REVIEW

YAARIV KHAYKIN, MD
Department of Cardiovascular Medicine, Section of Cardiac Pacing and Electrophysiology, The Cleveland Clinic

EDUARDO B. SAAD, MD
Department of Cardiovascular Medicine, Section of Cardiac Pacing and Electrophysiology, The Cleveland Clinic

BRUCE L. WILKOFF, MD
Department of Cardiovascular Medicine, Section of Cardiac Pacing and Electrophysiology, The Cleveland Clinic

Pacing in heart failure: The benefit of resynchronization

ABSTRACT

Cardiac resynchronization therapy involves pacing of the left ventricle alone or in concert with the right ventricle within a certain range of atrioventricular delay. It may help patients with systolic heart failure and conduction disturbances by optimizing myocardial performance.

KEY POINTS

Cardiac resynchronization therapy has been shown to improve functional status, quality of life, and cardiac function in patients with heart failure and to reduce hospitalizations, although its effect on mortality is still uncertain.

Even though many studies of cardiac resynchronization therapy have been done in various patient populations, who should receive it has not been fully resolved. We currently recommend it for patients with moderate or severe congestive heart failure (New York Heart Association class 3 or 4), poor left ventricular function (ejection fraction < 35%), and QRS duration > 130 ms.

Patients in New York Heart Association class 3 or 4 with a conduction disturbance who are undergoing open chest surgery for an independent reason should be considered for placement of a left ventricular epicardial lead.

The left ventricular lead is technically challenging to implant, and issues remain concerning patient selection and the best sites for pacing.

MANY PATIENTS with congestive heart failure (CHF) might benefit from a new type of pacemaker therapy that involves placing pacing leads in the right atrium, left ventricle, and sometimes the right ventricle. This new strategy, called *cardiac resynchronization therapy*, is aimed at correcting delays in conduction that result in different regions of the heart not working optimally in concert.

The US Food and Drug Administration recently approved this new therapy for patients with moderate CHF despite optimal medical therapy and with evidence of a significant intraventricular conduction delay.

This paper reviews the evidence (from more than 20 clinical trials) that cardiac resynchronization therapy is beneficial, who should receive it, and some unresolved clinical issues.

CHF TACKLED ON MANY FRONTS

CHF affects almost 5 million people in the United States.[1] Although 200,000 people die of it each year, the number of CHF patients is growing by 200,000 to 500,000 per year, thanks to improvements in its treatment that have lowered its mortality rate. The health care costs associated with the disease are estimated to exceed $20 billion per year.[1]

CHF has been the focus of intense research, and treatments include:

- **Medications** that address symptoms and myocardial remodeling[2–6]
- **Implantable defibrillators,** which prevent sudden death due to arrhythmias[7,8]
- **Surgery** for underlying coronary or valvular disease or to provide mechanical assistance for the ailing myocardium[9]
- **Transplantation,** which unfortunately is

not widely available, leaving many patients with intolerable symptoms.

RATIONALE FOR RESYNCHRONIZATION

The onset of left ventricular contraction should occur with less than 40 ms of variation throughout the wall.[10] The importance of this highly synchronized ventricular contraction has long been recognized.

In 1926, Wiggers[11] described left ventricular contraction as a "series of sequential fractionate contractions of muscle bundles." He proposed that a disturbance in the timing of contraction might be caused by interspersed areas of ischemia or fibrosis.

Nearly 40 years later, Harrison[12] noted that "disorganized contraction" or "asynergy" was frequently present on kinetocardiograms of patients with coronary heart disease. Soon after, Herman et al[13] found that more than 70% of patients who had abnormalities in their contraction patterns had clinical CHF.

Left bundle branch block leads to dyssynchrony

In 1983, Bramlet et al[14] recognized that people who had exercise-induced left bundle bunch block also had an exercise-induced decline in ejection fraction, even if their hearts were structurally normal.

Today, evidence is mounting that intraventricular conduction delay (ie, any degree of left bundle branch block on surface electrocardiography [ECG] with QRS duration > 120 ms) leads to disorganized left ventricular contraction, wasted myocardial stroke work, and adverse remodeling, generating areas of early and late activation.[15–17] More than 30% of patients with CHF may have such disorganized contractions.[18]

Dyssynchronous ventricular contraction is inefficient

Echocardiography,[19–24] nuclear imaging,[25] and tagged magnetic resonance imaging[26,27] show that in ventricular dyssynchrony, the interventricular septum typically contracts first, and the left ventricular free wall lags behind. As much as 20% of the contractile work is spent on chamber translocation rather than ejection.[28–30]

Furthermore, areas of the myocardium that are activated early may be paradoxically stretched when other areas contract later, which may further worsen myocardial performance by disrupting actin-myosin crossbridges. This stretching may have a proarrhythmic effect.[26,27,31,32] Late activation of other areas may impair ventricular relaxation.[33,34]

In addition, loss of synchrony between left atrial and left ventricular contractions may cause a conformational change in the mitral valve. This may lead to mitral insufficiency, further disrupting filling of the left ventricle and causing sudden atrial distention, left atrial dilatation, and ultimately, atrial tachyarrhythmias.[31,32,35,36]

Septal perfusion defect may cause dysfunction

A perfusion abnormality of the interventricular septum is seen in many patients with left bundle branch block during exercise and dobutamine stress perfusion testing. This is usually ascribed to imaging artifact,[37–39] but in fact it may represent a real functional perfusion defect that is partly responsible for the myocardial dysfunction and ventricular arrhythmias seen in patients with CHF who have a prolonged QRS interval.

Evidence for this theory comes from studies that compared different pacing sites as surrogates of conduction abnormalities. The velocity of blood flow in the left anterior descending and left circumflex arteries differed, depending on the pacing site.[40] The velocity in the left anterior descending artery was lower with pacing from the mid-right ventricle or its apex, but not with pacing from the right atrium or left ventricle.

The authors speculated that these velocity differences might be due to early activation of the areas perfused by the left anterior descending artery, particularly the interventricular septum, with pacing from the right side. If the region is activated early, it would not have to work as hard, and so it would consume less oxygen; consequently, the coronary flow to that region would decrease. Alternatively, the early-activated region may have a prolonged and less synchronous contraction, resulting in increased systolic resistance to coronary flow.[41]

Left ventricular contraction should occur with less than 40 ms of variation throughout the wall

Disappointing results with right-sided dual-chamber pacing

The first attempts at cardiac resynchronization involved placing leads in both the right atrium and right ventricle to restore atrioventricular synchrony, ie, right-sided dual-chamber pacing.[42,43] Although initial results were encouraging, long-term results were not.[35,44]

The reason may be that cardiac output is preserved over a broad range of atrioventricular delays,[45,46] in chronic atrial fibrillation compared with sinus rhythm,[47] and is independent of the interatrial delay.[48,49] Patients with CHF are already on the plateau of the Frank-Starling curve; thus, any marginal increase in preload caused by synchronized atrioventricular activation would not be expected to increase cardiac output very much.

Right ventricular apical pacing has even been shown to result in myocardial deterioration, mediated by further loss of left ventricular synchrony, similar to that seen in patients with intrinsic interventricular conduction delay.[50] Results have also been disappointing with leads in the right ventricular septum and the outflow tract.[46,51]

Dual-chamber right-sided pacing may actually make heart failure worse

At one center, up to 25% of CHF patients with pacemakers were shown to have a left ventricular ejection fraction less than 40% and New York Heart Association (NYHA) class 2 symptoms or worse.[52]

At The Cleveland Clinic, we noted worsening heart failure and ventricular arrhythmias during right ventricular pacing in patients with CHF within the first month of dual-chamber implantable cardioverter-defibrillator implantation.[53,54] Symptoms improved in some of these patients when we allowed intrinsic conduction by extending the programmed atrioventricular delay.

Similarly, the recent Dual Chamber and VVI Implantable Defibrillator (DAVID) trial randomized patients with a clinical indication for implantable cardioverter-defibrillator therapy (but not for pacing) to ventricular backup pacing or to dual-chamber rate-responsive pacing. Patients who received dual-chamber rate-responsive pacing were more likely to be hospitalized for CHF and had a trend towards a higher mortality rate.[55]

CARDIAC RESYNCHRONIZATION THERAPY

Cardiac resynchronization therapy involves pacing of the left ventricle alone or in concert with the right ventricle within a certain range of atrioventricular delay. It was hypothesized that this strategy would:

- Help to coordinate left ventricular contraction
- Improve left ventricular filling and relaxation
- Recover previously wasted stroke work without increasing myocardial energy demand
- Diminish mitral insufficiency and atrial tachyarrhythmias
- Reverse the remodeling of the left atrium and left ventricle.[56–58]

IMPLANTATION TECHNIQUES

In conventional dual-chamber pacing, leads are placed in the right atrium and right ventricle. In cardiac resynchronization therapy, an additional lead is placed over the free wall of the left ventricle so that the left and right ventricles are activated simultaneously.

