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# Retiming the Failing Heart: Principles and Current Clinical Status of Cardiac Resynchronization

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Left or biventricular (BiV) pacing, or cardiac resynchronization therapy, was proposed nearly 10 years ago as an adjunctive treatment for patients with advanced heart failure (HF) complicated by discoordinate contraction due to intraventricular conduction delay. Since then, both short-term and a growing number of long-term clinical trials have reported on the mechanisms and short- and mid-term efficacy of this approach, with encouraging results. Therapy is implemented with novel pacing systems incorporating an endocardial lead to stimulate the lateral free wall via a cardiac vein, and often a right ventricular (RV) apex lead to provide BiV stimulation. A third atrial sensing lead monitors intrinsic rhythm and provides timing data to ensure ventricular pre-excitation. Modulation of the electronic atrial-ventricular (AV) time delay can optimize contractile synchrony, enhance the contribution of atrial systole, and reduce mitral regurgitation. Individuals with advanced HF, a wide QRS complex often with an AV time delay, and evidence of contraction dyssynchrony in viable myocardium represent the target patient group. Short-term studies reveal systolic augmentation and chamber efficiency from pacing resynchronization that can be substantial. Long-term studies reveal improved symptoms and exercise capacity, and some report reversal of chronic cardiac dilation. However, important questions regarding long-term efficacy and mortality impact, optimal mode for pacing stimulation, and role of combined pacing/cardioverter/defibrillation devices remain unresolved. Here we review pathophysiologic mechanisms, short- and long-term clinical results, and future directions of this new and promising therapy. (J Am Coll Cardiol 2002;39:194–201) © 2002 by the American College of Cardiology

Over the past two decades, the focus of heart failure (HF) pathophysiology and treatment has shifted from abnormalities of chamber function and hemodynamics to changes affecting the myocardium itself. Current therapies target neurohormonal cascades and stress response signaling coupled to chamber remodeling, dilation, and progressive deterioration (1–5). Whereas many abnormalities are best understood at the myocardial level, key features remain determined by the integrated chamber. A prime example is the influence of electrical activation on the timing of atrial and ventricular systole and synchronous contraction of the muscle wall. Recent studies have revealed that intraventricular conduction block with or without prolonged atrial-ventricular (AV) delay adversely influences ventricular function due to discoordinate contraction (6–13). This is usually indicated on the surface electrocardiogram by widening of the QRS complex, a finding associated with increased morbidity and mortality in HF patients (14–16).

Both contractile discoordination and abnormal AV timing can be offset by non-conventional pacing stimulation in which leads are placed on the left ventricular (LV) free-wall or in a biventricular (BiV) configuration (second lead in the right ventricle [RV]) and pre-excitation is employed to restore physiologic AV timing (17–19) and contraction

synchrony (10,20–28). This therapy is increasingly being termed *cardiac resynchronization*, and over the past year alone, more than 20 studies have reported short- or long-term effects from the treatment, including recent studies with placebo controls. Based on the results, the Food and Drug Administration (FDA) recently approved the therapy for the treatment of moderate-to-severe HF in patients refractory to drug treatment who have contractile dyssynchrony due to conduction delay. This approval comes as larger multicenter trials continue with the important goal of assessing the impact of resynchronization therapy on mortality. In this review, we have aimed to summarize the underlying pathophysiologic mechanisms, clinical status, and future directions of this rapidly emerging and novel approach to HF treatment.

## PATHOPHYSIOLOGY OF ABNORMAL ELECTRICAL TIMING: DYSSYNCHRONY AND AV DELAY

The two primary targets of resynchronization therapy are the pattern of LV activation, and the delay between atrial and ventricular systole. The LV normally contracts synchronously with little more than 40 ms variation in the onset of electrical activation throughout the wall and very similar low-level variability in the timing of mechanical activation as well. Synchrony of contraction is important because it results in more effective and energetically efficient ejection. When a portion of the heart is prematurely stimulated, as for example with a left bundle branch block (LBBB) or single-site ventricular pacing, the activation sequence

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#### Abbreviations and Acronyms

