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Cardiac Resynchronization Therapy in Advanced Heart Failure: Predictors of Response and Optimization of Therapy

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Abstract

Heart failure affects a high percentage of the population, especially older patients. Cardiac resynchronization therapy is indicated in some patients with advanced heart failure. However, 20–40% of patients with implanted resynchronization device have no clinical response. In this chapter, we review factors related with the absence of a clinical response, recent technological advances that can reduce the failure rate, and an algorithm for management of patients without a clinical response.

Keywords: heart failure, cardiac resynchronization therapy, predictors of response to resynchronization, optimization of resynchronization, resynchronization-nonresponder-patients

1. Background

Heart failure affects more than 23 million people worldwide (2.4% of the adult population, with 11% that is older than 80 years) [1]. Its prevalence is increasing in recent years. It is a progressive disease, and its two leading causes of death are progressive heart failure and sudden death due to arrhythmia [2]. In an advanced stage of heart failure, patients have a limitation of their daily activity, frequent hospital admissions and medical treatment only slows the evolution of the disease. Cardiac resynchronization therapy (CRT) is indicated in some of these patients [3, 4].

2. Predictors of response to cardiac resynchronization therapy

Cardiac resynchronization is indicated in patients with heart failure, systolic dysfunction, and prolonged QRS interval since it could decrease mortality in this group of patients. Unfortunately, up to 40% do not experience clinical improvement to this therapy. **Table 1** shows the probable causes of this absence of response.

—   Presence of a large myocardial scar

—   Progressive heart failure

—   Noncompliance with pharmacological treatment

—   Not properly treated comorbidities (anemia, renal failure)

—   Suboptimal positioning of the electrodes

—   Suboptimal device programming

—   Absence of left ventricular dyssynchrony

—   Phrenic nerve stimulation

Table 1. Causes of the absence of response to cardiac resynchronization.

The prevalence of heart failure is higher in older patients. Many diseases show a lower response to treatment in older patients. Also, these older patients are usually excluded from clinical trials. The results of studies showing the effect of cardiac resynchronization therapy in elderly patients are contradictory. Some studies [5] do not show differences in mortality in older and younger patients. Other works [6] show that a greater age is a risk factor for higher mortality, together with other data (New York Heart Association functional class IV, impaired renal function, atrial fibrillation, and left ventricular ejection fraction <22%). With this doubt, the implantation of these devices could be considered in patients with advanced functional stages and older age.

Factors such as ischemic heart disease, monomorphic ventricular tachycardia, and the presence of moderate-to-severe mitral regurgitation have been associated with a decreased response to CRT [7].

The patients' baseline ECG, prior to implantation, also provides data that may help predict the response to resynchronization. The presence of a left bundle branch block (unlike right bundle branch block or other intraventricular conduction disorders) [8], atrial fibrillation, and a prolonged QRS interval is a factor related to a positive response to resynchronization treatment. The width of the QRS interval is another element to be evaluated. A QRS of 120–140 ms often occurs in left ventricular hypertrophy rather than in a true complete left bundle branch block; thus, the complete left bundle block is redefined as a QRS width >140 ms in men and >130 ms in women. A longer intraventricular conduction time is associated with a greater probability of echocardiographic inverse remodeling. An inverse relationship between QRS interval width and risk of death has been described [9]; in patients with QRS ≥145 ms, there is a benefit in survival, and there is no survival benefit in patients with ≤130 ms. Thus, according to

the recent guidelines [3], cardiac resynchronization is not recommended in patients with narrow QRS.

The presence of atrial fibrillation or atrial conduction delay is associated with a lower response to resynchronization; this second problem could be corrected with electrical activation with an electrode at the interatrial septum [8].

A 12-lead ECG recorded following implantation of a CRT device may also predict one's response to resynchronization therapy. Optimal biventricular pacing, which coordinates the systolic activity of the interventricular septum and free walls of the left ventricle, may be realized as a tall R wave (>0.4 mm) in lead V1 with a predominantly negative deflection in I (RV1SI pattern) and is accompanied by improvement in heart failure and a lower mortality [10, 11]. An increase in the size of the R wave in V1 and the deviation of the QRS from the right to the left in relation to baseline ECG is associated with lower left ventricular systolic volumes. The decrease of the width of the non-paced QRS complex after initiation of resynchronization, or electrical remodeling, may also be associated with a lower risk of ventricular arrhythmias and lower mortality [12, 13]. Despite the above criteria, there is no clear relationship between mechanical and electrical remodeling.