Percutaneous placement now available

During early trials, patients had to undergo thoracotomy for the left ventricular lead to be placed on the epicardial surface of the ventricle, but this lead can now be placed percutaneously in most patients. First described in 1998, this percutaneous technique is now widely used.[59]

In the new technique, the left ventricular lead is placed in one of the branches of the coronary sinus, using one of the commercially available sheath systems (FIGURE 1).

The best results have been achieved with the lead placed over the midlateral/posterior wall of the left ventricle.[60] This site may provide early excitation in the region with the greatest baseline delay in activation and can help reduce mitral insufficiency by prestimulating the papillary muscle. Placing multiple leads on the left ventricle (or multiple electrodes on one lead) on the left ventricle may provide further advantages, but this approach is still under investigation.[61]

TABLE 1

Randomized clinical trials of biventricular pacing

STUDY	N	INCLUSION CRITERIA	MAIN RESULTS, COMMENTS
PATH-CHF[*45,70,71]	53	NYHA class 3 or 4 QRS > 120 ms PR > 150 ms Sinus rate > 55	Improved hemodynamics (LV pacing had better acute hemodynamic results than biventricular pacing) Improved $Vo_{2\ max}$ Improved 6-minute walking distance
MUSTIC[*65,72,73]	58	NYHA class 3 QRS > 150 ms EF ≤ 35% LVEDD > 60 mm No pacing indications	Improved exercise capacity and quality of life Fewer hospitalizations for CHF 85% of patients preferred biventricular pacing Not designed to assess mortality, but showed a 5% reduction in mortality at 6 months, all in biventricular-paced patients
MIRACLE[74–77]	453	NYHA class 3 or 4 QRS ≥ 130 ms EF ≤ 35% LVEDD ≥ 55 mm No pacing indications	Improved NYHA class Improved 6-minute walking distance Improved quality of life Small improvement in ejection fraction About 2/3 of patients classified as improved, but 38% also improved despite no pacing therapy (placebo effect)
CONTAK CD[110]	490	NYHA class 2–4 QRS ≥ 120 ms EF ≤ 35% Standard ICD indications	Decreased progression of CHF (21%), but did not achieve the prespecified 25% reduction Improved $Vo_{2\ max}$ Improved 6-minute walking distance Improved quality of life
MIRACLE ICD[103,107,108]	636	NYHA class 2–4 QRS ≥ 130 ms EF ≤ 35% No pacing indications Standard ICD indications	Fewer CHF hospitalizations Improved 6-minute walking distance Improved ejection fraction Evaluated biventricular pacing in patients with CHF who needed an ICD
COMPANION[115]	1,520	NYHA class 3 or 4 QRS ≥ 120 ms EF ≤ 35% No indications for pacing or ICD Stable medical regimen	Stopped due to lower mortality and hospitalization rates First controlled study addressing mortality as primary end point Uses over-the-wire pacing system
InSync III[116,117]	264	NYHA class 3 or 4 QRS ≥ 130 ms EF ≤ 35% LVEDD ≥ 55 mm No pacing indications	Ongoing Device allows for differential ventricular pacing and programmable V-V interval
VECTOR		NYHA class II–IV QRS ≥ 140 ms EF ≤ 35% LVEDD ≥ 55 mm	Ongoing

*Crossover trials
NYHA = New York Heart Association, EF = ejection fraction, LV = left ventricular, $Vo_{2\ max}$ = peak oxygen consumption, CHF = congestive heart failure, LVEDD = left ventricular end-diastolic dimensions, ICD = implantable cardioverter-defibrillator

In contrast, placing the lead in the anterior venous system may actually worsen hemodynamic indices because this site is close to the right ventricular apex, and stimulating it can stimulate the intraventricular septum too early, with attendant loss of left ventricular synchrony.[45,62]

Technique is difficult

The implantation procedure is challenging, and in addition to the usual difficulties of pacemaker placement, it may be complicated by prolonged radiation exposure and coronary sinus dissection or perforation. Cardiac tamponade has been reported in up to 1% of patients undergoing lead implantation, and coronary sinus dissections may occur in as many as 2%.[10,63]

With practice, the likelihood of these complications diminishes and the success rate improves to over 85%.[59,64,65] A reasonable pacing threshold in the range of 1 to 1.5 volts may be achieved in 90% of patients.[10]

Better insertion systems, such as steerable coronary sinus introducer sheaths and lower-profile leads placed over the guidewire, may increase the number of target veins that can be reached, improve success rates, and reduce implantation times.[66]

Alternate percutaneous routes to the left ventricle across the septum or via the arteries have also been considered. However, these are complicated by the need for continuous anticoagulation and are fraught with the danger of stroke and systemic embolism.[67,68]

More options for those undergoing open chest surgery

One can still place a lead on the outside of the left ventricle surgically. This approach allows more freedom in selecting the pacing site while monitoring hemodynamics in the operating room. However, it requires general anesthesia and open chest surgery, which are associated with significant morbidity in patients with CHF.

Nevertheless, candidates for cardiac resynchronization who must undergo an open chest procedure for an independent reason should be considered for placement of a left ventricular epicardial lead.

BENEFITS OF CARDIAC RESYNCHRONIZATION THERAPY

TABLE 1 summarizes trials of biventricular pacing, some of which are reviewed below.

Patients improve clinically

The InSync study[69] enrolled 81 patients in Canada and Europe with NYHA class 3 or 4 symptoms, QRS duration longer than 150 ms, and left ventricular end-diastolic diameter greater than 60 mm who showed no clinical improvement despite best medical therapy for 1 month.

Biventricular pacing systems were successfully implanted in 68 patients. At 3 and 6 months, the patients' NYHA class, 6-minute walking distances, and quality of life measures had improved significantly.

The PATH-CHF study (Pacing Therapies for Congestive Heart Failure)[70,71] randomized 53 patients with moderate-to-severe CHF and interventricular conduction delay to undergo atrial synchronized biventricular pacing or best atrial-univentricular pacing. The right or left ventricle was selected depending on results of acute hemodynamic studies performed with the patient under general anesthesia during device implantation.

The success rate improves to over 85% with practice

After 4 weeks of pacing, all devices were switched to no pacing for 4 weeks. The patients were than crossed over to the alternate pacing mode for another 4 weeks and subsequently left in the best chronic pacing mode.

Contractility (as measured by the maximum rate of rise of left ventricular pressure; dP/dt_{max}) and pulse pressure improved: left ventricular pacing outperformed biventricular pacing, which was better than right ventricular pacing. Maximum oxygen consumption and the 6-minute walking distance improved with biventricular stimulation, and benefits were sustained at 1-year follow-up.[45,70,71]

The MUSTIC trial (Multisite Stimulation in Cardiomyopathy)[65,72,73] randomized 58 patients with NYHA class 3 symptoms, QRS interval greater than 150 ms, and left ventricular ejection fractions less than 35% to receive devices that were either set to atrial/synchronized biventricular pacing or to no pacing (ventricular backup pacing at 40

beats per minute). Patients crossed over to the other arm after 3 months of initial therapy. After another 3 months, devices were programmed according to patient preference.

Patients receiving biventricular pacing improved in NYHA class, 6-minute walking distance, quality-of-life measures, and hospitalizations needed. Most patients (85%) preferred the biventricular therapy, 4% preferred no pacing, and 10% had no preference.[65] Benefits were sustained at 1 year[72] and 2 years.[73]

The MIRACLE trial (Multicenter InSync Randomized Clinical Evaluation)[74–77] enrolled 453 patients with NYHA class 3 or 4 symptoms, left ventricular ejection fractions less than 35%, and QRS duration greater than 130 ms. In this double-blind study, patients were randomized to receive cardiac resynchronization therapy or no pacing for 6 months.

The resynchronization group improved significantly in their 6-minute walking distance, quality-of-life scores, and left ventricular ejection fraction, and fewer required hospitalization or intravenous therapy for CHF.[74] Benefits were sustained at 1 year.[75] A recent analysis demonstrated improvement in patients with ischemic and nonischemic cardiomyopathy[76]; the magnitude of response was greater in the latter group. Men and women responded similarly.[77]

Two small studies[78,79] also supported improved functional class and fewer hospitalizations with cardiac resynchronization therapy.