AV	= atrial-ventricular
BiV	= biventricular
HF	= heart failure
ICD	= implantable cardioverter-defibrillator
LV	= left ventricle/left ventricular
MR	= mitral regurgitation
NYHA	= New York Heart Association
RV	= right ventricle/right ventricular

changes markedly, generating regions of both early and delayed contraction (29–31). Early shortening at the stimulation site is wasted work because pressure is still low and no ejection is occurring. Late activation of the region remote to the stimulator occurs at higher stress because the paced territory has already developed tension, yet it is also characterized by wasted work because the early activated territory may now undergo paradoxical stretch (32). The net result is a decline in systolic function of about 20% with reduced cardiac output and increased end-systolic volume and wall stress (33,34), delayed relaxation (35,36), and decline in efficiency (37,38). The mechanical dysfunction arising from delayed intrinsic conduction delay (e.g., LBBB) versus single-site pacing (e.g., RV apex) is not necessarily equivalent. Rather, the data suggest the former has worse effects on contraction as a larger territory of myocardium is prematurely activated (39). Discoordination may also contribute to abnormal regional function and pro-arrhythmia (40,41). Late-systolic stretch of the myocardium, which is observed in the discoordinate septum (27,32), can lower force generation by rapidly disrupting cross-bridges. In addition, such mechanical stretch can trigger calcium release to induce after-contractions and arrhythmia (40,41).

In addition to intraventricular conduction, the AV time delay also influences net chamber mechanics—with too short or too long an interval resulting in sub-optimal chamber filling and contributing to mitral regurgitation (MR) (17). The latter occurs as the mitral valve re-attains an open midstream configuration during late diastole (after atrial contraction), which promotes regurgitation during the onset of ventricular systole (42). Experimental data in normal animals first showed a 15% decline in optimal cardiac output at either extreme of AV timing (43). However, translation of this behavior to the failing heart is non-trivial because such hearts often operate at high filling pressures, which reduces the volume contribution of atrial systole—even if optimally timed. In this situation, varying AV delay is less likely to affect net cardiac filling. Nonetheless, some studies have found linkage between optimal timing of atrial systole relative to the onset of ventricular activation and improved cardiac ejection in HF patients (44), and AV delay can have potent influences on the available diastolic filling time and pre-systolic MR (17). Finally, MR can also complicate atrial fibrillation owing to

irregular cycle lengths and thus sub-optimal valve positioning, and this might be offset by rate regularization via AV node ablation followed by synchronous stimulation.

#### ACUTE CLINICAL STUDIES: MECHANISMS

Initial clinical studies of pacing/stimulation therapy in HF patients focused on the effects of shortening AV delay. Small-scale trials indicated hemodynamic benefit for patients with a very long PR interval (often exceeding 300 ms) with pre-systolic MR and compromised diastolic filling time (17). However, this initial encouragement was not supported by subsequent studies (45). One potential factor was that in patients with an otherwise normal electrical activation sequence (narrow QRS complex), RV apical pacing generated de novo discoordination, thereby worsening function. Furthermore, in those patients who had dyssynchronous contraction with left free wall contraction delay, RV pacing did not correct the timing abnormality. High outflow tract pacing was also attempted, but the results were also generally disappointing (46). By the mid-1990s, the target changed from optimizing the AV delay to placing stimulation leads in those locations most likely to restore contractile synchrony.

Table 1 summarizes the recent clinical studies investigating the acute efficacy and mechanisms for biventricular (BiV) (and/or left ventricle [LV] only) stimulation effects. After the first report in 1983 involving four patients (47), it was nearly 13 years before the first systematic analysis was presented (21). Since then, BiV pacing has been shown to markedly improve cardiac output, increase systolic pressure, lower pulmonary wedge pressure (22,23), enhance ventricular systolic function as assessed by maximal rate of pressure rise (25,26) and pressure-volume loops (26), and improve the magnitude and synchrony of wall contraction (48,49). Furthermore, both BiV and LV-only pacing can generate systolic improvement while concomitantly reducing myocardial energy consumption, resulting in improved chamber efficiency (28). Short-term BiV pacing also reduces sympathetic activity, probably because of enhanced systolic function (50). For the majority of these studies, stimulation has been achieved with a dual-chamber pacing system in which the atrial lead senses activation and ventricular lead(s) prematurely excite the heart by means of a shortened AV delay. The target patients generally had severe HF (New York Heart Association [NYHA] functional class III–IV) with rest ejection fractions <20%, and most had a left bundle-branch conduction defect with QRS durations of 150 ms or more.

