Is Conventional Cardiac Pacing Harmful in Patients with Normal Ventricular Function?

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Abstract

Background: Right ventricular pacing may be deleterious in patients with left ventricular dysfunction, but in patients with normal function the impact of this stimulation triggering clinically relevant ventricular dysfunction is not fully established.

Objectives: To evaluate the clinical, echocardiographic findings of patients with previously normal left ventricular function underwent implantation of a pacemaker.

Methods: Observational, cross-sectional study with 20 patients, who underwent implantation of pacemaker, prospectively followed-up, with the following inclusion criteria: normal left ventricular function defined by echocardiography and ventricular pacing higher than 90%. Were evaluated functional class (FC) (New York Heart Association), 6-minute walk test (6MWT), B-type natriuretic peptide (BNP), echocardiographic assessment (conventional and dyssynchrony parameters), and quality of life questionnaire (QLQ) (SF-36). The assessment was performed at ten days (t1), four months (t2), eight months (t3), 12 months (t4) and 24 months (t5).

Results: Conventional echocardiographic parameters and dyssynchrony parameters showed statistically significant variation over time. The 6MWT, FC, and BNP showed worsening at the end of two years. QLQ showed initial improvement and worsening at the end of two years.

Conclusion: The implantation of conventional pacemaker was associated with worsening in functional class, worsening in walk test, increased BNP levels, increased duration of QRS, and worsening in some domains of the QLQ at the end of two years. There were no changes in echocardiography measurements (conventional and asynchrony measures). (Arq Bras Cardiol. 2013; 101(6):545-553)

Keywords: Pacemaker; Heart failure; Chagas Disease; Septal pacing; Asynchrony.

Introduction

Cardiac pacing is a treatment option for bradyarrhythmias[1], tachyarrhythmias[2,3] and heart failure[4]. However, conventional cardiac pacing in the right ventricle (RV), traditional for decades, has been questioned for its possible deleterious effects, especially in patients with previous left ventricular dysfunction[5].

In normal heart, the left ventricle (LV) contracts in a fast and synchronized manner. Stimulation anywhere in the RV alters the natural pattern of activation and, as a consequence, the ventricular contraction[6]. This may lead to induction of asynchrony with potential risk for the development of ventricular dysfunction[7].

In patients with normal ventricular function, the effects are not clearly defined. In a retrospective study, Silva et al[8] showed that in patients with pacemaker and normal ventricular function, no significant remodeling in the left ventricle occurs. In short-term study, Sá et al[9] showed no significant deleterious effects in patients with normal function. The mechanisms by which not all patients develop left ventricular dysfunction are not completely understood and may be related to stimulation site, duration of stimulation, age or underlying disease[10].

The aim of this study is to evaluate the clinical, laboratory, and echocardiographic effects of conventional cardiac pacing in patients with indication for pacemaker implantation and normal ventricular function, during two years of follow-up.

Methods

This study was approved by the Research Ethics Committee of the Hospital das Clinicas, Federal University of Goiás. This is a prospective, observational study. All patients participating in this study signed an informed consent form.

From March 2006 to July 2009, 178 patients were referred for pacemaker implantation. Of these, 23 patients were selected consecutively, with mean age of 11 ± 58 years and 60% male.

Inclusion criteria: 1) age over 18 years; 2) the indications for conventional pacemakers followed the guidelines of

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the Brazilian Society of Cardiology[11], being accepted those with high probability for right ventricular pacing: a) complete atrioventricular block; b) type II second-degree AV block; c) sinus node disease with first-degree AV block and PR interval > 200 ms; 3) normal ventricular function defined by echocardiography, performed immediately after implantation of the artificial cardiac pacemaker (normal ventricular diameters and normal ejection fraction).

Exclusion criteria: 1) severe disease with reduced survival probability; 2) inability to perform the tests proposed in the study; 3) patients who had right ventricular pacing of less than 90% during follow-up, whose analysis was performed by using the generator data.

After implantation, patients were followed for a period of two years, divided into five stages: ten days (t1), four months (t2), eight months (t3), 12 months (t4), and 24 months (t5).

We analyzed the following parameters: 1) functional class of the *New York Heart Association;* 2) Quality of Life questionnaire (SF-36); 3) 6-minutes walk test; 4) evaluation of the data stored in the generator; 5) ECG: duration of stimulated QRS; 6) levels of B-type natriuretic peptide (BNP); 7) echocardiogram (chamber diameters and volumes, and ejection fraction) and dyssynchrony.

