therapy

31

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Abstract

Congestive heart failure (CHF) continues to be a major source of morbidity, mortality, and health-care spending in today's society. In the past 20 years, device-based therapies such as implantable cardioverter defibrillators (ICDs), cardiac resynchronization therapy (CRT), and left ventricular assist devices have been developed and demonstrated to improve outcomes in patients with CHF and systolic dysfunction. These therapies treat two of the major causes of death associated with CHF, namely sudden cardiac death and pump failure. This chapter focuses on the application of CRT for treatment of CHF, with a focus on the therapeutic mechanisms, historical development, evolution of the technologies, implant techniques and patient follow-ups, clinical trials, evolving indications, approaches for optimizing therapies, and future directions.

Keywords

Cardiac resynchronization therapy • Physiologic pacing • Cardiac function • Implantable cardioverter defibrillator • Congestive heart failure • Biventricular pacing • Mechanical remodeling

Abbreviations

6MWD	6-minute hall walk distance
AF	Atrial fibrillation
AV	Atrioventricular
BiV	Biventricular
CCS	Clinical composite score
CHF	Congestive heart failure
CRT	Cardiac resynchronization therapy
CS	Coronary sinus
EP	Electrophysiology
ESV	End-systolic volume
ICD	Implantable cardioverter defibrillator
ICM	Ischemic cardiomyopathy
IPG	Implantable pulse generator
IVCD	Interventricular conduction delay
LBBB	Left bundle branch block
LGE	Late gadolinium enhancement
LV	Left ventricular
LVEF	Left ventricular ejection fraction
LVLED	Left ventricular lead electrical delay
MRI	Magnetic resonance imaging
NCM	Noncontact mapping
NICM	Nonischemic cardiomyopathy
NYHA	New York Heart Association
PEA	Peak Endocardial Acceleration
PNS	Phrenic nerve stimulation
QoL	Quality of life
RA	Right atrial
RBBB	Right bundle branch block
RV	Right ventricular
SPECT	Single-photon emission computed tomography
TDI	Tissue Doppler imaging

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P.A. Iaizzo (ed.), *Handbook of Cardiac Anatomy, Physiology, and Devices*, DOI 10.1007/978-3-319-19464-6_31

31.1 Introduction

Congestive heart failure (CHF) is a cardiovascular syndrome associated with high morbidity, mortality, and major healthcare expenditures. In general, it can be characterized by pump dysfunction, reduced functional capacity, neurohumoral imbalance, and/or myocardial remodeling [1]. The prevalence of CHF continues to grow, estimated in 2013, at approximately five million people in the USA alone [2]. As the number of patients with CHF grows, expenditures have also continued to climb, with estimated associated costs of $31 billion in the USA in 2012 [2]. Pharmacological treatments with beta-blockers, angiotensin-converting enzyme inhibitors, and/or angiotensin receptor blockers revolutionized therapeutic options in the 1980s and 1990s [3–7]. Also in the 1990s, interest in device-based therapies gained ground and led to the application of implantable cardioverter defibrillators (ICDs) and cardiac resynchronization therapy (CRT), which helped to reduce mortality and morbidity associated with CHF [8–12]. It should be noted that the development of new pacing leads that were able to reliably stimulate the left ventricle and new stimulator technologies enabled multisite pacemakers that could resynchronize the contractions of both ventricles and improve outcomes for CHF patients.

31.2 Development of CRT

By the early 1990s, in the decades preceding the development of CRT, advances in lead and pacing generator technologies led to reliable dual-chamber pacing systems. More specifically, the development of polyurethane leads with smaller and more lubricious lead bodies made it easier to implant two leads for both right atrial (RA) and right ventricular (RV) pacing [13]. Advances in tined lead design reduced the rate of atrial lead dislodgement from 14 % to less than 2 % [14]. Also noteworthy, lead tips with steroid elution reduced the foreign body response at the implant site, reducing chronic thresholds and the incidence of exit block [15]. Similarly, advances in integrated circuit technologies and microprocessor-based pacemakers led to the development of implantable pulse generators (IPG) with more sophisticated algorithms for novel treatments and monitoring, and the development of rate responsive pacemakers improved the quality of life and exercise capacity for patients with chronotropic incompetence [16].

Prior to development of CRT, multisite stimulation in the form of biatrial pacing had been proposed as a therapy to suppress atrial tachyarrhythmias (AT), by pacing the left atrium through the coronary sinus (CS) [17]. The Model 2188 CS lead (Medtronic plc, Minneapolis, MN, USA) was developed specifically for this purpose in collaboration with French investigators. In 1994, a patient with dilated cardiomyopathy, New York Heart Association (NYHA) class 4, QRS durations >150 ms, and left ventricular ejection fractions (LVEF) <35 % was implanted with a 4-chamber pacing system and subsequently experienced incredible improvement in symptoms [18]. The work of this group, as well as others, led to the adaptation of technologies for left ventricular (LV) stimulation, with associated intense research and development to establish CRT as a viable CHF therapy.

31.3 Mechanisms of CRT

31.3.1 Impact of Left Bundle Branch Block and CHF on Ventricular Electrical and Mechanical Functions

The native conduction system consists of the sinoatrial node, specialized atrial conduction fibers, atrioventricular (AV) node, His bundle, and right and left bundle branches which terminate in Purkinje fibers. This system provides rapid, orderly depolarization and contraction of the heart. The presence of *left bundle branch block* (LBBB) is associated with: (1) delayed contraction of the left ventricle; (2) reduced ventricular performance; and (3) widening of the QRS complex. LBBB typically leads to both interventricular and intraventricular dyssynchrony, with early depolarizations and contractions of the septum followed by delayed contractions of the LV free wall via slow cell-to-cell conductions. Overall mechanical pump function becomes reduced due to prolongations of isovolumic contractions and relaxations with shortening of the diastolic filling periods [19]. These changes in systolic and diastolic performance result in reduced LVEF. It should be noted that even the mild dyssynchronous contraction, illustrated by ventricular pacing within normal hearts, leads to differences in regional workload and oxygen consumption, with reduced workload near the septum due to early contractions against low pressures and stretching of remote, inactivated regions [20, 21]. Strain and regional work both increase the delayed segments which must contract against a higher afterload (i.e., pressure). Thus asynchronous contractions between ventricular segments with differing workload may lead to asymmetric remodeling, with thinning of the myocardial wall near early contracting segments and hypertrophy at the lateral wall [22].

The prevalence of LBBB has been reported as high as 25 % in patients with CHF [23]. LV depolarizations in LBBB are heterogeneous and may differ between patients with ischemic cardiomyopathy (ICM) and nonischemic cardiomyopathy (NICM). Endocardial mapping in patients with LBBB and normal hearts, NICM, or coronary artery disease all demonstrated that LV activation occurs after RV activation

via transseptal conduction [24]. All patients had at least one septal breakthrough site, with approximately one-third of patients having an additional site of early activation. LV activation times were significantly longer in patients with ischemic heart disease, possibly due to the impact of scar or slow-conducting tissues. Noncontact mapping (NCM) has provided further insights into LV conduction variations in patients with CHF. For example, Rodriguez et al. described two patterns of LV endocardial activation originating from the septum in LBBB and CHF: either slow conduction through a portion of the left bundle branch with mid-septal or apical breakthrough, or breakthrough at the high septum due to slow cell-to-cell conduction [25]. The former pattern tended to generate an apical and basal wavefront which met in the basal posterior lateral wall, while high septal breakthrough generated only one wavefront which spread toward the apex. These authors speculated these two patterns may also have different hemodynamic implications for the application of CRT. Aurrichio et al. also reported these differences in transseptal activation, but additionally described U-shaped conduction patterns caused by functional conduction blocks (e.g., not anatomical due to scar) in almost all CHF patients with LBBB [26]. Functional blocks were confirmed by demonstrating that the location of blocks (lateral, inferior, or anterior) could be altered by pacing from different sites. Patients with QRS durations ≤150 ms had shorter transseptal conduction times and more homogenous LV activations with a site of lateral block, while patients with longer QRS durations tended to have an anterior line of block.

NCM has also provided evidence that simultaneous biventricular (BiV) pacing can have dramatically different effects on LV conduction patterns depending on the individual. In the study by Pratola et al., LV endocardial conduction in one patient was almost completely dominated by the RV-paced wavefront during BiV pacing, i.e., due to a long delay between LV epicardial-paced activations and LV endocardial depolarizations [27]. In contrast, LV conduction in another patient was almost entirely due to the LV pacing, the result of long transseptal conduction times. In yet another patient, only BiV pacing eliminated the identified U-shaped activations and created homogenous LV depolarizations. This technique has also been used to demonstrate that LV pacing in areas of slow conduction, which are often present in patients with ICM, is associated with suboptimal hemodynamic responses [28]. Pacing in an area of normal conduction or preactivating the LV via VV delay can improve hemodynamic responses to CRT and reduce total LV activation times.