These short-term studies also revealed at least three unexpected and intriguing findings. One was that the immediate effects of single-site LV activation were often similar or even more prominent than those from BiV stimulation (23,25,26). To date, the latter has involved simultaneous stimulation of RVs and LVs, and this is not necessarily optimal, particularly in dilated failing hearts.

**Table 1.** Short-Term Studies With Temporary LV or BiV Pacing in Patients With Intraventricular Conduction Delay

Reference	Study Date	No. of Patients	Pacing Modes Compared	Primary Output	Results vs. Baseline or AAI
De Teresa (47)	1983	4	no pacing/LV	radionuclide imaging	LVEF: +25% in LV
Cazeau (21)	1996	8	no pacing/RV/BiV	hemodynamics	CI: +28% in BiV / PCWP: -16% in BiV
Blanc (23)	1997	23	no pacing/BiV/LV	hemodynamics	SBP: +7% / PCWP: -22%/V wave: -30% in BiV and LV
Leclercq (22)	1998	18	AAI/RV/BiV	hemodynamics	CI: +35% / PCWP: -18%/V wave: -21% in BiV
Saxon (48)	1998	11	no pacing/RV/LV/BiV	echocardiography	fractional area change: +19% in BiV
Kass (26)	1999	18	no pacing/RV/LV/BiV	hemodynamics	dP/dt +23% / PP: +18% in LV dP/dt +13% / PP: +15% in BiV LV > BiV
Auricchio (25)	1999	27	no pacing/RV/LV/BiV	hemodynamics	dP/dt +15% / PP: +7.5% in LV dP/dt +14% / PP: +6.5% in BiV LV > BiV
Nelson (27)	2000	22	no pacing/LV	hemodynamics MRI imaging	dP/dt +35% / PP: +16% in LV predictive + factors: QRS >155 ms + dP/dt <700 mm Hg/s
Nelson (28)	2000	10	no pacing/LV	hemodynamics ENERGETICS	dP/dt +43% / PP: +19% in LV $\Delta AV_{O_2}$ : -4% / $MV_{O_2}$ : -6% in LV
Kerwin (49)	2000	13	no pacing/BiV	radionuclide	LVEF: +29% / IVS +48% in BiV
Hamdan (50)	2000	13	RV/LV/BiV	SNA neurography	SNA: -11% in LV/-15% in BiV

AV<sub>O</sub><sub>2</sub> = arterial-coronary sinus oxygen difference; BiV = biventricular; CI = cardiac index; CO = cardiac output; IVS = interventricular synchrony; LV = left ventricular; LVEF = left ventricular ejection fraction; MV<sub>O</sub><sub>2</sub> = myocardial oxygen consumption; PCWP = pulmonary capillary wedge pressure; PP = pulse pressure; SBP = systolic arterial pressure; SNA = sympathetic nerve activity; SVR = systemic vascular resistance.

Although LV pacing alone pre-excites the lateral wall and thus might seem to simply shift electrical delay to the right side, the mechanical effects appear different. This may relate to the requirement for intramyocardial spread of electrical conduction from the LV pacing site, versus intra-fascicular conduction in the preserved right bundle. In addition, BiV pacing has thus far been studied with synchronous stimulation of both ventricles. This does not recapitulate normal activation and may be suboptimal. Second, whereas modifying AV delay influenced the net systolic response to LV or BiV pacing, this was a more modest effect compared with the pacing site itself. Over a broad range of delays (PR interval from 110 to 140 ms), the mechanical responses to BiV and LV-only pacing appear similar (25,26), and both are greater than with RV pacing. Finally, studies have not revealed short-term benefits (or detriments) on cardiac diastolic function as indexed directly by the isovolumic relaxation time constant and the diastolic pressure-volume curve (26).