The echocardiography was performed in the equipment Toshiba Xario, under two-dimensional harmonic mode, and 2.5 MHz sector transducer. All examinations were performed by a single physician. Patients remained in the left lateral position and were monitored with electrocardiogram. All measurements were performed with the patient in expiratory apnea. The measurements of the LV, RV, the diameters of the left atrium, and aorta were performed by one-dimensional mode, according to the recommendations of the American Society of Echocardiography[12].

In the assessment of intraventricular dyssynchrony the following criteria were employed: M mode: difference between the onset of QRS complex and the peak contraction of the septal wall, and then obtained from the time between the onset of the QRS complex and the peak contraction of the posterior wall, being considered dyssynchrony values greater than 130 ms; Pulsed Doppler: measurement of the onset of QRS complex up to the onset of aortic flow, being considered dyssynchrony values greater than 140 ms; tissue Doppler: difference between the onset of QRS complex and the S wave peak of the basal region of the lateral, anterior, septal and inferior walls, being considered dyssynchrony values greater than 65 ms[13,14].

To assess the mean quantitative variables of normal distribution which changed over time, we used the method of analysis of variance (ANOVA) with repeated measures followed by multiple comparisons via Tukey-Kramer method, if applicable. The assumption of sphericity was assessed via Mauchly test. When the assumption was not met, the Huyn-Feldt correction was applied. The normality assumption was evaluated by visual inspection of histograms and D'Agostino-Pearson *omnibus* normality test.

The change profile of quantitative variables with asymmetric distribution over time was analyzed with Friedman nonparametric test, followed by multiple comparisons according to the Conover method.

The calculation of sample size was determined from the ejection fraction variable which best represented the primary endpoint.

The ANOVA for repeated measures with an intraindividual factor (t1, t2, t3, t4 and t5) was planned in the statistical analysis. For an average absolute difference of at least 5%, the sample size of 20 patients would be appropriate to obtain a 90% statistical power in order to detect an average absolute difference of at least 5% of EF between two arbitrary means over time (t1, t2, t3, t4 and t5). The analysis of repeated measures for variable of ordinal response was conducted with Cochran-Mantel-Haenszel test.

Missing data of a patient at t5 were imputed according to the last observation carried forward method *(LOCF)*. Quantitative variables with normal and asymmetric distributions were described as mean ± standard deviation and median (interquartile range), respectively.

All significance probabilities (p values) are of bilateral type, and values lower than 0.05 were considered as statistically significant. The software SAS 9.2 *(Statistical Analysis System, Cary, NC, USA)* was applied for statistical analysis of data.

Results

In the initial sample of 23 patients, three were excluded due to ventricular pacing lower than 90%. The most frequent etiology was Chagas Disease (80%). Complete AV block or type 2 second-degree AV block accounted for 70% of the sample. The electrode was implanted in the septal region in 70% of the cases. The clinical features are shown in Table 1. The follow-up period of two years was performed in 19 patients. One patient died of heart failure at 14 months of follow-up.

The percentage of ventricular pacing was obtained from each patient by analyzing the data stored in the generator. The average percentage of stimulation was 99%. There was no statistically significant difference between the medians over the times t1, t2, t3, t4 and t5 ($p = 0.4405$).

All patients started the protocol in functional class I, and during the course seven patients showed worsening of functional class ($p < 0.001$) (Figure 1). The walk test showed worsening over time, being observed between t2 and t3, and between t2 and t5 ($p = 0.02$) (Figure 2).

The duration of stimulated QRS complex increased by 12 ms over time ($p = 0.0001$), this difference was observed between t1 and t5.

Table 2 shows the data regarding conventional echocardiographic parameters: systolic and diastolic diameters of LV, systolic and diastolic volumes of the LV, and left atrial dimension. No statistical differences were observed over time. The average ejection fraction at baseline was 64.50% and at the end was 60.65%, but there was no statistical difference ($p = 0.1602$) (Figure 3).