31.3.2 Improvement of Cardiac Function with CRT

In its simplest conception, CRT can improve cardiac performance by restoring coordinated contractions between the ventricular septum and LV lateral wall. This is most commonly achieved by stimulating the RV with a standard endocardial pacing lead and the LV via a transvenous lead placed in a coronary vein (Fig. 31.1). The addition of an RA lead allows control of ventricular stimulation prior to intrinsic, delayed conduction during atrial sensing and pacing. The immediate hemodynamic impact of CRT can be reflected in significant increases in maximum rate of LV pressure rise (LV dP/dt_{max}) and systolic blood pressure [29, 30]. These changes are accompanied by improvements in systolic and diastolic time intervals. In one study, AV optimization with a

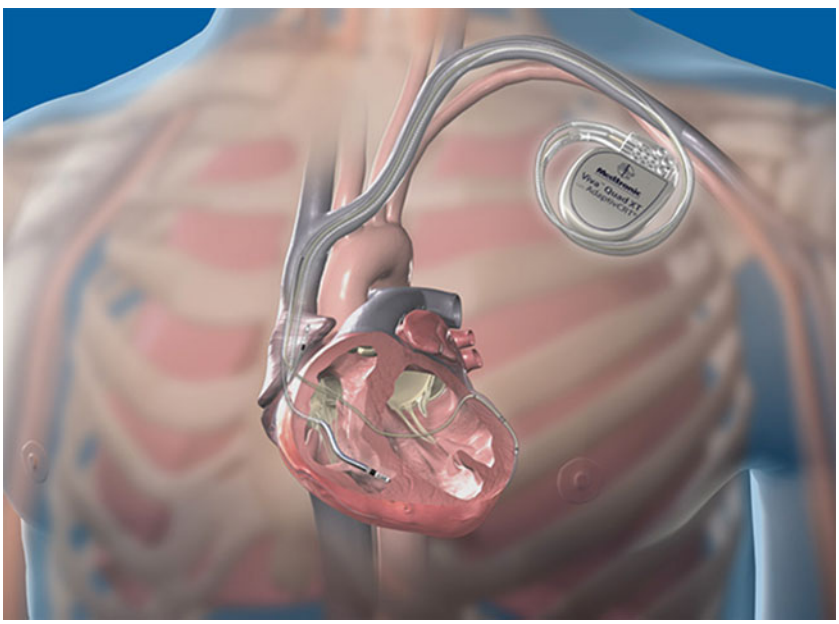

Fig. 31.1 Illustration of an implanted CRT system with right atrial, right ventricular, and left ventricular leads. Courtesy of Medtronic plc

mitral inflow method and simultaneous BiV pacing was shown to significantly increase normalized LV filling time ($p<0.001$), shorten interventricular mechanical delay ($p<0.001$), and shorten isovolumic contraction ($p<0.05$) in patients with CRT compared to controls [31]. Reduction in severity of mitral regurgitation may also occur with CRT due to improved coordination of the papillary muscle contractions, LV synchrony, and hemodynamic closing forces [32–35]. The beneficial effects of CRT have also been noted to be accompanied by a reduction in sympathetic nerve activity, which is frequently elevated in CHF patients. Reduction in sympathetic activity after CRT has, in turn, been associated with improved peak oxygen consumption (peak VO_2), LVEF, LV end-systolic volume index (ESVi), and NYHA class [36, 37]. Acute improvements are maintained chronically and further promote improvements in LV structure and volumes, termed *reverse remodeling*. In the MIRACLE study, it was shown that CRT reduced LV volumes, improved LVEF, and reduced severity of mitral regurgitation up to 12 months postimplant [38]. These changes were accompanied by reduced dyssynchrony, reflected by increased diastolic filling time, and reduced interventricular mechanical delay.

31.4 Implantation of CRT

Implantation of a CRT system typically involves delivery of an RA lead, an RV lead, and an LV lead. The RV lead is typically positioned first to allow backup pacing if the AV node is temporarily blocked during CS cannulation and delivery of the LV lead. To date, the RV apex has been the most common implant site, but other locations such as the RV septum are also used. The first step for implanting the LV lead is cannulation of the CS. A combination of an outer sheath with or without a guidewire may be used, as well as an electrophysiology (EP) catheter. An EP catheter may also be used with recording of EGMs for guidance. Once CS access is obtained, an occlusive coronary venous angiography may be performed by introducing a balloon catheter through the delivery sheath, to determine coronary veins suitable for LV lead delivery. Venography is often recorded with cine fluoroscopy in one or two views (Fig. 31.2). Some implanters may only "puff" contrast through the sheath, or not introduce contrast at all out of concern for toxicity in patients with poor kidney function or to reduce the number of steps in the procedure [39]. The LV lead can then be delivered via stylet or guidewire to the target vein. Telescoping catheter systems consisting of an inner and outer sheath can also be used to aid in the delivery of the LV lead with greater support (Fig. 31.3). These systems may reduce the number of failed implants, improve LV lead implant location, and shorten LV positioning time [40]. A lateral or posterolateral vein is often

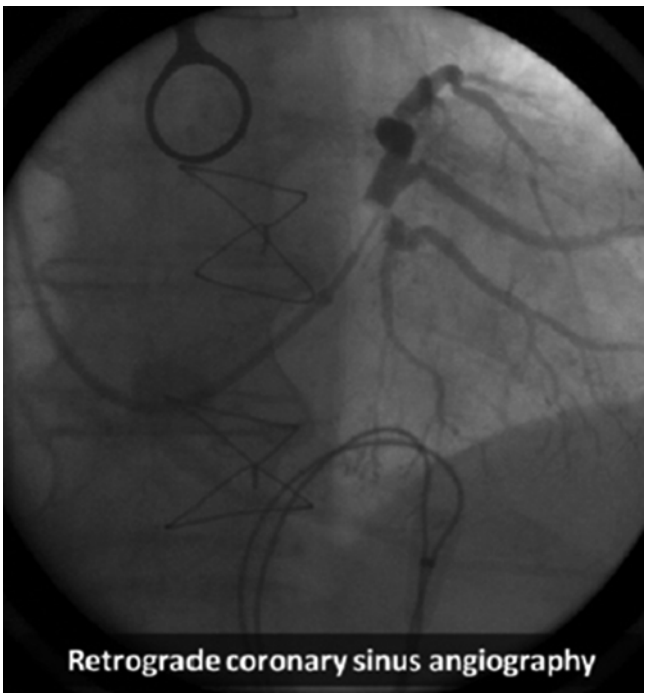

Fig. 31.2 Retrograde coronary sinus venography showing multiple coronary venous branches. Modified from Merkely et al. [166], available under a Creative Commons Attribution license. http://creativecommons.org/license/by/3.0

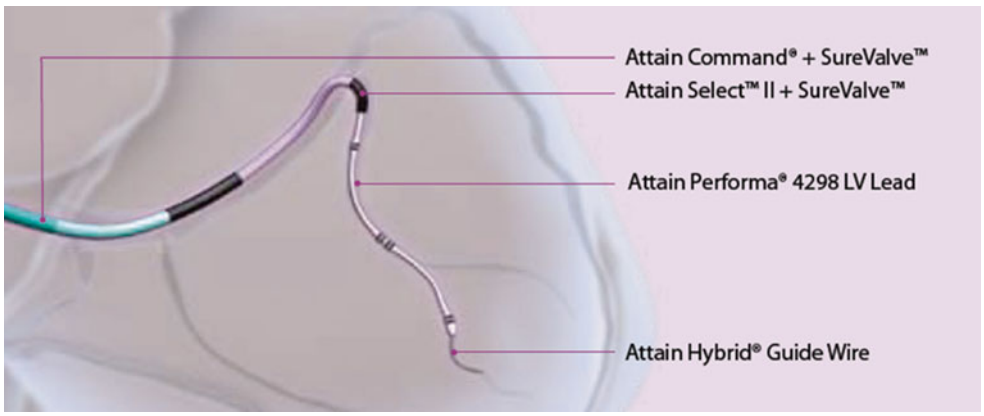

Fig. 31.3 Illustration of Attain Command® coronary sinus cannulation catheter, Attain Select™ II subselection catheter and Attain Performa® LV lead with guidewire. Courtesy of Medtronic plc

preferred for implant, based on studies that suggest these branches are more likely to be beneficial for CRT therapy than anterior positions [41, 42]. Implanters also prefer to avoid the apex for permanent LV pacing, as this location has been associated with inferior outcomes in studies such as MADIT-CRT [43]. Once a stable position is attained, electrical testing for acceptable pacing capture thresholds and phrenic nerve stimulation (PNS) is performed. An LV pacing capture threshold $\leq$2.5 V, and a difference (i.e., margin) between PNS threshold and LV capture threshold of at least 3 V, is preferred to avoid complications [44]. Note that the potential for PNS is often tested by pacing at maximum outputs (e.g., 10 V). Multiple vectors may be tested to find an acceptable configuration before resorting to repositioning the lead, i.e., when such leads have multiple pacing electrodes (see below). The delivery catheter(s) are removed after the lead position is deemed acceptable. Removal requires slitting the length of the sheath using a slitting tool or separating the sheath by hand in the case of peelable catheters. The LV lead thresholds are often retested prior to insertion into the pacing device to ensure that electrical performance has not deteriorated during removal of the implant tools. If an LV lead cannot be implanted via the transvenous approach, a common alternative is to place an epicardial lead surgically, if the procedure can be tolerated by the patient.