**Identifying patients likely to respond.** A central issue for resynchronization therapy is the identification of candidates most likely to benefit. The primary variable has been QRS duration—an electrical marker for spatially dispersed mechanical activation. Experimental studies have shown that the greater the degree of pacing-induced LV discoordination and dysfunction, the wider the associated electrical complex (33), and patients with wider QRS complexes have a greater immediate mechanical response to resynchronization therapy (25–27,51,52). Additionally, the worse the cardiodepression, perhaps itself reflecting dyssynchrony, the greater the resynchronization response (27). This dysfunction may be indexed by ejection fraction (22), basal dP/dt<sub>max</sub> (27), Doppler echocardiographic indexes of diastolic-to-

cycle-length ratio (53), or Doppler measures of isovolumic contraction. Direct analysis of dyssynchrony may also be feasible by means of magnetic resonance imaging (27), tissue Doppler strain analysis (54), or contrast echocardiography (55). Such measures appear to provide the strongest correlate with responsiveness to resynchronization (27). One aspect that has been somewhat controversial is whether QRS narrowing with BiV or LV stimulation can be used to indicate treatment efficacy. Short-term studies have not found this correlation, which is probably related to the intramyocardial conduction that exists with pacing regardless of the more global synchrony that may be produced. However, some long-term studies have suggested that a narrower QRS correlates with better long-term efficacy (56), and these issues remain to be reconciled.

Simple mechanical measures might also be employed to examine the efficacy of resynchronization therapy—such as artery pulse pressure or cardiac output. Preliminary data suggests that short-term enhancement of some parameters correlates with long-term improvement; this relationship is being clarified by several ongoing studies. It might be useful to measure a mechanical response when placing the lead to improve pacing-site selection, although this has rarely been done thus far.

## CHRONIC CLINICAL STUDIES

There are now a half-dozen completed clinical studies involving long-term multisite (BiV) cardiac stimulation for the treatment of advanced dilated cardiomyopathy with underlying conduction delay (QRS > 120 to 150 ms). These studies are summarized in Table 2. Early experience began in Europe with the work of Bakker et al. (57), Cazeau

**Table 2.** Studies With Permanent Cardiac Multisite Pacing

Study (Reference)	Beginning/ End	No. of Patients	Randomized	Placebo Controlled	Follow-up (Months)	NYHA		Endo/Epi	Results With Multisite Pacing
						Functional Class (Mean)	SR/AF		
French Pilot (56)	1994/1998	50	no	no	15.4 ± 10.2	III/IV	36 only 99/14	43 endo 7 epi endo	-1.5 NYHA functional class; +40% in peak V <sub>O<sub>2</sub></sub> ; Mortality: 40%
Insync	1997/1998	103	no	no	12	III/IV (3.7)			1.2 NYHA functional class; +40% QOL; +25% in 6 WT; Mortality: 20%
InSync Italian Registry (58)	1998/2000	190	no	no	10 ± 5	II-IV (3.3)	158/32	endo	NYHA class; +31% in 6 WT; +60% in QOL; Mortality: 7%
PATH-CHF (59)	1995-1998	42	yes	no	3	III/IV (3.1)	SR only	epi	22% in 6 WT; +43% QOL; 20% peak V <sub>O<sub>2</sub></sub> ; Mortality: 20%
MUSTIC SR (60)	1998-1999	67	yes/crossover	yes	3/3	III (3.1)	SR only	endo	-23% in 6 WT; +32% QOL; 8% peak V <sub>O<sub>2</sub></sub> ; Mortality (7.5 months): 7.5%
MUSTIC AF (63)	1998-1999	43	yes/crossover	yes	3/3	III	AF only	endo	+9.3% in 6 WT; 13% peak V <sub>O<sub>2</sub></sub> ; Mortality (9 months): 10.9%
MIRACLE (61,62)	1998-2000	266	yes/parallel	yes	6	III/IV (3.1)	SR only	endo	+13% in 6 WT; 13% in QOL; Mortality: non-available

AF = atrial fibrillation; NYHA = New York Heart Association; QOL = quality of life; 6 WT = 6-min walking test; SR = sinus rhythm.

et al. (21), and others (58). To date, three placebo control studies have been completed: the PATH-CHF trial (59), the MUSTIC trial (60), and the MIRACLE trial (61,62). In the PATH-CHF study, patients were first assigned to four weeks of active pacing (LV or BiV), then four weeks of no pacing, then a second four-week active pacing period—continued for the ensuing year. This was a single-blind study and required surgically implanted leads and two stimulators. Importantly, exercise performance (e.g., maximal oxygen consumption) rose significantly only during the two periods of active pacing. This finding in the third month (after a month of no-pacing) was somewhat more difficult to ascribe to a placebo effect.