In Table 3, we observe the data regarding the echocardiographic assessment of the ventricular dyssynchrony. By M mode, there was no significant difference in average time between septal activation and posterior wall activation over time. Average value observed at the onset (t1) was 35.50 ms and at the end of two years (t5) was 41.00 ms. By pulsed Doppler method, the

Table 1 - Baseline Clinical Characteristics of the patients studied

1.	45	M	CD	SND + AVB 1°	septal	DDC
2.	64	M	CD	CAVB	septal	DDC
3.	68	M	CD	AVB 2° Mobitz 2	septal	DDC
4.	45	M	CD	SND + AVB 1°	apical	DDC
5.	70	F	FCS	CAVB	septal	DDC
6.	43	M	CD	SND + AVB 1°	septal	DDC
7.	67	M	CD	AVB 2° Mobitz 2	septal	DDC
8.	45	F	CD	SND + AVB 1°	apical	DDC
9.	69	F	FCS	CAVB	septal	DDC
10.	59	F	CD	SND + AVB 1°	apical	DDC
11.	55	M	CD	SND + AVB 1°	septal	DDC
12.	64	M	CD	CAVB	apical	DDC
13.	78	F	FCS	CAVB	septal	DDC
14.	76	M	CD	CAVB	septal	DDC
15.	59	F	CD	CAVB	septal	DDC
16.	67	F	FCS	CAVB	apical	DDC
17.	45	M	CD	CAVB	septal	DDC
18.	38	M	CD	CAVB	septal	DDC
19.	54	M	CD	AVB 2° Mobitz 2	septal	DDC
20.	64	F	CD	CAVB	apical	DDC

CD: Chagas disease; FCS: fibrosis of the conduction system; CAVB complete AV block; SND: sinus node disease; AVB 1: first-degree AV block; DDC: dual chamber.

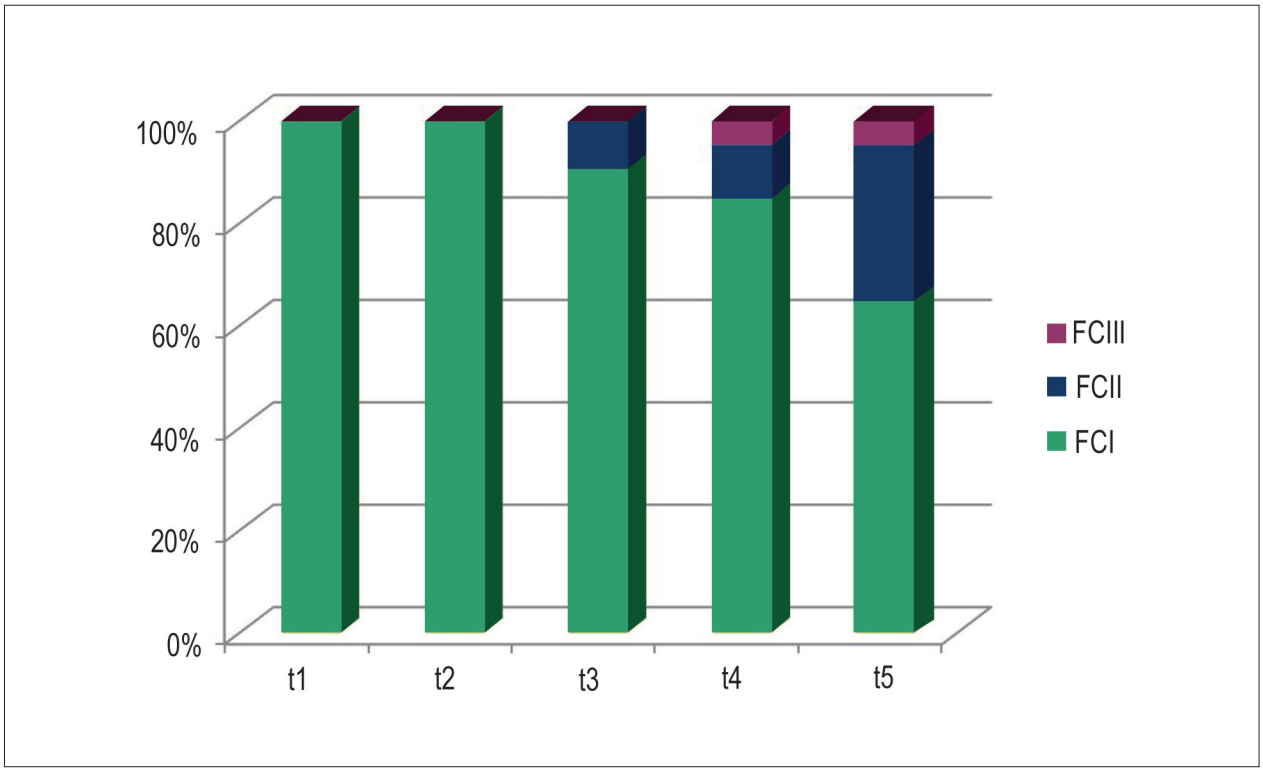

Figure 1 - *Changes in functional class at t1 (10 days), t2 (four months), t3 (eight months), t4 (12 months), and t5 (24 months). Worsening between t1 and t4 and t1 and t5 ($p < 0.0001$).*