31.4.1 Left Ventricular Leads

Currently, a variety of lead body shapes and electrode configurations are available for LV leads. The majority of LV leads employ passive fixation, meaning the lead body shape primarily holds the lead in place. Typical shapes include compound cants, sigmoidal S-shapes, spirals, and straight leads with tines. Since dislodgement remains a concern for all lead systems, LV leads with active fixation components have also been developed. For example, the Attain Starfix® (Model 4195, Medtronic plc) lead was developed specifically to address dislodgement by incorporating deployable lobes on the lead body (Fig. 31.4) [45]. The lobes are deployed by using a tool to push the outer lead body tubing distally and forcing the lobes to expand. More recently, the Attain Stability® (Model 20066, Medtronic plc) lead has been developed with a side helix for fixation, and it has demonstrated acceptable performance through 12 months in humans (Fig. 31.5) [46]. This lead was designed to be positioned in a

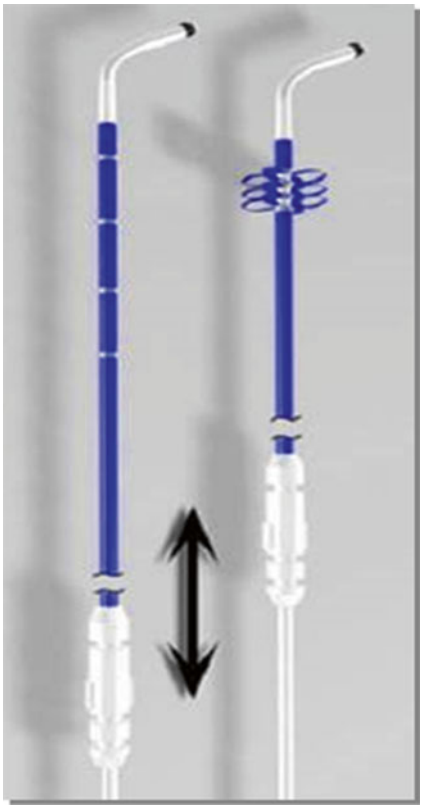

Fig. 31.4 Illustration of Attain StarFix® Model 4195 lead design with deployable lobes for fixation. Courtesy of Medtronic plc

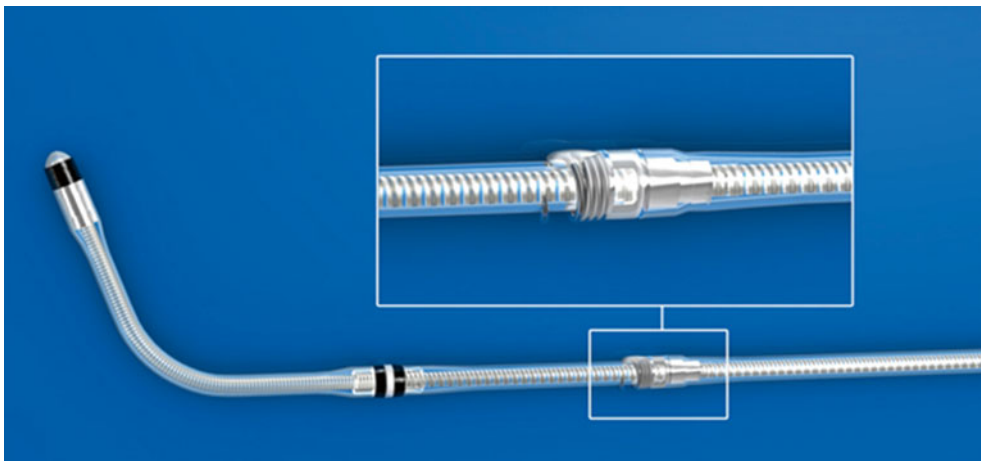

Fig. 31.5 Illustration of Attain Stability® Model 20066 lead design with co-radial helix for fixation. Courtesy of Medtronic plc

wider range of vein sizes with enhanced extractability if required.

A key characteristic of LV leads is the polarity or number of electrodes. Options include unipolar, bipolar, and quadripolar leads (Fig. 31.6). Unipolar leads are still commercially available but are less attractive due to limited options for programming LV stimulation. Bipolar leads are more common and allow three to six stimulation vectors, depending on the capabilities of the pulse generator. More recently, quadripolar LV leads have been developed to further increase the number of pacing vectors, to help manage problems such as high pacing thresholds, PNS, and/or dislodgement [47]. In contrast to unipolar and bipolar leads, quadripolar leads have a newer connector pin which conforms to the ISO 27186:2010 (E) four-pole connector standard (Fig. 31.7). This standard was developed to ensure interchangeability of leads and devices between manufacturers.

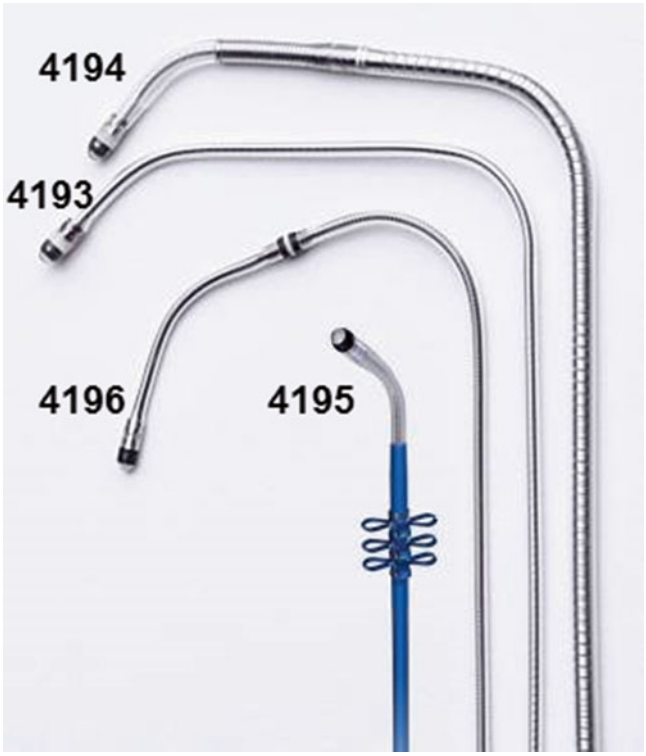

Fig. 31.6 Example of unipolar (4193 & 4195) and bipolar (4194 & 4196) LV leads. Courtesy of Medtronic Inc.

31.4.2 Complications Associated with CRT

Complications related to CRT can be divided into either acute or chronic events. Acute complications during implant include: (1) CS dissection; (2) high pacing thresholds; (3) dislodgement; and (4) stimulation of the phrenic nerve. Coronary sinus dissection occurs when the venous wall is damaged, and this is often visualized after injection of contrast. Common causes for this include the advancement of the cannulation catheter, guidewire, lead, or other implant tools into difficult anatomies. Though dissection rarely requires additional treatment intervention, the trauma may be extensive enough to prevent LV lead implantation or it may be severe enough to require pericardiocentesis to prevent tamponade. Left ventricular lead dislodgement may occur during removal of implant tools or it may be due to unstable implant positions. PNS may sometimes occur along the entire length of the target vein. Therefore, dislodgement, high thresholds or inability to capture, and PNS may cause implant failure in some cases.

Complications related to CRT have declined considerably since the therapy was introduced. For example, in one report, implant success rates by French investigators improved from 60 % without dedicated tools in the early years to 98 % by the end of the 1990s; this was accompanied by a reduction in LV lead dislodgements from 30 to 12 % during the same time period [48]. Other studies have demonstrated a learning

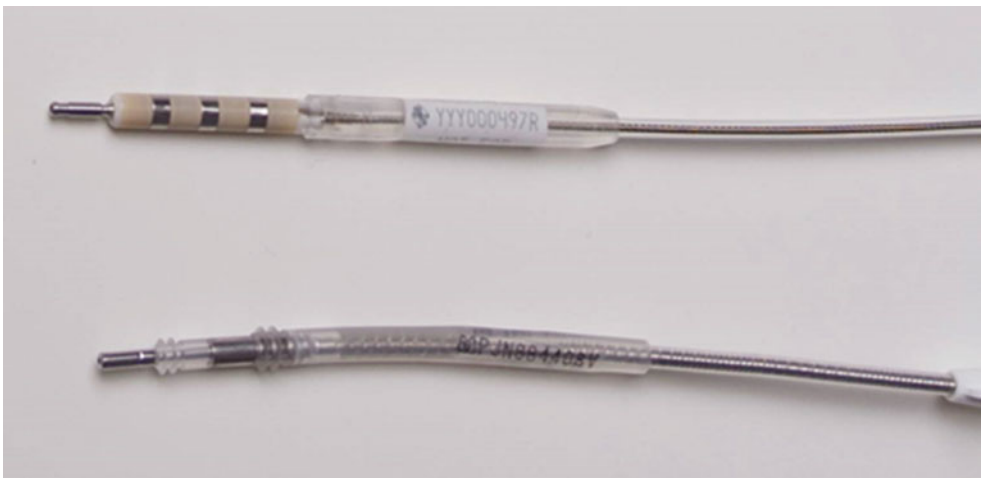

Fig. 31.7 Examples of an IS4 lead connector (*top*) and IS1 connector (*bottom*). Courtesy of Medtronic Inc.

curve for CRT, with greater implant success and lower complication rates occurring as implanting center and operator experience increases [48, 49]. Today, implant success rates of greater than 95 % are not uncommon with transvenous CRT systems, especially when repeated implant attempts are considered [50–52]. Yet, it should be noted that the etiology of CHF may also impact LV lead implant success. For example, Macias et al. found that ICM was the only independent predictor of a failed LV lead implant at a preferred empirical lateral site [52]. This may be due to lack of veins secondary to scar formation in ICM, since 50 % of ICM patients with a failed lateral implant had no target vein in this region; note that the inability to deliver the lead to the target vein was the most common reason for failed implants in NICM patients. Procedure-related complication rates have reduced over time, from 24 % of patients in the MIRACLE, MIRACLE ICD, and Insync III studies [49] to approximately 16 % in the CARE-HF study [50]. The need for LV lead reintervention after implant varies from 5 to 10 % in studies with up to 1-year follow-up [49, 51, 53]. The most frequent cause of reintervention is dislodgement in approximately 7–10 % of patients; however intractable PNS, high capture thresholds, and infections have also been noted. To date, data on coronary vein thrombosis and implant success rates after LV lead revision are relatively limited. Yet, Borleffs et al. reported an 86 % first success LV lead revision rate at a median of 85 days, and the same branch as the original implant could be used in 57 % of the cases [51]. Additionally, Biffi et al. reported that the original branch could only be used in 33 % of patients with the majority of LV lead revisions occurring less than 6 months post-implant [53].

