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CARDIOLOGY Rounds™

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Resynchronization therapy: the arrival of a new cardiac device indication

BY DAVID NEWMAN, MD

In general, physicians using implanted device therapy have paid relatively little attention to the exact effects of pacing on left ventricular mechanical function. However, over the last 10 years, intense research and development efforts have led to a new Health Canada-approved device indication. The new indication is to utilize low output pacing stimuli, delivered via coronary epicardial wires to the left ventricle, to improve left ventricular dysfunction in patients with dilated ventricles and congestive heart failure (CHF). With the recent announcement of results from a large Phase III randomized trial, it is clear that advances in "biventricular" (ie, conventional right ventricle + left ventricle) or resynchronization pacing therapy are dramatic and have led to a stronger union between device-based electrophysiologists and CHF clinicians.

The chief hallmark of CHF is impaired left ventricular systolic function. As the heart dilates due to a variety of disease processes, it has been known for some time that a significant amount of cardiac dyssynchronous activation occurs. In dilated cardiomyopathy (of any etiology), this is manifested by prolonged QRS duration with an interventricular conduction defect, usually an incomplete or complete left bundle-branch block. Cardiac dyssynchrony leads to a remarkable delay in activation of the base of the left ventricle, the area that is normally activated earliest. As a result, portions of the left ventricular anterolateral wall may be still moving slowly inward while mitral filling is occurring. The altered mechanics of left ventricular function contribute to significantly increased wall strain in myocardial contracting elements. Along with these mechanical abnormalities of myocardial function, dilated cardiomyopathy is also characterized by significant amounts of AV valve regurgitation – particularly mitral regurgitation – and a worsening mismatch of myocardial energetics due to increased left ventricular dimensions. Finally, it has long been appreciated that as the heart dilates, first degree heart block may develop, contributing further to mitral regurgitation.

Early attempts to improve left ventricular systolic function with pacing used conventional right-sided dual chamber pacing. The hypothesis was that markedly shortened atrioventricular (AV) intervals would allow earlier contraction of the left ventricular base, thereby preventing mitral valve regurgitation. The problem was the time it took for impulses to traverse from the right ventricular apex to the left ventricular base; it was so long that a remarkably short AV delay was required. This, in turn, abbreviated the time for left ventricular filling excessively. Despite encouraging anecdotal case reports, controlled randomized trials of right-sided dual chamber pacing with very short AV delays were found to be deleterious, or at best ineffective, for improving myocardial dysfunction.

Nonetheless, the search was on to find a way of using pacing techniques to cause the very slow and delayed activation of the left ventricular anterobasal segments to occur earlier than usual in the disease process and closer to normal myocardial contraction. It was appreciated that if the AV delay could be shortened somewhat, while allowing left ventricular anterobasal segments to contract earlier, the magnitude of dyssynchrony of ventricular contraction would be less and result in improved cardiac function. Furthermore, a narrowed biventricular paced QRS duration with a decrease in mitral regurgitation should produce a net progressive improvement over time in myocardial contractile function (Figure 1).

To do this, direct pacing of the left-ventricular basal segments was required. The initial proof of concept studies used epicardial pacing wires attached to the left-ventricular anterobasal segments at the time of open-heart surgery. In crossover trial designs, these initial pioneering efforts

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Figure 1: Example of biventricular pacing on 12-lead ECG. Panel A shows native 12-lead of typical recipient with LBBB; QRS duration of 160 ms; PR interval of 240 ms in patient with NYHA Class III CHF. Panel B shows the 12-lead of biventricular pacing. Note the QRS duration has decreased to 140 ms and that the paced AV delay is 80 ms. Six months after starting biventricular pacing, patient had improved to NYHA Class II with a 75 m increase in 6 min hall walk.