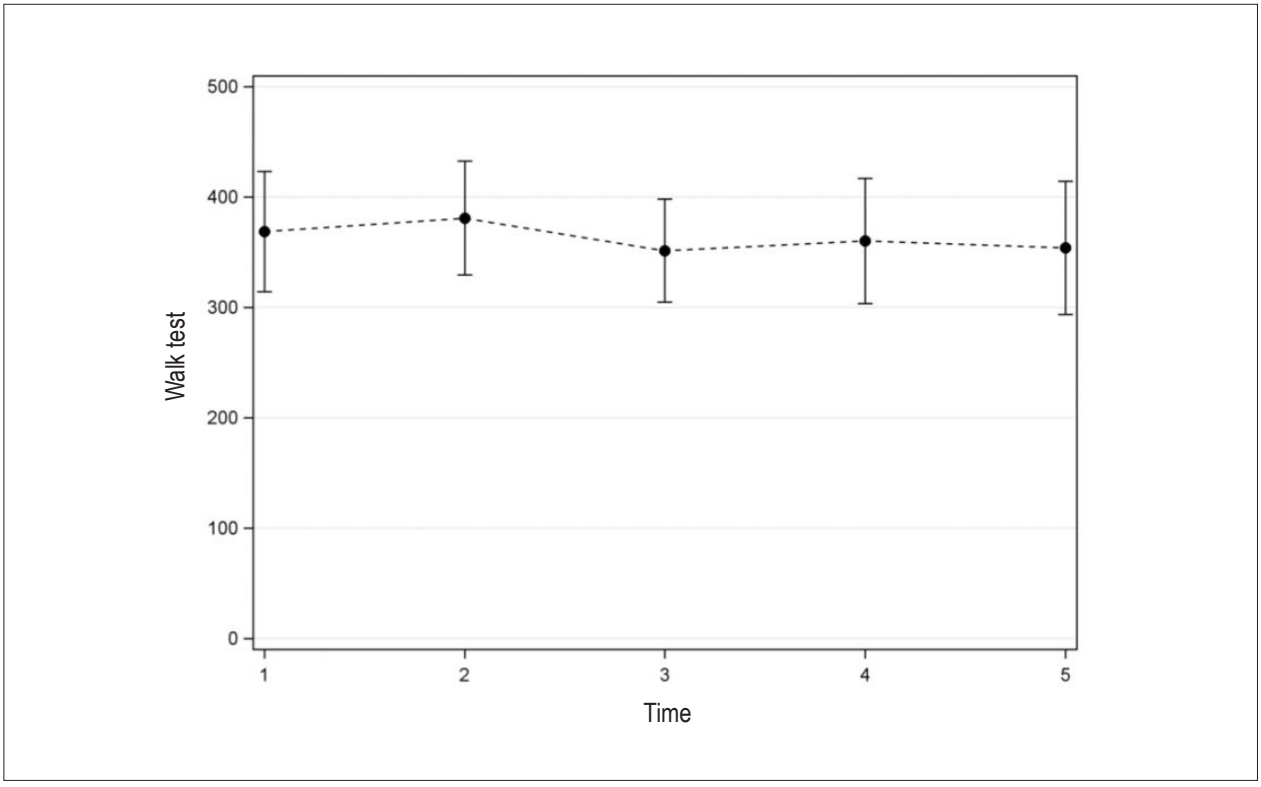

Figure 2 - *6-minute walk test in meters (difference between t2 and t3, and between t2 and t5), p = 0.0212.*

