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REDUCED EJECTION FRACTION AND CARDIAC RESYNCHRONIZATION THERAPY

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Abstract: Introduction: cardiac resynchronization therapy (CRT) is a therapeutic modality for patients with heart failure (HF) refractory to optimized pharmacological treatment. **Goal:** This study aimed to analyze the main indications for the use of CRT in HFrEF available in the literature. **Methods:** This is a literature review in the following databases: New England Journal of Medicine, American Heart Association, SCIENSE, JACC. Articles in English during the period 2002 -2013 were selected. The Brazilian Guideline for Chronic and Acute Heart Failure was also consulted. **Discussion:** CRT has established itself as an important therapy in the treatment of HF, mainly in patients with NYHA functional class III and IV. Its effectiveness has been widely documented in several clinical trials, which have shown clinical benefits related to symptom improvement, reduced hospital admissions and improved survival. **Conclusion** : from the analysis of the studies presented in this literature review, it is possible to conclude that CRT, when well indicated, is capable of reducing mortality and morbidity, in addition to showing favorable impacts on improving the quality of life and, consequently, the functional class.

Keywords: Cardiac resynchronization therapy; Cardiac insufficiency; Recommendation.

INTRODUCTION

Heart failure (HF) is characterized as a difficult-to-control syndrome, in which the heart gradually loses its ability to pump blood to the rest of the body, either due to contraction or relaxation deficits, leading to implications throughout the body. The varied etiologies have structural or functional cardiac alterations as pathophysiological substrate, and by peculiar signs and symptoms, which promote a reduction in cardiac output or cause high filling pressures at rest or during exertion. [1]

Traditionally. the most important classification to define heart failure consists of Left Ventricular Ejection Fraction (LVEF), which divides patients into two categories: those patients with normal LVEF (≥ 50%), called Insufficiency with Preserved Ejection Fraction (HFpEF), and those with reduced LVEF (< 40%), identified as Heart Failure with Reduced Ejection Fraction (HFrEF). [1]

Despite all the advances in the available therapies for the treatment of HF, it still remains in the 21st century, as a serious public health problem accounting for more than 23 million people worldwide. On average, after five years of diagnosis, survival decreases by 35%. In addition, depending on the age of the individual, the prevalence increases, reaching 1% in patients aged between 55 and 64 years, up to 17.4% in patients aged 85 years or older. [1]

Cardiac Resynchronization Therapy (CRT) then emerged as a therapeutic modality for patients with decompensated HF and that no longer respond to drug treatment. The first scientific evidence on the subject began to emerge in the 1990s, but it was only in the 2000s that larger and more consistent clinical trials began to show the efficacy and safety of CRT. [two]

It is an invasive therapeutic procedure, which aims to correct electromechanical dysfunctions through artificial cardiac stimulation, in patients with symptomatic and refractory HF. In recent years, several studies have sought to establish its benefits and determine its indications, according to the functional class and symptomatology, in addition to other variables, such as the duration of the QRS complex on the electrocardiogram. Most of these studies have shown promising results in patients with advanced HF (functional class III-IV). CRT has been able to bring about consistent improvements in quality of life, functional class and exercise capacity, in addition to reducing

hospitalizations and mortality rates.[two]

Due to the success of this therapeutic modality, more studies were developed to evaluate the expansion of CRT for patients with functional class I and II. In this context, CRT emerges as a promising and safe therapeutic option. Although it is still a controversial topic in these patients. [2]

However, although CRT is a promising intervention for decompensated HF, there is still a small group that does not benefit from this therapy. However, there must be a consensus, research with a greater number of patients and studies that better define the clinical parameters, for the identification of non-responders to CRT, in order to avoid unnecessary expenses, due to its high cost. [2]

The interest in the subject was motivated by the experience acquired in the follow-up for approximately 3 months of a 48-year-old patient, who remained hospitalized for 68 days in a tertiary hospital in Teresópolis, in December 2019. The patient had HF (idiopathic). who was symptomatic despite all therapeutic optimization. Due to the prolonged hospitalization time. the psychosocial factors highlighted, led to a worsening of the condition, but culminated in a greater and better doctor-patient relationship. She underwent CRT implantation and is undergoing cardiological follow-up.