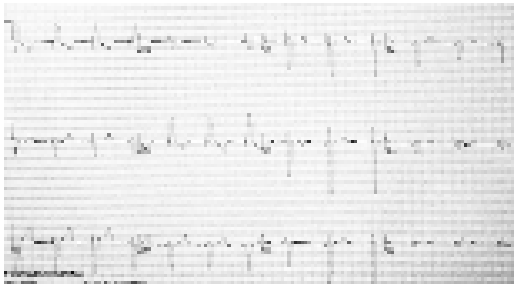


Figure 1, Panel A

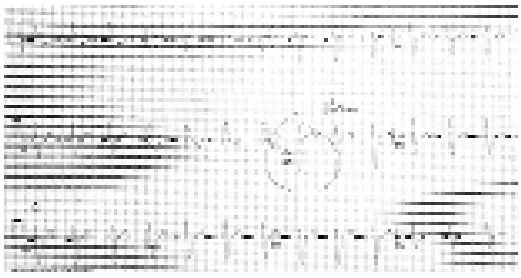


Figure 1, Panel B

showed significant promise and led to the search for chronic transvenous access of left ventricular epicardial pacing sites. Pioneering efforts by Daubert and colleagues in France[1] demonstrated that after coronary sinus opacification, epicardial branches of coronary sinus veins could be identified and selectively cannulated with chronically implanted pacing leads. These chronic pacing leads could be used as part of a system of biventricular (RV + LV) pacing, with narrowing the QRS. Simultaneous with the pioneering efforts to achieve chronic, stable, implanted, left-ventricular epicardial pacing systems, a variety of acute left ventricular epicardial and endocardial pacing studies were performed. These studies established the plausibility and provided mechanistic insights to support the effort for chronic transvenous biventricular pacing systems.

Kass *et al* used conductance catheters to provide continuous accurate recordings of left ventricular volume combined with Millar catheters to construct pressure-volume loops in dilated ventricles in acute hemodynamic studies.[2] It was found that left ventricular anterobasal pacing provided the greatest improvement in myocardial function. Coincident with an improvement in left ventricular pressure-volume area, there was a 20%-40% improvement in dP/dt. Since pressure-volume area is also a measure of myocardial oxygen consumption, these investigators and others have shown that left ventricular pacing offers a significant improvement in myocardial energetics. It was shown, for example, that the improvement in contractility (as measured by dP/dt) that occurs with left ventricular anterobasal pacing, is accompanied by a decrease in myocardial oxygen consumption, while dobutamine infusion (titrated to the exact same improvement in dP/dt) leads to a doubling of myocardial oxygen consumption.[3]

The exact mechanism behind these mechanical benefits is not completely clear. There is a decrease in myocardial oxygen consumption, improvement in myocardial energetics, and a decrease in left ventricular strain and mitral regurgitation. In addition, chronic studies have shown the salutary effects of resynchronization (biventricular pacing) therapy on a variety of endpoints generally associated with the pathophysiological sequellae of heart failure (eg, a decrease in ANF, norepinephrine, sympathetic neuronal traffic, and lung water).

Once acute mechanistic trials suggested benefit, and once chronic transvenous left ventricular pacing could be achieved, a variety of trials (some still ongoing) were undertaken to establish long-term efficacy, largely in terms of symptom relief and functional improvement rather than effects on mortality (see below).

Software and hardware design issues

To date, so-called 'first generation' biventricular pacing systems for heart failure utilize a conventional dual chamber pacing platform with a bifurcation of the ventricular output signal. This bifurcated ventricular output signal is used both for pacing and for sensing. From a pacing point of view, this generates simultaneous activation of both left and right ventricle, with subsequent narrowing of QRS duration upon successful pacing. It also requires careful analysis of the paced ECG QRS vector to identify noninvasively whether there is loss or capture of left ventricle, right ventricle, or both ventricles with pacing stimulus. From a design point of view, sensing from a wide 'bipole' of two sites may yield problems. It is expected that in the near future, 2-, 3-, and perhaps even 4-lead pacemakers with dedicated outputs for each chamber where a lead is placed, will be available, packaged in devices with brady or implantable cardioverter defibrillator (ICD) functions.

In addition to device hardware advances, there are still challenges with implant technique related to reliable coronary sinus cannulation and identification of target veins, as well as with the technology available to navigate into these veins. Current methods now utilize both over-the-wire and side-rail type angioplasty methods.