Table 2 - Echocardiography parameters

	EF	Delta D	LVDD	LVSD	LVEDV	LVESV	LA
t1	64.50 ± 5.56	35.05 ± 4.03	50.25 ± 3.44	32.20 ± 3.44	124.85 ± 29.91	43.70 ± 12.50	32.60 ± 3.23
t2	62.65 ± 7.23	34.10 ± 5.27	50.70 ± 5.50	33.45 ± 5.09	125.90 ± 27.81	47.35 ± 16.53	32.70 ± 3.16
t3	61.55 ± 7.65	33.40 ± 5.90	51.25 ± 5.24	34.10 ± 5.51	129.85 ± 32.57	50.35 ± 19.27	32.95 ± 3.86
t4	61.80 ± 6.57	32.95 ± 4.59	50.55 ± 4.88	34.15 ± 5.22	127.95 ± 29.02	49.90 ± 17.93	32.70 ± 4.03
t5	60.65 ± 8.68	32.60 ± 6.10	50.55 ± 7.18	34.45 ± 7.39	131.10 ± 33.10	51.60 ± 18.32	33.10 ± 4.05
p	p = 0.1602	p = 0.2654	p = 0.7559	p = 0.0270	p = 0.1592	p = 0.1400	p = 0.09141

EF: ejection fraction; LVDD: LV end-diastolic diameter; LVSD: LV end-systolic diameter; LVEDV: LV end-diastolic volume; LVESV: LV end-systolic volume; LA: left atrium.

average value observed was 105.40 ms at t1, and 122.00 ms at t5. By tissue Doppler the average value observed was 38.55 ms at t1, and 44.45 ms at t3. There was no significant difference in the mean between the septal activation and posterior wall activation over time.

In BNP tests, there was a significant difference between the average levels over time. The average level was 19.75 pg / ml at t1, and 167 pg/ml at t5, this difference being found between t1 and t5 (p = 0.0002) (Figure 4).

Table 4 shows the data regarding the answers to the Quality of Life Questionnaire (SF-36). In the domains of functional capacity, pain, vitality, emotional aspects, limitations due to physical aspects, general health status, and limitation due to social aspects, the patients had improvement between t1 and t4. There was worsening between t2 and t5, but no difference between t1 and t5. In the mental health domain there was no difference over time.

Discussion

For 50 years, since its introduction[15], the right ventricular pacing, especially in the apical region, has been the preferred site due to the ease of implantation and its stability. However, such stimulation has been extensively revised to be related to induction of ventricular dysfunction[16].

The main etiology in our study was Chagas Disease, whose pathophysiology is complex[17]. The installation of a bradyarrhythmia may simply be a marker of inflammatory