The effects of cardiac resynchronization on neurohormones are similar to those of drug therapy

Hemodynamic measures improve

Cardiac resynchronization therapy has been shown to:

- Lower left ventricular filling pressures and peripheral vascular resistance
- Increase contractility, expressed as pressure-volume loops and dP/dt_{max}
- Improve coordination of left ventricular contraction
- Raise cardiac output and systolic blood pressure.[25,45,46,56,80–82]

In one study,[83] the maximum hemodynamic improvement in patients who responded to cardiac resynchronization therapy occurred at an atrioventricular delay that did not raise the left ventricular end-diastolic pressure and when there was no latency period between left atrial systole and the onset of left ventricular isovolumic contraction. This resulted in optimum pulse pressure.

On the other hand, patients who did not respond to cardiac resynchronization therapy had worsening hemodynamic measures with a shorter left atrial-left ventricular delay. This suggests that they depend more on higher left ventricular end-diastolic pressure to maintain adequate cardiac output, or that the resynchronization was inadequate.

Furthermore, in a study of patients with poor left ventricular function (ejection fraction < 30%) and left bundle branch block, cardiac output increased to a similar extent with cardiac resynchronization therapy or dobutamine infusion. However, the difference in oxygen saturation between the coronary arteries and coronary sinus declined with cardiac resynchronization therapy (indicating a decrease in oxygen consumption), whereas oxygen consumption rose as expected with the dobutamine infusion.[84]

This indicates that cardiac resynchronization therapy, unlike the other positive inotropic therapies currently available, improves left ventricular efficiency by recovering stroke work lost without increasing myocardial oxygen demand. Both biventricular pacing and left ventricular pacing alone had these effects.

Although smaller studies indicated that left ventricular pacing alone may be superior to biventricular pacing,[46,82,85] large clinical trials to date have employed simultaneous left ventricular-right ventricular activation in their protocols.

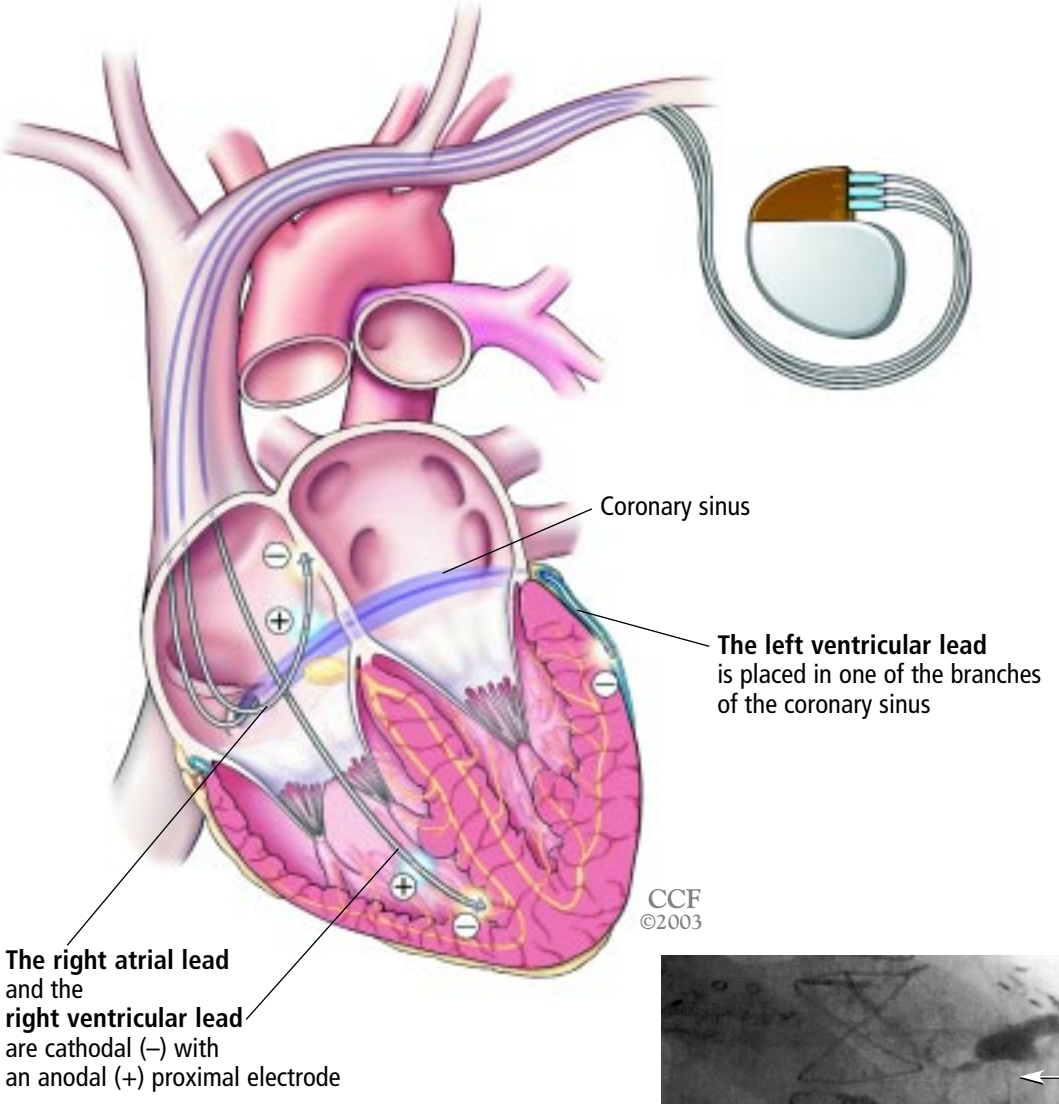
Reduced neuroendocrine activation

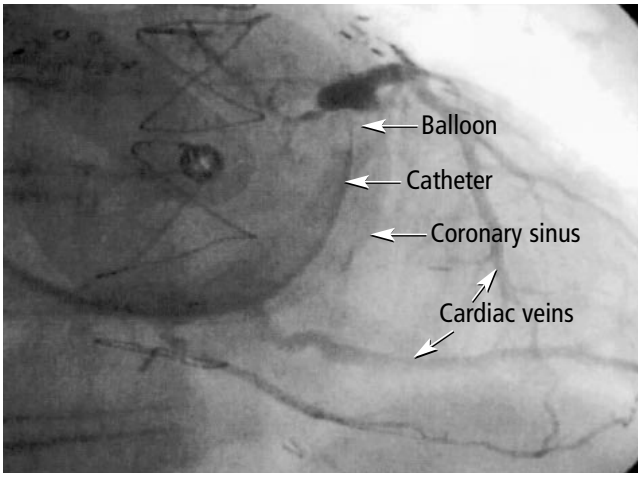
In CHF, the sympathetic and renin-angiotensin-aldosterone systems are activated, resulting in adverse hemodynamic consequences, myocardial remodeling, and fibrosis.[86] The best medical therapy in CHF, which includes beta-adrenergic blockers,[5] angiotensin-converting enzyme inhibitors,[2,3] and spironolactone,[6] improves symptoms and outcomes by suppressing this neuroendocrine cascade.

Cardiac resynchronization therapy shows effects similar to medical therapy, with a decrease in the levels of circulating norepi-

Resynchronization therapy in heart failure

Many patients with congestive heart failure might benefit from a new type of pacemaker therapy called cardiac resynchronization therapy, aimed at correcting delays in conduction that result in different regions of the heart not working optimally in concert.





Retrograde coronary sinus angiogram in the anteroposterior projection using a balloon-tip catheter. After cannulation, the balloon is inflated to occlude the main coronary sinus, allowing for better retrograde filling of the venous branches.

FIGURE 1.

nephrine after a mean of 12 weeks of biventricular pacing.[87,88] Microneurographic assessment found cardiac resynchronization therapy to suppress sympathetic activation in CHF better than right ventricular pacing alone, regardless of QRS duration.[89,90] Analysis of heart-rate variability in patients receiving cardiac resynchronization therapy revealed a shift towards higher parasympathetic and lower sympathetic tone modulation.[91,92]

Beneficial remodeling

A number of studies[72,74,93–95] reported a decline in left ventricular end-systolic and end-diastolic dimensions, left atrial size, and mitral insufficiency with cardiac resynchronization therapy, suggesting that it can reverse the mechanical remodeling seen in CHF.