GOALS

This study aimed to analyze the main indications for the use of CRT in HFrEF available in the literature, where aspects inherent to this therapeutic modality were addressed.

METHODS

This is a literature review, which aims to add content on the subject The Reduced Ejection Fraction and Cardiac Resynchronization Therapy. The following databases were consulted: New England Journal of Medicine, American Heart Association, SCIENSE, JACC, searching for articles in English and also the Brazilian Guideline for Chronic and Acute Heart Failure.

During the pre-selection of the articles, 335 were found, using the following descriptors: Cardiac Resynchronization Therapy, Heart Failure and Indication. As inclusion criteria, studies carried out in humans were selected, limited to clinical trials of greater relevance in the given period (2002 to 2013), in addition to having well-described methods with well-defined follow-up and that answered the question: when to indicate CRT ? Articles that were not in line with the theme of this review and other pathologies that also benefit from the use of CRT or that did not answer the question were excluded. Thus, 15 articles were selected, considering their statistical relevance and full inclusion in the inclusion criteria.

DISCUSSION

The role of CRT has been extensively documented in several clinical trials. Over the years, indisputable clinical benefits associated with the improvement of symptoms and quality of life, with a decrease in the return to the hospital, and improvement in the issue of morbidity and mortality, have been evidenced. In general, the participants in these studies had HF and moderate to severe symptoms, were using specific medications and had systolic LVEF < 3 5%, in addition to intraventricular conduction disorders with QRS complex duration > 120 ms. With the progressive increase in the use of CRT, there are studies focused on determining clinical

variables linked to excellent feedback on the response to CRT, such as female gender, non-ischemic cause, typical pattern of Left Bundle Branch Block (LBBB) with QRS complex duration > 150 ms. [1]

As already mentioned, CRT has proven support and benefit in patients with HFrEF. The first randomized clinical trial on the subject was published in June 2002 by the journal of the Journal of the American College of Cardiology, whose title was Cardiac resynchronization therapy in patients with heart failure and ventricular conduction delay (PATH-CHF). This study had a great impact that year, and its main objective was to compare the short- and long-term clinical effects of univentricular and biventricular pacing in patients with HF and ventricular conduction delay. The study adopted a crossover, randomized, controlled multicenter trial as methodology. A total of 36 patients were recruited and followed up for a period of 12 months. For inclusion in this study, patients had to be classified as NYHA III or IV for at least 6 months, and present sinus heart rhythm with heart rate greater than 55 bpm, QRS complex > 120 ms in at least two leads and PR interval > 150 ms. The analyzed outcomes were the peak $O_{2\ consumption}$ during exercise, the anaerobic threshold of $O_{2\ consumption}$ and the distance covered in the six-minute walk test. The PATH-CHF study was designed to evaluate the long-term outcomes of univentricular and biventricular pacing in patients with functional class III or IV. The result showed that CRT produces an improvement in clinical symptoms, quality of life, functional class, in addition to improvement in the walk test and a decrease in the number of days hospitalized due to heart failure decompensation in the long term, in patients with HF with ventricular conduction delay. There was no significant difference between the application of biventricular and univentricular therapy. [3]

Also in June 2002, The New England Journal of Medicine published one of the pioneering studies in the evaluation of CRT through atriosynchronous biventricular pacing. This is MIRACLE, this study aimed to evaluate whether biventricular cardiac resynchronization therapy produced clinical benefits in patients with HF with delay in intraventricular conduction. It was a randomized, multicenter clinical trial with all analyzes guided by intention to treat. During the years 1988 to 2000, 453 patients were followed for a period of six months. They must have HF in NYHA functional class III or IV, ejection fraction < 35%, left ventricular diastolic diameter > 55mm, QRS complex > 130ms, six-minute walk test < 450 meters. Patients using a pacemaker or implantable cardio-defibrillator, history of a cardiac or cerebral event in the last 3 months, atrial arrhythmia in the last month, systolic blood pressure >170mmHg or <80mmHg, heart rate greater than 140 bpm were excluded from the study. serum creatinine > 3.0mg/dl, liver enzymes above the upper limit of normality. During the follow-up of the study, changes in the six-minute walk test, changes in quality of life, fewer hospitalizations, and changes in NYHA functional class were considered as the primary outcome. Secondary outcomes were: change in peak $O_{2\ consumption.}$ change in QRS complex duration, and improvement in ejection fraction. Considering the primary and secondary outcomes, the study concluded that CR is capable of providing significant clinical improvement in patients with moderate to severe HF and intraventricular conduction delay. The study was sponsored by Medtronic. [4]