Several case reports have exposed the detriment of selecting an inappropriate candidate for CRT device insertion. Investigators have described [14] the clinical course of a patient with a dilated cardiomyopathy, narrow QRS with anterosuperior hemiblock pattern, advanced heart failure, and absence of dyssynchrony. The implantation of a CRT device was followed by a widening of the QRS complex, since pacing of the right ventricle did not achieve adequate fusion with the ventricular complex itself and worsened heart failure. The patient's clinical status improved by optimizing the atrioventricular delay, resulting in a narrowing of the QRS complex. It is very difficult to select resynchronization candidates only by echocardiographic asynchrony or by wide QRS.

The interrogation of the device can provide several abnormal pacing data: defective implantation or failure of capture of the left ventricular electrode, delayed ventricular electrical conduction due to ventricular disease, or fusion beats between paced and spontaneous beats [10]. Electrophysiologists can correct some alterations, for example, by shortening atrioventricular delay or by varying the pacing interval between left and right ventricle. Pseudofusion, or ventricular pacing that start simultaneously with native complexes, and ineffective pacing, may be alleviated in part with medication that increases atrioventricular block or even with atrioventricular node ablation.

Heart failure is a progressive disease; however, stabilization of the clinic course may indicate a positive response to CRT. CRT nonresponders exhibit a progressive worsening of their heart failure (**Figure 1**), following device implantation. On the other end of the spectrum are the super-responders, who exhibit a significant improvement in the echocardiographic parameters of heart failure (100% increase of the left ventricular ejection fraction, or a final value of this parameter of at least 45%, 12 months after the implantation). The most frequently observed characteristics associated with the super-responders are extreme intraventricular conduction delays with QRS width ≥150 ms, typically with a complete left bundle branch block, female

gender, non-ischemic cardiomyopathy, lower body mass index, and a smaller left atrial size [15, 16]. These data may help to screen patients who will reap the greatest benefit associated with resynchronization therapy, although the necessary optimization of the medical treatment of heart failure cannot be forgotten.
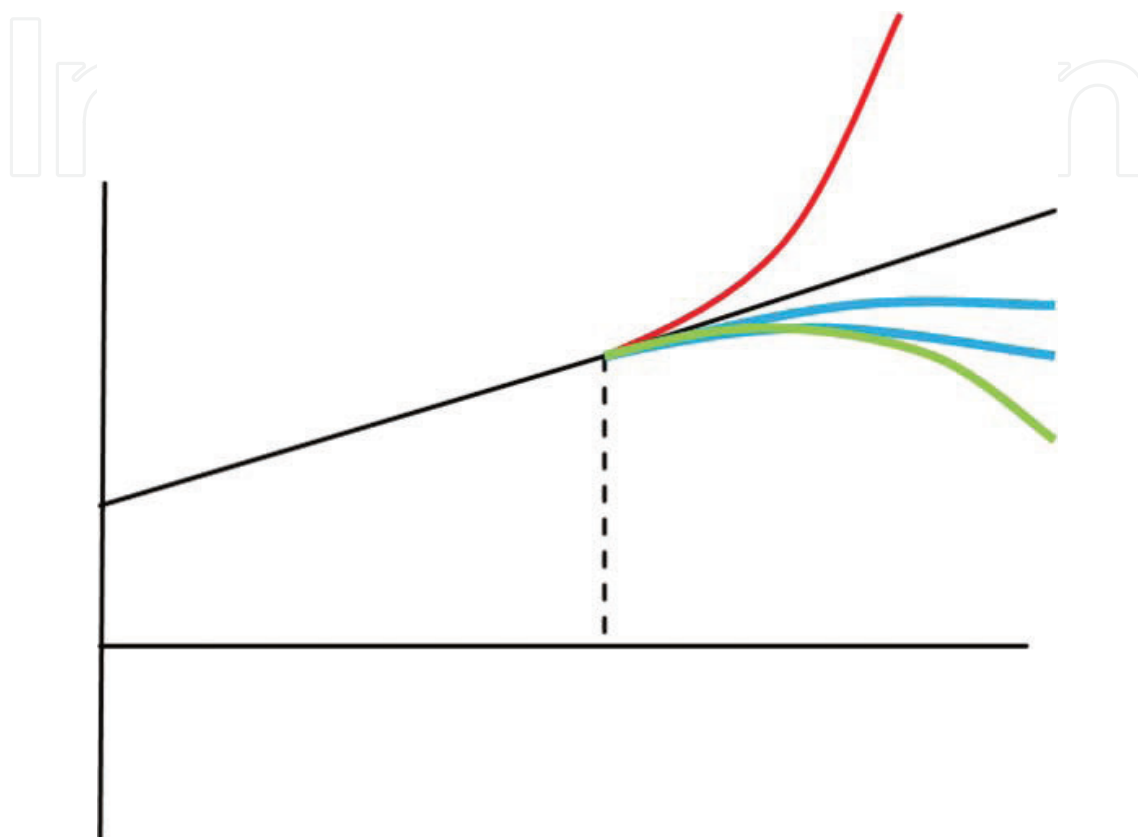
Figure 1. Graphical representation of the progression of heart failure (ordinates) as a function of time (abscissa). Dotted line, time of implantation of the resynchronization device; red line, negative responder; black line, nonresponder; blue lines, responders; green line, super-responder.

