Cardiac resynchronization therapy (CRT) is one of the major therapeutic advances to have taken place in cardiology over the past decade. The benefit of CRT is obtained on top of optimal drug treatment, primarily in patients with left ventricular (LV) dysfunction, wide QRS and severe heart failure (NYHA class III and IV) and, more recently, with moderate heart failure (NYHA class II) [1]. It is noteworthy that over the same period many attempts to improve outcome have been performed using different pharmacological drugs, but without real success, with the exception of ivabradine and eplerenone.

Even after 15 years of CRT many questions remain to be answered. One such question relates to the fact that despite thousands of implantations of CRT devices worldwide, the proportion of patients who do not benefit from CRT — the so-called the non-responders — has remained unchanged. The rate of non-response, according to the definition based on clinical or echocardiographic criteria, ranges from 30 to 55% [2], which is unacceptably high for an invasive and costly therapeutic procedure. We have to recognize, however, that not all patients respond to drug therapy either, but the issue of non-responders to pharmacological therapy tends to be discussed less frequently.

To reduce the rate of non-responders to CRT, we have to refine patient selection. Patients who will not respond or who are poor responders need to be identified and eliminated from selection; but we also need to improve the pacing modalities and optimize the programming and follow-up of these fragile patients, and use the haemodynamic data provided by these devices.

For patient selection, the definition of ventricular dyssynchrony is based on the QRS width on a surface ECG — an apparently simple but probably too simplistic criterion. First of all, we have to recognize that there is no standardization when measuring QRS duration. An interesting study showed inter- and intraobserver variability in the measurement of QRS duration, and hence the poor reliability of this variable [3]. Data from randomized controlled trials have shown consistently that the magnitude of response to CRT is higher in patients with a very wide QRS (> 150 ms) and/or the presence of left bundle branch block [2]. Current European guidelines, updated in 2010, consider only the QRS duration for the definition of ventricular dyssynchrony, with different cut-offs according to the severity of the heart failure (120 ms for NYHA class III or IV patients and 150 ms for NYHA class II patients), but without any consideration for the type of conduction disorder (i.e. LBBB vs non-LBBB) [1]. New European guidelines are under construction and should consider not only QRS duration but also the absence or presence of LBBB when selecting candidates for CRT. Interestingly, recent guidelines published by the Heart Failure Society of America integrate the type of ventricular conduction disorder [4]. Despite many encouraging
reports from single-centre studies, it is noteworthy that imaging techniques are not implemented in the guidelines to improve the selection of patients. This statement is related to the inconclusive results of the Predictors of Response to CRT (PROSPECT) trial, but we can expect that imaging techniques (not only echocardiography!) with new, more sensitive, reproducible and less operator-dependency will play an important role in the selection of patients for CRT. Another important criterion is the nature of the underlying cardiomyopathy. The extent of myocardial scarring may play a role and be associated with reduced CRT responsiveness. Data are insufficient to support a specific recommendation, but clinicians should weigh the risks against the potential benefits of CRT implantation in patients with extensive myocardial scar, particularly in the location of the LV lead placement. Imaging techniques with fusion of data may be very helpful. Finally, the presence of a dysfunction of the right ventricle appears to be an important predictive factor of non-response to CRT, suggesting the need for careful evaluation of the right ventricle in the selection of candidates for CRT.

The position of the LV lead may have an important impact on the clinical and echocardiographic outcomes of CRT patients. Classically, the recommended LV lead location is the lateral or postero-lateral LV wall-based on previous haemodynamic studies [2]. However, data from three clinical trials showed that the lateral position was not necessarily associated with a better clinical outcome compared with posterior or anterior positions [5–7]. These observations reinforce the need for individual positioning of the LV lead in respect of the pattern of ventricular activation and the presence of scar and/or fibrosis.

Some authors have suggested that providing more pacing sites in the right or left ventricles would improve the correction of cardiac dyssynchrony and thus improve response to CRT. In an acute study in 21 patients, Yoshiida et al. showed that triple-site pacing using one LV lead and two right ventricular leads, one at the apex and one at the right outflow tract, significantly improved LV haemodynamics compared with conventional biventricular pacing [8]. Another triple pacing site configuration with two LV leads positioned in the coronary sinus has been studied. Mid-term results from small studies have shown promising results [9,10]. These encouraging results have to be confirmed by further randomized trials such as the TRUST CRT (Triple-site versus standard cardiac resynchronization therapy) study, conducted in de novo CRT patients [9]. The V3 trial, designed to assess the potential efficacy of a second LV lead in non-responders, is ongoing [11].