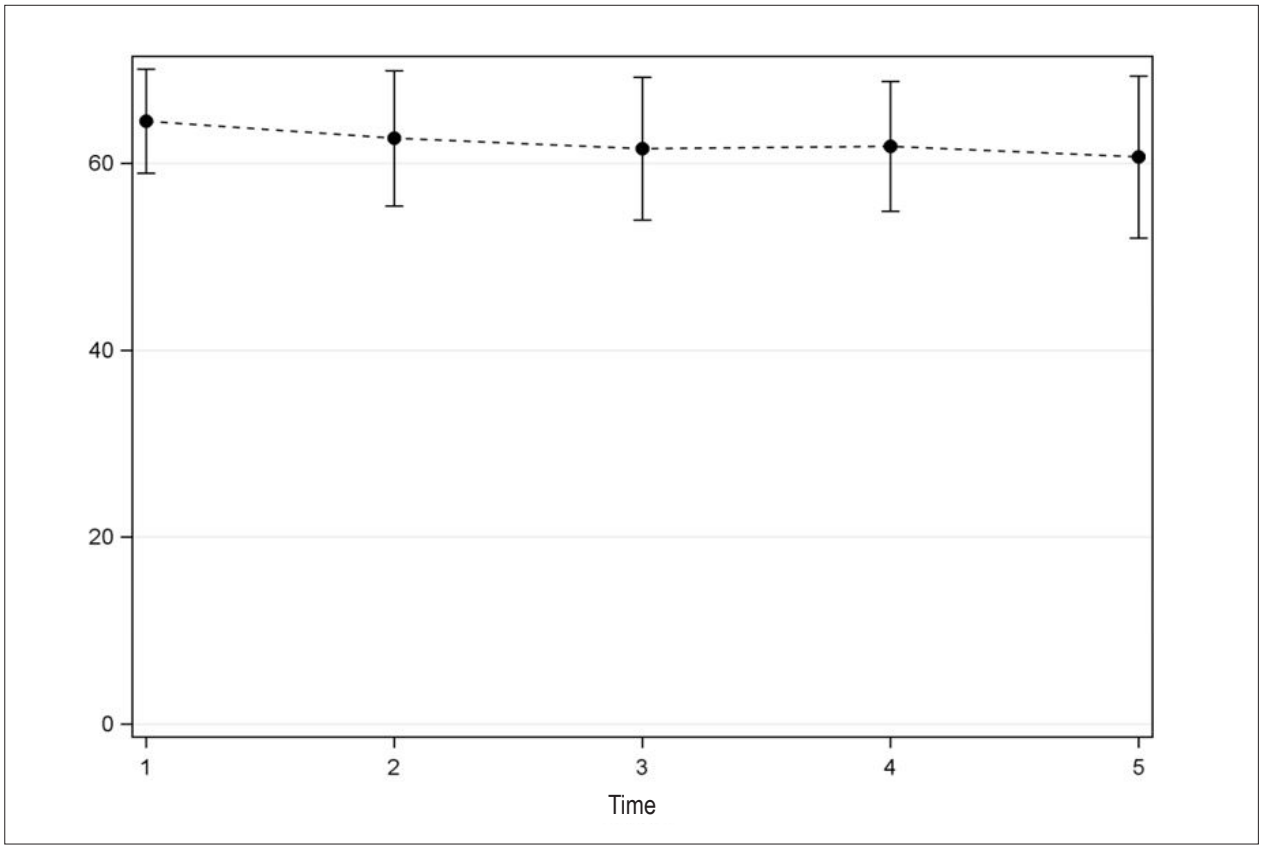

Figure 3 - *Ejection fraction did not change significantly over time (p = 0.1602).*

Table 3 - Echocardiography parameters related to intraventricular dyssynchrony

	M mode	Pulsed Doppler	Tissue Doppler
t1	35.50	105.40 ± 20.89	38.55 ± 14.14
t2	42.00	118.40 ± 24.53	40.62 ± 19.02
t3	41.00	117.20 ± 15.86	42.45 ± 16.21
t4	39.00	118.05 ± 29.78	42.35 ± 16.20
t5	41.00	122.10 ± 28.48	44.45 ± 17.20
p	p = 0.6619	p = 0.0988	p = 0.6921

changes and the evolution to ventricular dysfunction can occur independently of the presence of a pacemaker.

Functional class and walk test showed significant worsening at the end of the two years, indicating clinical deterioration over time. The stimulation time is an important factor in the induction of ventricular dysfunction and risk for heart failure. Sweeney et al[18], in the MOST study, demonstrated that RV pacing > 80% for more than two years increased the risk for heart failure. In addition, they assessed the duration of the QRS complexes and their relationship with mortality in patients undergoing implantation of a pacemaker for sinus node disease. The presence of paced QRS complex with duration greater than or equal to 120 ms was associated with a death risk of 34%[19].

Zhang et al[20], in a retrospective study with an eight-year follow-up showed that in patients with complete AV block, the predictive factors for developing heart failure were age, apical pacing, duration of QRS complex pacing, and the presence of coronary artery disease. In our sample, no increase was observed in QRS duration over time. In studies on resynchronization, patients with higher QRS duration have greater benefit from this therapy[21]. In addition, patients with wider QRS complexes have worse prognosis[22]. Therefore, we can assume that an increased QRS duration over time may be associated with a higher dyssynchrony.

