Upgrade is independently associated with short-term mortality after cardiac resynchronization therapy.

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Title: Upgrade is independently associated with short-term mortality after cardiac resynchronization therapy.

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ABSTRACT

Background: Cardiac resynchronization therapy (CRT) improves outcomes in heart failure (HF) patients with left bundle branch block (LBBB). However, the benefits of CRT in patients with previous pacing are still uncertain. The aim is to compare the short-term mortality between upgrade and De novo-CRT implantation.

Methods: Prospective cohort study that included HF patients indicated for CRT with left ventricular ejection fraction (LVEF) of less than 35%. Data were collected to investigate mortality predictors after 1 year. The overall survival was calculated by the Kaplan-Meier method and multivariate analysis using Cox's regression model was performed. A value of $p<0.05$ was considered as significant.

Results: 93 patients were evaluated with a mean follow-up of 1.0±0.6year. Of these, 22 (23.7%) were upgraded from right ventricular pacing. Chagas Disease (CD) was the most prevalent cause of HF with 29 (31.2%) individuals. LVEF at 6 months increased after CRT: 24,0%±7.8 to 30.3%±11.5, p=0.007, and there was no difference between upgraded patients and De novo CRT, p=0.26. Overall mortality at 1-year was 30.1% (28 patients). In univariate analysis, CD and upgraded therapy were associated with high mortality, HR: 3.9, CI 1.8-8.4, p=0.001 and HR: 4.7, CI: 2.2-9.9, p<0.001, respectively. In the multivariate model,

only upgraded therapy remained independently associated with the outcome, adjusted HR: 2.9, CI 1.2-7.2, p=0.02.

Conclusion: In this specific HF population, with a high prevalence of chagas cardiomyopathy, upgraded therapy was independently associated with worsened 1-year survival after CRT implantation.

Key words: implantable cardioverter-defibrillator, resynchronization therapy, heart failure, left bundle branch block, Chagas's cardiomyopathy.

Introduction

Randomized controlled trials supports the clinical efficacy and safety of cardiac resynchronization therapy (CRT) in patients with moderate or severe heart failure and ventricular dyssynchrony.[1-2]Guidelines from international cardiology societies provide strong recommendations for CRT specially in symptomatic patients with left bundle branch block (LBBB) and a QRS duration >150ms.[3] However, some questions remain about its effectiveness in specific etiologies, such as Chagas Cardiomyopathy (CC), since most of the published trials about on the subject did not include a significant number of this population.

Upgrade for a CRT from a conventional pacemaker have become increasingly common in HF patients, since right ventricular pacing may aggravate left ventricular function.[4] Despite this, there are still concerns about this practice, considering that the decision to proceed to upgrade is supported by small observational studies. Recent studies suggest that clinical response and survival are impaired in patients undergoing CRT upgrade compared to de novo implantations.[5-6]

Thus, the aim of this study is to compare the short-term mortality between upgrade and de Novo CRT implantation in a population with heart failure and clinical indication for this device, comparing its results between individuals with Chagas Cardiomyopathy and not.

Methods

Population

Prospective cohort study between May 2017 and September 2019. We included consecutive outpatients over 18 years, followed at the heart failure unit in a tertiary hospital in Bahia, Brazil. The indication for CRT was based on the following criteria: patients age over 18 years, under appropriate medical treatment, presenting NYHA II to IV with left ventricular ejection fraction (LVEF) less than 35% and a QRS duration > 150ms or 120–150ms with proven dyssynchrony by echocardiogram (??). Patients with previously implanted pacemakers or implantable cardioverter-defibrillators (ICD) who developed this criteria, with or without need for continuous ventricular pacing, were also considered for CRT (upgrade group).