One such study[96] categorized patients as "responders" or "nonresponders," depending on whether their left ventricular end-systolic volume declined with therapy by more than 10%. Although responders had greater left ventricular dyssynchrony at baseline, they also had relatively lower plasma B-type natriuretic peptide and endothelin levels. This suggests that cardiac resynchronization therapy may benefit patients before they reach end-stage biochemical heart failure.[96] The magnitude of the changes in left ventricular end-diastolic volume and dimension predicted changes in the NYHA functional class.[97]

Sudden cardiac deaths account for up to 50% of deaths in patients with severe CHF

Pacing thresholds were reduced after long-term biventricular stimulation in another study,[98] suggesting reduced wall stress with cardiac resynchronization therapy and beneficial electrical remodeling.

Reduced ventricular arrhythmias

On cardiac resynchronization therapy, the incidence of ventricular arrhythmias decreases, as measured by how many times the patient's implantable cardioverter-defibrillator discharges and by the frequency of documented ventricular ectopy.[99,100]

In one study,[101] frequent episodes of ventricular tachycardia were completely suppressed, and another showed less likelihood of inducing ventricular tachycardia during electrophysiological testing if biventricular pacing was substituted for right ventricular pacing alone.[102]

This phenomenon may be explained by diminished paradoxical stretch of the early-activated myocardium with its attendant calcium flux, and by reduced heterogeneity of ventricular refractoriness.

Although studies indicate that antitachycardia pacing or implantable cardioverter-defibrillator shocks occur as often in patients treated with cardiac resynchronization therapy as in other patients, biventricular antitachycardia pacing has been shown to be more effective than conventional right ventricular antitachycardia pacing.[94,103–105] Adding defibrillator function to the cardiac resynchronization therapy pacing system may further reduce the number of sudden cardiac deaths, which account for up to 50% of deaths in patients with severe CHF.[106]

The MIRACLE-ICD study[103,107,108] enrolled patients who lacked a conventional indication for pacing but warranted implantable cardioverter-defibrillator placement for primary or secondary prevention of sudden death. Other enrollment criteria included NYHA class 2, 3, or 4 symptoms, a left ventricular ejection fraction less than 35%, and QRS duration greater than 130 ms.

Of 636 patients, 567 had a coronary sinus lead successfully implanted. Three to 7 days later, 554 patients were randomized to have their pacemakers turned on or off. All patients received an InSync implantable cardioverter-defibrillator system (Medtronic), with right ventricle-only sensing and right ventricle/left ventricle pacing capability. Implantable cardioverter-defibrillator functions remained active throughout the study.

Patients improved in the 6-minute hall-walk test, quality-of-life scores, left ventricular end-systolic and end-diastolic dimensions, and fractional shortening, but the change was statistically significant only in patients with NYHA class 3 or 4 symptoms.[107] Ventricular tachyarrhythmias were appropriately detected and treated in all cases, with no episodes of double-counting or inappropriate shocks. Biventricular-delivered antitachycardia pacing was more effective than right ventricular antitachycardia pacing alone.[103] At 6 months, left ventricular volume, ejection fraction, maximum oxygen

consumption, NYHA functional class, and quality-of-life indicators had improved.[108,109]

The VIGOR/VENTAK CHF trial[93] studied changes in clinical, echocardiographic, and neurohormonal measures in 53 patients with a cardiac resynchronization therapy system with an epicardial left ventricular lead. Subjects had dilated cardiomyopathy with NYHA class 3 or 4 symptoms, QRS duration greater than 120 ms, left ventricular ejection fraction less than 30%, and PR intervals greater than 160 ms. Patients were randomized to receive cardiac resynchronization therapy or to a control group 1 to 2 weeks after implantation. Patients in the control group had their pacemakers reprogrammed to deliver cardiac resynchronization therapy after the initial 6-week phase.

At 12 weeks, patients receiving cardiac resynchronization therapy had decreased left ventricular and left atrial dimensions and improved cardiac output, and at 3 months, fewer episodes of ventricular tachyarrhythmias. No effect on neurohormonal markers was seen. The study was terminated early because it did not utilize transvenous left ventricular leads: once transvenous leads were available, it was difficult to recruit patients into a study requiring a thoracotomy.

In small case series, improvement in sleep apnea was noted after resynchronization therapy

The CONTAK-CD trial[110] randomized 490 patients with NYHA class 2, 3, or 4 symptoms, QRS greater than 120 ms, left ventricular ejection fractions less than 35%, and indications for an implantable cardioverter-defibrillator. Preliminary analysis after 3 months demonstrated decreased left ventricular dimensions with cardiac resynchronization therapy but no effect on neurohormonal markers.

However, the therapy did not achieve the desired end point (a 25% reduction in CHF progression at 6 months). This may have been because some of the patients were relatively healthy, ie, those with NYHA 2 symptoms and relatively short QRS duration at baseline. Almost 30% of the patients had the left ventricular lead implanted in the anterior circulation, further diminishing the success of cardiac resynchronization therapy. Adding the defibrillator function to cardiac resynchronization therapy resulted in a trend to improved survival at 10-month follow-up.

A meta-analysis of the VENTAK, MIRACLE, and MUSTIC trials presented at the 2002 meeting of North American Society of Pacing and Electrophysiology[111] showed a strong trend towards a lower mortality rate with cardiac resynchronization therapy (odds ratio 0.7, 95% confidence interval 0.4–1.2).

Cardiac resynchronization and atrial fibrillation

Although some studies suggested that cardiac resynchronization therapy is useful in patients with atrial fibrillation,[112] an intention-to-treat analysis of a subset of MUSTIC trial patients with chronic atrial fibrillation and atrioventricular node ablation did not show any differences in outcomes with right ventricular vs biventricular pacing.[113] The Left Ventricular-Based Cardiac Stimulation Post AV Node Ablation Evaluation (PAVE) trial is investigating this issue.

Cardiac resynchronization and sleep apnea

In a small case series,[114] patients who received cardiac resynchronization therapy had significant improvements in both central and obstructive sleep apnea, which are common in CHF patients. Cheyne-Stokes breathing was significantly diminished. Larger studies are needed to explore this issue further.

ONGOING STUDIES

The COMPANION study (Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure)[115] is a randomized, open-label trial comparing three treatments: cardiac resynchronization therapy, cardiac resynchronization therapy with additional implantable cardioverter-defibrillator capability, and optimal medical therapy alone.

Investigators planned to enroll 2,200 patients with NYHA class 3 or 4 symptoms, left ventricular ejection fraction less than 35%, and QRS duration greater than 120 ms.[115] However, the data and safety monitoring board stopped the trial after only 1,520 patients were enrolled because the resynchronization therapies were more effective than the medical therapy in reducing the end points of hospitalizations and deaths.

These findings should be interpreted with

TABLE 2

Current trends in biventricular pacing

Ideal patient selection
- Severely symptomatic congestive heart failure (New York Heart Association class 3 or 4) despite optimal medical therapy
- Wide QRS complex (> 130 ms) with left bundle branch block morphology
- Prolonged PR interval
- Ejection fraction < 35%

Technical aspects
- Coronary sinus angiography is extremely helpful to detect available venous branches
- Posterolateral venous branches appear to be the best targets
- Different approaches to coronary sinus navigation have not been directly compared
- Other approaches to left ventricular pacing are still underdeveloped, eg, transcutaneous pericardial approach

Expected results
- Improved hemodynamic indices
- About 2/3 of adequately selected patients improve in functional capacity and quality of life
- Possibly decreased incidence of ventricular arrhythmias
- Possibly decreased sympathetic activation
- No data available on mortality benefits

Current indications:
- **Moderate or severe CHF**
- **Poor LV function**
- **QRS > 130 ms**

caution, since the study has not yet been published.

The InSync III study[116,117] is designed to assess the safety and efficacy of the InSync III pacemaker (Medtronic), the first device to allow separate programming of the right and left ventricles with modulation of right ventricular-left ventricular timing. Patients have no standard indications for pacing but have NYHA class 3 or 4 symptoms, QRS duration greater than 130 ms, and left ventricular ejection fraction less than 35%. Primary end points include NYHA class, 6-minute walking distance, and quality-of-life measures.

