

# Impact of serum troponin I in the long-term evolution of patients submitted to resynchronization with biventricular stimulation: follow-up of up to 59 months

*Impacto da troponina I cardíaca sérica na evolução tardia de pacientes submetidos a ressincronização com estimulação biventricular: seguimento de até 59 meses*

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## Abstract

**Objective:** To analyze the evolution and prognostic influence of the cardiac troponin I serum levels in patients with congestive heart failure (CHF) submitted to interventricular resynchronization (VR) over a 59-month follow-up period.

**Method:** Thirty-three patients with idiopathic dilated cardiomyopathy in NYHA functional classes III and IV were submitted to VR. The pre- and post-operative quality of life (QoL) was analyzed using the Minnesota Code and the left ventricle function was assessed by echocardiography. The cardiac troponin I levels were compared in 23 patients utilizing the Fisher exact test to analyze the correlation with death and the Kaplan-Meier curve was used to analyze the survival rate.

**Results:** The QoL was better after VR with a median of 73 points in the pre-operative period and 36 in the postoperative

period (p-value < 0.0001). The left ventricle diastolic diameter (LVDD) reduced from 65 mm in the preoperative period to 60 mm in the postoperative period (p-value = 0.0014) with an increase in the ejection fraction from 37 to 47% (p-value = 0.0004). In 15 patients with normal cardiac troponin I levels, no deaths occurred and of the 8 patients with high levels, six died (p-value = 0.0003). The actuarial survival curve showed a survival rate of  $47.1 \pm 13.3\%$  at the end of 59 months.

**Conclusion:** VR in patients with CHF improves the QoL and echocardiographic parameters (ejection fraction and LVDD). It is a good alternative for functional class III and IV patients. The serum levels of cardiac troponin I are predictors of risk to life.

**Descriptors:** Troponin. Arrhythmia. Heart failure, congestive. Pacemaker, artificial.

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### Resumo

**Objetivo:** Analisar evolução e a influência prognóstica dos níveis séricos da troponina I cardíaca nos pacientes com insuficiência cardíaca congestiva (ICC) submetidos a ressincronização interventricular (RV), com seguimento de até 59 meses.

**Método:** Foram analisados 33 pacientes com miocardiopatia dilatada idiopática em classe funcional III/IV da NYHA, submetidos a RV. A qualidade de vida (QV) foi analisada pré e pós-operatoriamente com o *Minnesota Code* e a função ventricular através da ecocardiografia. Os níveis séricos da troponina I foram dosados em 23 pacientes, utilizando o teste exato de Fischer para avaliar sua relação com o evento óbito, e a curva de Kaplan-Meier para análise da taxa de sobrevivência.

**Resultados:** A QV foi significativamente melhor após a RV,

com mediana de 73 pontos, no pré e 36, no pós ( $p < 0,0001$ ). O diâmetro diastólico do VE (DDVE) apresentou redução de 65mm, no pré para 60mm, no pós ( $p = 0,0014$ ), com aumento da fração de ejeção (FEVE) de 37 para 47% ( $p = 0,0004$ ). Nos 15 pacientes com valores normais de troponina, não ocorreram óbitos e dos oito pacientes com valores elevados, seis faleceram ( $p = 0,0003$ ). A curva atuarial de livres de óbitos mostrou uma taxa de sobrevivência de  $47,1 \pm 13,3\%$ , ao final de 59 meses.

**Conclusões:** A RV em pacientes com ICC melhora a QV e os parâmetros ecocardiográficos. Constitui uma boa alternativa para os pacientes em classe funcional III/IV NYHA. Os níveis séricos elevados da troponina I cardíaca foram preditores de risco para óbito.

**Descritores:** Troponina. Arritmia. Insuficiência cardíaca congestiva. Marca-passo artificial.

## INTRODUCTION

Heart failure (HF) is characterized by structural, biological and functional changes in the cardiocirculatory system and not only the involvement of the contraction of the myocardial fibers, but also the dynamical and progressive profile of the syndrome should be taken into consideration [1]. In the transition of asymptomatic HF to symptomatic HF, remodeling of the myocardium, collagen and of the vascular structures occurs. The activation of the sympathetic nervous, rennin-angiotensin and other neuro-humoral systems is highly relevant in myocardial remodeling. The progression of HF results in a deterioration of the quality of life and increases the risk of death, with mortality rates being reported of between 40% and 60% in patients with III and IV functional classes (NYHA) one year after the appearance of the symptoms [2-4]. Medicinal therapies offer good results in the improvement of functional class. The use of beta-blockers, in particular carvedilol, which act against myocardial remodeling by an anti-noradrenaline action, causes a reduction of approximately 30% in mortality. The spiro lactone reduces myocardial fibrosis, inhibiting aldosterone and the angiotensin conversion enzyme (ACE) inhibitors and the angiotensin I receptor blockers (AT1) antagonizing myocardial remodeling and apoptosis [5,6]. In the evolution of HF electrical changes occur, which contribute to the hemodynamical instability with the left branch blockade (LBB) being the main alteration in the infranodal electrical conduction, causing asynchronous interventricular contractions. This myocardial dyssynchronism provokes disorders in the systolic functioning, in closing the aortic valve and, specifically, in delaying the opening of the mitral valvar, thereby reducing

the time of left ventricular filling [7]. Bleeker et al. [8] evaluated the relationship between the duration of the QRS and left myocardial dyssynchrony in patients with congestive heart failure (CHF), concluding that patients with a QRS  $< 120$  ms or  $= 120$  ms presented 27 % and 70% of dyssynchronism, respectively.