CRT devices may delay the need for a left ventricular assist device, in patients with advanced cardiac failure, who are hospitalized in need with inotropic support [17]. There may be up to 16% of response rate, especially in those patients with a complete left bundle branch block and a smaller left atrium.

3. Relationship between mechanical and electrical resynchronization

The concepts of mechanical and electrical remodeling refer to two distinct concepts: the first one is the mechanical improvement of the heart, and the second one is the electrical changes that tend to produce a less variegated electrical pattern.

This mechanical remodeling of the heart has already been observed previously in patients with optimal treatment for heart failure. Cardiac resynchronization produces a level of inverse

echocardiographic remodeling added to that achieved with appropriate pharmacologic therapy [18]. On an anatomopathologic level, there is a decrease in the degree of myocardial fibrosis [19].

Previous investigators have described how intraventricular conduction delay causes dyssynchronous cardiac contraction [18], with mechanical asynchrony (obtained by tissue Doppler) and delayed electrical activation of the left ventricular free wall. This has been observed in patients with a dilated cardiomyopathy, poor left ventricular function, and a complete left bundle branch block. However, many studies have shown a poor correlation between echocardiographic and electrographic data [20]. The PROSPECT study [21] showed that standard measures performed with conventional echocardiography do not distinguish between responders and nonresponders to CRT. Therefore, echocardiographic parameters were not useful in predicting clinical response. Studies using real-time three-dimensional echocardiography attempted to improve discrimination as compared to conventional 2D echocardiography, and found the systolic dysincrony index, a parameter that evaluates ventricular hemodynamics globally and may help predict changes in hemodynamics with a sensitivity greater than 80% [22].

Cardiac dyssynchrony has also been described in patients who have undergone the insertion of a permanent pacemaker. Stimulation from the right ventricular apex in patients with a decreased left ventricular ejection fraction may increase mortality and worsen congestive heart failure, dyssynchrony caused by several mechanisms. Dyssynchrony may occur by increasing the delay between right and left ventricular contraction, worsening of ventricular remodeling, increasing the propensity of developing atrial fibrillation, and worsening of mitral insufficiency. Attempts at pacing from the interventricular septum or right ventricular outflow tract, to mitigate these changes, especially in patients with preserved left ventricular ejection fraction, may produce dyssynchrony similar to that observed with right ventricular apical stimulation [23]. Further studies are needed to fully assess this patient cohort.

At the present time, the decision to implant a CRT device is based on clinical and electrocardiographic data (wide QRS with an LBBB pattern) and not on echocardiographic criteria. Sporadic cases have described the benefit of CRT in patients with dyssynchrony and a narrow QRS, with improvement of LV function; however, this has not gained universal acceptance.

Despite the limited usefulness of echocardiographic techniques, an imaging technique (transthoracic echocardiography, three-dimensional echocardiography, or contrast angiography) has been described to guide the electrode location, assessing the asynchrony achieved with the active device [24]. Several data from classical transthoracic echocardiography may help to predict clinical improvement after the implantation of the resynchronization device: delayed septal and posterior wall contraction (≥130 ms) observed in M-mode and intraventricular dyssynchrony, defined as the difference between peak systolic contraction in contralateral walls >40 ms and a maximum delay >65 ms between anterior, inferior, septal, and basal lateral walls with tissue Doppler [25]. These methods have two problems: the low coincidence rate between observers (kappa index 0.1–0.39), and, as suggested in the PROSPECT study [21], no value was significantly associated with a higher clinical response.

