

«Cardiac Resynchronization» in Heart Failure: Well-Established Therapy or New Approach With Unanswered Questions?

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Biventricular pacing is a new development in the treatment of ventricular failure associated with intraventricular conduction delays, and the term «ventricular resynchronization» has been coined, implying for many authors that synchronous right and left ventricular activation and contraction are the goal of therapy. However, there is ample evidence that isolated left ventricular stimulation may be at least as efficacious as biventricular stimulation, and the mechanisms of functional improvement remain speculative. The role of mitral regurgitation and its modification with «resynchronization» has not been fully evaluated. Long-term prognosis, effect on mortality and predictors of a positive response are important unanswered questions. It is clear that a narrow-based QRS complex is not a good indicator of a favorable response. We need to better understand the effect of the activation sequence on left ventricular contraction dynamics, including mitral valve function, to refine the technique and indications for «resynchronization therapy».

Key words: *Cardiac resynchronization. Biventricular pacing. Heart failure.*

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Biventricular pacing (BVP) constitutes an exciting new field of therapy for patients with advanced heart failure and intraventricular conduction abnormalities whose symptoms persist in spite of optimal pharmacological treatment.^{1,2} Early research showed improvements in specific parameters of ventricular function. This is supported by clinical observation of

«Resincronización ventricular» en la insuficiencia cardíaca: ¿un método bien establecido o una línea de progreso con muchos interrogantes?

La estimulación biventricular ha supuesto una línea nueva de desarrollo para el tratamiento de los pacientes con insuficiencia cardíaca asociada a retrasos de la conducción intraventricular, y el término «resincronización ventricular», acuñado por muchos autores, implica que la sincronía entre la activación y contracción del ventrículo izquierdo y derecho es el objetivo de esta terapia. Sin embargo, existen amplias evidencias de que la estimulación aislada del ventrículo izquierdo puede ser, al menos, tan efectiva como la estimulación biventricular, haciendo que los mecanismos de mejoría citados sean especulativos. El papel de la insuficiencia mitral y sus cambios con la «resincronización» no han sido completamente evaluados. El pronóstico a largo plazo, el efecto en la mortalidad y los predictores de respuesta positiva son cuestiones importantes todavía no resueltas. Está bastante claro que perseguir un complejo QRS estrecho con la estimulación no es un buen indicador de una respuesta favorable, y que necesitamos comprender mejor el efecto que supone la secuencia de activación ventricular izquierda sobre la contracción, incluyendo el efecto sobre la función de la válvula mitral para, con ello, poder mejorar la técnica y las indicaciones de la terapia de «resincronización».

Palabras clave: *Resincronización cardíaca. Estimulación biventricular. Insuficiencia cardíaca.*

mid-term improvements in functional capacity. Research into the influence of BVP on survival rates is currently under way.

These initial results have led to the optimistic assumption that BVP is the perfect means of improving ventricular function. Improvement is taken to be a consequence of the simultaneous activation of both ventricles, known as «resynchronization». The objective of resynchronization is to reduce the duration of the QRS interval. Consequently, new products that are capable of stimulating both ventricles and both auricles too, are now on the market. Some of these are even able to defibrillate. However, detailed reading of the

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bibliography and clinical reports leaves a number of questions unanswered. In response, we conclude that resynchronization therapy has yet to be fully researched so the results available to date are incomplete. In addition, we find that many patients do not respond for no apparent reason. Even the very idea of resynchronizing activation and contraction in both ventricles begins to look a barely justifiable working hypothesis.

HOW DOES DELAY IN ACTIVATION INFLUENCE VENTRICULAR FUNCTION?

We know that the existence of an intraventricular conduction abnormality (especially left bundle branch block [LBBB]) implies an adverse prognosis for patients with ventricular dysfunction. In theory, an alteration in septal function and the consequent interventricular asynchrony have a negative effect on patients' already depressed global systolic functions. When early septal shortening occurs, delayed activation and end-systolic contraction of the free posterolateral wall expands the already relaxed septum.³ The net result is a depressed systolic function with a reduced ejection fraction and increased end-systolic volume. Delayed contraction of the lateral wall can also alter papillary muscle function and cause mitral insufficiency. Cases of severe mitral insufficiency leading to acute heart failure have been described in connection with intermittent LBBB.⁴ Finally, a prolonged systole leads to a reduction in filling time that can aggravate diastolic dysfunction. Similarly, adverse effects of right ventricular (RV) pacing, so-called «induced LBBB», have been observed in left ventricle (LV) systolic and diastolic function, perfusion, and neurohormonal status,⁵ although severe ventricular failure is rarely linked to mitral insufficiency.⁶

However, data exist that question generalizations about these mechanisms. Firstly, in clinical practice few patients present severe adverse effects due to RV pacing. This is especially surprising as RV pacing is considered a model of chronic induced LBBB even in patients with heart failure. Isotopic ventriculography of patients with heart failure shows that in the absence of LBBB, RV apical pacing deteriorates LV function. But in patients with LBBB it leads to an improvement.⁷ Right ventricular pacing produces clinical improvements in comparison to baseline values in spite of delayed LV activation.⁸ This is particularly, but not exclusively found in patients with right bundle branch block and in those with an especially prolonged PR interval.⁹

RESYNCHRONIZATION OF BOTH VENTRICLES OR LEFT VENTRICULAR ACTIVATION?