The use of multiple site pacing for hemodynamical support, introduced in 1994, is giving clinical benefits with significant reductions in the number of days in hospital due to HF, improvement in the 6-minute exercise test, in the quality of life and in the functional class [9]. Based on these results, biventricular resynchronization has become an option in the treatment of HF, obtaining a faster depolarization with the stimulation of different strategic sites and consequently, recovery of the interventricular synchronism.

In HF, changes of the intracellular morphology determine discontinuous areas of myonecrosis and fibrous sites. The left ventricular dysfunction and the increase in mortality during the evolution of HF are associated with high cardiac troponin serum levels. This increase comes from myofibrillar degradation, which determines the potential of specificity and sensitivity of cardiac troponin I as a serum biomarker in severe congestive heart failure (CHF) [10]. Cardiac troponin I is a biomarker of myocardial lesions, as its location is in the myocardial contractility complex in the sarcomere [11].

The objective of this study is to analyze the quality of life using the Minnesota Code, the pattern of echocardiographic parameters, the survival rate (Kaplan-Meier curve) and the prognostic influence of cardiac troponin I serum levels, in patients with congestive heart failure submitted to interventricular resynchronization, with a follow-up of up to 59 months.

**METHOD**

The study analysed 20 male (60.6%) and 13 female patients with idiopathic dilated heart disease in NYHA functional classes III and IV. The ages ranged from 41 to 84 years (mean  $65 \pm 30.4$  years; median 64 years). All presented with advanced heart failure with dyspnea and fatigue on small and moderate efforts. They were under optimized medicinal therapy for CHF using digital, diuretic agents, ACE and AT1 inhibitors, beta-blockers and antiarrhythmic agents to control the heart frequency and ectopic focus in some patients. Complementary diagnostic examinations were performed including echocardiogram, Holter, a hemodynamic study of the heart and isotopic ventriculography.

Ventricular resynchronization was achieved with the endovenous implantation of right atrial and ventricular electrodes (left cephalic vein), and with the implantation of a left ventricle electrode in the epimyocardium, by left anterior minithoracotomy. The left ventricular dyssynchronism with QRS greater than 120 ms were present in 70% of the patients, of whom the majority suffered from LBB. All presented in sinusal rhythm.

The quality of life was analysed using the Minnesota Code questionnaire, which determines the health conditions and an echocardiogram was used to evaluate the left ventricular function in the pre- and post-procedure periods. The echocardiographic parameters utilized were the left ventricular ejection fraction (LVEF) evaluated using the Simpson method and the left ventricle diastolic diameter (LVDD). Measurement of the cardiac troponin I serum level was performed after the procedure using the chemiluminescence technique with  $< 0.1$  ng/mL considered normal. The statistical methods utilized were the Mann-Whitney test to compare parameters between the pre- and postoperative periods, both for the Minnesota Code and the echocardiographic measurements. The Fischer exact test was used to evaluate event-related deaths and increases in the cardiac troponin I serum levels and the Kaplan-Meier curve was employed to evaluate the survival rate. The present study was approved by the Ethics Research Commission of the Domingo Braille Institute.

**RESULTS**

The follow-up after the implantation of the biventricular resynchronizer varied from 1 to 59 months (mean  $24 \pm 14.5$  months; median = 24 months). The quality of life according to the Minnesota Code was significantly better after implantation, with a median of 73 points in the preoperative period and 36 points in the last evaluation ( $p < 0.0001$ ; Figure 1).

The left ventricle diastolic diameter reduced from 65 mm to 60 mm in the post-implantation period ( $p = 0.0014$ ) and the ejection fraction increased from 37% to 47% ( $p = 0.0004$  - Figure 2). There was a clear correlation between deaths and cardiac troponin I serum levels above normal values. From the thirty-three patients studied, the troponin I was measured in 23 patients after the procedure. Of these, a group of eight patients presented troponin I above normal levels, six of whom died. In the fifteen patients with normal troponin levels no deaths occurred during of follow-up period ( $p = 0.0003$ ). The actuarial survival curve of patients submitted to the implantation of biventricular resynchronizer demonstrated a survival rate at the end of 59 months of  $47.1 \pm 13.3\%$  (Figure 3).