There is no set method to optimally program AV delay for three-chambered pacing systems. One manufacturer uses a proprietary formula based on a variety of measured variables (PR interval, paced atrium to ventricle interval, and QRS duration). Another uses a published and validated algorithm based on an analysis of mitral filling patterns from an echocardiogram performed after implantation. With either of these methodologies, patients receiving biventricular pacing tend to have relatively short AV delays, averaging 90-100 ms for a paced AV delay, ensuring that ventricular pacing occurs all the time with a relatively narrow QRS. However, there is as yet no consensus on whether a patient-specific, echocardiogram-guided, or an arbitrarily chosen programmed AV delay is optimal.

Table 1: Key studies of resynchronization therapy

COMPLETED TRIALS:

Study Name/ Sample Size	Design	Main Result	Reference
InSync I N=68	case series	↑ 6 min walk, QOL, NYHA class	Gras *et al*. *PACE* 1998[4]
VIGOR CHF N=73	epicardial lead 2:1 randomization, parallel design 6 week intervention	functional capacity, 6 min walk	Saxon *et al*. *AJC* 1999[9]
PATH-CHF N=42	epicardial lead (surgical placement) 3 month, crossover design	functional capacity ↑ VO_2, 6 min walk, QOL	Auricchio *et al*. *AJC* 1999[10]
Contak CD N=581	ICD + biV pacing 6 month, parallel design	↓ need for ICD shock	Higgins *et al*. *JACC* 2000[11]
MIRACLE N=463	6 month, parallel RCT	↑ 6 min walk, QOL, NYHA class	design: Abraham. *J Card Fail* 2000[6]
MUSTIC N=67	3 month, crossover design	↑ 6 min walk, QOL	Cazeau *et al*. *NEJM* 2000[5]

PENDING TRIALS (IN PROGRESS):

Study Name/ Sample Size	Design	Primary Endpoint	Reference
PACMAN N=328 (2001)	6 month, parallel RCT	6 min walk, QOL, NYHA	
CART-HF N=72 (2002)	ICD + vs. – biV 2° prevention 6 month intervention Canadian trial	LV end systolic volume	
MIRACLE ICD N=500 (2002)	ICD + vs. – biV 1° + 2° prevention 6 month intervention	NYHA class, QOL, 6 min walk, VO_2	
COMPANION N=2200 (2002-03)	3-way randomization between medical therapy, biV, and 1° prevention biV + ICD	primary endpoint is all-cause mortality and hospitalization	design: Bristow *et al*. *J Card Fail* 2000[7]
PAVE N=856 (2003)	biV vs. RVA only vs. LV only in AV junction ablation patients with permanent Afib	6 min walk, adverse event rates, safety	
BELIEVE N=74 (2003)	biV + ICD 1° + 2° prevention LV vs. biV pacing	6 min walk, QOL, NYHA	
Name pending N=900 (2003-04)	2:1 randomization, medical vs. 1° prevention biV + ICD Canadian trial	all-cause mortality, CHF admission	
CARE-HF N=800 (2003-04)	open label randomization usual care vs. biV 18 months	mortality	

biV: biventricular or resynchronization pacing
ICD + vs. - biV: implantable cardioverter defibrillator with, compared to without biventricular pacing enabled
RCT: randomized controlled trial either as crossover or parallel design (ie, with placebo device therapy)
VO_2: exercise O_2 consumption
QOL: quality of life
1° prevention: ICD given to patients only at risk for malignant arrhythmias
2° prevention: ICD given to patients who have survived a malignant arrhythmia

The relative contribution of the presence and timing of right ventricular pacing simultaneously with the left ventricular pacing impulse is unclear. Some investigators feel that right ventricular pacing may not always be necessary, while others emphasize the importance of right ventricular outflow tract or proximal septal pacing with simultaneous left ventricular basal pacing to maximally narrow the paced QRS complex. Some suggest that the latter is a marker of response.