The recently published MUSTIC study (60) used a cross-over design, with patients randomized to three months' stimulation on or off and the mode then switched for the second three-month period. In sinus rhythm patients, exercise capacity improved only during active treatment (+23% in 6-min walking distance,  $p < 0.001$ ), improved symptoms (32% in quality-of-life questionnaire,  $p < 0.001$ ) and increased maximal oxygen consumption (+8%,  $p < 0.03$ ). Interestingly, this study did not observe a placebo effect. A separate component of this study evaluated patients with chronic atrial fibrillation, each patient undergoing AV nodal ablation prior to receiving a BiV stimulation system (63). Intention-to-treat analysis failed to reveal significant differences between pacing on and off data, although limitations due to study design and loss of effective pacing in several subjects contributed to this. In the subset of subjects in which pacing was effectively delivered, the results suggested improvement, but this needs more definitive testing.

The recently completed MIRACLE trial is the largest study to date. Preliminary data have been reported (61,62), and a full publication is pending. This six-month parallel-design trial randomized 228 patients to resynchronization therapy and another 225 patients to a placebo control arm. All patients were in normal sinus rhythm and were stable NYHA functional class III or class IV. The primary findings showed an improvement in the 6-min walk test, quality-of-life score, and NYHA functional class (a combined end point was also examined). Secondary end points were also assessed in a subset of patients, and the data support a diminished diastolic and systolic chamber size in the active resynchronization treatment but not in the placebo group. Mortality was <10% in both treatment arms at six months. Rehospitalization rates and number of days hospitalized were both significantly and substantially lower in the active treatment group. The investigators reported a placebo effect with respect to quality of life but not for exercise or cardiac-function parameters.

In addition to these main trials, several smaller studies have reported improved quality of life (64), reduced hospitalization (65), and antiarrhythmic activity (66,67) from resynchronization therapy. The level of enhanced exercise capacity is nontrivial, and it compares favorably with that

**Table 3.** Ongoing Trials With Multisite Cardiac Pacing

	Inclusion	Objectives	Randomized	Primary End Point
COMPANION	Class III/IV; LVEF < 35% QRS > 140 ms	no pacing vs. BiV vs. BiV + ICD	yes follow-up: 2 years	Death/All hosp
CARE-HF	Class III/IV; LVEF < 35% QRS > 150 ms or QRS > 120 ms + dyssynchrony Echocardiography criteria	no pacing vs. BiV vs. BiV + ICD	yes follow-up: 1.5 years	Death/CV hosp
PACMAN	Class III; LVEF < 35% QRS > 150 ms	no pacing vs. BiV + ICD if indicated	yes cross-over 6 months	6 WT
PATH-CHF 2	Class II-IV; LVEF < 35% QRS > 120 ms	optimized pacing vs. no pacing + ICD if indicated	yes cross-over 6 months	6 WT and CPX
Ventak	Class II-IV; LVEF < 35% QRS > 120 ms	no pacing + ICD vs. BiV + ICD	yes cross-over 3 months	CPX
VECTOR	Class II-IV; LVEF < 35% QRS > 140 ms	no pacing vs. BiV	yes cross-over 6 months	6 WT and QOL
PAVE	AV node ablation/chronic AF	RV vs. LV vs. BiV	yes/3 arms/6 months' follow-up	6 WT and QOL
BELIEVE	Class II-IV; LVEF < 35% QRS > 130 ms + ICD indication	LV + ICD vs. BiV + ICD	yes/1-year follow-up	Echocardiography
INSYNC III	Class III-IV; LVEF < 35% QRS > 130 ms + ICD indication	safety/efficacy new device	no/6 months' follow-up	6 WT and QOL
MIRACLE ICD	Class II-IV; LVEF < 35% QRS > 130 ms + ICD indication	no pacing + ICD vs. BiV + ICD	yes cross-over 6 months	6 WT and QOL
OPTSITE	AV node ablation/chronic AF	RV vs. LV vs. BiV	yes/3 arms/6 months' follow-up	6 WT and QOL