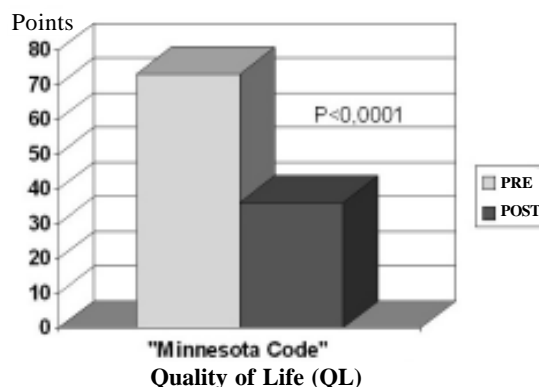


Fig. 1 - Pattern of the evaluation of the quality of life using the Minnesota Code, in patients with advanced heart failure submitted to ventricular resynchronizer implantation.

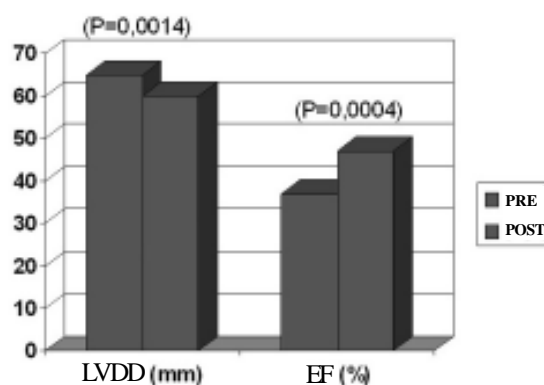


Fig. 2 - Pattern of the left ventricular diastolic diameter (LVDD) and the Left ventricular ejection fraction (LVEF), in patients with advanced heart failure submitted to ventricular resynchronizer implantation.

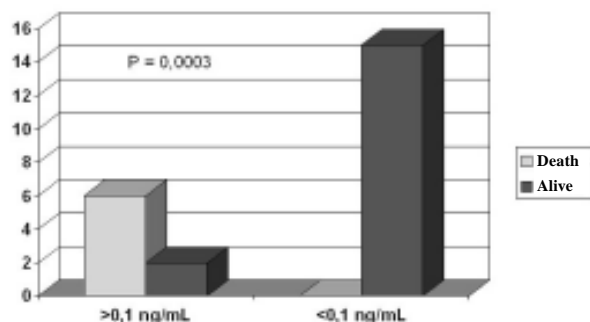


Fig. 3 - Number of deaths of patients with advanced heart failure submitted to ventricular resynchronizer implantation, compared to the cardiac troponin I serum levels in the initial evaluation.

#### COMMENTS

In heart failure, the activation systems of ventricular function are changed, cardiomyofibrils undergo changes in the micro-organelles and the length of the QRS tends to increase [10]. In the arsenal of therapies for patients with congestive heart failure with optimized clinical treatment, resynchronizer implantation with biventricular pacing has proved to be a safe and effective alternative. Resynchronization of the ventricles proposes a simultaneous contraction of the ventricles and reduction of the atrioventricular delay, thereby helping in the medicinal treatment of left ventricular dysfunction.

The etiological cause seems not to interfere in the results. In the current study, chagasic and ischemic patients were excluded, although patients with obstructive coronary disease do not respond well to resynchronization treatment [12]. Randomized studies with the biventricular resynchronizer demonstrated an improvement in the left ventricle ejection fraction and diastolic diameter and also an improvement in the six-minute exercise test, in the functional class and in the quality of life. However, the mortality rate did not reduce [9,13,14].

The PATH-CHF study, with a limited number of patients, demonstrated an improvement in physical capacity however, the same performance was not seen in high capacity physical exercise testing, when comparing univentricular and biventricular stimuli in follow-ups of up to 12 months [15]. The MIRACLE and MUSTIC studies also demonstrated an improvement in the quality of life, in the LVEF and number of hospitalizations [13]. However, from 20% to 30% of the patients submitted to resynchronizer implantation responded little to the functional improvement. The lengthened QRS does not

act as a good predictor of the presence of dyssynchrony. Alternatives are appearing to better identify and stratify left ventricle dyssynchrony and the responsive myocardium for the use of the resynchronizer [14].

In this evaluation, it was possible to demonstrate improvements in the LVEF, the LVDD and the quality of life, but the lack of a good hemodynamic response in some patients also justifies attempts to identify patients more responsive to the resynchronizer. Missov et al. [10] evidenced the importance of the cardiac troponin I in the evolution of ventricular dysfunction in patients with CHF, in consequence of cellular degeneration and multiple sites of myonecrosis. Troponins I and T, as heart enzymes with high specificity for myocardial lesions, are factors that contribute to the prognostic evaluation of patients submitted to heart resynchronizer implantation [11].

#### CONCLUSIONS

Cardiac resynchronization in patients with dilated HF improves the echocardiographic parameters (LVEF and LVDD) and the quality of life according to the Minnesota Code. This is an effective and safe alternative for patients in functional classes III and IV (NYHA) under optimized medicinal treatment with a survival rate at the end of 59 months of  $47.1 \pm 13.3\%$ . It was possible to demonstrate that high cardiac troponin I serum levels may be considered risk predictors for death.

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