Clinical trials (Table 1)

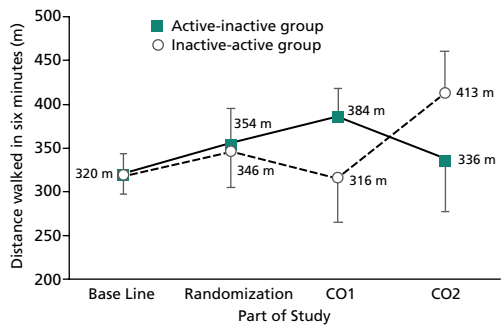
Following the success of small sample crossover designs using an epicardial pacing system, larger scale studies have been performed. The largest Phase II trial was the Medtronic InSync trial of 103 patients, all of whom received biventricular pacing.[4] Measurements of myocardial contractile function, 6-minute hall walk duration, and quality of life all improved when compared from baseline to post-implant values. Importantly, no patient had an opportunity for crossover, and no randomization occurred.

As a result, the opportunity for a placebo effect remained quite strong. Phase III trials resolved to assess the magnitude of this placebo effect. One smaller series, the MUSTIC trial, used a crossover design to demonstrate an improvement in 6-minute hall walk in a group of 67 patients, with a 3-month crossover between biventricular pacing, on or off (Figure 2).[5] The problem with such a design was that, although it allowed each patient to be his/her own control, there were concerns for a carryover effect, as well as a change of the disease state in a longitudinal fashion. Accordingly, pivotal trials include the recently presented MIRACLE trial and others that are ongoing or awaiting publication.

The MIRACLE trial

In the Multi-Center InSync Randomized Clinical Evaluation (MIRACLE) trial,[6] which was preliminarily reported at the recent American College of Cardiology 2001 meeting, with further data presented at the North American Society of Pacing and Electrophysiology (NASPE) 2001 meeting, 460 patients were randomized in a double-blind fashion to 6-months of biventricular pacing therapy, turned on or turned off. To enter the trial, patients had to have NYHA class III or IV heart failure, a left ventricular end diastolic diameter of >55 mm, an ejection fraction of <35%, and a QRS duration >130 ms. As well, all patients had to be on a stable drug regimen for at least one month prior to study entry. Therefore, 55% of patients were on beta-blockers and 91% were on ACE-inhibitor therapy or angiotensin receptor blocker (ARB). The control arm received a sophisticated 3-chambered pacing system with the device turned to a low rate of VDD, a rate of 30 bpm for safety support only. The treatment arm received the same device and implant technique with biventricular pacing turned on. In this group therefore, biventricular pacing occurred with narrowing of the QRS duration. After 6 months, the trial was completed and patients who were randomized to resynchronization therapy that was turned off, had the opportunity for it to be turned on. All concerns with respect to lead performance and safety were satisfactorily resolved with a 93% implant success rate at the 44 participating centres.

Figure 2: From the MUSTIC trial,[5] a crossover study design in 67 patients. In the active phase (biventricular pacing ON), the mean distance walked in 6 minutes was 23% longer than in the inactive phase (p<0.001).



The MIRACLE trial had three validated measures for improvement in congestive heart failure as its primary endpoint:

- 6-minute hall walk
- Minnesota Living with Heart Failure Scale, and
- improvement in New York Heart Association (NYHA) functional class.

The study was adequately powered to split the alpha three ways and still have an ability to detect meaningful improvements in the 3 parameters. The trial results demonstrated significantly strong improvements in all 3 of these parameters. At the end of 6 months, 69% of study patients vs. 34% of controls improved more than one NYHA class, and study patients, on average, walked 2 min longer on a Naughton protocol. Using any combination of primary endpoints, there were still significant and clinically meaningful benefits.

The protocol employed a variety of secondary endpoints and all showed significant improvement in favor of biventricular pacing therapy. These included a statistically significant improvement in exercise peak VO_2, in measurements of ANF, norepinephrine, and in overall ejection fraction. As well, some mechanistic insight was obtained from the echocardiogram substudy, demonstrating that resynchronization therapy was associated with a 5 mm decrease in left ventricular end diastolic diameter and an overall 50% reduction in mitral regurgitation jet area in patients with regurgitation at baseline. These dramatic results have established the efficacy of 3-chambered pacing for heart failure.

Many questions remain. Which patients will benefit from this therapy? And the corollary, how do you identify the 20%-30% of patients who will not benefit? Two sets of data reveal that the magnitude of QRS duration prolongation at baseline did not identify a group with particular benefit. It has been suggested that QRS narrowing in response to pacing or an increase in pulse pressure may help predict improvement. Another suggestion is that severe mitral regurgitation or perhaps excessive end diastolic dimensions of >75 mm may predict the patients who fail to respond to 'conventional' biventricular pacing.