Alternative LV pacing modalities to the coronary sinus route have been proposed, especially in case of failure of LV lead implantation [2]. Epicardial LV pacing using a mini-invasive thoracotomy or thoracoscopy can be performed. Another promising approach is endocardial biventricular pacing, which provides a more physiological electrical activation since the activation originates in the endocardium and spreads towards the epicardium. Different routes have been proposed, mainly using an interatrial septum or transapical routes. A recent acute study based on the measurement of LV dp/dt reported that there is a considerable intervariability in the location of the optimal endocardial pacing site, suggesting again a tailored, individualized approach for each patient [12]. However, there are safety issues to consider such as thromboembolism or infection of the endocardial pacing lead or the impact of the mitral valve functioning. Further studies are warranted to evaluate the safety and superiority of these alternative strategies over conventional biventricular pacing in the future.

The follow-up of patients implanted with a CRT device should focus on a multidimensional approach to maximize clinical response to the therapy. This includes a systematically executed optimization procedure of the device itself. Recent data suggest that a high percentage of biventricular pacing (>92%) is mandatory for the clinical success of the therapy [2]. Basic device parameters such as the basal pacing rate, the upper limit rate as well as the need for a rate-responsive function have to be carefully evaluated in each patient. The lack of optimization of the atroventricular (AV) intervals has been suggested recently as an important cause of non-response to CRT [6]. However, the Freedom (Frequent Optimization Study Using the QuickOpt Method) and SMART-AV (SmartDelay determined AV optimization: a comparison to other AV delay methods used in cardiac resynchronization therapy) trials comparing IEGN-based algorithms or echo-based AV optimization have suggested that the ‘out-of-the-box’ setting (i.e. the default parameters ensuring biventricular pacing) may work sufficiently [13,14]. However, it is still a matter of debate if these studies will have limitations in their design, pre-study assumption and power calculations. Current CRT devices provide the possibility to optimize the interventricular (VV) delay, allowing simultaneous biventricular pacing or sequential pacing with different degrees of VV delays or VV delays preexcitation. Up to now, there is still controversy about whether an individual AV/VV optimization protocol is necessary in every implanted CRT patient or only for non-responders.

Today, cardiac resynchronization devices record and provide important information about different ‘haemodynamic’ parameters [2]. We may have easy access to the patient’s activity, their night-time and daily heart rate, and heart rate variability, but we also have important information about the pulmonary fluid status via the transthoracic impedance or the respiratory status [2]. However, the reliability of the monitoring of the pulmonary fluid status remains controversial with the current technology [2]. The devices also provide data about the occurrence and the prevalence of atrial and ventricular arrhythmias as well as another important parameter, the percentage of biventricular pacing. In non-responders, knowledge of these parameters may identify the cause of non-response and thus the most appropriate action necessary. However, to be more efficient, knowledge of all of these parameters has to be delivered in a timely manner to the patient’s physician. The development of remote monitoring improves the monitoring of the device but also provides information about the status of the patient. With this technology, information on body weight and blood pressure — very simple but important factors in the follow-up of heart failure patients — is transmitted to the physician. Some preliminary data are encouraging in terms of improving follow-up of these patients [15,16]. New devices not incorporated into the CRT device are dedicated to assess directly the pressure in the pulmonary artery or in the left atrium [17,18]. However, today, there is no strong evidence
that the monitoring and transmission of all of this haemodynamic information improves the outcome of non-responders. Further investigations are therefore needed.

**Conclusion**

CRT is definitively a major treatment in patients with LV systolic dysfunction, wide QRS and mild to severe heart failure refractory to optimal pharmacological treatment, but the proportion of non-responders needs to be reduced. This can be achieved by better selection of candidates but also by improving LV lead implantation. The future should also confirm the benefit of CRT in different populations, such as patients with atrial fibrillation or requiring permanent right ventricular pacing. Furthermore, new indications are of potential interest, such as patients with a narrow QRS and patients with moderate LV systolic dysfunction (LV ejection fraction > 35%).

**Disclosure of interest**

The author has not supplied his declaration of conflict of interest.

**References**