Demographic, laboratory and echocardiographic data were collected at the time of the hospitalization for the procedure. All patients were hospitalized electively for the procedure and the New York Heart Association (NYHA) functional class was assessed at the time of the hospitalization. Left ventricular ejection fraction was measured on transthoracic echocardiograms using the Simpson's method at the time of the CRT implantation, and after 6 months. Chronic renal disease was defined as renal clearance, estimated using Cockroft and Gault's formula, <60mL/min/1.73m2. Atrial fibrillation was defined at the time of the procedure by baseline electrocardiogram. Chagas disease was confirmed by serology (ELISA and IFI).

Patients were excluded if they had a chronic systemic inflammatory disease, malignant neoplasia under treatment, who declined to give informed consent or who refused the procedure.

Follow-up and outcomes

Patients were followed through regular outpatient visits at the institution after hospital discharge. Echocardiogram was performed after 6 months of the procedure. Hospitalization for heart failure was assessed at follow-up. Super responders were considered patients with LVEF > 50% at 6-month. Those patients who did not return within 1 year after CRT implantation were contacted by telephone. The primary outcome was to

assess short-term mortality between upgrade and De novo-CRT implantation. Survival was assessed as the time from CRT implantation to all-cause mortality.

Ethics Committee

The local ethics committee approved the study, and all procedures were performed according to the Helsinki statement.

Statistical analysis

The Kolmogorov-Smirnov test was used to verify the normal distribution of continuous variables. Variables with normal distribution were described by means and standard deviations and compared by paired Student's t-test. For comparison of the mean LVEF after 6 months between the groups, the unpaired t test was performed. Non-parametric variables were described as medians and interquartile range and compared with the the Wilcoxon test. Categorical data were presented as the number of patients and percentage of the total sample and were compared by the Fisher's exact test. The overall survival was calculated by the Kaplan-Meier method and the log-rank test was used to compare the survival curves. A value of P <0.05 was considered as statistically significant. To identify the variables that are independently predictive of overall mortality, a subsequent stepwise multivariate analysis using Cox's regression model was performed, including variables that had a predictive value of P-value < 0.10 in the univariate analysis of overall survival (log-rank test). The Statistical Package for the Social Sciences (SPSS) version 20.0 was used for the analysis of all data.

Results

One hundred patients were evaluated for CRT implantation, seven of them were excluded due to a LVEF higher than 35% prior the procedure. Of the remaining 93 patients, Chagas cardiomyopathy was the most prevalent cause of HF with 29 (31.2%) individuals, followed by idiopathic dilated cardiomyopathy with 28 (30.1%) patients. There was no lost of follow-up for the main outcome, with a mean duration of 1,0 (±0.6) year.

Patients upgraded from a right ventricular pacing (upgrade group) were 22 (23.7%), of those, 4 (18.2%) had previously an implantable cardioverter-defibrillator. Baseline demographic characteristics of groups upgrade and *de novo* are in Table 1. Chagas cardiomyopathy was more prevalent in the upgraded patients, with 16 (72.7%) vs 13 (18.3%), p<0.001. Other demographic, clinical characteristics and medical treatment for heart failure with evidence-based medical therapies were similar in both groups.

Only 6 (6.5%) patients underwent CRT implantation with non-LBBB (induced or spontaneous), five of whom had Chagas disease and a right bundle branch block (RBBB). Among patients with CC, 13 (44.8%) had induced LBBB, 11 (37.9%) had spontaneous LBBB and 5 (17.2%) had a RBBB.

Echocardiographic measurements at baseline and 6 months of follow-up were available in 78 (83.9%) patients. Both groups had an improvement in LVEF after 6 months of implantation, 22.3% (± 7.1) to 27.1% (± 9.5), p < 0.001, for upgrade and 24.4% (± 7.6) to 31.1% (±11.9), p < 0.001, for De novo CRT, but there was no difference of ΔLVEF improvement between the two groups, p = 0.246. Four (4.3%) patients had echocardiographic criteria for super-responder after CRT, 3 (4.2%) in De novo CRT group and 1 (4.5%) in the upgrade group, p = 0.999. No patient underwent heart transplantation during the study period.