Clinically relevant PNS is observed in approximately 20 % of patients when the LV lead is placed in a lateral or posterolateral position [54, 55]. The rate of PNS varies considerably by anatomical zone of the LV lead implant. A retrospective analysis of over 1000 patients found that a lateral lead position was associated with greater than four times the risk of PNS than an anterior position, and the apical position was associated with greater than six times the risk [53]. Pacing systems with multiple programmable cathode and anode combinations provide an effective means to avoid high pacing threshold and PNS [54, 55]. Bipolar pacing from a closely spaced electrode, recently incorporated into a quadripolar lead design (Fig. 31.8), has also been demonstrated to avoid PNS by reducing the size of the stimulating electrical fields. The resulting increases in PNS thresholds with minimal change in LV pacing thresholds thus increases the safety margin, and has been demonstrated in both preclinical and human studies [56, 57]. For more specific information about cardiac venous anatomy, see Chap. 8.

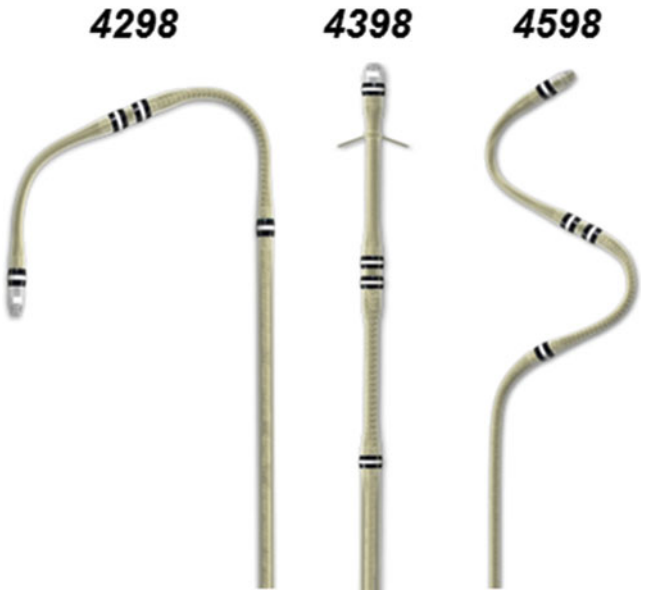

Fig. 31.8 Attain Performa® quadripolar LV lead family. Courtesy of Medtronic plc

31.5 Clinical Trials in CRT

31.5.1 Moderate-to-Severe CHF

Multicenter clinical studies of CRT began in the latter half of the 1990s. MUSTIC was a multicenter study which enrolled 67 patients with QRS durations ≥150 ms, LVEFs <35 %, and NYHA class III while receiving optimal medical therapy for at least 1 month [58]. The primary endpoint of this single-blinded, randomized, crossover study was a 6-minute hall walk distance (6MWD). Secondary endpoints included quality of life (QoL), peak oxygen consumption, CHF hospitalization, and mortality. Patients underwent a period of inactive and active pacing for 3 months each. Distance walked during the active phase was 23 % longer than during the inactive phase ($p<0.001$). Quality of life and peak oxygen consumption significantly improved during pacing, and CHF hospitalizations were reduced. PATH-CHF was a single-blinded, randomized, crossover study that enrolled 42 patients. Patients were in NYHA classes III or IV, with QRS durations >120 ms and sinus rhythms; the use of chronic univentricular or BiV pacing configuration was determined by invasive hemodynamic optimization, using aortic pulse pressure and LV dP/dt_{max} [30]. Notably, in patients with BiV therapy, LV end-systolic and end-diastolic volumes decreased, NYHA class improved, and LVEF increased from 22±7 % to 26±9 % ($p=0.03$) [59]. Around the same time period, larger randomized, double-blinded studies were initiated to definitively

demonstrate the effectiveness of CRT. The Multicenter InSync Randomized Clinical Evaluation (MIRACLE) study enrolled patients with LVEF ≤35 %, QRS duration ≥130 ms, and individuals with moderate-to-severe CHF (NYHA class III or IV) [8]. Patients were randomized to CRT or control (no pacing therapy) for 6 months. Patients receiving CRT had significantly improved 6MWD, QoL, time during treadmill exercise, and LVEF. CRT also reduced LV end-diastolic dimensions and mitral regurgitation. More patients were classified as improved (67 % vs. 39 %) by Packer's clinical composite score (CCS) and fewer patients were worsened (16 % vs. 27 %) than in the control group ($p<0.001$). Further, CHF-related hospitalizations, as well as a combined endpoint of death or CHF hospitalizations, were also reduced in the CRT group. This study led to FDA approval of CRT pacemaker (CRT-P) therapy in August 2001.

The next progression in the use of this therapy was the initiation of trials with combined CRT and defibrillator therapy (CRT-D); these were initiated to determine the additional potential benefits of CRT in patients indicated for ICD. The double-blinded CONTACT CD approval study randomized 490 patients in NYHA classes II–IV, with LVEF ≤35 % and QRS duration ≥120 ms, to either CRT-D or ICD therapy alone for up to 6 months [60]. The primary endpoint was a composite of all-cause mortality, CHF hospitalization, and occurrence of VT/VF requiring ICD therapy. Secondary endpoints included peak levels of VO_2, 6MWD, relative NYHA class, QoL, and echocardiographic changes. There was a nonsignificant 15 % reduction in the primary endpoint of the CRT group ($p=0.35$). In some patients the NYHA class improved prior to CRT because optimal medical therapy was instituted for 1 month prior to randomization. In the group with NYHA class I–II, there were no significant improvements in any secondary endpoint. In contrast, there were significant improvements in peak VO_2, 6MWD, NYHA class, and QoL in patients in NYHA classes III–IV. Based on this study, CRT-D therapy was approved by the FDA in February 2002 for patients with moderate-to-severe CHF (NYHA classes III–IV), LVEF ≤35 %, and QRS duration ≥120 ms.

Subsequently, clinical trials with longer study durations demonstrated the benefits of CRT on mortality. The Comparison of Medical Therapy, Pacing, and Defibrillation in CHF (COMPANION) trial randomized 1520 patients in NYHA classes III–IV, LVEF ≤35 % and QRS duration ≥120 ms into three groups: optimal medical therapy, CRT-P, or CRT-D [10]. The primary endpoint was time to all-cause death or hospitalization, with a secondary endpoint of all-cause death. The primary endpoint was reduced in both the CRT-P (HR = 0.81, $p=0.014$) and the CRT-D groups (HR = 0.80, $p=0.01$) with 12 months follow-up. The risk of death or hospitalization due to CHF was reduced by 34 % with CRT-P ($p<0.002$) and 40 % with CRT-D ($p<0.001$). CRT-D reduced the risk of all-cause mortality by 36 % ($p=0.003$), although the 24 % reduction with CRT-P did not reach significance ($p=0.06$). Next, the Cardiac Resynchronization-Heart Failure (CARE-HF) study demonstrated that CRT alone (CRT-P) reduced the risk of death beyond the benefits of optimal medical therapy [11]. In this trial, 813 patients in NYHA classes III–IV, LVEF ≤35 %, and with QRS duration ≥120 ms were randomized into optimal medical therapy or CRT-P. Patients with QRS intervals between 120 and 149 ms were required to meet 2 of 3 mechanical dyssynchrony criteria for inclusion. The primary endpoints were time to all-cause death or unplanned hospitalization associated with a major cardiovascular event. With a mean follow-up of 29.4 months, 39 % of patients with CRT reached the primary endpoint vs. 55 % of patients receiving only optimal medical therapy (HR = 0.63, $p<0.001$). For the principal secondary endpoint of death from any cause, the rates were 20 % in the CRT group vs. 30 % for those patients receiving optimal medical therapy (HR = 0.64, $p<0.002$). It was also noted in this trial that CRT improved interventricular mechanical delay, LV ESV, mitral regurgitation, LVEF, and QoL, which was in agreement with previous studies.

