Cardiac resynchronisation therapy in daily practice and loss of confidence in predictive techniques to response

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Cardiac resynchronisation therapy (CRT) aims to restore left ventricular electrical/mechanical dyssynchrony, which can underlie impaired systolic left ventricular (LV) function and congestive heart failure. Several large prospective studies were able to document clearly that chronic electrical synchronisation does improve the systolic dysfunction and ameliorates symptoms, patient functioning and prognosis. If the conventional criteria are applied, this positive response can be observed in roughly 70% of patients, depending on the definition used for 'positive response'.

Faced with patients suffering from severe congestive heart failure due to depressed systolic left ventricular function, despite conventional medical therapy, the 2008 pacing guidelines show ways to ameliorate their prognosis as well as quality of life.¹ A reduced LV ejection fraction (<35%) and a widened QRS complex (>120 ms) with diminished physical functioning (NYHA III-IV) remain the rules of thumb to apply cardiac resynchronisation therapy (CRT), in sinus rhythm as well as in atrial fibrillation.² According to these guidelines, loss of LV intraventricular or inter-ventricular mechanical synchrony is not incorporated in the decision to implant a biventricular pacer.

According to this concept, in the Netherlands hundreds of patients have been treated annually with CRT. A retrospective analysis of a large series of CRT recipients from the general hospital in Arnhem by Rolink et al., published in this issue, represents a typical example of the development and history of CRT in the past decade.³ Initially, only the above-mentioned conventional criteria were used, whereas later tissue Doppler echocardiographic images (TDI) were also applied to examine electromechanical delays. Technical failure of biventricular device implantation was low

(<3%) and cumulative survival at two years was approximately 80%, consistent with previous large-scale data. Death was mainly of cardiac origin (12.6%) whereas deterioration of heart failure, arrhythmias and device complications constituted the most frequent reasons for hospitalisation after implantation. Unfortunately, the authors do not report any baseline and follow-up TDI findings, neither positive nor negative outcomes to CRT in terms of clinical improvement and their correlation, as the authors fairly admit. Thus, essential information on the full benefit of CRT in this series of patients is lacking and this report should be interpreted as a local, incomplete interim analysis of the quality of pacing and heart failure care in the past years in this hospital.

In the past decade, prediction of CRT responders and methods to improve CRT with pacing (re)programming has been extensively explored with Doppler echocardiographic studies as well as with MRI, nuclear cardiac tracer studies and invasive examinations in experimental and clinical conditions. An overwhelming amount of literature tries to convince us about the superiority of a specific parameter or cut-off value in terms of validity and ease of use. Given this worldwide confusion about the most trustworthy Doppler echocardiographic parameter, a prospective study of predictors of CRT response (PROSPECT trial) was carried out, which revealed that none of the 12 examined parameters of dyssynchrony showed sufficient diagnostic power to improve patient selection or quantify responses to CRT.⁴

Although some parts of the methods and results of the PROSPECT trial can be questioned, the message of this study includes that despite all efforts, we are again bound to rely on the conventional CRT selection criteria as provided by the 2008 guidelines. This is also disappointing because the main therapeutic mechanism of CRT is thought to be the correction of dyssynchronous myocardial contraction, and if current echocardiographic dyssynchrony parameters are unsuited in CRT selection, we need to explore new mechanical markers for LV dyssynchrony. These modalities must be robust, have a high accuracy and be suitable for use in everyday clinical practice. A better

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insight must be given into the differences between, and the extent of regional dyssynchrony and scarring. Probably Doppler strain imaging⁵ and two-dimensional speckle tracking⁶ will do this, because they are less affected by tethering or translation induced by the rocking motion of the heart and more reliable for measurements of regional myocardial contraction and dyssynchrony. Also the implementation of 3D echocardiography appears to provide better quantification of LV ejection fraction and volumes.⁵ Moreover, the issue of nonresponders caused by factors as inappropriate left ventricular lead location, right ventricular dysfunction, severe valvular disease, ischaemia or left ventricular scar tissue is not addressed by the PROSPECT trial. In addition, this study does not emphasise the necessity to optimise AV and VV delays with echocardiography to diminish the number of nonresponders. As a consequence, new dyssynchrony markers should also guide synchronisation of the CRT device after implantation.

In retrospect, it is not surprising that in the publication by Rolink et al. data on responsiveness to CRT are missing. In the past the definition of responsiveness using clinical, functional or echocardiographic parameters varied widely between trials. In daily practice, functional and clinical improvement following bi-ventricular pacer implantation will be readily recognised as a positive response. Furthermore, sophisticated Doppler echocardiographic imaging was or is not available in all cardiology departments, whereas time constraints for recordings are obvious. Faced with the outcome of the PROSPECT trial, the confusion is almost complete because the TDI indexes often applied appear to be unreliable, MRI can only be done before implant and invasive optimisation with dP/dt^7 can never become a routine procedure. In addition, a large proportion of the 30% nonresponders can also be elicited by an unfavourable LV pacing site. Regarding the pacing site, the current epicardial stimulation via the coronary sinus branches appears rather primitive whereas LV endocardial pacing offers a much more normal spread of activation and thus better synchronisation. Scars and nonviable areas delaying the pacing impulse to the desired site of delayed activation can also negatively affect the response to CRT, as neglecting optimisation after implantation.

The loss of confidence raises the question how to proceed further. Must we classify all the results reported by single or multicentre studies that propose dyssynchrony measurements to predict outcome in CRT, as worthless? Can we not transfer the findings of experimental studies, which invented the word dyssynchronopathy⁸ as an important underlying mechanism of heart failure, to our heart failure patients? Finally, it cannot be excluded that there are reasons why the

dyssynchrony determinants examined and used in the PROSPECT are not appropriate for a multicentre approach because of unavoidable technical differences.

To bridge the gap now created, we propose that whenever possible CRT candidates are referred to centres with specific knowledge and high-quality echocardiographic imaging facilities (3D strain imaging and speckle tracking) for initial screening and yearly follow-up examinations. Echocardiography must have an ongoing role in helping us to understand how CRT essentially works, while it is likely that there are inter-related mechanisms involved, rather than a single mechanism in LV dyssynchrony. A prospective national CRT registry that records, besides baseline and follow-up data, easily collected parameters of responsiveness to CRT can produce new insight towards the validity and ease of use of these new imaging methods. In the meantime the conventional guidelines for CRT selection should be applied because many patients with severe drug-refractory heart failure cannot be denied the benefits of cardiac resynchronisation therapy, which until now are unfortunately unpredictable. ■

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