Future trials

The European PACMAN trial is pending and is similar to the MIRACLE trial. The COMPANION trial is another ongoing larger trial that is assessing, in a 3-way randomization, the relative contribution of 3-chambered pacing (with and without defibrillator function) to medical therapy in 2200 patients.[7] This trial will be adequately sized to assess issues of functional and class improvement, and mortality and heart failure hospitalizations, as well. The COMPANION trial, and two other trials (MIRACLE ICD and CART-HF), will establish the efficacy of 3-chambered pacing in ICD platforms.

Combining 3-chambered pacing with an ICD has intuitive logic since ICD therapy in dilated ventricles may impact premature arrhythmic death, while the 3-chambered pacing component will benefit symptoms. In conjunction with a large, ongoing, prophylactic, single-chamber ICD trial (versus amiodarone or placebo) in dilated ventricles (SCD-HeFT, recruitment to end July 2001), it may be revealed that prophylactic ICD therapy has a significant role in mortality prevention alone. If so, coupling this with 3-chambered therapy to improve symptoms at the same time would likely be a compelling direction for further research. QRS duration is an independent predictor of mortality. As a result, 3-chambered brady platforms which narrow QRS duration may have prognostic (mortality) benefit. Future trials will assess this question directly, or use appropriate ICD shock delivery as a surrogate measure.

Future directions

To generalize this new therapy will require new data and improvements from both the technical and clinical viewpoints.

Technical

Trials are needed to establish the optimal timing of both V-V pacing intervals and AV delay. New advances in echocardiography and in the assessment of cardiac function will likely be used to establish acute measures of optimization. In the MIRACLE trial, successful implant rates ultimately occurred in 94% of patients; however, the first procedure success rate was in the range of 88%, similar to a recent registry report using angioplasty techniques to place the LV pacing leads. A variety of advances in lead design and other technical issues will be needed with respect to the simple, straightforward, and reliable positioning of a chronic left ventricular pacing lead. At the same time, there will probably be significant hardware advances for dedicated output to the variety of leads deployed in the heart. The exact role and location of right ventricular pacing will need to be further defined and this may require advances in lead fixation and stability.

Clinical

Data on patient selection are needed with respect to identifying responders and those in whom chronic biventricular pacing may retard or prevent progression of CHF. In addition to advances in patient selection, advances in maneuvers to predict or enhance response at implant and in follow-up are needed.

Finally, further research is required on the health-economic issues of 3-chambered pacing in either brady or ICD platform devices. Clearly, devices will result in significantly increased up-front costs in terms of hardware, in the time involved for implantation, and in iterative implantation after dislodgment or infection. This may well be counterbalanced by significant savings – already documented – in healthcare costs with respect to physician visits, hospitalizations, and according to some published series, to preventing transplantation. The number of possible recipients is huge; one study estimated that up to 10% of all CHF admissions are potential candidates using the restricted criteria of current trials.[8]

Summary

A remarkable international scientific and industry-based research effort has culminated in the clear understanding that biventricular pacing to resynchronize cardiac contraction can be reliably delivered to the dilated human ventricle. With this delivery, there are proven and clinically important improvements in a variety of measures related to left ventricular function, including better physical capacity, exercise duration, and health-related quality of life. All of these improvements are associated with decreased neurohumoral activation and cavity dimensions, while improving overall myocardial energetics in dilated cardiomyopathy from any cause. The improvements are dramatic, and to some degree, unique in the annals of heart failure therapy. To date, heart failure therapy has largely depended on diuretics (and to a lesser degree nitrates and glycosides) as the only agents to improve symptoms. With little in the way of extra technological hardware; current and future platforms will add the prognostic and antiarrhythmic benefits of ICD therapy to the benefits of resynchronization therapy. A variety of protocols are now underway that will establish who will be the best recipient of resynchronization therapy, with or without ICD therapy. The benefit for the patient with a lesser degree of heart failure symptoms, and the relative importance and location of right ventricular pacing, are important aspects that are also being investigated.