There were four in-hospital deaths, all of them directly associated with the procedure and all from the upgraded group. In the follow-up, overall mortality occurred in 28 (30.1%) patients, with more frequent death in upgraded group when compared to De novo CRT implantation, 14 (63.6%) vs 14 (19.7%), p < 0.001 (log rank), figure 1. In the univariate analysis, Chagas cardiomyopathy and upgraded therapy were associated with overall mortality at follow-up, HR: 3.9, CI: 1.8-8,4, p = 0.001 and RR: 4.7, CI: 2.2-9.9, p < 0.001, respectively. In the multivariate model including both variables, and combined therapy with CRT-D, only upgraded therapy remained independently associated with the outcome, adjusted HR: 2.9, CI: 1.2-7,1, p=0.019), Table 2.

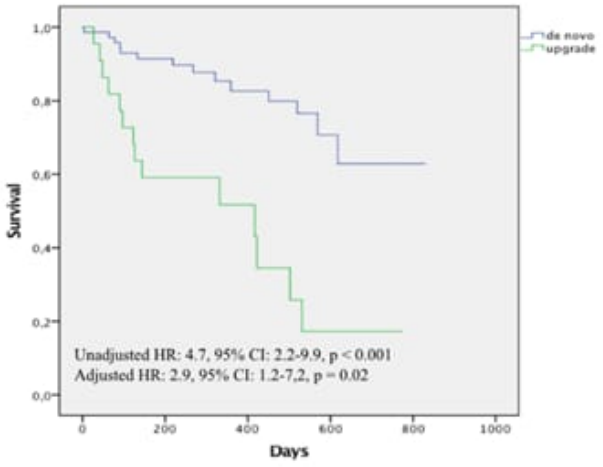

Figure 1: This is a caption

Discussion

In this prospective cohort of patients with heart failure and classic indication for CRT, with a high number of individuals with Chagas cardiomyopathy, upgraded therapy was independently associated with worsened 1-year survival after CRT implantation. Besides that, CC was also associated with worse prognosis in follow-up.

Patients submitted to the upgraded CRT implantation had similar clinical, echocardiographic and demographic characteristics when compared to the population of De novo CRT, only differing with a higher prevalence of Chagas cardiomyopathy. We observed a high prevalence of patients with advanced HF, with a mean LVEF below 25% and most patients classified as NYHA III-IV. There was no loss of follow-up and use of evidence-based medical therapies was higher than most previous CRT-trials. [7-8] Furthermore, the indication for CRT was consistent with guideline-based recommendations, with almost all patients presenting with LBBB (induced or spontaneous) and QRS> 150ms. Unlike previous studies comparing De novo CRT vs upgraded, we found no difference regarding the prevalence of atrial fibrillation or QRS duration between both groups. [5,9]

In general, CRT was effective in improving systolic performance with a significant increase in LVEF. This left ventricular reverse remodeling occurred consistently in both groups, and it is in accordance with a recently published meta-analysis that demonstrated similar rates of improvement in LVEF in patients undergoing upgraded and *de novo* -CRT. [10]

We observed a high overall mortality in 1-year follow-up of 30.1%, mainly in the upgraded-CRT group. In univariate analysis, Chagas disease and upgraded-CRT were directly associated with overall mortality in 1-year. The principal find of our study was that in the multivariate model, upgraded therapy was the only variable associated with the primary outcome. This result, and the excessive mortality-rate in the upgraded group, is consistent with the study of Vamos M et al, that followed 552 CRT implantations, including 177 upgrade procedures, and found a 1.65-fold increased mortality.[5] Similarly, the cohort of Beca B et al, found a long-term mortality rate 2.86-fold increased.[11] On the other hand, this data differs from previously mentioned meta-analysis, and the European CRT survey, that demonstrated that CRT upgrade is associated with similar risk for all-cause mortality compared to De novo resynchronization therapy.[9]

