Efficacy, Safety, and Performance of Isolated Left vs. Right Ventricular Pacing in Patients with Bradyarrhythmias: A Randomized Controlled Trial

Elizabeth Sartori Crevelari, Katia Regina da Silva, Caio Marcos de Moraes Albertini, Marcelo Luiz Campos Vieira, Martino Martinelli Filho, Roberto Costa

Instituto do Coração (InCor) do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HCFMUSP), São Paulo, SP – Brazil

Abstract

Background: Considering the potential deleterious effects of right ventricular (RV) pacing, the hypothesis of this study is that isolated left ventricular (LV) pacing through the coronary sinus is safe and may provide better clinical and echocardiographic benefits to patients with bradyarrhythmias and normal ventricular function requiring heart rate correction alone.

Objective: To assess the safety, efficacy, and effects of LV pacing using an active-fixation coronary sinus lead in comparison with RV pacing, in patients eligible for conventional pacemaker (PM) implantation.

Methods: Randomized, controlled, and single-blinded clinical trial in adult patients submitted to PM implantation due to bradyarrhythmias and systolic ventricular function ≥ 0.40. Randomization (RV vs. LV) occurred before PM implantation. The main results of the study were procedural success, safety, and efficacy. Secondary results were clinical and echocardiographic changes. Chi-squared test, Fisher's exact test and Student's t-test were used, considering a significance level of 5%.

Results: From June 2012 to January 2014, 91 patients were included, 36 in the RV Group and 55 in the LV Group. Baseline characteristics of patients in both groups were similar. PM implantation was performed successfully and without any complications in all patients in the RV group. Of the 55 patients initially allocated into the LV group, active-fixation coronary sinus lead implantation was not possible in 20 (36.4%) patients. The most frequent complication was phrenic nerve stimulation, detected in 9 (25.7%) patients in the LV group. During the follow-up period, there were no hospitalizations due to heart failure. Reductions of more than 10% in left ventricular ejection fraction were observed in 23.5% of patients in the RV group and 20.6% of those in the LV group (p = 0.767). Tissue Doppler analysis showed that 91.2% of subjects in the RV group and 68.8% of those in the LV group had interventricular dyssynchrony (p = 0.022).

Conclusion: The procedural success rate of LV implant was low, and the safety of the procedure was influenced mainly by the high rate of phrenic nerve stimulation in the postoperative period. (Arq Bras Cardiol. 2019; 112(4):410-421)

Keywords: Cardiac Pacing, Artificial; Bradycardia; Arrhythmias, Cardiac; Pacemaker, Artificial; Ventricular remodeling.

Introduction

Artificial cardiac pacing is the only treatment for acquired atrioventricular blocks.[1-3] Conventional pacemakers (PM), which stimulate the right ventricle (RV), via unicameral or atrioventricular pacing, have been the most widely used devices to treat these bradyarrhythmias.[1-4] Owing to its proven effectiveness in reducing symptoms caused by low cerebral and systemic blood flow, as well as its increased survival rate, this clinical indication represents 55.1% and 83.4% of all implants performed in the United States of America and Brazil, respectively.[5,6]

Nevertheless, deleterious effects of chronic right ventricular pacing have been described. Examples include proarrhythmic mechanisms, intra- or interventricular electromechanical dyssynchrony, and ventricular remodeling, which may lead to heart failure refractory to drug treatment.[7-14] Changing the mode of pacing from RV to biventricular has been reported to reverse these events.[15-20]

Isolated atrial synchronous left ventricular pacing has been used for the correction of cardiac dyssynchrony in patients with severe left ventricular dysfunction and left bundle branch block, with results similar to those obtained by atriobiventricular pacing.[21-25] There is, however, no evidence to date that the use of isolated left ventricular pacing, in comparison with right ventricular pacing, may reduce the rate of ventricular remodeling in patients with acquired atrioventricular blocks, regardless of the presence or absence of previous left ventricular dysfunction.