The following year, the PATH-CHF2 and MIRACLE ICD study was published, continuing training on the application of CRT and providing better reliability for the

management of patients with HF in whom the therapy in question is chosen. The PATH-CHF2 study evaluated the clinical efficacy of CRT with left ventricular pacing, and analyzed the impact of severity on baseline conduction delay in relation to the magnitude of benefit. This study gains importance because it alters a topic that is still a matter of debate today, which is the selection of the most suitable candidate for the use of ventricular resynchronization therapy. PATH-CHT2 was a study with a relatively small number of patients enrolled, only 86 and including those with an ejection fraction <30% and a wide QRS complex in at least two leads. The study proved the effectiveness of ventricular resynchronization therapy, especially in patients with substantial QRS prolongation, having an impact on improving exercise tolerance and quality of life. [5]

MIRACLE IDC had. as publication vehicle. JAMA magazine. The focus of the study was to evaluate the efficacy and safety of combined therapy with an implantable cardioverter-defibrillator (ICD) and biventricular resynchronization therapy (BRT) in patients with functional class III or IV and in appropriate clinical treatment with the use of Angiotensin-Converting Enzyme (ACE) or Angiotensin Receptor Blockers (ARBs) and beta-blockers. The MIRACLE IDC study had a very similar design to the MIRACLE study. To be included in the study, the patient had to be 18 years of age or older, class III or IV heart failure, history of cardiac arrest due to ventricular fibrillation or ventricular tachycardia, ejection fraction <35%, QRS complex greater than 130ms, and left ventricular end-diastolic diameter greater than or equal to 55mm. [6]

This study showed improvement in HF functional class, restoration of quality of life and progress in the six-minute walk test. Secondarily, the duration of the stress test, left ventricular ejection fraction, end-diastolic and systolic volumes of the Left Ventricle (LV), severity of mitral insufficiency, duration of the QRS complex and neurohormonal concentrations were analyzed, verifying that the magnitude of the benefit was very close to that of the previous study, suggesting that patients with heart failure who had an indication for an ICD benefited as much from cardiac resynchronization therapy as those without an indication for an ICD. The effectiveness of anti-tachycardia biventricular pacing was significantly greater than that observed in the univentricular configuration (right ventricle only). In view of the analyzed outcomes, the study concluded that VRT has the potential to restore quality of life, functional capacity and tolerance to physical exercise in patients with moderate to severe heart failure, in addition to reducing the incidence of arrhythmias. life-threatening. [6] MIRACLE IDC was also sponsored by Medtronic [R] and all devices were made available by this company. [6]

In May 2004, the use of CRT was advanced with a study published by The New England Journal of Medicine. This is the COMPANION study, whose objective was to assess whether prophylactic CRT in the form of biventricular pacing with a pacemaker or with an ICD reduced the risk of death and hospitalization in patients with advanced chronic HF and intraventricular conduction delay. COMPANION adopted, as a methodology, a randomized, multicenter, controlled clinical trial, and all analyzes were by intention to treat. A total of 1520 patients were selected and followed up for a period of 12 months. Such patients were divided into three groups, 308 of them underwent clinical treatment, 617 underwent CRT + pacemaker and 595 underwent CRT + ICD. Those selected for this study must have HF NYHA functional class III or IV, ejection fraction <35%, QRS

complex>120ms, PR interval>150ms, sinus rhythm and no indication for pacemaker or ICD use. Patients with unexplained syncope, unstable angina, refractory chronic atrial tachyarrhythmias, uncorrected primary valvopathies, cardiac amyloidosis, pregnant women, low life expectancy (less than 6 months), systolic blood pressure > 160mmHg or < 85mmHg or diastolic blood pressure were excluded from the study. > 90mmHg. [7]