Many studies define the relationship between a reduction in left ventricular end-systolic volume of at least 10% and a reduction in the width of the non-stimulated QRS (from 163 to 153 ms) and the stimulated QRS after implantation (from 146 to 121 ms) [26]. These data point at the same direction that those from other studies [27] and heighten the importance of placing the left ventricular electrode in the appropriate site and of properly programming the device, to achieve a narrow-paced QRS complex.

4. Optimization of resynchronization therapy

The problem of lack of response to resynchronization is complex. These devices would only be a priori indicated in the patients with greater probability of positive response. Patients with complete left bundle branch block and idiopathic dilated cardiomyopathy, with relative integrity of the His-Purkinje system, have a greater response than patients with left ventricular dysfunction of ischemic origin, with involvement of the conduction system by extensive areas of necrosis [28].

The absence of myocardial viability in the lateral region of the left ventricle, evaluated by magnetic resonance, makes more improbable positive response after cardiac resynchronization therapy, even though there are no echocardiographic data of asynchrony [29]. In addition, not every electrode implanted through the coronary sinus that stimulates the left ventricle has resynchronization capacity accompanied by clinical benefit.

The programming of the devices is important mainly in two parameters: the atrioventricular interval and the interventricular interval. It seems necessary to optimize the atrioventricular interval because an excessive elongation of the interval between atrial and ventricular systoles can lead to decreased cardiac output [30]. A direct observation of the transmitral flow pattern should be made by transthoracic echocardiography, attempting to separate the E and A waves and eliminate diastolic mitral regurgitation. Programming the interventricular interval sometimes produces nonsimultaneous biventricular pacing, which may be more effective than simultaneous pacing. It is more important to assess the echocardiographic response of the patient than the degree of QRS narrowing induced by therapy (which is a poor marker of clinical response to resynchronization). Interventricular delay can be measured by conventional pulsed Doppler and intraventricular asynchrony by the delay between peak septum and left ventricular posterior wall contraction in M-mode. It is not clear whether these intervals should be optimized in all patients and the order in which they should be done. But it should be emphasized that this optimization should not be done according to an algorithm, but individualized based on the response of each patient [30].

A survey carried out in Spain by the implantation centers of cardiac resynchronization devices [31] showed that the main obstacles for implantation are the difficulty in introducing the electrode in the selected vein (51%) and the poor electrode stability (26%). Seventy-three percent of centers do not perform any technique to optimize the point of stimulation prior to implantation. The clinical response rate is 74 ± 9%. For nonresponders, 15% of electrophysiologists replaced the electrode at a different point, 39% placed an electrode via

the epicardial route with thoracotomy, 3.5% performed multifocal stimulation in the left ventricle, and about half (47.6%) admitted that it has no alternative to optimizing medical treatment.

The best position of the electrode has traditionally been a vein in the lateral and basal region of the coronary sinus, which is accompanied by an improvement in echocardiographic resynchronization parameters [32]. The initial objective of the electrophysiologists, years ago, was the implantation of the electrocatheter in those veins. In the present moment, this approach is overcome, because the areas of maximum electrical delay are not always areas of greater alteration of contractility. Several electrical parameters have been described during implantation that can predict reverse remodeling/favorable clinical response [33, 34], such as non-paced QRS intervals (151 versus 126 ms) and delayed right ventricle-left ventricle activation interval (93 versus 69 ms), greater in responders. One study [35] describes that the implantation of the electrocatheter in the right ventricle guided by the maximum electrical delay in the outflow tract, apex, or septum increases the response rate to the standard right ventricular apex implant.

Alternative stimulation points have been evaluated, which may be indicated in some patients where there may be inadequate functioning due to anatomical data, inadequate stimulation thresholds, electrode twisting or anchorage electrode, etc. The efficacy of left ventricular pacing from the lateral wall has been described [36]. Transeptal access may be useful in patients with difficulty in localizing the coronary sinus [37, 38], although it has the drawbacks of requiring long-term anticoagulation and the possibility of increasing mitral insufficiency [39]. Triangular stimulation can also be performed, with two electrodes implanted in the right ventricle (apex and outflow tract) and one in the left ventricle [40–42]. We can think about this pacing technique in patients in whom the left ventricular electrode cannot be placed endocardially, or in patients with heart failure, with extensive transmural myocardial scarring in posterior and lateral walls of the left ventricle, or even in patients with previous classic pacemaker with indication of upgrading/improvement of their performance. Although this technique seems to be less aggressive, its benefit appears smaller. Other authors [43, 44] use His-bundle pacing, which may be effective in patients with non-wide QRS, and may induce a greater QRS narrowing, although this is not always accompanied by an improvement in LV function. Few studies [45] describe Purkinje fiber pacing, which is similar to conventional pacing, and may be useful in patients with ischemic heart disease, with more stable stimulation in cases of myocardial damage.