AF = atrial fibrillation; AV = atrioventricular; BiV = biventricular; CPX = cardiopulmonary exercise; hosp = hospitalization; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; QOL = quality of life; 6 WT = 6-min walking test.

reported with angiotensin-converting enzyme inhibitors and beta-blockers (68,69). Long-term follow-up data from these trials have not yet been published, although preliminary results have been presented at recent national meetings. For the MUSTIC trial, functional benefit was sustained during the one-year follow-up period; for the PATH-CHF study, two- and three-year mortality rates have been reported at 86% and 75%, respectively (70).

Additional trials are currently underway in the US and Europe to address important unanswered issues (Table 3). Several studies are evaluating the efficacy of combining internal defibrillation with BiV resynchronization (MIRACLE ICD, CONTAK CD, INSYNC ICD, BELIEVE). Data from one such study reported that implantable cardioverter-defibrillator (ICD) firings were significantly less frequent during the randomized period when resynchronization therapy was applied (66,67), although this has not yet been confirmed in larger trials. Other studies are addressing whether resynchronization therapy improves mortality (COMPANION, CARE-HF, PACMAN). The COMPANION study is the largest, with a target recruitment of 2,200 patients (71), and it is powered to determine a mortality benefit of 25% in patients with dilated cardiomyopathy and a basal QRS duration >120 ms. It includes a placebo group, a combined ICD and resynchronization therapy group, and a group receiving resynchronization therapy only. Finally, studies are planned to test the relative merits of single-site LV pacing versus BiV pacing for resynchronization (BELIEVE, PAVE and OPTSITE). Preliminary data from the PATH-CHF 1 study have not found significant differences between these modes.

## IMPLEMENTATION: NEW TECHNOLOGIES

As of April 2001, more than 1,000 individuals involved in various trials have received some form of resynchronization pacing therapy. The vast majority of these patients received an endocardially placed coronary venous lead system (72). This application has required the development of novel leads that can better reach the target site (often lateral cardiac wall), maintain lead stability after placement, and provide acceptable pacing thresholds.

The question of precisely where on the LV optimal pacing is achieved remains incompletely resolved and is likely to vary somewhat from patient to patient. Butter et al. (73) reported that short-term systolic response did depend on the LV pacing site, with the mid-part of the LV lateral wall generally providing the greatest improvement in most patients (73). One potential explanation is that pre-excitation of the left lateral wall optimally offsets the region with the greatest basal delay in activation and may also help ameliorate MR by pre-stimulating the papillary muscle. Multiple LV sites may be even better than a single site (74), but this remains to be more fully studied.

Initial lead placement was surgical, and although surgical mortality was low (Auricchio A, personal communication, 2001), the approach was largely abandoned owing to attendant morbidity from the surgery itself. A transvenous approach was introduced by Daubert et al. in 1998 (75), and this approach has since become the mainstream method, employing specifically designed leads to assist in placement. With these improvements, implantation success has risen from 50% to 85% or higher (76,77). The target location

(i.e., a lateral or posterolateral vein in mid-cavity position) can be reached in a majority of patients (about 75%), and similar results have been reported by several groups using various technologies (78,79).

Implantation of an LV lead via the coronary sinus poses some technical challenges, most often related to a dilated right heart anatomy and/or variable or suboptimal coronary venous anatomy. Both can render coronary sinus cannulation and lead placement more difficult. Although overall reported complication rates have been generally low, one must keep in mind that most of these data have come from centers with extensive experience, and there is a well-recognized and important learning curve involved with implantation. Furthermore, HF patients ill-tolerate complications related to arrhythmia or perforation, so care and caution are always indicated. The major serious complications are dissections or perforations of the coronary sinus (or cardiac vein), which result in cardiac tamponade. In the series by Ricci et al. (78), the latter complication occurred in 0.9% of 190 patients treated. In the Rennes Hospital experience, the rate of coronary sinus dissection was 2% (out of 102 patients), but none of these instances led to further adverse clinical consequences. Pacing thresholds in the 1–1.5-V range are achieved in approximately 90% of subjects, and many maintain such thresholds over the long term. Further improvements in lead technology and in the coronary sinus introducer sheaths should improve on these statistics. Steerable sheaths, which assist in negotiating the dilated right heart anatomy that often complicates coronary sinus cannulation, may also improve success rates. Several alternative approaches such as a transeptal (80) or pericardial-epicardial approach may be useful in cases with coronary sinus or venous anatomy failure. The surgical epicardial approach may still be considered useful in appropriate candidates for whom heart surgery is already indicated, or for those with failed transvenous lead implantation due to anatomic or technical difficulties.