The first 264 patients showed significant improvements in left ventricular systolic volume, NYHA class, quality-of-life measures, and 6-minute walking distance compared with the MIRACLE trial control group at 3 months.[116] Placing the right ventricular lead in the septum vs the apex did not affect functional performance.[117]

The VECTOR trial (Ventricular Resynchronization Therapy Randomized trial) is looking at exercise performance, adverse event rates, and pacing system performance in patients with CHF, QRS duration greater than 140 ms, and left ventricular ejection fraction less than 35%. The patients receive a St. Jude Frontier 3x2 pulse generator and are randomized to receive cardiac resynchronization therapy or no pacing for 6 months.

The CARE-HF study (Cardiac Resynchronization in Heart Failure)[118] is randomizing 800 patients to cardiac resynchronization therapy or a control group and following them for at least 18 months. It will assess the effect of cardiac resynchronization therapy on a composite end point of all-cause mortality and unplanned cardiovascular hospitalization in patients with CHF due to left ventricular systolic dysfunction. Results should be available in 2004.[118]

WHO SHOULD RECEIVE CARDIAC RESYNCHRONIZATION THERAPY?

Despite the many studies of cardiac resynchronization therapy in various patient populations, who should receive it has not been fully resolved. Nevertheless, we currently recommend it for patients with all of the following:
- Moderate or severe CHF (NYHA class 3 or 4)
- Poor left ventricular function (ejection fraction < 35%)
- QRS duration greater than 130 ms with left bundle branch block morphology (TABLE 2).

While it is logically less likely that

TABLE 3

Unanswered issues in biventricular pacing

What are the exact mechanisms of hemodynamic improvement?

What are the best predictors of a favorable response?

Do patients with right bundle branch block derive the same benefit as those with left bundle branch block?

What is the best left ventricular stimulation site or sites?

Is left ventricular pacing alone as beneficial as biventricular pacing?

Can biventricular pacing reverse left ventricular remodeling?

Does biventricular pacing have a preventive role in earlier stages of patients with congestive heart failure and conduction defects (prevent left ventricular remodeling)?

Can isolated right ventricular pacing cause long-term deterioration in left ventricular function?

Is defibrillation capability beneficial for patients without standard indications for an implantable cardioverter-defibrillator?

Will short-term benefits be maintained after long-term follow-up?

Can biventricular pacing reduce mortality in patients with congestive heart failure?

patients with right bundle branch block would benefit from cardiac resynchronization therapy, and they were underrepresented in clinical studies, there is some evidence that they might benefit from biventricular pacing.[119] A baseline QRS duration greater than 160 ms correlated with a favorable acute hemodynamic response in PATH-CHF,[45] but in the InSync trial, significant QRS narrowing seen during biventricular pacing did not correlate with clinical response to therapy.[69]

New imaging tools can directly measure left ventricular mechanical dyssynchrony; these include magnetic resonance imaging,[26,27] echocardiography,[19–24] nuclear imaging,[25] and three-dimensional contact[120] and noncontact[121] electro-anatomical mapping.

Investigators using these tools advocate baseline dyssynchrony as the best predictor of response to cardiac resynchronization therapy. Real-life correlates of this, including QRS duration greater than 150 ms and dP/dt_{max} less than or equal to 700 mm Hg/sec, consistently predict a positive response to biventricular pacing.

Models for tomorrow: Individualize pacing sites

Work is underway to establish better ways of screening patients likely to benefit from cardiac resynchronization therapy and to find ideal pacing sites. It is unlikely that a single left ventricular lead placement area would benefit all CHF patients with left bundle branch block.

Ideally, we need to quantify the baseline dyssynchrony of left ventricular contraction in each patient, then apply a mathematical computer model to identify the best site of early activation that would improve the mechanical properties of the left ventricle. This model should take into account whether and how well the target area can contract, based on the degree of myocardial scarring and blood supply present. In addition, some form of contact or noncontact endocardial activation mapping may be useful to identify and avoid areas with slowed conduction.[121]

We should then be able to create an overlay of coronary veins available for lead implantation in the region of interest and model the degree of cardiac functional improvement, provided a lead could be secured at one of these locations with or without concomitant right ventricular lead placement. Such technology would help us reject patients not expected to improve from cardiac resynchronization therapy, optimize cardiac resynchronization therapy in suitable patients, and abandon an implantation procedure early if a target position could not be engaged.

New imaging tools can directly measure left ventricular mechanical dyssynchrony

FUTURE RESEARCH DIRECTIONS

Among the unanswered questions about cardiac resynchronization therapy (TABLE 3) are the following.

- *Who might need true biventricular pacing?* Right ventricular contractile synchrony may help some preload-dependent patients with impaired right ventricular function or those with primary clinical right heart failure, but it may offer minimal hemodynamic benefit to other patients. Right ventricular pacing may, in fact, be detrimental if it continues to contribute to left ventricular dyssynchrony despite left ventricular free-wall pacing.

If concomitant right ventricular pacing is found to be effective, the questions of ideal right ventricular pacing sites and right ventricular-left ventricular stimulation timing would need to be addressed. The Medtronic InSync III stimulator can be programmed to deliver left and right ventricular stimulation separately, and its use is currently being studied.

- *Can cardiac resynchronization benefit patients with atrial fibrillation?* The issue is still under investigation, with positive preliminary results.[112]

Use of cardiac resynchronization for atrial fibrillation is under investigation

- *Will adding defibrillator capability to the cardiac resynchronization therapy system protect CHF patients from sudden death?* Ongoing studies will tell. However, the practice of routinely adding a coronary sinus lead via a Y-adapter to a dual-chamber implantable cardioverter defibrillator should be discouraged. During nonpaced modes, these systems may double-count ventricular potentials, owing to the temporal separation of right and left ventricular signals, leading to inappropriate shocks.[122]
- *Can cardiac resynchronization therapy prevent dyssynchrony?* CHF patients with an independent indication for pacing may deteriorate further from right ventricular pacing alone and could benefit from cardiac resynchronization therapy to prevent rather than treat left ventricular dyssynchrony,[53] but this needs to be further investigated.

Patients with CHF and indications for cardiac resynchronization therapy undergoing open chest surgery for an unrelated reason may routinely have an epicardial lead placed in the operating room to circumvent the challenge and risk of transvenous left ventricular lead placement.

- *How to remove a coronary sinus lead?* This question has not been well studied to date. It is reasonable to assume that some patients with cardiac resynchronization therapy systems may develop infection and would benefit from complete extraction. However, transvenous extraction of the coronary sinus lead may be challenging and carries a risk of coronary sinus perforation and tamponade, requiring open heart surgery to remove the lead.

CARDIAC CONTRACTILITY MODULATION PACING

Some patients may not be able to have a resynchronization system implanted successfully. They may instead benefit from cardiac contractility modulation pacing, which is also under investigation.

This modality uses nonexcitatory, subthreshold diastolic electrical stimuli to augment calcium flux from the sarcoplasmic reticulum, increasing intracellular calcium available for sarcomere contraction. It has been shown to be beneficial in animals, but its application in humans is still in its infancy.[123,124]

REFERENCES

1. **Heart Failure Society of America (HFSA) practice guidelines.** HFSA guidelines for management of patients with heart failure caused by left ventricular systolic dysfunction—pharmacological approaches. J Card Fail 1999; 5:357–382.
2. **The CONSENSUS Trial Study Group.** Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 1987; 316:1429–1435.
3. **The SOLVD Investigators.** Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991; 325:293–302.
4. **The Digitalis Investigation Group.** The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med 1997; 336:525–533.
5. **Bristow MR.** Beta-adrenergic receptor blockade in chronic heart failure. Circulation 2000; 101:558–569.
6. **Pitt B, Zannad F, Remme WJ, et al.** The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999; 341:709–717.
7. **Buxton AE, Lee KL, Fisher JD, et al.** A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter Unsustained Tachycardia Trial Investigators. N Engl J Med 1999; 341:1882–1890.
8. **Moss AJ, Zareba W, Hall WJ, et al.** Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002; 346:877–883.