The study also took into account, in the primary analysis of the results, death from any cause and hospitalization from any cause and, secondarily, death from any cause, death from a cause directly related to cardiac function and hospitalizations due to cardiac causes. Ultimately, COMPANION concluded that, in patients with advanced heart failure and wide QRS, CRT reduces the risk of death from any cause or hospitalization and, when combined with ICD, significantly reduces mortality. It is noteworthy that the study was sponsored by Guidant. [7]

In 2005, the CARE-HF was published in The New England Journal of Medicine, being considered, until today, one of the studies with more consistent data aimed at specifically evaluating myocardial resynchronization therapy, showing benefits both in relation to morbidity and mortality, thus placing resynchronization as a safe therapy in patients with indications. The main objective of this study was to evaluate the impacts of myocardial resynchronization on the morbidity and mortality of patients with heart failure. CARE-FH was a randomized, multicenter, prospective, controlled clinical trial, and all analyzes were performed by intention to treat. A total of 813 patients were selected and divided into two groups: clinical treatment (404 patients) and CRT (409 patients). To be included in the study, patients must be over 18 years old and diagnosed with HF at least six months ago, with NYHA functional class III or IV, ejection fraction <35%, QRS complex >120ms and ventricular diastolic diameter left>30mm. Patients with pacemaker or ICD indication, HF requiring continuous intravenous medication and patients with a cardiovascular event in the last six weeks were excluded from the study. The possibility of improving the functional class and increasing the survival of patients with end-stage HF with cardiac resynchronization had already been suggested in the COMPANION study, but it is worth mentioning that in that study there was an association with implantable cardioverter defibrillator. Thus, it is evident that CARE-HF had a unique study design and, therefore, its results represent an important gain for evidence-based medical practice. [8]

In view of the advances in the use of CRT, in November 2004, the MIRACLE ICD II study was published in Circulation, characterized as the first randomized clinical trial that proposed to assess whether CRT is capable of limiting the progression of heart failure and providing improvement in quality of life in patients with NYHA class II HF. The study recruited 186 patients and followed them for a period of six months. The following inclusion criteria were established: age greater than or equal to 18 years, HF NYHA II, ejection fraction <35%, QRS complex >130ms, left ventricular end-diastolic diameter greater than 55 mm and formal indication for ICD implantation. [9]

After four years, the Journal of the American College of Cardiology published, in December 2008, the CR study in patients with asymptomatic or mildly symptomatic HF (REVERSE), addressing a different perspective. As with the MIRACLE ICD II, the target of the study were patients with heart failure with minor symptoms (NYHA I or II). The sample had 610 patients, which were divided: 419 with active desynchronization therapy and 191 with inactive desynchronization therapy.

It was a randomized, prospective, multicenter clinical trial and all analyzes were by intention to treat. Inclusion criteria were: HF NYHA I or II for at least 03 months, sinus rhythm, QRS complex >120ms, ejection fraction <40% and all patients must be receiving optimized clinical treatment with ACE inhibitors or ARBs and beta-blockers for at least three months. The patients were followed up for one year and it could be observed that in patients with mildly symptomatic heart failure, the use of CRT does not reduce the proportion of patients who worsen, but it was noted that it delayed the time until the first hospitalization for heart failure. Significant reverse remodeling of the left ventricle was also observed. However, overall, the study showed no difference in mortality rates. Despite showing some benefits, the role of CRT in patients with mildly symptomatic heart failure remains unclear. [10]