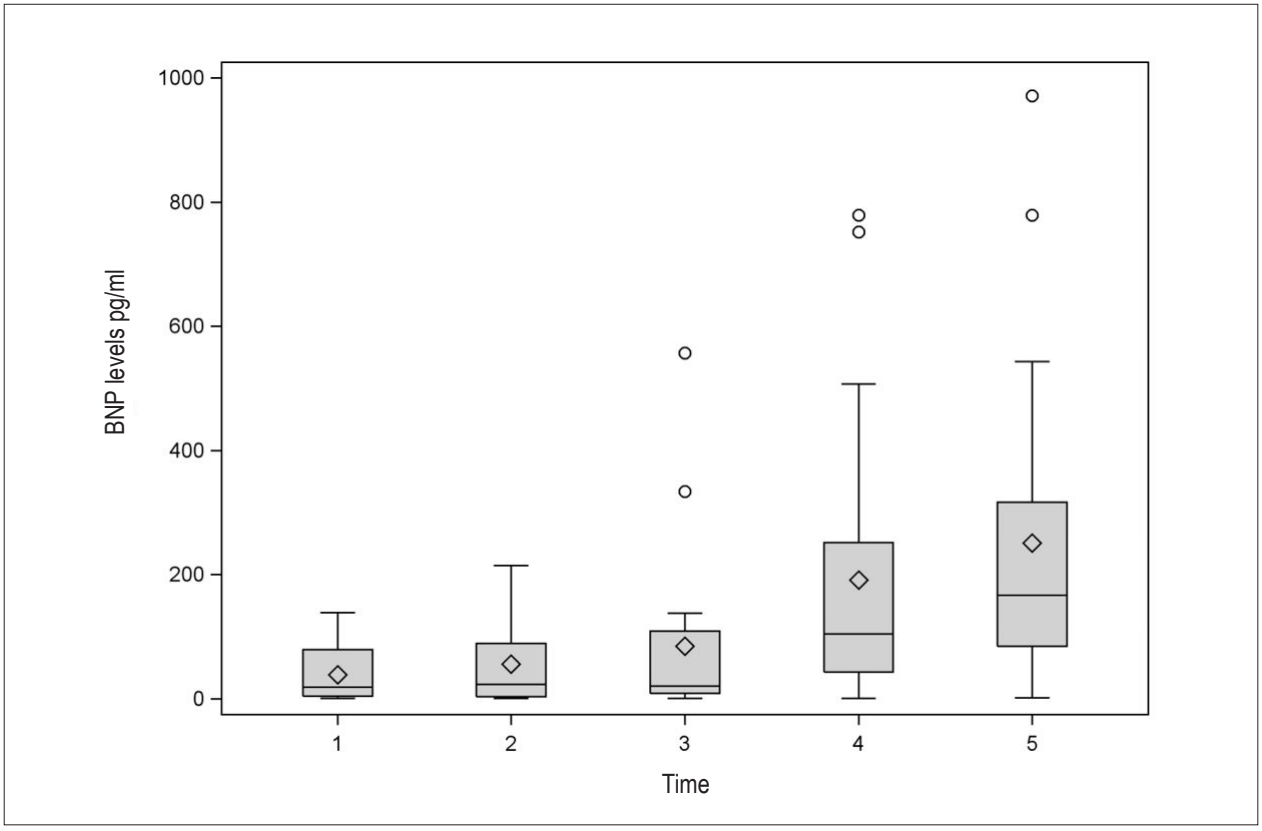

Figure 4 - *Box-plot of BNP levels; significant increase between t1 and t5 (p = 0.0004).*

Table 4 - Test of quality of life SF-36

	FC	LPA	Pain	GHS	Vitality	SA	EA	Mental Health
t1	90	50	73 ± 21	75 ± 19	73 ± 21	75	100	76± 20
t2	97	87	78 ± 21	77 ± 16	84 ± 12	100	100	87± 9
t3	95	100	86 ± 12	87 ± 11	84 ± 13	100	100	86± 8
t4	97	100	90 ± 10	90 ± 10	83 ± 11	97	100	87± 10
t5	85	50	82 ± 19	77 ± 19	68 ± 23	94	67	75± 19
p	p < 0.0001	p < 0.0001	p = 0.0110	p < 0.0001	p < 0.0021	p = 0.0021	p < 0.0001	p = 0.0108

FC: Functional capacity; LPA: Limitations due to physical aspects; GHS: General health status; SA: Social aspects; EA: Emotional aspects.

In the SF-36 questionnaire, initial improvement was observed in the following domains: functional capacity, social aspects, and general health status. The improvement arises from the correction of bradycardia by cardiac pacing in this group of patients previously limited. The MOST[23] and PASE[24] studies, comparing dual-chamber pacing versus single-chamber pacing, used the SF-36 questionnaire. The authors observed a significant improvement in quality of life after pacemaker implantation in both groups, but less effective in patients over 75 years old. In our study, after 24 months there was a worsening in these parameters, corroborating the functional class and walk test data.

In our study there was a prevalence of septal pacing. The apical pacing has been more clearly associated to the deleterious effects[25]. However, the cardiac pacing anywhere in the RV alters the cardiac activation, since the stimulus conduction is slower through the ventricular myocardium compared to His-Purkinje system. The stimulation on outflow tract[26], septal region[27], hissian region or para-hissian region[28] has been investigated, but without consistent results regarding major outcomes, such as total mortality and cardiovascular mortality.