9. **Rose EA, Gelijns AC, Moskowitz AJ, et al.** Long-term mechanical left ventricular assistance for end-stage heart failure. N Engl J Med 2001; 345:1435–1443.
10. **Leclercq C, Kass DA.** Retiming the failing heart: principles and current clinical status of cardiac resynchronization. J Am Coll Cardiol 2002; 39:194–201.
11. **Wiggers CJ.** Are ventricular conduction changes important in the dynamics of left ventricular contraction? Am J Physiol 1926; 74:12–30.
12. **Harrison TR.** Some unanswered questions concerning enlargement and failure of heart. Am Heart J 1965; 69:100–115.
13. **Herman MV, Heinle RA, Klein MD, Gorlin R.** Localized disorders in myocardial contraction. Asynergy and its role in congestive heart failure. N Engl J Med 1967; 277:222–232.
14. **Bramlet DA, Morris KG, Coleman RE, Albert DCobb FR.** Effect of rate-dependent left bundle branch block on global and regional left ventricular function. Circulation 1983; 67:1059–1065.
15. **Prinzen FW, Augustijn CH, Arts T, Allessie MA, Reneman RS.** Redistribution of myocardial fiber strain and blood flow by asynchronous activation. Am J Physiol 1990; 259:H300–H308.
16. **Prinzen FW, Hunter WC, Wyman BT, McVeigh ER.** Mapping of regional myocardial strain and work during ventricular pacing: experimental study using magnetic resonance imaging tagging. J Am Coll Cardiol 1999; 33:1735–1742.
17. **Wyman BT, Hunter WC, Prinzen FW, McVeigh ER.** Mapping propagation of mechanical activation in the paced heart with MRI tagging. Am J Physiol 1999; 276:H881–H891.
18. **Stevenson WG, Stevenson LW, Middlekauff HR, et al.** Improving survival for patients with advanced heart failure: a study of 737 consecutive patients. J Am Coll Cardiol 1995; 26:1417–1423.
19. **Zhou Q, Henein M, Coats A, Gibson D.** Different effects of abnormal activation and myocardial disease on left ventricular ejection and filling times. Heart 2000; 84:272–276.
20. **Ansalone G, Giannantoni P, Ricci R, et al.** Doppler myocardial imaging in patients with heart failure receiving biventricular pacing treatment. Am Heart J 2001; 142:881–896.
21. **Nelson GS, Fetics BJ, Murabayashi T, Rochitte CE, Talbot M, Berger RD.** Cardiac variability imaging enables detection of pacing improved contractile coordination in patients with dilated cardiomyopathy and left bundle-branch block [abstract]. Circulation 2000; 120:539.
22. **Yu CM, Chau E, Sanderson JE, et al.** Tissue Doppler echocardiographic evidence of reverse remodeling and improved synchronicity by simultaneously delaying regional contraction after biventricular pacing therapy in heart failure. Circulation 2002; 105:438–445.
23. **Breithardt OA, Stellbrink C, Kramer AP, et al.** Echocardiographic quantification of left ventricular asynchrony predicts an acute hemodynamic benefit of cardiac resynchronization therapy. J Am Coll Cardiol 2002; 40:536–545.
24. **Kawaguchi M, Murabayashi T, Fetics BJ, et al.** Quantitation of basal dyssynchrony and acute resynchronization from left or biventricular pacing by novel echo-contrast variability imaging. J Am Coll Cardiol 2002; 39:2052–2058.
25. **Kerwin WF, Botvinick EH, O'Connell JW, et al.** Ventricular contraction abnormalities in dilated cardiomyopathy: effect of biventricular pacing to correct interventricular dyssynchrony. J Am Coll Cardiol 2000; 35:1221–1227.
26. **Nelson GS, Curry CW, Wyman BT, et al.** Predictors of systolic augmentation from left ventricular preexcitation in patients with dilated cardiomyopathy and intraventricular conduction delay. Circulation 2000; 101:2703–2709.
27. **Curry CW, Nelson GS, Wyman BT, et al.** Mechanical dyssynchrony in dilated cardiomyopathy with intraventricular conduction delay as depicted by 3D tagged magnetic resonance imaging. Circulation 2000; 101:E2.
28. **Park RC, Little WC, O'Rourke RA.** Effect of alteration of left ventricular activation sequence on the left ventricular end-systolic pressure-volume relation in closed-chest dogs. Circ Res 1985; 57:706–717.
29. **Littmann L, Symanski JD.** Hemodynamic implications of left bundle branch block. J Electrocardiol 2000; 33(suppl):115–121.
30. **Grines CL, Bashore TM, Boudoulas H, et al.** Functional abnormalities in isolated left bundle branch block. The effect of interventricular asynchrony. Circulation 1989; 79:845–853.
31. **Sarubbi B, Ducceschi V, Santangelo L, Iacono A.** Arrhythmias in patients with mechanical ventricular dysfunction and myocardial stretch: role of mechano-electric feedback. Can J Cardiol 1998; 14:245–252.
32. **ter Keurs HE, Zhang YM, Davidoff AW, et al.** Damage induced arrhythmias: mechanisms and implications. Can J Physiol Pharmacol 2001; 79:73–81.
33. **Heyndrickx GR, Vantrimpont PJ, Rousseau MF, Pouleur H.** Effects of asynchrony on myocardial relaxation at rest and during exercise in conscious dogs. Am J Physiol 1988; 254:H817–822.
34. **Ariel Y, Gaasch WH, Bogen DK, McMahon TA.** Load-dependent relaxation with late systolic volume steps: servo-pump studies in the intact canine heart. Circulation 1987; 75:1287–1294.
35. **Brecker SJ, Xiao HB, Sparrow J, Gibson DG.** Effects of dual-chamber pacing with short atrioventricular delay in dilated cardiomyopathy. Lancet 1992; 340:1308–1312.
36. **David D, Michelson EL, Naito M, et al.** Diastolic "locking" of the mitral valve: the importance of atrial systole and intraventricular volume. Circulation 1983; 67:640–645.
37. **Larcos G, Gibbons RJ, Brown ML.** Diagnostic accuracy of exercise thallium-201 single-photon emission computed tomography in patients with left bundle branch block. Am J Cardiol 1991; 68:756–760.
38. **Caner B, Rezaghi C, Uysal U, et al.** Dobutamine thallium-201 myocardial SPECT in patients with left bundle branch block and normal coronary arteries. J Nucl Med 1997; 38:424–427.
39. **Tighe DA, Hutchinson HG, Park CH, et al.** False-positive reversible perfusion defect during dobutamine-thallium imaging in left bundle branch block. J Nucl Med 1994; 35:1989–1991.
40. **Amitzur G, Manor D, Pressman A, et al.** Modulation of the arterial coronary blood flow by asynchronous activation with ventricular pacing. Pacing Clin Electrophysiol 1995; 18:697–710.
41. **Dresing TJ, Natale A.** Congestive heart failure treatment: the pacing approach. Heart Fail Rev 2001; 6:15–25.
42. **Hochleitner M, Hortnagl H, Ng CK, Gschnitzer F, Zechmann W.** Usefulness of physiologic dual-chamber pacing in drug-resistant idiopathic dilated cardiomyopathy. Am J Cardiol 1990; 66:198–202.
43. **Auricchio A, Sommariva L, Salo RW, Scafuri A, Chiariello L.** Improvement of cardiac function in patients with severe congestive heart failure and coronary artery disease by dual chamber pacing with shortened AV delay. Pacing Clin Electrophysiol 1993; 16:2034–2043.
44. **Linde C, Gadler F, Edner M, et al.** Results of atrioventricular synchronous pacing with optimized delay in patients with severe congestive heart failure. Am J Cardiol 1995; 75:919–923.
45. **Auricchio A, Stellbrink C, Block M, et al.** Effect of pacing chamber and atrioventricular delay on acute systolic function of paced patients with congestive heart failure. The Pacing Therapies for Congestive Heart Failure Study Group. The Guidant Congestive Heart Failure Research Group. Circulation 1999; 99:2993–3001.
46. **Kass DA, Chen CH, Curry C, et al.** Improved left ventricular mechanics from acute VDD pacing in patients with dilated cardiomyopathy and ventricular conduction delay. Circulation 1999; 99:1567–1573.
47. **Leon AR, Greenberg JM, Kanuru N, et al.** Cardiac resynchronization in patients with congestive heart failure and chronic atrial fibrillation: effect of upgrading to biventricular pacing after chronic right ventricular pacing. J Am Coll Cardiol 2002; 39:1258–1263.
48. **Porciani MC, Sabini A, Colella A, et al.** Interatrial delay does not affect clinical outcomes of cardiac resynchronization therapy [abstract]. PACE 2002; 24:561.
49. **Di Pede F, Gasparini G, Raviele A, et al.** Effect of atrial stimulation site on the contractile function of heart failure patients with DDD biventricular pacing [abstract]. PACE 2002; 24:670.
50. **Tantengco MV, Thomas RL, Karpawich PP.** Left ventricular dysfunction after long-term right ventricular apical pacing in the young. J Am Coll Cardiol 2001; 37:2093–2100.
51. **Victor F, Leclercq C, Mabo P, et al.** Optimal right ventricular pacing site in chronically implanted patients: a prospective randomized crossover comparison of apical and outflow tract pacing. J Am Coll Cardiol 1999; 33:311–316.
52. **Thackray SD, Witte KK, Nikitin NP, Cleland JG.** The prevalence of heart