Some factors may justify these findings, firstly, it has been suggested that CRT upgrade procedures are associated with increased peri-procedural complications. In fact, all in-hospital deaths of our study occurred in the upgraded-CRT group and was directly related to the procedure. However, our sample size was not

sufficient to test this hypothesis. Data comparing the rates of complications following CRT upgrade versus *de novo* CRT are limited and inconsistent. In a large European CRT Survey of 11088 patients, and 2396 (23.2%) upgrade procedures, overall peri-procedural complication rates were similar between upgraded-CRT and De novo CRT.[12] In contrast, Cheung JW et al, using the United States National database, identified a significantly higher rate of complications in CRT upgrade patients compared to de novo CRT patients with a two-fold increased risk of in-hospital mortality.[6]

Another hypothesis is that patients in the upgrade group had more advanced heart disease and more comorbidities. In our series, upgraded patients had a trend to be older, with slightly lower left ventricular ejection fraction and higher prevalence of NYHA III and IV, despite the lack of statistical significance when they were compered to De novo CRT group. Perhaps, the indication for biventricular pacing was too late in this group and was associated to a worse prognosis.

Finally, the presence of Chagas cardiomyopathy may interfere in patient survival. CC has more severe heart dysfunction and worse clinical management, mainly due to its etiopathogenesis and worse ventricular remodelling, with a higher incidence of death from advanced heart failure and arrhythmic causes.[13-14] Particularly in patients undergoing CRT, it has been consistently demonstrated that Chagas cardiomyopathy has a worse prognosis when compared to other dilated cardiomyopathies. Martinelli et al showed that Chagas disease had a two-fold higher risk of death in one-year compared to the others dilated cardiomyopathy.[15] Simirlaly, Passos, et al also demonstrated a worse prognosis in combined events in patients with Chagas cardiomyopathy after CRT.[16]

It is important to emphasize that, since intrinsic LBBB in Chagas heart disease is uncommon, and it is considered an arrhythmogenic cardiomyopathy characterized by a wide variety of abnormalities of the conduction, it is expected a higher incidence of upgraded-CRT implantation in this patients. In fact, in the cohort presented by Martinelli et al, there was a 73.9% incidence of induced-LBBB in Chagas' disease patients undergoing CRT.[15] In our study, 72.7% of patients undergoing upgraded-CRT implantation had Chagas cardiomyopathy.

This is the first study that analysis the impact of the upgraded-CRT on mortality in a population where Chagas disease is a prevalent cause of cardiomyopathy. In fact, it is known by previous publications that CC was directly associated with an increase in short-term mortality after CRT implantation. However, after multivariate analysis adjusted for potential confounders in our analysis, it is suggested that this worse prognosis may be due to the higher incidence of upgraded-CRT. Studies with larger cohorts of patients with Chagas cardiomyopathy are necessary to confirm this hypothesis. Until then, considering the current scientific evidence, patients with HF secondary to Chagas disease and previous ventricular pacing, must have the indication for the upgrade procedure evaluated with great caution.

This study has some limitations. We emphasize the unicentric design of the study, which may impact in its external validity. Additionally, it is a non-randomized study that generates hypothesis and is exposed to confounding bias. Finally, the limited sample size makes the study vulnerable to type 1 error.

Conclusion

In this heart failure cohort of patients with high prevalence of Chagas disease cardiomyopathy, survival was less-favorable in patients undergoing CRT upgrade compared to *de novo* implantations. Until further evidence is available, this result should be taken into account when evaluating upgrade therapy in Chagas disease patients with previous ventricular pacing.

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Conflicts of Interest

None declared

References:

1. Cleland JG, Abraham WT, Linde C, Gold MR, Young JB, Claude Daubert J, et al. An individual patient meta-analysis of five randomized trials assessing the effects of cardiac resynchronization therapy on morbidity and mortality in patients with symptomatic heart failure. Eur Heart J. 2013; 34(46):3547-56.

2. Zareba W, Klein H, Cygankiewicz I, Hall WJ, McNitt S, Brown M, et al. Effectiveness of cardiac resynchronization therapy by QRS morphology in the multicenter automatic defibrillator implantation trial-cardiac resynchronization therapy (MADIT-CRT). Circulation. 2011; 123(10):1061-72.