In the literature, acute hemodynamic data always show that for the majority of patients optimal hemodynamic parameters are obtained by LV

stimulation⁸⁻¹⁰ and not simultaneous BVP. These studies show that the degree of acute functional improvement is not related to the reduction in QRS width achieved by stimulation. Clearly, these findings contradict the view that biventricular resynchronization is needed to achieve an improvement in heart function. Recent clinical follow-up studies support the idea that LV pacing is what matters and not simultaneous BVP.¹¹ These findings are crucial as they contradict the belief that achieving a very narrow QRS complex by pacing is an adequate objective for resynchronization therapy for heart failure, a conclusion highlighted recently in a follow-up study.^{9,12}

Biventricular pacing does reduce asynchrony between both ventricles in isotopic phase analysis studies, but the data in inconsistent regarding the reduction in intraventricular asynchrony.¹³ Astonishingly, recent findings indicate that simultaneous stimulation of both ventricles produces worse results than stimulation involving a slight time lapse.¹⁴

WHAT IS THE MECHANISM THAT IMPROVES LEFT VENTRICULAR FUNCTION THROUGH STIMULATION?

Research into the mechanism that improves LV function is essential. It will help us understand why a significant number of patients do not improve with stimulation and indicate how we can best select potential responders so as to avoid unnecessary implants.

Optimizing the AV interval by stimulation contributes to improvement⁸ even though it does have a significant effect on ventricular function. This is evident in the improvement noted in patients with atrial fibrillation and AV node ablation.¹⁵ However, the fact that LV pacing alone with a wide QRS complex produces optimal results contradicts the belief that it is the synchronization of the two ventricles or simply the reduction in total ventricular activation time that improves ventricular function. This means we need to find another explanation for the improvement in mechanical synchronization. The discrepancy between electric synchronization and mechanical synchronization has recently been confirmed under experimental conditions.¹⁶ In magnetic resonance studies of LV function, dyskinesia in an animal model of heart failure and LBBB was corrected by both BVP and isolated LV pacing. However, the lack of electric synchrony is much greater in LV pacing. These authors recently published similar clinical results using a new method of echo-contrast enhanced endocardial visualization.¹⁷ They show how the action of LV pacing alone (7 out of 10 patients) or of BVP, improves septal function without producing significant changes in the lateral wall.

Biventricular pacing improves systolic and diastolic functions. In the latter case, this is attributed to reduced isovolumetric contraction time and increased filling

time.¹⁸ Research to ascertain whether isolated LV pacing produces the same results has yet to be carried out.

PREDICTORS OF THE EFFICIENCY OF CARDIAC RESYNCHRONIZATION

In all clinical studies, some 30% of patients do not improve as a result of BVP. The precise cause of this has not been identified. These findings show how little we understand about the mechanisms involved in using BVP.

An initial explanation for the different responses is that LBBB brings together different activation abnormalities and that the hypothetical delay in activation and contraction in the lateral wall is an oversimplification. Endocardial activation studies of LBBB show a significant degree of heterogeneity among patients. Mode of onset, duration and termination of ventricular activation especially in the presence of infarcts,¹⁹ would lead us to expect different patterns of contraction and, consequently, different responses to changes in activation. Some authors suggest that a lack of response to resynchronization is more frequent in patients with ischemic heart disease.¹² Studies of LBBB using 3D echocardiography and tissue Doppler imaging show a delay in lateral segment shortening in the majority of patients with dilated cardiomyopathy and a septal delay in the majority of ischemic patients.¹⁴ The degree of asynchrony can be quantified by calculating the phase angle of the Fourier transform. Thus, the degree and type of contractile dysfunction is more accurately linked to the effects of resynchronization.²⁰ These studies suggest that LBBB with delayed lateral shortening is that which most benefits from resynchronization (in most cases with LV pacing), although patients with other types of dysfunction also improve.