failure in the permanently paced population and the utility of BNP as a screening tool [abstract]. J Am Coll Cardiol 2002; 39:160A.
53. **Pavia SV, Perez-Lugones A, Lam C, et al.** Symptomatic deterioration post dual chamber cardioverter-defibrillator implantation: a retrospective, observational study. J Am Coll Cardiol 2001; 37:89A–90A.
54. **Saad EB, Marrouche NF, Martin DO, et al.** Frequency and associations of symptomatic deterioration after dual-chamber defibrillator implantation in patients with ischemic or idiopathic dilated cardiomyopathy. Am J Cardiol 2002; 90:79–82.
55. **Wilkoff BL, Cook JR, Epstein AE, et al.** Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: the Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial. JAMA 2002; 288:3115–3123.
56. **Saxon LA, Kerwin WF, Cahalan MK, et al.** Acute effects of intraoperative multisite ventricular pacing on left ventricular function and activation/contraction sequence in patients with depressed ventricular function. J Cardiovasc Electrophysiol 1998; 9:13–21.
57. **Etienne Y, Mansourati J, Touiza A, et al.** Evaluation of left ventricular function and mitral regurgitation during left ventricular-based pacing in patients with heart failure. Eur J Heart Fail 2001; 3:441–447.
58. **Kim WY, Sogaard P, Mortensen PT, et al.** Three dimensional echocardiography documents haemodynamic improvement by biventricular pacing in patients with severe heart failure. Heart 2001; 85:514–520.
59. **Daubert JC, Ritter P, Le Breton H, et al.** Permanent left ventricular pacing with transvenous leads inserted into the coronary veins. Pacing Clin Electrophysiol 1998; 21:239–245.
60. **Butter C, Auricchio A, Stellbrink C, et al.** Should stimulation site be tailored in the individual heart failure patient? Am J Cardiol 2000; 86:K144–K151.
61. **Pappone C, Rosanio S, Oreto G, et al.** Cardiac pacing in heart failure patients with left bundle branch block: impact of pacing site for optimizing left ventricular resynchronization. Ital Heart J 2000; 1:464–469.
62. **Butter C, Auricchio A, Stellbrink C, et al.** Effect of resynchronization therapy stimulation site on the systolic function of heart failure patients. Circulation 2001; 104:3026–3029.
63. **Ricci R, Ansalone G, Tosacano S, et al.** Cardiac resynchronization: materials, technique, and results. The InSync Italian Registry. Eur Heart J 2000; 2:J6–15.
64. **Alonso C, Leclercq C, d'Allonnes FR, et al.** Six year experience of transvenous left ventricular lead implantation for permanent biventricular pacing in patients with advanced heart failure: technical aspects. Heart 2001; 86:405–410.
65. **Cazeau S, Leclercq C, Lavergne T, et al.** Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. N Engl J Med 2001; 344:873–880.
66. **Gurley J, Lamba S, Moulton K, et al.** Does the availability of left-heart lead and delivery system options matter for cardiac resynchronization therapy? [abstract]. PACE 2002; 24:597.
67. **Jais P, Takahashi A, Garrigue S, et al.** Mid-term follow-up of endocardial biventricular pacing. Pacing Clin Electrophysiol 2000; 23:1744–1747.
68. **Garrigue S, Jais P, Espil G, et al.** Comparison of chronic biventricular pacing between epicardial and endocardial left ventricular stimulation using Doppler tissue imaging in patients with heart failure. Am J Cardiol 2001; 88:858–862.
69. **Gras D, Mabo P, Tang T, et al.** Multisite pacing as a supplemental treatment of congestive heart failure: preliminary results of the Medtronic Inc. InSync Study. Pacing Clin Electrophysiol 1998; 21:2249–2255.
70. **Auricchio A, Stellbrink C, Sack S, et al.** The Pacing Therapies for Congestive Heart Failure (PATH-CHF) study: rationale, design, and endpoints of a prospective randomized multicenter study. Am J Cardiol 1999; 83:130D–135D.
71. **Auricchio A, Stellbrink C, Sack S, et al.** Long-term clinical effect of hemodynamically optimized cardiac resynchronization therapy in patients with heart failure and ventricular conduction delay. J Am Coll Cardiol 2002; 39:2026–2033.
72. **Linde C, Leclercq C, Rex S, et al.** Long-term benefits of biventricular pacing in congestive heart failure: results from the MUltisite STimulation in cardiomyopathy (MUSTIC) study. J Am Coll Cardiol 2002; 40:111–118.
73. **Leclercq C, Linde C, Cazeau S, et al.** Sustained clinical efficacy of biventricular pacing in patients with advanced heart failure and stable sinus rhythm. 2 year follow-up from the MUSTIC study [abstract]. PACE (II) 2002; 24:601.
74. **Abraham WT, Fisher WG, Smith AL, et al.** Cardiac resynchronization in chronic heart failure. N Engl J Med 2002; 346:1845–1853.
75. **Abraham WT, Fisher W, Smith A, et al.** Long-term improvement in functional status, quality of life and exercise capacity with cardiac resynchronization therapy: the MIRACLE trial experience [abstract]. J Am Coll Cardiol 2002; 39:159A.
76. **St John Sutton M, Kokovic D, Plappert T, et al.** Cardiac resynchronization therapy results in reverse remodeling in both ischemic and non-ischemic heart failure patients. PACE 2002; 24:716.
77. **Conti J, Curtis A, Aranda J Jr, Abraham WT, Petersen-Stejskal S, Paulsen D.** Are there differences in gender response to cardiac resynchronization therapy? Analysis of the MIRACLE trial [abstract]. PACE 2002; 24:694.
78. **Lupi G, Brignole M, Oddone D, et al.** Effects of left ventricular pacing on cardiac performance and on quality of life in patients with drug refractory heart failure. Am J Cardiol 2000; 86:1267–1270.
79. **Braunschweig F, Linde C, Gadler F, Ryden L.** Reduction of hospital days by biventricular pacing. Eur J Heart Fail 2000; 2:399–406.
80. **Foster AH, Gold MR, McLaughlin JS.** Acute hemodynamic effects of atrio-biventricular pacing in humans. Ann Thorac Surg 1995; 59:294–300.
81. **Leclercq C, Cazeau S, Le Breton H, et al.** Acute hemodynamic effects of biventricular DDD pacing in patients with end-stage heart failure. J Am Coll Cardiol 1998; 32:1825–1831.
82. **Blanc JJ, Etienne Y, Gilard M, et al.** Evaluation of different ventricular pacing sites in patients with severe heart failure: results of an acute hemodynamic study. Circulation 1997; 96:3273–3277.
83. **Auricchio A, Ding J, Spinelli JC, et al.** Cardiac resynchronization therapy restores optimal atrioventricular mechanical timing in heart failure patients with ventricular conduction delay. J Am Coll Cardiol 2002; 39:1163–1169.
84. **Nelson GS, Berger RD, Fetics BJ, et al.** Left ventricular or biventricular pacing improves cardiac function at diminished energy cost in patients with dilated cardiomyopathy and left bundle-branch block. Circulation 2000; 102:3053–3059.
85. **Mansourati J, Etienne Y, Gilard M, et al.** Left ventricular-based pacing in patients with chronic heart failure: comparison of acute hemodynamic benefits according to underlying heart disease. Eur J Heart Fail 2000; 2:195–199.
86. **Packer M.** New concepts in the pathophysiology of heart failure: beneficial and deleterious interaction of endogenous haemodynamic and neurohormonal mechanisms. J Intern Med 1996; 239:327–333.
87. **Saxon LA, Boehmer JP, Hummel J, et al.** Biventricular pacing in patients with congestive heart failure: two prospective randomized trials. The VIGOR CHF and VENTAK CHF Investigators. Am J Cardiol 1999; 83:120D–123D.
88. **Spaziani D, Pagani M, del Rosso G, De Servi S, Grassi G, Mancia G.** Reduction of norepinephrine levels with biventricular pacing but recurrence of arrhythmic events in patients with biventricular ICD and cardiomyopathy [abstract]. J Am Coll Cardiol 2002; 39:78A.
89. **Hamdan MH, Zagrodzky JD, Joglar JA, et al.** Biventricular pacing decreases sympathetic activity compared with right ventricular pacing in patients with depressed ejection fraction. Circulation 2000; 102:1027–1032.
90. **Hamdan MH, Barbera S, Kowal RC, et al.** Effects of resynchronization therapy on sympathetic activity in patients with depressed ejection fraction and intraventricular conduction delay due to ischemic or idiopathic dilated cardiomyopathy. Am J Cardiol 2002; 89:1047–1051.
91. **Alonso C, Leclercq C, Mabo P, Lavergne T, Daubert JC.** Atriobiventricular pacing improves heart rate variability in patients with severe heart failure. Eur J Heart Fail 2001; 3:24.
92. **Sinha A, Zarse M, Markus KU, et al.** Effects of cardiac resynchronization therapy on heart rate variability in patients with heart failure and left bundle branch block [abstract]. PACE 2002; 24:624.
93. **Saxon LA, De Marco T, Schafer J, Chatterjee K, Kumar UN, Foster E, for the VIGOR Congestive Heart Failure Investigators.** Effects of long-