Recent advances in design and materials of electrocatheters and guides have been accompanied by higher success rates in the implant [46]. The steerable positioning system of the catheter-guided catheter [47] achieves a nonsignificant improvement in the success rate of transvenous implant (93.7% versus 91.2% of the conventional method), with shorter implant time and less use of radiographic contrast. Easy maneuvers [48] may facilitate the progression of the electrocatheter through an unfavorable venous tree; with a second hydrophilic guide mounted in parallel with another one, the coronary sinus is accessed with a catheter of wide curvature, an angiography is done to assess the nature of the obstacle, and the first guide is inserted into the chosen vein to achieve the advance of the electrocatheter. Anatomical

abnormalities such as the presence of a Thebesian valve, a fenestrated Thebesian valve, or an inadequate ratio of its size to the diameter of the ostium of the coronary sinus can be solved mostly with these two strategies [49].

A significant advance in this field is the quadripolar electrocatheter of the left ventricle [50]. Four electrodes are arranged along the 4.7 cm distal, allowing up to ten stimulation configurations, which means a greater probability of achieving an effective stimulation without the need to reposition the electrode. It has several advantages: adequated pacing thresholds, greater electrocatheter stability with low rates of electrode displacement, infrequent pacing of the phrenic nerve, pacing from basal left ventricle positions—apparently with better performance and ability to pacing around the scar tissue of the myocardium—and improved cardiac output in the medium to long term. Multipoint stimulation improves cardiac contractility to a greater extent than classical biventricular pacing [51], with an increase in the left ventricular ejection fraction of 12.7% compared to 6.7% in classic resynchronization [52].

Several intelligent resynchronization therapy algorithms have been recently developed. The algorithm called adaptive CRT pacing stimulates the left ventricle synchronously only when there is intrinsic activation of that ventricle, producing a fusion beat. This more physiological electrical programming gets different results [53, 54], so it cannot yet be widely recommended.

In the 80s and the early 90s, there was no routine optimization of the device after its implantation. Unlike in recent years, optimization of the therapy is performed a few weeks after implantation, using simple echocardiographic measurements, since the atrioventricular and interventricular intervals may be different in each individual and change over time. Several studies [55–57] show improved cardiac failure data and even improved survival in patients with scheduled post-implant visits. At these visits, problems can be detected with early correction and improvement of the prognosis of these patients (malignant ventricular arrhythmias, atrial fibrillation, ventricular pacing time of less than 90–95%, diaphragmatic pacing, inadequate electrode pacing, etc.). One work with methodological problems [58] found no such improvements with scheduled visits after the implant. It seems, therefore, that the option of frequent monitoring after the implant is better. The RESPOND CRT clinical trial (Clinicaltrials.gov: NCT01534234) is currently being conducted to evaluate the effectiveness of automatic optimization algorithms versus optimization based on echocardiographic criteria.

Remote monitoring is a technology that is increasingly used today and that may be more important in the future. The transmission of programmed and patients' response data is performed from a device implanted to the specialist's office [59]. It makes a closer follow-up in order to optimize the therapy and relieves the saturation of specialists' offices. The IN-TIME study [60] shows less worsening of cardiac failure data and nonsignificant mortality reduction in patients with implantable cardioverter defibrillator or mixed—resynchronization + defibrillator—devices. Recent clinical guidelines of the Spanish Society of Cardiology [4] recommend the implantation of devices with remote monitoring functionality (recommendation IIa, level of evidence A).

5. Treatment of resynchronization nonresponder patients

The evaluation of the patient who does not respond to resynchronization should be systematic (**Table 2**), taking into account the elements of the device, and cardiac and extracardiac patient data [61].

1. To assess the ECG with and without pacemaker/resynchronization, arrhythmias

2. To interrogate the device: sensing and capturing atrial and ventricular thresholds, atrioventricular and interventricular delays, physiological sensors

3. To check the position of the electrodes: chest X-ray, fluoroscopy

4. To verify the effect of resynchronization by echocardiography: Doppler parameters, mitral flow, dP/dt, intraventricular and interventricular dyssynchrony, atrioventricular and interventricular delay optimization

5. To check for proper intake of basal medication

6. To check for comorbidities

Table 2. Stepwise approach of the patient who does not respond to cardiac resynchronization.