3. Normand C, Linde C, Singh J, Dickstein K. Indications for Cardiac Resynchronization Therapy: A Comparison of the Major International Guidelines. JACC Hear Fail. 2018; 6(4):308-16.

4. Curtis AB, Worley SJ, Adamson PB, Chung ES, Niazi I, Sherfesee L, et al. Biventricular Pacing for Atrioventricular Block and Systolic Dysfunction. N Engl J Med. 2013; 368(17):1585-93.

5. Vamos M, Erath JW, Bari Z, Vagany D, Linzbach SP, Burmistrava T, et al. Effects of upgrade versus de novo cardiac resynchronization therapy on clinical response and long-term survival: Results from a multicenter study. Circ Arrhythmia Electrophysiol. 2017; 10(2):e004471.

6. Cheung JW, Ip JE, Markowitz SM, Liu CF, Thomas G, Feldman DN, et al. Trends and outcomes of cardiac resynchronization therapy upgrade procedures: A comparative analysis using a United States National Database 2003–2013. Hear Rhythm. 2017; 14(7):1043-50.

7. St. John Sutton MG, Plappert T, Abraham WT, Smith AL, DeLurgio DB, Leon AR, et al. Effect of cardiac resynchronization therapy on left ventricular size and function in chronic heart failure. Circulation. 2003; 107(15):1985-90.

8. Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, et al. Cardiac-Resynchronization Therapy for the Prevention of Heart-Failure Events. N Engl J Med. 2009; 361(14):1329-38.

9. Bogale N, Witte K, Priori S, Cleland J, Auricchio A, Gadler F, et al. The European Cardiac Resynchronization Therapy Survey: Comparison of outcomes between de novo cardiac resynchronization therapy implantations and upgrades. European Journal of Heart Failure. 2011; 13(9):974-83.

10. Kosztin A, Vamos M, Aradi D, Schwertner WR, Kovacs A, Nagy KV, et al. De novo implantation vs. upgrade cardiac resynchronization therapy: a systematic review and meta-analysis. Heart Failure Reviews. 2018; 23(1):15-26.

11. Beca B, Sapp JL, Gardner MJ, Gray C, AbdelWahab A, MacIntyre C, et al. Mortality and Heart Failure After Upgrade to Cardiac Resynchronization Therapy. CJC Open. 2019; 1(2):93-9.

12. Linde CM, Normand C, Bogale N, Auricchio A, Sterlinski M, Marinskis G, et al. Upgrades from a previous device compared to de novo cardiac resynchronization therapy in the European Society of Cardiology CRT Survey II. Eur J Heart Fail. 2018; 20(10):1457-68.

13. Mady C, Cardoso RHA, Pereira Barretto AC, Da Luz PL, Bellotti G, Pileggi F. Survival and predictors of survival in patients with congestive heart failure due to Chagas' cardiomyopathy. Circulation. 1994; 90(6):3098-102.

14. Oliveira-Filho J, Viana LC, Vieira-De-Melo RM, Faiçal F, Torreão JA, Villar FAGA, et al. Chagas disease is an independent risk factor for stroke: Baseline characteristics of a Chagas disease cohort. Stroke. 2005; 36(9):2015-7.

15. Martinelli Filho M, Peixoto GDL, De Siqueira SF, Martins SAM, Nishioka SAD óri., Pedrosa AAA, et al. A cohort study of cardiac resynchronization therapy in patients with chronic Chagas cardiomyopathy. Europace. 2018; 20(11):1813-8.

16. Passos LCS, Melo RMV de, Lira YM, Oliveira NFC de, Trindade T, Carvalho W, et al. Chagas disease is associated with a poor outcome at 1-year follow-up after cardiac resynchronization therapy. Rev Assoc Med Bras. 2019; 65(11):1391-6.

Figure Legends

Figure 1 - Kaplan–Meier estimates of survival by implantation type. CI indicates confidence interval; and HR, hazard ratio.