31.5.2 Mild CHF

The next major focus of clinical trials and the expansion for indications for CRT was the treatment of patients with milder CHF. The Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) trial was a double-blinded, randomized study of patients in NYHA classes I–II, QRS ≥120 ms, and LVEF ≤40 % [61]. In this trial, 610 patients were implanted and randomized to CRT, on or off. The primary endpoint was a CHF CCS, and the prospectively powered secondary endpoint was LV ESVi. There were no significant differences in the percentage of patients categorized as "worsened" between CRT on and off over 12 months of follow-up (16 % worsened with CRT on vs. 21 % with CRT off, $p=0.10$). However, patients programmed to CRT elicited significant improvements in LV ESVi and had longer time to first CHF hospitalization (HR = 0.47, $p=0.03$). The larger Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) trial randomized 1820 patients in NYHA classes I–II, with QRS duration ≥130 ms and LVEF ≤30 % in a 3:2 ratio to CRT-D or ICD alone [62]. The primary endpoint was a composite of all-cause death or nonfatal CHF events. This primary endpoint was reached in 17.2 % of patients implanted with CRT-D vs. 25.3 % in the ICD group, with an average follow-up of 2.4 years (HR = 0.66, $p=0.001$). This was primarily driven by a 41 % reduction in risk of CHF events with CRT, which was greater

in a prespecified group of patients with QRS ≥150 ms. The annual mortality rates in each group were similar at approximately 3 %. Improvements in LV volumes and LVEF, from baseline to 1 year, were also significantly greater in the CRT group.

The double-blinded, Resynchronization–Defibrillation for Ambulatory Heart Failure Trial (RAFT) extended these results to patients in sinus rhythm or with rate-controlled permanent atrial fibrillation (AF) or atrial flutter [63]. Altogether, 1798 patients in NYHA classes II–III, QRS duration ≥120 ms, and LVEF ≤30 % were randomized to either CRT-D or ICD. The original protocol was later revised to enroll only patients in NYHA class II, resulting in a total of 20 % of patients in NYHA class III. The primary endpoint of all-cause death or CHF hospitalization was lower in the CRT-D group (33.2 %) than in the ICD group (40.3 %). Time to first primary endpoint was significantly prolonged with CRT-D (HR = 0.75, $p < 0.001$). Both death and CHF hospitalizations were significantly lower in the CRT-D group, though this was associated with approximately twice the number of adverse events at 30 days postimplant.

31.5.3 Mechanical Dyssynchrony, Narrow QRS Duration, and AV Block

The role of mechanical dyssynchrony for improving patient selection for CRT remains controversial. The multicenter, nonrandomized Predictors of Response to CRT (PROSPECT) study evaluated the ability of 12 echocardiographic indices of dyssynchrony to predict CRT responses at 6 months [64]. A positive response was defined as an improved CCS, with at least a 15 % reduction in LV ESV. These indices provided only modest sensitivity and specificity, and the investigators reported large variability in quantification of dyssynchrony. Mechanical dyssynchrony has also been used to select CRT candidates with a narrow QRS duration ≤120 ms, with limited success in randomized multicenter studies. The earliest of these studies, the Cardiac Resynchronization Therapy in Patients with Heart Failure and Narrow QRS (RethinQ) study, was a double-blinded, randomized study of patients in NYHA class III, LVEF ≤35 %, and QRS duration ≤120 ms with evidence of mechanical dyssynchrony [65]. Tissue Doppler imaging (TDI) or M-mode delay between opposite cardiac wall segments were used to determine the presence of dyssynchrony. The primary endpoint of improved peak VO_2 at 6 months was not significantly improved with CRT. There were no significant differences in QoL, 6MWD, or cardiac structure and function between CRT-on and CRT-off, although more patients experienced significant improvement in NYHA class with CRT (54 % vs. 26 %, $p = 0.006$). It should be noted that these findings were in contrast to smaller, single center studies reporting benefits in patients with narrow QRS duration [66–68]. The largest study in this population, the Echocardiography Guided Cardiac Resynchronization Therapy (EchoCRT) study, randomized 809 patients implanted with CRT-D to CRT-D or ICD therapies only [69]. Patients in NYHA classes III–IV, LVEF ≤35 %, and QRS duration ≤130 ms with evidence of mechanical dyssynchrony (defined by TDI or speckle tracking radial strain) were enrolled. The primary efficacy endpoint was all-cause death or CHF hospitalization. This study was stopped for futility, with a potential for harm based on recommendations from the data and safety monitoring board in 2013. The differences in the primary endpoint were not different between the CRT and ICD groups (28.7 % vs. 25.2 %, HR = 1.2, $p = 0.15$). Yet, there was a significantly higher rate of death in the CRT group (11.1 % vs. 6.4 %, HR = 1.81, $p = 0.02$), with more deaths due to cardiovascular causes, and there were no differences at 6 months in NYHA class or QoL. This study further reinforced the importance of QRS duration over mechanical dyssynchrony as the more important determinant of CRT responses.

One potential group of patients with CHF and narrow QRS durations that may benefit from CRT are those with AV block who then require a high percentage of ventricular pacing. The prospective, double-blinded, randomized Biventricular versus Right Ventricular Pacing in CHF Patients with AV Block (BLOCK HF) study enrolled patients in NYHA classes I–III, LVEF ≤50 %, and a standard class I or IIa indication for pacing due to high-degree AV block [70]. In this trial, 691 patients were implanted with CRT-D or CRT-P, randomized to CRT or RV pacing, and followed for an average of 37 months. The primary endpoint was time to event, which included death from any cause, urgent care visits for CHF requiring IV therapy, or ≥15 % increase in LV ESV index. It was shown that 55.6 % of patients in the RV pacing group met the primary endpoint, significantly more than the 45.8 % patients in the CRT group (HR = 0.74). The secondary endpoints of death from any cause or urgent care CHF visits, death or CHF hospitalization, and CHF hospitalization were also significantly reduced with CRT. This trial led to an expanded indication in April 2014 for use of CRT devices in patients in NYHA classes I–III with AV block and LVEF ≤50 % who are expected to require a high percentage of ventricular pacing. The Biventricular Pacing for AV Block to Prevent Cardiac Desynchronization (BioPace) study is an ongoing trial in a similar patient cohort. Approximately 1900 patients with a class I indications for permanent ventricular pacing and high likelihood of ventricular pacing ≥66 %, without restriction on LVEF, were randomized and implanted with a CRT or RV pacing systems [71]. The primary endpoints include all-cause mortality and time to first CHF hospitalization.

31.6 Factors Influencing CRT Responses

31.6.1 QRS Duration, Morphology, and QRS to LV EGM Onset (QLV)

The relative QRS duration provides powerful prognostic value for patients with CHF and is a primary indicator of eligibility for CRT. A cut-off of 120 ms for QRS duration was established in the initial guidelines, based on randomized trials of CRT, although smaller studies suggested that patients with a QRS duration <150 ms had limited benefit from CRT [30]. Evidence obtained from REVERSE, MADIT-CRT, and RAFT trials, as well as recent meta-analyses, has concluded that patients with QRS durations of at least 150 ms derive greater benefit from CRT. Patients with QRS durations <140 ms did not experience significant reverse remodeling in the REVERSE trial [72]. Analysis of the prespecified subgroup of patients with QRS durations <150 ms did not elicit significant reductions in death or CHF in the MADIT-CRT [62] or RAFT [63] trials. Similarly, meta-analyses of COMPANION, CARE-HF, RAFT, MADIT-CRT, and REVERSE concluded that CRT did not reduce clinical events in patients with QRS durations <150 ms [73]. Analysis of almost 15,000 patients in the Medicare ICD registry, implanted between 2005 and 2006, identified that patients with QRS durations >150 ms had significantly lower mortality and combined mortality or CHF hospitalizations at both 1 and 3 years after CRT [74]. A prospective 10-year observational registry study demonstrated that mortality after CRT benefits were similar between patients with QRS durations of 120–149 ms and those of 150–199 ms, with significantly increased mortality in patients with QRS durations of 200 ms and greater [75]. This finding is not inconsistent with studies concluding that patients with QRS durations of 150 ms and greater benefit more with CRT, since CRT may offset the greater mortality rate associated with increasing QRS durations.

Recent studies have also concluded that patients with LBBB are more likely to respond to CRT than those with right bundle branch block (RBBB) or nonspecific interventricular conduction delays (IVCDs). This is somewhat intuitive, since correction of delayed lateral wall contraction with early activation of the septum in LBBB is the hallmark of CRT. An LBBB morphology was the only baseline ECG characteristic that was significantly associated with improved clinical composite score (CCS) and reverse remodeling in a sub-study of PROSPECT [76]. CRT reduced the risk of CHF hospitalization or death by 53 %, relative to ICD in patients with LBBB in MADIT-CRT, with no significant reduction in patients with non-LBBB morphology [77]. It should be noted that similar findings were found in the RAFT trial [63]. Meta-analyses of COMPANION, CARE-HF, MADIT-CRT, and RAFT data have demonstrated greater benefits in reduction of mortality and morbidity in patients with LBBB vs. IVCD or RBBB [78]. Analyses of the Medicare ICD registry also revealed that patients with RBBB had significantly greater mortality than those with LBBB after adjusting for baseline covariates [74]. Recently, Adelstein et al. also reported that patients with RBBB elicited less reverse remodeling, lower improvement in NYHA at 6 months, and had lower survival and fewer transplants or LVADs than patients with LBBB [79].