It is desirable that biventricular stimulation be active about 100% of beats, even during exercise. The atrioventricular or interventricular intervals with echocardiographic control may be optimized, with pre-excitation of the left ventricle or simultaneous biventricular contraction. These changes may increase cardiac output in relation to the intrinsic cardiac rhythm and factory settings of the device.

The presence of atrial fibrillation leads to loss of left ventricular catheterization or to fusion/pseudofusion beats with ineffective resynchronization. Fusions or pseudofusions may not be detected by the device, so the percentage of stimulation may be falsely normal. This data should be exposed by reviewing the paths recorded in the device memory. If the sinus rhythm cannot be recovered, it is important to control the ventricular rate to ensure ventricular capture, sometimes even with an atrioventricular node ablation. The presence of frequent ventricular extrasystoles can inhibit pacing of the left ventricular lead and thus reduce the effectiveness of resynchronization; therefore, a percutaneous ablation can be considered.

Some nonresponder patients have loss of catheter capture. The beats produced by biventricular stimulation have a QRS axis in the upper right quadrant of the frontal plane and a dominant R wave in V1. If we observe a predominantly negative complex in V1 lead, we should suspect loss of capture or nonoptimal position of the left ventricular electrode, and its replacement can be considered.

The localization of the left ventricular lead may influence the response to resynchronization. Chest X-ray (posteroanterior and lateral projection images) and fluoroscopy are the methods of choice. The recommendation is to implant the electrode in a collateral branch of the coronary sinus (from basal to mediolateral or posterolateral) if there is an adequate vein to host the electrode.

The anterior position of the electrode is accompanied by a lack of response. And, the apical pacing can induce heterogeneous activation of the left ventricle. Electrocardiographic patterns of the left or right branch block, or intraventricular conduction disorder, can add greater variability in the activation pattern, so an implant should be performed by assessing the response in an individualized way.

In patients without positive clinical response to a left ventricular electrode in a nonoptimal position, the option of implanting a second electrode should be assessed. Computed tomography can be done to assess the anatomy of the branches of the coronary sinus. If the endocardial implant is not feasible, an epicardial approach via a mini-thoracotomy or a transeptal endocardial implant should be assessed. Before, an evaluation of the a priori morbidity of this new implant and the degree of compensation of other comorbidities of the patient should be made.

Despite the described limitations, it is mandatory to perform an echocardiography of the patient who does not improve with resynchronization. It is recommended to evaluate several aspects:

- The transmitral filling profile, which can improve acutely with the resynchronization. If the transmitral filling period is too short, less than 40–45% of the cycle duration, it can be optimized by prolonging atrioventricular delay. If the atrioventricular interval is too long, it may improve the resynchronization response by shortening that period. These data are not static and change over time, so it is suggested to optimize it preferably with echocardiography every 6 months.

- We can find data of favorable response to resynchronization, such as immediate reduction of functional mitral regurgitation, acute increase of left ventricular dP/dt (contractility index), and disappearance of the initial systolic inward movement of the interventricular septum [62].

- Another element of favorable response is the decrease in intraventricular dyssynchrony, measured as a decrease in the difference in the interval of aortic and pulmonary preeyection. In these cases an individual optimization of the interventricular interval is recommended. If there is no improvement, consider changing the position or the performance of the left ventricular electrode, or even cancel it/remove it.

One final aspect, but not less important, is the verification of compliance with the medication for treating heart failure. Up to 25% of patients without a resynchronization response do not take their prescribed medication [63].

There may be involuntary medication suppression, due to progressive renal insufficiency or adverse effects, with worsening of the condition. In addition, patients with arrhythmias may require antiarrhythmic treatment. The comorbidities of these patients (diabetes, ischemic heart disease, vascular and cerebral diseases) may attenuate the beneficial effects of resynchronization. Worsening renal function, anemia, and arterial hypotension are associated with poor prognosis in resynchronized patients. It has already been commented that the inverse remodeling is more pronounced in non-ischemic patients than in ischemic patients.

Optimizing the response to resynchronization, with that patient-focused individual approach (**Table 2**), can maximize the beneficial effect of cardiac resynchronization.

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