In the same line of research as the MIRACLE IDC II and REVERSE studies, in which the focus was to assess whether functional class I or II patients would benefit from the use of cardiac resynchronization therapy, the MADIT CRT study was published in September 2009, by The New England Journal of Medicine, with 1820 patients divided into two groups: the first, with 1089 patients who used CRT+ICD, and the second with 731 others, who used only ICD. Such patients were followed up for a period of 2.4 years. The MADIT CRT evaluated the benefit of CRT+ICD in relation to the ICD, only in patients with severe HF (ejection fraction <30%), oligosymptomatic and with QRS complex prolongation. Based on the analysis of primary and secondary outcomes, the study showed that the group that used CRT + ICD had lower all-cause HF mortality rates, with a Number Need to Treat (NNT) of 12. the study was able to clarify the questions raised by CARE-HF and expanded the indication of CRT for patients with functional class I and II. [11]

The following year, at MADIT-CRT, The New England Journal of Medicine published the Cardiac resynchronization study for patients with mild to moderate heart failure-RAFT, which evaluated whether the addition of CRT to the ICD and optimized clinical treatment reduces death and hospitalization for HF. when compared to ICD and optimized clinical treatment only in patients with NYHA II and III HF, left ventricular dysfunction and widened QRS complex. The RAFT was a randomized, multicenter, controlled clinical trial with all intention-to-treat analyzes. Those included in the study must have HF NYHA II or III, be on optimized clinical treatment, LVEF<30%, QRS>120ms, and be planning ICD implantation for primary or secondary prevention. 1798 patients were recruited and followed up for 40 months. The results of the RAFT study point to CRT implants for patients with a lower functional class, therefore with less advanced disease, however, irreversible. In this context, the study concluded that, in patients with NYHA III or IV HF, wide QRS complex and left ventricular systolic dysfunction, CRT associated with the ICD significantly reduced the rates of death and hospitalization for heart failure. However, it is worth mentioning a greater number of adverse effects. [12]

With the aim of expanding the indications for the use of CRT, some studies began to analyze the use of CRT in patients with different criteria from previous studies. In 2007, The New England Journal of Medicine published the RethinQ study, whose main objective was to evaluate the response to CRT in patients with HF with narrow QRS. It was a randomized, prospective, multicenter, controlled clinical trial, with analyzes performed by intention to treat. 172 patients were followed up for a period of six months, and had to meet the following

criteria: heart failure (ischemic or non-ischemic), ventricular ejection fraction <35%, NYHA functional class III using optimized drug therapy, QRS complex < 130ms and electromechanical dyssynchrony evaluated by echocardiography. [13]

QRS complex duration has been used as a marker of electromechanical dyssynchrony, but so far it has not been possible to demonstrate its ability to predict clinical response. The analyzed outcomes were: an increase of at least 1ml/kg/min in peak oxygen consumption in the ergospirometric test after six months and changes in the quality of life, NYHA functional class and ejection fraction questionnaires. The study concluded that there was no benefit from the use of CRT in patients with a QRS complex <130ms. [13]

Considering all the scientific evidence about the effectiveness of CRT when properly indicated, studies were developed that analyzed which variables are predictors of good response to CRT in general, grouping patients with a broader clinical profile and with a greater number of variables analyzed. thus allowing for a more individualized selection of CRT candidates. In this context, in May 2008, the study Predictors of Response to Cardiac Resynchronization Therapy (PROSPECT) was published in the journal Circulation, which aimed to evaluate pre-defined parameters for echocardiographic evaluation of CRT. It was a multicenter, observational, non-randomized study that evaluated 12 variables among two-dimensional echocardiogram measurements, M-mode and tissue Doppler in patients undergoing CRT. [14]

The echocardiographic analysis was compared with clinical response and reduction in left ventricular end-systolic volume. The study does not detail how the sample calculation was performed. A total of 462 patients were selected and followed up for six months. They must have ventricular ejection fraction <35%, HF NYHA functional class III or IV, therapy with Angiotensin Converting Enzyme (ACE) inhibitors or Angiotensin Receptor Blockers (ARB) and optimized beta-blocker, QRS complex >130ms. The study analyzed, as favorable outcomes, the CRT response, the functional improvement in the ejection fraction and the reduction of more than 15% in the end systolic volume of the left ventricle. Of the 426 patients, 69% showed improvement in functional class, 15% showed no changes and the rest of the patients did not respond to treatment. This was the first multicenter study that showed sufficient sensitivity and specificity to allow a clinical decision based on the echocardiogram. The evaluation of dyssynchrony using electrocardiographic criteria still does not have sufficient predictive value to anticipate the response to treatment with cardiac resynchronization. However, such data can be used as selection criteria for resynchronizer implantation. [14]