term biventricular stimulation for resynchronization on echocardiographic measures of remodeling. Circulation 2002; 105:1304–1310.
94. **Kuhlkamp V.** Initial experience with an implantable cardioverter-defibrillator incorporating cardiac resynchronization therapy. J Am Coll Cardiol 2002; 39:790–797.
95. **Stellbrink C, Breithardt OA, Franke A, et al.** Impact of cardiac resynchronization therapy using hemodynamically optimized pacing on left ventricular remodeling in patients with congestive heart failure and ventricular conduction disturbances. J Am Coll Cardiol, 2001; 38:1957–1965.
96. **Yu CM, Nicholls GM, Sanderson JE, et al.** Echocardiographic and neurohormonal predictors of left ventricular reverse remodeling after biventricular pacing for heart failure [abstract]. J Am Coll Cardiol 2002; 39:96A.
97. **St. John Sutton M, Plappert T, Abraham WT, et al.** Echocardiographic predictors of functional class changes during cardiac resynchronization therapy: results from the MIRACLE trial [abstract]. J Am Coll Cardiol 2002; 39:107A.
98. **Greenberg JM, Ransom S, DeLurgio DB, Mera FV, Leon AR.** Left ventricular remodeling during cardiac resynchronization therapy: effect on ventricular dimension and stimulation threshold chronically after biventricular pacing [abstract]. J Am Coll Cardiol 2002; 5:107A.
99. **Walker S, Levy TM, Rex S, et al.** Usefulness of suppression of ventricular arrhythmia by biventricular pacing in severe congestive cardiac failure. Am J Cardiol 2000; 86:231–233.
100. **Higgins SL, Yong P, Sheck D, et al.** Biventricular pacing diminishes the need for implantable cardioverter defibrillator therapy. Ventak CHF Investigators. J Am Coll Cardiol 2000; 36:824–827.
101. **Garrigue S, Barold SS, Hocini M, et al.** Treatment of drug refractory ventricular tachycardia by biventricular pacing. Pacing Clin Electrophysiol 2000; 23:1700–1702.
102. **Zagrodzky JD, Ramaswamy K, Page RL, et al.** Biventricular pacing decreases the inducibility of ventricular tachycardia in patients with ischemic cardiomyopathy. Am J Cardiol 2001; 87:1208–1210.
103. **Liem L, Leon A, Young JB.** Effectiveness of bi-ventricular antitachycardia pacing in CHF patients receiving cardiac resynchronization therapy [abstract]. PACE 2002; 24:647.
104. **Krater L, Lamp B, Heintze J, et al.** Influence of antitachy pacing location on the efficacy of ventricular tachycardia termination [abstract]. J Am Coll Cardiol 2002; 39:124A.
105. **Kumar V, Higgins SL, Putz EJ, et al.** Effect of chronic resynchronization therapy on ICD therapies [abstract]. PACE 2002; 24:558.
106. **de Teresa E, Alzueta J, Jimenez-Navarro M.** Profiling risk from arrhythmic or hemodynamic death. Am J Cardiol 2000; 86:K126–K132.
107. **Young JB, Abraham WT, Liem L, Leon AR.** Cardiac resynchronization therapy benefits patients with ICD indications—results of the InSync ICD trial [abstract]. PACE 2002; 24:694.
108. **St. John Sutton M, Plappert T, Young J, Hilpisch KE, Hill MRS.** Cardiac resynchronization therapy results in improvement in echocardiographic parameters in heart failure patients with an indication for an ICD: evidence from the InSync trial [abstract]. PACE 2002; 24:648.
109. **Abraham WT, Young J, Kocovic D, et al.** Cardiac resynchronization therapy benefits patients—combined results of the MIRACLE and MIRACLE ICD trials [abstract]. PACE 2002; 24:558.
110. **Daoud E, Hummel J, Higgins S, et al.** Does ventricular resynchronization therapy influence total survival? [abstract]. PACE 2001; 24:539.
111. **Al-Khatib SM, Hassleblad V.** Does cardiac resynchronization therapy improve survival of patients with symptomatic congestive heart failure? [abstract]. PACE 2002; 24:669.
112. **Leclercq C, Victor F, Alonso C, et al.** Comparative effects of permanent biventricular pacing for refractory heart failure in patients with stable sinus rhythm or chronic atrial fibrillation. Am J Cardiol 2000; 85:1154–1156.
113. **Daubert JC, Linde C, Cazeau S, Kappenberger L, Sutton R, Bailleul C.** Clinical effects of biventricular pacing in patients with severe heart failure and chronic atrial fibrillation: results from the Multisite Stimulation in Cardiomyopathy (MUSTIC) study group II [abstract]. Circulation 2000; 102(suppl 2):II-693.
114. **Gabor JY, Hanly PJ, Khaykin Y, et al.** The effect of biventricular pacing for heart failure on sleep: a possible further mechanism of benefit [abstract]. Can J Cardiol 2002; 18:186B.
115. **Bristow MR, Feldman AM, Saxon LA.** Heart failure management using implantable devices for ventricular resynchronization: Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure (COMPANION) trial. COMPANION Steering Committee and COMPANION Clinical Investigators. J Card Fail 2000; 6:276–285.
116. **Leon AR, Brozena S, Liang CS, et al.** Effect of cardiac resynchronization therapy with sequential biventricular pacing on Doppler-derived left ventricular stroke volume, functional status and exercise capacity in patients with ventricular dysfunction and conduction delay: the US InSync III trial [abstract]. PACE 2002; 24:558.
117. **Kanuru NK, DeLurgio DB, Ransom S, et al.** Right ventricular septal versus right ventricular apical pacing in biventricular pacing systems does not affect patient functional improvement [abstract]. PACE 2002; 24:648.
118. **Cleland JG, Daubert JC, Erdmann E, et al.** The CARE-HF study (CArdiac REsynchronisation in Heart Failure study): rationale, design and endpoints. Eur J Heart Fail 2001; 3:481–489.
119. **Aranda JMJ, Curtis AB, Conti JB, Peterson-Stejskal S.** Do heart failure patients with right bundle branch block benefit from cardiac resynchronization therapy? Analysis of the MIRACLE study [abstract]. J Am Coll Cardiol 2002; 39:96A.
120. **Auricchio A, Geller C, Reek S, Goette A, Klein HU.** Delayed electrical activation of the left septum and lateral wall in left bundle branch block: insight from 3-D electroanatomical mapping [abstract]. J Am Coll Cardiol 2002; 39:96A.
121. **Lambiase PD, Rinaldi A, Hauck J, et al.** Do areas of slow activation limit the benefit of biventricular pacing? A non-contact left ventricular endocardial mapping study [abstract]. PACE 2002; 24:579.
122. **Schreieck J, Zrenner B, Kolb C, Ndrepepa G, Schmitt C.** Inappropriate shock delivery due to ventricular double detection with a biventricular pacing implantable cardioverter defibrillator. Pacing Clin Electrophysiol 2001; 24:1154–1157.
123. **Pappone C, Vicedomini G, Salvati A, et al.** Electrical modulation of cardiac contractility: clinical aspects in congestive heart failure. Heart Fail Rev 2001; 6:55–60.
124. **Sabbah HN, Haddad W, Mika Y, et al.** Cardiac contractility modulation with the impulse dynamics signal: studies in dogs with chronic heart failure. Heart Fail Rev 2001; 6:45–53.

ADDRESS: *Bruce L. Wilkoff, MD, Department of Cardiovascular Medicine, Section of Cardiac Pacing and Electrophysiology, F15, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44122; e-mail wilkofb@ccf.org.*