Left ventricular lead placement at a site of latest electrical delay, measured by local EGM, is also associated with an increased probability of a positive response to CRT (Fig. 31.9). Some of the earliest evidence supporting this concept was demonstrated in the PATH-CHF-II study, where the difference in LV conduction delay between the free wall and anterior coronary veins was correlated with the difference in

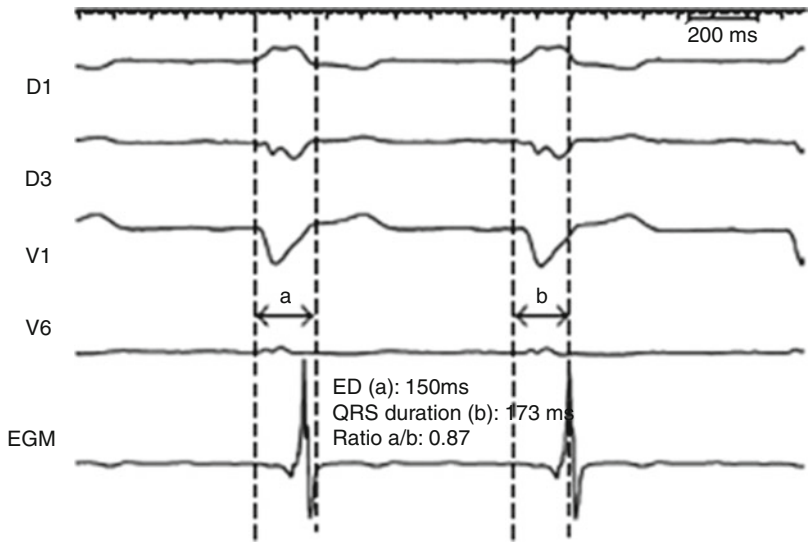

Fig. 31.9 QLV electrical delay (*a*) and QRS duration measurement. Modified from Fatemi et al. [167], available under a Creative Commons Attribution license. http://creativecommons.org/license/by/2.0

improved LV dP/dt_{max} while pacing within each vein [41]. Another study found that both RV to LV conduction and QLV (i.e., QRS onset to LV EGM) correlated with improved LV dP/dt_{max} during optimized BiV pacing; yet no clear cut-off was identified to predict acute hemodynamic response [80]. Normalizing the QLV by QRS duration, termed LV lead electrical delay (LVLED), was also shown to correlate with Doppler-derived dP/dt values, and an LVLED greater than or equal to 50 % was associated with significantly greater reductions in all-cause death or CHF hospitalization at 12 months follow-up in patients with ICM or NICM [81]. The same group of investigators later showed that LVLED was similarly associated with improved outcomes in patients with apically placed LV leads. An LVLED of at least 50 % with an apical LV lead placement was associated with greater freedom of all-cause deaths, CHF hospitalizations, and need for transplant at 2 years (81 % vs. 30 %, $p=0.007$), as well as greater reductions in LV ESV and increased LVEF [82]. Similarly, Gold et al. also found that longer QLVs were associated with improvements in reverse remodeling and QoL in a subanalysis of SMART-AV [83]. A QLV of 120–195 ms was associated with 3.2 times greater odds of reverse remodeling compared to a QLV <70 ms, via multivariate analysis. However, the ability of QLV-guided LV lead placement to improve outcomes after CRT remains to be tested in prospective, randomized studies.

31.6.2 LV Lead Position, Scar, and Mechanical Dyssynchrony

Left ventricular lead position has been recognized as an important determinant for response to CRT since the initial development of this therapy. Initially, acute studies demonstrated greater improvements in hemodynamics during LV free wall pacing than during anterior stimulation, thus providing the basis of empirical targeting of lateral or posterolateral veins [41]. In this series of studies, pacing anterior locations actually decreased LV dP/dt_{max} and pulse pressures below baseline levels in approximately one-third of patients. However, a lateral position cannot be assumed to provide the maximal benefit for all patients. For example, Dekker et al. demonstrated that even though pacing the mid-lateral or basal LV segments corresponded to the best hemodynamic function during surgical epicardial mapping in the majority of patients, these regions corresponded to the worst function in other patients [42]. Expanding on these findings, Gold et al. tested multiple pacing locations within a lateral or anterior vein to determine the impact of activating different sites within a vein [84]. They observed large individual variations in the hemodynamic responses between apical and basal regions, with no significant differences between both regions on average. Additional acute studies investigating the benefits of LV endocardial pacing have confirmed that the location of the optimal pacing site varies significantly between patients, supporting a strategy of individualized LV lead placement to maximize the benefit of CRT [85, 86].

Retrospective analyses of large clinical studies have provided additional insights as to the role of anatomical LV lead positions on chronic outcomes after CRT. Multiple studies have concluded that a more apical LV lead position carries a negative prognosis, while the role of circumferential lead position is less certain. An apical lead position was associated with significantly increased risk for CHF hospitalizations or death after adjusting for clinical covariates in MADIT-CRT [43]. Similar impacts of apical LV lead positions on CHF hospitalization and death were demonstrated in other retrospective single center and multicenter studies [87–89]. Apical lead placement has also been associated with lower levels of subsequent reverse remodeling and a smaller improvement in the patient's assessed NYHA class [87, 88]. Anterior LV lead positions have traditionally been avoided, but data on the impact of circumferential position on chronic outcomes after CRT are conflicting. For example, in one assessment there were no significant differences in outcome between lateral, anterior, and posterior lead positions in MADIT-CRT [43]. Changes in 6MWD, QoL, and percentage of patients with improved NYHA class were similar between lead positions in COMPANION [90]. Similarly, there were no differences in all-cause mortality or CHF hospitalizations, though risk of all-cause mortality or all-cause hospitalizations was not significantly reduced in patients with posterior leads. In contrast, two retrospective analyses found that lateral lead positions were associated with lower incidence of death or first hospitalizations [87] and two to three times less risk for a non-response, death, or necessary transplant [91].

31.6.2.1 Role of Baseline Mechanical Dyssynchrony, Scar, and Implications for LV Lead Position

Corrections of AV, interventricular, and intraventricular dyssynchrony are believed to be the major mechanisms of action for improved cardiac function with CRT. Numerous studies have concluded that the presence of baseline dyssynchrony improves the likelihood of a patient's CRT response. For example, an interventricular mechanical delay of at least 40 ms was an independent predictor of response in a subanalysis of the CARE-HF trial [92]. Though the PROSPECT study reported a relatively weak ability of echocardiographic measures of dyssynchrony to predict outcomes after CRT, subsequent analyses concluded that patients who experienced improvement in both CCS and reverse remodeling had greater baseline dyssynchrony [93]. Furthermore, a recent study utilizing speckle tracking radial strain showed that a lack of baseline radial strain was associated with worse freedom from death, transplant, or LVAD [94]. Cardiac magnetic

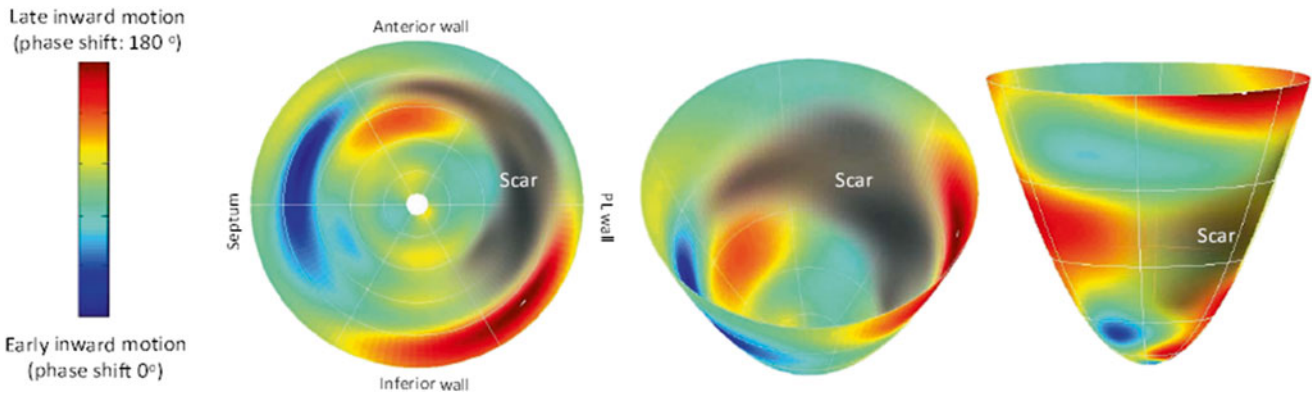

Fig. 31.10 Inward radial motion timing fused with myocardial scar from late gadolinium enhancement on cardiac magnetic resonance imaging. Modified from Foley et al. [168], available under a Creative Commons Attribution license. http://creativecommons.org/license/by/2.0

resonance imaging (MRI) and single-photon emission computed tomography (SPECT) are also useful for the quantification of mechanical dyssynchrony, tissue viability and scar (Fig. 31.10) [95, 96].