Another study with this perspective, to evaluate the therapeutic response to CRT and prognostic factors, was the Efficacy of low-dose Dobutamine stress-echo cardiography to predict cardiac resynchronization therapy response (LODO-CRT), being a multicenter, prospective and observational study, designed to determine whether Left Ventricular Contractile Reserve (LVSR) is able to predict the clinical and echocardiographic response to CRT. Left contractile reserve was defined as an increase in LVEF >5% on a dobutamine stress test. Clinical response was defined as the absence of major cardiovascular events and echocardiographic response as a reduction in LV end-systolic volume >10%. A total of 221 patients with HF class III-IV, QRS ≥ 120ms, left ventricular dilation and LVEF ≤ 35% were followed for 15 ± 5 months. Patients were randomized according to the presence (n=177) and absence (n=44) of LVCR. The

study demonstrated that the percentage of clinical responders was 88% and 75% in the groups with and without CEVR, respectively. The analysis of primary and secondary endpoints showed a significant improvement in cardiac survival and reduction in hospitalization rates in the CEVR group. The proportion of echocardiographic responders was 87% and 42% in the groups with and without ECVR respectively. The concomitant presence of clinical and echocardiographic response showed sensitivity of 83% and specificity of 99%. Thus, the LODO-CRT concluded that the presence of LVCR can be considered a variable in predicting the clinical and echocardiographic response to CRT. [15]

FINAL CONSIDERATIONS

As mentioned at the beginning, CRT is an invasive therapeutic procedure that aims to correct electromechanical dysfunctions through artificial cardiac stimulation in patients with HF. This therapeutic modality represents a breakthrough in the arsenal for the treatment of HF and emerges as a therapeutic variant, saving lives for patients who are refractory to optimized clinical treatment.

With the consolidation of CRT, questions arise about its benefits in patients with functional class I and II. Thus, several studies were developed and, based on the results obtained, the use of CRT was gradually expanded. It must be noted that such expansion is due, in part, to a period in which pharmacological therapies practically stagnated. In the current context, in addition to the growth of new technologies that increasingly improve CRT, the emergence of new drugs with the potential to reduce mortality and morbidity is also notable, as shown by the PARADIGM-HF study using sacubitril-valsartan. Thus, the prospects are that both therapies will advance in the coming years and that treatment will increasingly become individualized.

From the analysis of the studies presented in this literature review, it is possible to conclude that the effectiveness of CRT is proven by the finding of clinical benefits shown in several studies related to the improvement of symptoms and quality of life, reduction of hospitalizations and increased survival. In most of the study that was discussed, a favorable result was obtained, the selected patients had symptomatic HF, despite optimized drug therapy, and with severe systolic dysfunction (LVEF < 30% or < 35%) and widened QRS. At first, the benefit was only proven for patients with functional class III and IV, and later, some benefits were also observed in NYHA I and II patients. However, it is worth mentioning that, in patients with a narrow QRS complex, no favorable outcome was observed with the use of CRT. Currently, studies have been developed with the intention of evaluating the expansion of indications in the use of CRT and better defining which clinical variables are most correlated with better outcomes. The prospect is that resynchronization therapies will increasingly become more accessible and with increasingly individualized indications.

In view of the experience with the patient mentioned in the Introduction, which aroused interest in understanding more about the subject, this review, through the results, impacts, repercussions and perspectives of this revolutionary treatment, confirms all expectations, and which allows us to say that the application of CRT, in the indicated cases, provides well-being and quality of life, enhancing patients' self-esteem, comfort and hope for better living conditions.

CONFLICT OF INTEREST

There is no conflict of interest.

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