We still need to develop a simple method of studying segment contractility that will show the extent to which this is linked to the activation sequence and acts as a guide to pacing. Methods based on the movement of the endocardial border^{17,20} and tissue Doppler velocities¹⁸ fail to distinguish between active movement (thickening) and passive movement. Methods based on M mode are limited to radial movement and basal segments.²¹

EFFECT OF LEFT VENTRICULAR PACING ON MITRAL REGURGITATION

The effect of pacing on mitral insufficiency (MI) is seldom evaluated even though it affects many patients. Data exist that suggest mitral regurgitation is an important factor in explaining functional improvement.

In LV dysfunction, mitral regurgitation can be caused by a variety of factors. These include changes in mitral valve apparatus geometry due to ventricular

dilatation, papillary muscle dysfunction, and alterations in the contraction sequence and the global systolic function produced by intraventricular conduction delay. Researchers have linked improvement in the degree of mitral regurgitation to mid-term improved functional capacity.^{18,22} In one BVP study, the improvement was directly related to the degree of baseline mitral regurgitation.¹²

These data make it clear that we need more information about the relationship between mitral valve function and LV activation. We may find that the severity of mitral regurgitation can be used as a marker of positive response to LV pacing. A better understanding of the relationship might also increase our knowledge of the complex mechanisms involved in mitral valve closure.

RESYNCHRONIZATION GUIDED BY QRS COMPLEX WIDTH?

What we have said so far should make it easier to understand why a narrowing of the QRS complex does not predict improvement^{9,12} despite the fact that many authors propose this as a referent for effective cardiac resynchronization. Clearly, we need to develop a means of directly measuring ventricular function to estimate the effect of stimulation. However, the type of measure required is not clear. Several researchers have used a simple, quick protocol that evaluates changes in systolic arterial pressure and/or LV systolic dP/dt in series of 5 stimulated cycles.^{8,9} This is easy to repeat, so the effect of stimulation at different sites can be identified quickly. However, it is not clear how these changes are related to the physiological changes caused by stimulation. Other authors¹⁰ measure pressure and cardiac output, apparently a better method even though it is more complex to apply. By using these methods, some 20% of patients are classified as nonresponders⁸ with reference to the acute effect alone.

We know nothing about the relationship between acutely observed improvements and subsequent clinical progress. Follow-up of acute studies with short series of stimulation shows a lack of mid-term clinical response in as many as 40% of patients initially classified as responders in the acute test.^{12,22,23} Clearly we must evaluate methods of predicting long-term response before and during implanting to optimize indications and results in responders. As things stand, we cannot confirm that either the most complete hemodynamic studies, tissue Doppler analysis of segment contraction, or changes in the severity of mitral regurgitation provide us with data that actually improve selection.

UNRESOLVED TECHNICAL ISSUES

LV pacing involves significant technical problems. Careful selection of pacing sites involves complex

exploration of the coronary venous system. Additional difficulties can arise involving electrode stabilization in sites with good lead thresholds. Generally, unipolar electrodes are preferred because they are more manageable. However, they increase the risk of problems involving unipolar configurations, especially those of left auricle detection by the coronary sinus vein electrode, which can make stimulation impossible as it inhibits the channel. New electrodes for this specific application are continually being developed but in approximately 13% of patients problems of access, lead displacement or loss of ventricular capture make satisfactory implantation impossible.¹

The technique is far from risk-free. Serious complications occurred in 6.8% of the 571 patients in the recently published MIRACLE study.² Complications included complete auriculoventricular block, coronary sinus artery dissection-perforation, and two procedure-related deaths. Moreover, the physical stability of electrodes in the coronary venous system is unknown, as is that of long-term epicardial thresholds. Nor do we have much experience with the consequences of long-term coronary venous system implants.

IS LEFT VENTRICULAR PACING A DEFINITIVE TREATMENT?

Although it seems to have been demonstrated that a good number of patients improve their functional class^{1,2} and we are even beginning to see data on the effects of ventricular remodeling with reduced ventricular volume,^{18,23} cardiac resynchronization cannot yet be said to improve survival rates. However, work in progress (CARE-HF, COMPANION) may cast light on this issue. For the moment, LV pacing, alone or associated with RV pacing, is an option available for some patients who are not candidates for a heart transplant. It may also constitute a bridging therapy prior to transplant. Long-term results whether in terms of positive effects or of possible complications or technical deficiencies, are unknown.

Once we improve our understanding of the mechanisms by which alterations in ventricular synchrony cause heart failure and of the way that these can be antagonized by selective LV pacing, RV pacing or BVP, we may be able to define groups of patients for whom resynchronization therapy would be «almost a cure». Meanwhile, resynchronization should be considered a line of research under study. Resynchronization is still being developed and can only be offered to patients with caution and without an unfounded optimism that might lead to frustration if good results are not obtained.

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