CHF etiology and scar size also impact the probability and extent of a positive CRT response. Though patients with NICM and ICM may receive benefits from CRT, the magnitude of response tends to be reduced in the ICM patients. After 6 months of CRT in the MIRACLE study, LV volumes were significantly reduced in both groups, but magnitudes were almost twice as large in the NICM group [38]. These differences remained significant after adjusting for covariates. Reverse remodeling was also lower in patients with ICM in the MADIT-CRT and REVERSE studies [72, 97]. However, the primary endpoint of all-cause death or nonfatal CHF events was not significantly different between patients with ICM and NICM in MADIT-CRT [62]. A longitudinal database study, as well as analyses of the Medicare ICD registry identified that ICM patients had significantly higher mortality than NICM patients after receiving CRT-D [74, 98]. This apparent difference in survival may reflect the worsening prognoses for ICM observed in studies of patients without CRT [99–101]. The presence of scar in patients with ICM may limit the effectiveness of CRT, especially if the LV lead is placed in the scar or if there is a limited amount of myocardium recruitable by pacing. The location of a myocardial scar also appears to be a critical factor. A transmural scar, defined as scar >50 % of the LV wall thickness on late gadolinium enhancement (LGE) MRI, is associated with reduced efficacy of CRT. A posterolateral transmural scar was associated with nonresponse and a lack of improvement in mechanical dyssynchrony after CRT [102]. In one report, Chalil et al. observed that a posterolateral scar measured by LGE MRI was the strongest predictor of CV death or CHF hospitalizations after CRT (HR = 3.06, $p < 0.0001$) [103]. A lack of anteroseptal or posterolateral scars accompanied by septal-to-lateral dyssynchrony on MRI was significantly associated with improved CCS in another study [104]. Similarly, patients with LV leads positioned at transmural scars experienced no improvement in LVEF, ESV, QoL, and 6MWD after CRT [105], and pacing on scar was associated with higher mortality and morbidity [103]. In contrast, patients with LV leads positioned outside of scarred regions by MRI guidance had reduced risk of death and CHF hospitalization compared to leads positioned inside scar [106]. High scar burden (i.e., the percentage of LV mass comprised of scar) is also associated with reduced CRT response. Numerous studies have demonstrated that increased scar burden measured by LGE MRI or by low amplitude echocardiographic speckle tracking strain is associated with less reverse remodeling after CRT [95, 107–109]. A scar burden of 15 % or less by LGE MRI was reported to predict clinical response with an 85 % sensitivity and 90 % specificity [110]. Adelstein et al. found that patients with ICM and low scar burden had survival free of death, transplant, or LVAD similar to patients with NICM [111]. Patients with ICM and high scar burden in that study had significantly reduced survival and lack of improvements as assessed by echocardiographic function.

While mechanical dyssynchrony, scar burden, and LV lead position appear to influence the effectiveness of CRT therapy separately, additional studies have further highlighted their relative importance by considering these factors simultaneously. An acute hemodynamic study in an animal model of LBBB demonstrated that the maximal improvement in pump function was similar in ICM and NICM at the optimal LV site and AV delay, although the optimal LV pacing site varied depending on scar location in the ICM animals and hemodynamics were more sensitive to AV delay than in animals with NICM. [112]. Wong et al. found that dyssynchrony at the LV pacing site was not predictive of reduction in LV ESV, while LGE-MRI scar at the LV and RV lead sites was associated with volumetric nonresponse [113]. Another study concluded that LV lead placement

at a late contracting segment with normal amplitude identified by speckle tracking echo, but not baseline dyssynchrony, predicted a reduction in LV ESV of at least 15 % [114]. Retrospective analysis of 389 patients with ICM and speckle tracking radial strain revealed that LV lead placement remote from the latest contracting segments (HR = 2.086, $p = 0.001$) or scar (HR = 2.913, $p < 0.001$) was associated with higher all-cause mortality on multivariate analysis with a small but statistically significant benefit of baseline dyssynchrony (HR = 0.995, $p = 0.001$) [115]. The prospective, randomized, double-blinded, controlled TARGET and STARTER studies investigated the impact of echocardiographic speckle tracking radial strain guided LV lead placement on CRT outcomes [116, 117]. LV lead placement in the echo-guided arm was targeted to a delayed contracting segment with either explicit or implicit avoidance of low amplitude or abnormal strain, while standard of care implant was performed in the control group. The echo-guided group in TARGET had superior volumetric responses (70 % vs. 50 %, $p = 0.031$). Higher proportions of patients improved at least 1 NYHA class (83 % vs. 65 %, $p = 0.003$), and they demonstrated lower rates of all-cause mortality and CHF hospitalizations. Similarly, the echo-guided group in STARTER had higher freedom from first CHF hospitalizations or death (HR = 0.48, $p = 0.0006$), and elicited greater reverse remodeling. Placement of the LV leads on or adjacent to the latest contracting segments, regardless of randomization, was associated with improved event-free survival (HR = 0.40, $p = 0.002$). In summary, these studies suggest avoidance of scar tissue at the LV pacing site while targeting a latest contracting site is a viable strategy to improve the probability of benefit after CRT (Fig. 31.11).

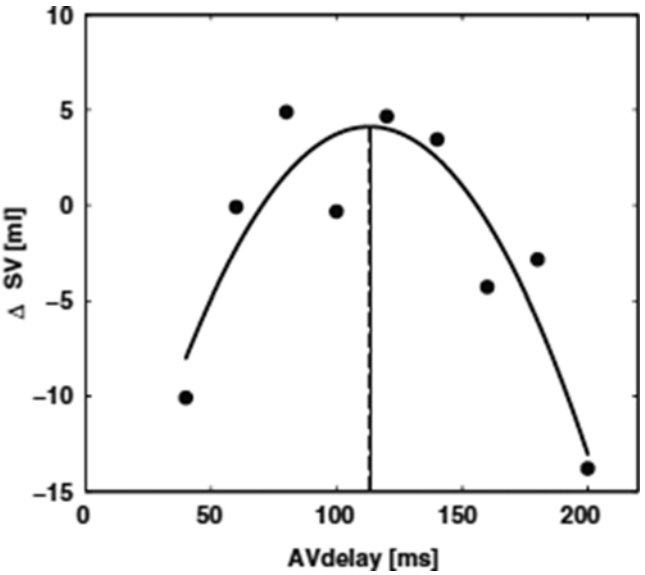

Fig. 31.11 Changes in stroke volume with AV delay. The optimal setting is indicated by the peak of the curve. Modified from Molenaar et al. [169], available under a Creative Commons Attribution license. http://creativecommons.org/license/by/2.0

31.6.3 AV and VV Optimization

Individualized programming of the AV and VV intervals is not typically performed in most patients in normal clinical practice, and it has been primarily reserved for nonresponders [118]. A survey of investigators in the FREEDOM trial found that echocardiography was the most common method used for optimization, yet almost 20 % of respondents never performed optimization. Mullens et al. described a multidisciplinary approach to managing non-responders to CRT at the Cleveland Clinic [119]. The most common factor contributing to suboptimal CRT was impaired filling due to inappropriate AV delay settings in 47 % of patients. In contrast to general clinical practice, the majority of major clinical CRT trials required AV optimization, often using the Doppler mitral inflow technique to maximize filling [8, 11]. The value of individualized tailoring of the AV and VV intervals is somewhat difficult to ascertain, due to the different methods used for verifying optimization and also variable criteria used to characterize CRT response [120–125]. Single point-in-time device optimization algorithms based on analyses of conduction properties from EGMs have demonstrated limited value over fixed programming or standard of care in the general population of patients receiving CRT. The FREEDOM trial randomized 1647 patients to empiric programming, which could have included one-time optimization, or the QuickOpt™ algorithm (St. Jude Medical, St. Paul, MN, USA), a programmer-based feature which provides recommended AV and VV delays based on EGM measurements [126]. Patients were followed for 12 months, with repeated optimizations in the QuickOpt™ group every 3 months. There were no significant differences between groups in the primary endpoint of the number of patients with improved CCS. Only 32 % of the patients in the empiric programming group were echo-optimized, highlighting the lack of AV and VV optimizations in clinical practice. The SMART-AV trial randomized 980 patients to echo-optimized AV delay, a fixed delay of 120 ms, or an AV optimization with the EGM-based SmartDelay® feature (Boston Scientific, Natick, MA, USA) [127]. After 6 months of pacing, there was no significant difference in the primary endpoint of reduction in ESV between groups. Additionally, changes in NYHA class, QoL, 6MWD, LV EDV, and LVEF were also not significantly different. The investigators concluded that while the routine use of AV optimization techniques studied in the trial did not translate to improved outcomes, optimization may still provide benefit to individual non-responders. In contrast to EGM-based methods, an optimization algorithm based on the Peak Endocardial Acceleration (PEA)

sensor (SonR®, Sorin CRM SAS, Clamart, France) contained in the RV or RA lead has been developed. The PEA sensor measures mechanical vibrations associated with cardiac contraction [128]. This algorithm provides manual AV and VV intervals via the programmer with weekly automatic AV interval optimizations. The randomized, single-blinded CLEAR pilot study randomized 238 patients to SonR® or standard of care optimization [129]. The primary endpoint at 1 year—the percentage of patients defined as improved by a composite of all-cause death, CHF hospitalizations, NYHA class change, and QoL—were all significantly higher in the PEA group (76 % vs. 62 %, $p=0.0285$). This difference was mainly driven by an unblinded assessment of the given patient's NYHA class. The results of this study are being confirmed in the randomized, double-blinded RESPOND-CRT study [130]. AdaptivCRT™ (aCRT), a fully automated and ambulatory AV and VV optimization algorithm based on EGM conduction measurements, has recently been developed (Medtronic plc). This algorithm measures AV conduction every minute and provides LV-only pacing synchronized to RV conduction when AV conduction is normal. In cases of long AV conduction, the algorithm provides AV and VV optimized BiV pacing. The double-blinded Adaptive CRT study randomized 522 patients to the aCRT algorithm or mandatory AV and VV echo optimization in 2:1 ratio [131]. Noninferiority of AdaptivCRT™ to echo at 6 months was achieved for the three primary endpoints, which included the number of patients with improved CCS. Further analyses of this trial data demonstrated an absolute 12 % improvement in CCS in the AdaptivCRT™ study arm over historical controls by propensity score analysis [132]. Another retrospective analysis of this same study found that AdaptivCRT™ in patients with normal AV conduction was associated with lower risk of death or CHF hospitalizations than in the echo-optimized control group (HR = 0.52, $p=0.044$) [133]. The percentage of patients with improved CCS was also higher in the AdaptivCRT™ group at 6 months (81 % vs. 69 %, $p=0.041$). The potential superiority of the aCRT algorithm over standard of care CRT in patients with normal AV conduction and LBBB is being prospectively studied in the AdaptResponse trial.