Although data on short-term pacing effects of BiV versus LV stimulation show equivalence or slight superiority to LV pacing, BiV pacing remains the dominant method under clinical study. In this regard, the optimal placement of the right heart lead is itself somewhat controversial. For most trials, this lead is placed at the RV apex. However, alternative locations, such as the mid-upper RV septum, are feasible and may or may not provide additional improvement. This potentially important question needs to be resolved.

Initial studies employed a Y-adaptor and existing DDDR pacing systems to link both ventricular leads to the single ventricle outport. This resulted in a substantial number of technical failures, but current generator systems with three dedicated ports have largely resolved this problem. However, only recently has the output to both ventricles been truly independent. Most existing and ongoing studies involve systems tying both leads to a common internal current source. This runs the risk of an impedance mismatch that could result in only RV or only LV pacing, rather than both.

New devices have two independent channels and further add programmability of the RV–LV stimulation delay. These are under current investigation.

## UNSOLVED ISSUES, FUTURE DIRECTIONS

Although much has been learned over the past several years regarding resynchronization therapy, many important questions remain unanswered. Clearly, there are major important questions about whether there is a sustained benefit on morbidity and reduced hospitalization and whether there is a favorable effect on overall and cardiac mortality. In this regard, it is important that the ongoing trials such as COMPANION, which are addressing these key questions, proceed to completion so that the role of this therapy can be properly and fully evaluated. The mortality impact of resynchronization may ultimately be tied in with ICDs, particularly if the results of ongoing multicenter trials show survival benefits from such devices in HF.

Another question relates to the prospective identification of responders. New methods examining regional wall motion hold promise for generating a dyssynchrony index that could improve on current, more indirect methods. The optimal method of therapy itself is unresolved. As noted, questions remain as to whether BiV stimulation is needed, whether multisite left-heart stimulation would enhance the efficacy, or, if an RV lead is to be placed, where the optimal location is and what the best timing delay is between RV and LV stimulation.

A large unresolved question is whether this therapy is going to be useful in patients with atrial fibrillation. Some studies have suggested utility (81), although larger trial data remain inconclusive (64). Unlike the sinus rhythm patients, in which there is some degree of freedom in the AV delay to optimally time a resynchronization effect, the AV node in atrial fibrillation patients is generally ablated, and then patients are treated using a BiV pacing mode. This involves regularization of the heart rate with rate-responsive generators, as well as activation of both lower chambers. Rate response serves to simulate normal effects of autonomic tone, but it is not a perfect replacement for physiologic control. Furthermore, in patients without an existing conduction delay, BiV pacing may not yield as good a response as that with His-Purkinje conduction. More studies are clearly needed in these patients.

Finally, the existing evidence indicating deterioration of systolic function and energetic efficiency with pacing-induced dyssynchrony suggests that standard RV apex pacing in individuals with cardiac failure may not be the ideal approach. In patients with cardiodepression but a narrow QRS complex and normal intraventricular conduction who need pacing for rate control, a BiV system may prove superior, but this clearly needs to be tested.

## SUMMARY

Substantial data now support the hypothesis that LV or BiV stimulation can improve cardiac function and efficiency in

HF patients with discoordinate contraction due to abnormal conduction. Several recent modest-sized placebo-controlled trials suggest that the long-term benefits can be substantial (60–62); and based on these data, this therapy recently received FDA approval in selected HF patients. Its ultimate utility and acceptance into HF management will depend on fully establishing its indications and long-term therapeutic value, refining the targeting of patients most likely to benefit and enhancing the treatment delivery systems and technologies to achieve these goals. Much exciting work has already been done, but there is much more still to do.

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