Tables

Table 1 – Demographic data and baseline clinical characteristics

	Upgrade group n=22	*de Novo* **group n=71**	**P**
Heart failure etiology			
Chagas, n (%)	16 (72.7%)	13 (18.3%)	<0.001*
Idiopathic, n (%)	1 (4.5%)	27 (38.0%)	0.003*
Ischemic, n (%)	1 (4.5%)	14 (19.7%)	0.109*
Age, years, mean (±SD)	62.4 (±13.8)	56.6 (±11.4)	0.080 +
Male gender, n (%)	15 (68.2%)	36 (50.7%)	0.220*
LVEF, mean (±SD)	22.3 (±7.1)	24.4 (±7.6)	0.249+
NYHA class III or IV, n (%)	19 (86.4%)	57 (80.3%)	0.754*
Atrial fibrillation, n (%)	5 (22.7%)	15 (21.1%)	0.999*
QRS > 150ms, n (%)	21 (95.5%)	64 (90.1%)	0.675*
QRS duration, mean (±SD)	158.2 (±14.7)	160.1 (±22.5)	0.636+
non-LBBB, n (%)	1 (4.5%)	5 (7.0%)	0.999*
Myocardial infarction, n (%)	2 (9.1%)	10 (14.1%)	0.725*
Stroke, n (%)	3 (13.6%)	4 (5.6%)	0.350*
Hemoglobin, g/dL median (IQ)	13.0 (11.0 – 13.0)	13.0 (12.0 – 14.0)	0.147++
Chronic kidney disease, n (%)	8 (36.4%)	17 (23.9%)	0.278*
Diabetes, n (%)	7 (31.8%)	23 (32.4%)	0.999*
CRT-D	14 (63,6%)	29 (40,8%)	0.086*
Medications			
ACEI, ARB or ARNI	20 (90.9%)	61 (85.9%)	0.725*
Beta-blocker	21 (95.5%)	65 (91.5%)	0.999*
Spironolactone	18 (81.8%)	63 (88.7%)	0.469*

LVEF, left ventricular ejection fraction; LBBB, left bundle branch block; NYHA, New York Heart Association; CRT-D, Cardiac resynchronization therapy combined with cardiodefibrillator (CRT-D) ARNI, angiotensin receptor neprilysin inhibitor; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; SD, standard deviation; IQ: interquartile range

* Fisher's exact test; + unpaired Student's t-test; ++ Wilcoxon test

Table 2: Univariate and multivariate predictors of death from any cause by Cox's regression model

Univariate analysis Multivariate analysis

	HR (95% CI)	**P**	**HR (95% CI)**	**P**
Age, years	1.0 (0.9 – 1.0)	0.808	-	-
Stroke	1.2 (0.3 – 4.9)	0.839	-	-
NYHA class III or IV	1.2 (0.4 – 2.8)	0.354	-	-
LVEF, baseline (%)	0.9 (0.9 – 1.0)	0.335	-	-
QRS duration (ms)	1.0 (0.9 – 1.0)	0.648	-	-
Chronic kidney disease	0.7 (0.3 – 1.7)	0.510	-	-
Hemoglobin (g/dL)	1.0 (0.8 – 1.2)	0.657	-	-
Atrial fibrillation	0.9 (0.4 – 2.2)	0.895	-	-
CRT-D	0.6 (0.2 – 1.0)	0.055	0.7 (0.3 – 1.4)	0.283
Chagas cardiomyopathy	3.9 (1.8 – 8.4)	0.001	2.1 (0.9 – 5.3)	0.106
Ischemic cardiomyopathy	2.1 (0.6 – 7.0)	0.224	-	-
Upgrade	4.7 (2.2 – 9.9)	< 0.001	2.9 (1.2 – 7.1)	0.019

LVEF, Left ventricular ejection fraction; NYHA, New York Heart Association; CRT-D, Cardiac resynchronization

therapy with defibrillator