The use of cardiac resynchronization therapy prophylactically, i.e. prevention of asynchrony and its deleterious effects as a consequence, have been tested. Albertsen et al[29] selected 50

patients with complete AV block, which were randomized to biventricular pacing or conventional pacing. After one year of follow-up, they found that biventricular pacing minimizes asynchrony (assessed by echocardiography with tissue Doppler), preserves the left ventricular function, and presents lower BNP levels. There was a reduction in ejection fraction by 2% in the DDD group, with no repercussions on functional class or walk test. This study included patients with and without left ventricular dysfunction.

Another strategy has been to minimize ventricular pacing through new pacing algorithms[30], because a higher percentage of stimulation is associated with risk for heart failure[31]. The SAVE PACe study[32] performed in patients with sinus node disease randomized 1065 patients to receive conventional dual-chamber pacing or dual-chamber minimal ventricular pacing. There was a 40% reduction in atrial fibrillation, with no difference in mortality. The INTRINSIC RV study[33] in patients with indication for ICD, compared DDDR modes (70 bpm) x VVI (40 bpm) with respect to mortality and hospitalization for HF, and no significant difference has been observed. However, patients with complete AV block or high-grade block do not benefit from this strategy because they require ventricular stimulation.

In our group, we observed a significant increase in BNP levels at the end of the two years of follow-up. The average level at the end of the two years was 167 pg/ml. This value correlates to mild ventricular dysfunction[34]. Abreu et al[35] showed that in patients with conventional pacing, intraventricular dyssynchrony was an independent predictor of increased BNP levels, after adjustment for age and ejection fraction. On the other hand, Nikoo et al[36] found no correlation between BNP levels and pacing site (apical versus non-apical).

In our population, there was no worsening of conventional echocardiography parameters and dyssynchrony measurements, but downward trend in ejection fraction, a value that did not reach statistical difference. The sample size may have been insufficient to detect subtle changes in ejection fraction. Silva et al[37] evaluated ventricular remodeling in patients with ventricular apical pacing. The remodeling was defined as echocardiographic changes documented for at least six months after implantation: > 10% increase in left ventricular diastolic diameter and > 20% decrease in ejection fraction. The variables analyzed were: underlying heart disease, functional class, duration of ventricular pacing and QRS duration. Researchers have observed that patients without ventricular dysfunction and undergoing RV apical pacing showed low ventricular remodeling.

A model to evaluate ventricular dysfunction related to the use of pacemaker is the congenital complete AV block without associated heart disease, as it excludes other potentially confounding variables. Thambo et al[38] evaluated 23 patients with congenital complete AV block and previously normal left ventricular function, under at least five years of cardiac pacing. The following parameters were analyzed: ventricular filling time, cardiac output, severity of mitral regurgitation, interventricular dyssynchrony, intraventricular dyssynchrony, and exercise stress test. The results indicate that prolonged ventricular pacing was associated with left ventricular dilation, LV asymmetric hypertrophy, and low physical capacity. However, from the clinical point of view, the impact of these changes has not been evaluated. Kim JJ et al[39] evaluated patients with congenital complete AV block and showed after 20 years of follow-up that 92% of patients had no ventricular dysfunction assessed by echocardiography and clinical parameters. This suggests that ventricular pacing should not be considered as the only factor inducing ventricular dysfunction. In our study, clinical worsening was not clearly associated with asynchrony, suggesting evolution of the underlying heart disease.

The limitation of this study was the sample size, which is small and powerless to detect small changes in echocardiographic measurements and major clinical outcomes. The prevalence of patients with Chagas Disease, whose clinical course is variable, may also be a confounding factor. In addition, in the evaluation of the generator data by telemetry it is not possible to exclude patients with pseudofusion.

The paradigm change in the current implant mode requires solid data, especially in relation to clinically relevant outcomes. It will be important to clearly define risk subgroups because the reason why some patients develop ventricular dysfunction or not requires further investigation and probably is not related exclusively to ventricular pacing.

Conclusion

In patients with normal left ventricular function, implantation of conventional pacemaker was associated with change in functional class, worsening in walk test, increased BNP levels, increased duration of QRS, and worsening in some domains of the QLQ (SF-36) at the end of two years. There were no changes in echocardiography measurements (conventional and asynchrony measurements).

Author contributions

Conception and design of the research, Analysis and interpretation of the data and Critical revision of the manuscript for intellectual content: de Sá LAB, Rassi S; Acquisition of data and Writing of the manuscript: de Sá LAB, Batista MAL; Statistical analysis: de Sá LAB,

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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