31.6.4 Atrial Arrhythmias, AF, and Percentage of Biventricular Pacing

Atrial fibrillation (AF) can eliminate some of the benefits of improved filling with CRT by eliminating AV synchrony, as well as by reducing the ability to provide consistent BiV capture and effective CRT due to fast rates and irregular AV nodal conduction. The prevalence of AF increases with NYHA class, with rates <10 % in NYHA class I and increasing to approximately 50 % in NYHA class IV [134]. In the 2009 European CRT survey, 23 % of patients receiving CRT were reported to be in AF [135].

Patients with AF have been underrepresented in trials of CRT, prompting interest in how the benefits of CRT in AF may differ from patients in sinus rhythm. A meta-analysis by Upadhyay et al. of 1164 patients from 5 studies concluded that patients in both AF and sinus rhythm benefited from CRT, though patients in AF seemed to benefit less [136]. Importantly, there were no significant differences between groups in mortality or change in NYHA classes at 1 year. However, patients in sinus rhythm elicited significantly greater improvements in both 6MWD and QoL. A larger, more recent meta-analyses of 7495 patients from 33 observational trials included 25.5 % patients with AF [137]; patients with AF had higher all-cause mortality (10.8 %/year vs. 7.1 %/year, $p=0.015$) and higher risk of nonresponse (34.5 % vs. 26.7 %, $p=0.001$). Similar to the analysis by Upadhyay et al., AF was associated with smaller improvements in 6MWD, QoL, and ESV but with no differences in LVEF. These analyses also identified that AV junctional ablations were associated with lower risk of non-response (RR = 0.40, $p<0.001$). Two studies also found a mortality benefit of AV junctional ablation, likely due to increased delivery of BiV pacing in patients with competing intrinsic conduction during AF [138, 139].

Ensuring a high percentage of BiV pacing is a main determinant of improved mortality and CHF hospitalization with CRT. Koplan et al. found that the greatest benefits in terms of mortality and CHF hospitalization were associated with BiV pacing more than 92 % of the time [140]. They also found a significant interaction between history of atrial arrhythmias and percent BiV pacing. An analysis of almost 37,000 patients from the LATITUDE Patient Management System (Boston Scientific) found that the greatest benefit of reduced mortality was found in patients with greater than 98 % pacing, emphasizing that the goal for BiV pacing should be as close to 100 % as possible [141]. Recognition and resolution of low percent BiV pacing remains challenging. A holter monitoring study of 19 patients with permanent AF found that only 47 % had effective BiV pacing, defined as greater than 90 % fully paced beats [142]. In the remaining 10 patients, 16 % ± 5 % beats were fusion and 24 ± 9 % were pseudo-fusion (i.e., pacing with no evidence of capture). Additionally, device diagnostics may be useful in determining reasons for loss of BiV pacing. In an analysis of almost 81,000 patients enrolled in the CareLink Network (Medtronic plc), device-diagnosed AT/AF was the most frequent identifiable cause of reduced BiV pacing [143]. The contribution of AT/AF was more pronounced in patients with BiV pacing <90 %. Management of patients with permanent or persistent AF and intact AV conductions to ensure a high percentage BiV pacing remains challenging. Patients with permanent, persistent, and paroxysmal AF defined by device diagnostics

had a prevalence of 8 % each in a remote monitored group of almost 55,000 patients [144]. In terms of percent BiV pacing, 69 % of patients diagnosed with permanent AF and 62 % with persistent AF had BiV pacing <98 %. Using multivariate analysis, patients with AF had higher mortality than patients with little or no AF after adjusting for factors including BiV pacing (HR = 1.28, $p < 0.001$ for permanent AF; HR = 1.51, $p < 0.001$ for persistent). Similarly, mortality was higher in patients with BiV pacing 90–98 % (HR = 1.20, $p < 0.001$) and <90 % (HR = 1.32, $p < 0.001$) compared to patients with BiV pacing >98 %.

These findings highlight the potential benefits of improving the overall percentage of BiV pacing in patients with frequent AT/AF. In patients whose AV conduction cannot be pharmacologically controlled and have a low percentage of BiV pacing, the 2013 ESC guidelines recommend that AV junctional ablation should be performed [145]. The largest comparison of CRT in patients with AF and AV junctional blocks ($n = 443$), AF with rate-slowing drugs ($n = 895$) and patients in sinus rhythm ($n = 6046$) was reported from the prospective, multicenter, observational CERTRIFY registry [146]. In this study, there was no significant difference in all-cause or cardiac mortality between patients in sinus rhythm and those with AF and AV junctional block. In contrast, mortality was significantly higher in patients receiving rate-slowing drugs with AF, both before and after these multivariate analysis (HR = 1.52, $p < 0.001$ for total mortality; HR = 1.57, $p < 0.001$ for cardiac mortality). These findings were in agreement with the meta-analysis of 768 patients from 7 trials that evaluated differences in CRT outcomes between AV junctional block and rate control [147]. AV junctional block was associated with significantly reduced all-cause mortality (RR = 0.42), cardiovascular mortality (RR = 0.44), and NYHA class reduction (RR = −0.52).

31.7 Future Directions

Future developments in CRT technology will likely focus on improved systems for delivering CRT pacing and new implant techniques. Advances in pacing multiple LV sites, LV endocardial pacing, leadless technologies, and image guidance for lead placement (e.g. fusion of functional imaging and anatomy) will likely play roles for improving the benefits of CRT and reducing complications. Early data on multisite LV pacing suggested that pacing two LV sites in different veins could improve acute hemodynamics more than pacing either site alone [148]. Only a handful of studies have investigated the chronic benefits of CRT with two LV pacing leads (i.e. "TriV pacing"), in part due to the technical complexity of implanting two LV leads and adapting the leads to IPGs which are not designed for the additional LV lead. A small, nonrandomized single center study demonstrated that such systems could be implanted with an approximately 87 % success rate and reported a 96 % response rate in 27 patients at 3 months [149]. The results from the prospective, randomized, single-blinded, crossover TRIP-HF study in 26 patients did not meet the primary endpoint after 3 months of pacing, but reduction in LV ESV was significantly greater with TriV pacing [150]. This approach is being further studied in the prospective, randomized, single center, single-blinded TRUST-CRT study [151]. The development of quadripolar LV leads has opened the possibility of pacing more than one LV site via a single lead. At present, it is unclear if pacing two LV sites along a quadripolar LV lead is superior to an optimized, single LV site [152, 153]. A study in patients with TriV pacing concluded that pacing multiple LV sites significantly improved hemodynamics more than the best single site, but not when pacing the best single LV site at an optimized AV interval [154]. Currently, the relative safety and efficacy of multisite LV pacing with a quadripolar LV lead is being studied in the MPP IDE study.

LV endocardial pacing has been suggested as an alternative implant approach in CRT nonresponders or patients with failed coronary sinus implants. Various implant techniques have been described to introduce a lead inside the LV including (1) an atrial transseptal puncture [155], (2) a ventricular transseptal puncture [156], and (3) a transapical puncture [157]. Acute preclinical and clinical studies of ICM and NICM suggest that LV endocardial pacing improves hemodynamics more than epicardial pacing [85, 86, 158, 159]. These superior hemodynamic responses may be due to a more physiological endocardial to epicardial conduction activation, as well as greater access to LV pacing sites and faster endocardial conduction with a smaller path length [160]. Anticoagulation is considered mandatory for LV endocardial pacing since the major risk associated with this lead placement technique is the risk of thromboembolism due to the presence of a lead in the systemic circulation. Further, required lead extractions and potential interactions of the lead with cardiac structures (such as the mitral valve apparatus) are additional concerns. Recently, the safety and efficacy of a totally superior atrial transseptal approach using a deflectable catheter system and RF puncture wire was reported [161]. Future advancements in pacing technology miniaturization and leadless pacing devices may help overcome some of these issues. For example, a small 0.05 cc ultrasound powered leadless electrode and pacing system (WiCS®-LV, EBR Systems Inc., Sunnyvale, CA, USA) is currently undergoing clinical study in the SELECT-LV trial. The receiver electrode is designed to endothelialize and minimize the risk of thromboembolism.

New techniques of integrating functional and anatomic imaging during CRT implantation are also being explored. Preprocedural targeting and implantation at the latest contracting regions, identified from 3D transesophageal

echocardiography with fusion of rotational CS anatomy, was highly successful (>90 %) and associated with a 90 % clinical response and an 80 % echocardiographic response [162]. This approach has also been used to guide implantation of two LV leads to separate late activated regions with associated improvements in clinical symptoms and reduced dyssynchrony [163]. Intraoperative technologies using fluoroscopy or electroanatomical mapping systems combined with preprocedural imaging are also being explored. Feasibility of delivering an LV lead to a site free from scar, determined by LGE-MRI, while navigating on a virtual venogram from electroanatomical mapping has been described [164]. Fusion of preprocedural anatomy from CT or MRI with live fluoroscopy has also been developed to improve targeted LV lead placement, including in those patients with previously failed implants [165].

31.8 Summary

This chapter discussed the application of CRT for the treatment of CHF, highlighting various technologies and implant techniques along with clinical trial findings. Furthermore, future directions were proposed in the arena of CRT.

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