It is likely that in the next 5 years, all level I implant centres will acquire the expertise to insert and follow patients with resynchronization biventricular pacing systems. Access to this hardware awaits the understanding of healthcare economic data, with respect to efficacy, and technical advances in implantation and follow-up. Nonetheless, the positive results from a variety of pivotal Phase II and III trials suggest that these and other advances in pacing therapy for heart failure are inevitable.

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Abstracts of Interest

Non Synchronous vs Synchronous Biventricular Stimulation May Induce Further Increase in Ventricular Systolic Performance

PEREGO GB, CHIANCA R, FACCHINI M, ET AL. MILAN ITALY.

Synchronous biventricular stimulation (BIV) can improve left ventricular (LV) systolic performance in dilated cardiomyopathy associated with intraventricular conduction delay. We tested the hypothesis that further improvement can be obtained by non synchronous BIV with optimization of both atrioventricular and interventricular delay.

Methods: 7 biventricular implants (FE <30%, QRSd >150 msec) were associated with LV catheterization. LV dP/dt was acutely measured during BIV with different atrioventricular and interventricular intervals: right atrium (RA) to right ventricle (RV) interval (AVi) ranged from 80 to 160 msec and RV to LV interval (VVi) from -60 to +40 msec.

Results: For each stimulation mode we selected the intervals which were associated with the maximum LV dp/dt; the average AVI were similar both for VVi=0 and VVi≠0. The values at which the LV dP/dt was maximum are presented in the table.

N=7	VVi (msec)	AVi (msec)	LV dP/dt
Synch.	0	110±32	130±19
RV to LV delay	-30±-20*	116±29	140±20§

LVdP/dt is expressed as % of baseline. § p<0.01 vs. maximum value with VVi=0: *p<0.01 vs. 0 In no case maximum LV dP/dt was obtained for single ventricle LV stimulation. In no case maximum LV dP/dt was obtained at the step with the narrowest QRS.

Conclusions: A significant increase of LV dP/dt can be obtained by non synchronous BIV mode of stimulation as compared to the synchronous one. The highest LV dP/dt is obtained when LV is stimulated before RV. The extent of the anticipation is about 30 msec but is variable from patient to patient.

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Mechanisms of Exercise Capacity Improvement Induced by Biventricular Pacing in Congestive Heart Failure (CHF)

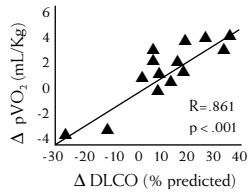
PEREGO GB, BLENGINO S, MALFATTO G, ET AL. MILAN, ITALY.

In CHF one of the factors limiting exercise capacity is respiratory muscle fatigue. This has been attributed both to generalized muscle impairment and to the increase of lung stiffness due to increase of lung water (LW). Biventricular pacing (BIV) improves rest hemodynamics and exercise capacity. The aim of our study was to define possible improvements in pulmonary function and investigate about the mechanisms of increase of exercise capacity.

13 Pts with CHF and QRS >150 msec underwent rest respiratory function tests and cardiopulmonary stress test with arterial and femoral vein blood sampling before (pre) and 1 month after (F.up) biventricular implantation.

Results:

	pVO2 (ml/Kg/?)	DLCO (% pred)	A Sat %	FV Sat %
Pre	10.3±2.5	53.2±18.3	93.2±6.1	20±9
F.up	12.6±2.1§	62.1±17.6	92.6±4.0 n.s.	21±10n.s.



pVO_2 =VO_2 at peak ex.; Asat and FVSat; radial artery and femoral vein Hb saturation; DLCO=Pulmonary diffusion of CO; § p<0.01 (2-tailed paired (test=pre vs. post implantation). D= variation pre vs post

Conclusions: 1) BIV was associated with a significant increase of DLCO suggesting a decrease of LW. 2) pVO_2 increase was not due to an increase of O_2 extraction. Instead an increase in peak exercise blood flow to exercising muscles (and cardiac output) must be hypothesised to justify our data. 3) The correlation between DLCO and pVO_2 suggests that a decrease in LW can play an additional role in increasing exercise capacity. The improvement of pulmonary mechanics would remove one of the reason of exercise limitation and allow full expression of the hemodynamic reserve.

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