Notwithstanding the possible clinical-functional benefits that may be expected from the use of left ventricular pacing, in comparison with right ventricular pacing, there are other factors that may influence this comparison, especially those related to the operating technique and its complications. The technique of implanting PM with endocardial RV pacing is well established and its results and complications have long been known. On the other hand, implants in the left ventricle

Mailing Address: Roberto Costa •
Av. Dr. Enéas de Carvalho Aguiar, 44, Postal Code 05403-900, Cerqueira César, São Paulo, SP – Brazil
E-mail: rcosta@incor.usp.br
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(LV), via epicardial or transvenous access, presents specificities both with regard to the anesthetic technique and the skills required to perform them, either via thoracotomy or coronary sinus catheterization.[26-32] Among these aspects, the viability of using coronary sinus tributary veins in individuals with normal or slightly enlarged heart is still unknown, notwithstanding the significant experience already achieved with this means of access in patients with cardiomegaly and an accentuated increase in the left ventricular cavity.

In view of this concern regarding the deleterious effects of chronic right ventricular pacing, the hypothesis of the present study was that the use of an active-fixation coronary sinus lead will allow for safe isolated left ventricular pacing for patients with atrioventricular blocks who are indicated for conventional PM implantation.

Objectives

The objective of the present study was to evaluate the safety, efficacy, and effects of left ventricular pacing, using an active-fixation coronary sinus lead (*Medtronic Attain StarFix® Model 4195 OTW*),[33] in comparison with right ventricular pacing in patients who were indicated for conventional PM implantation and who had normal or slightly altered left ventricular function, with the aim of determining:

- The procedural success rate of coronary sinus lead implantation;
- The safety and efficacy of left ventricular pacing;
- Cardiac synchrony and the occurrence of remodeling and left ventricular dysfunction.

Methods

Study design

This is a randomized controlled clinical trial that compared the use of right ventricular pacing (RV Group) with relation to unifocal left ventricular pacing (LV Group) in patients with bradyarrhythmias.

This study was performed in a high complexity cardiology hospital. It received approval from the Institution's Research Ethics Committee. All participants signed an informed consent form. This study was registered at *ClinicalTrials.gov*.

Study Population

Adult subjects who met the following criteria were considered eligible for the study: (1) Indication of initial implantation of a definitive conventional PM by the transvenous technique; (2) Systolic ventricular function ≥ 0.40; (3) Agreement to participate in the study.

Individuals who presented at least one of the following criteria were not included in the study: (1) Impediment of venous access through tributaries of the superior vena cava due to: uncorrected intracardiac defects, absence of venous access, tricuspid valve prosthesis, or need for radiotherapy in the thorax; (2) > 85 years of age; (3) Pregnancy in progress; (4) Contraindication for use of iodinated contrast during the surgical procedure (serum creatine ≥ 3.0 mg/dL).

Patients were consecutively selected from those with indication for conventional PM implantation. After the indication of surgical treatment, the individuals who fulfilled the eligibility criteria were submitted to a preoperative evaluation, consisting of medical history, clinical, laboratory and echocardiographic assessment. (Figure 1)

Composition of study groups

Before the surgical procedure, patients were allocated into two groups in a random distribution list generated by a computer: (1) composed of patients who were submitted to conventional RV lead implantation; (2) LV Group: composed of patients who received implantation of an active-fixation coronary sinus lead in the LV.

The random distribution list was generated by the computer program *Statistical Analysis System* (SAS), with a 2:1 ratio of LV implants. To guarantee a balanced distribution of patients, we opted for block randomization, generating a list with blocks of 10 to allocate patients into the two study groups.

Allocation was performed by means of sealed, opaque envelopes, which were numbered sequentially. Patient allocation always occurred the night before the surgical procedure, following adequate assessment of the study's eligibility criteria. The process of preparing and sealing the envelopes was performed by an independent individual who was not involved in any other steps of the study.

Blinding of all patients and the investigator responsible for assessing the study results was guaranteed during all phases of the study. Due to the surgical intervention protocol, it was not possible to blind the surgical staff and the team responsible for the PM evaluations and programming.

Study interventions

The two main interventions performed during this study were conventional right ventricular (RV Group) and left ventricular (LV Group) implantations. The surgical procedure for PM implantation was always performed through the transvenous route, in accordance with our institution's routine practice.

In patients allocated into the RV Group, the *Medtronic CapSureFix Novus® 5076-58* lead was preferably implanted in the middle portion of the interventricular septum, always under indirect vision using fluoroscopy. When it was not possible to obtain adequate fixation, stimulation, or sensitivity in the mid-septum position, the ventricular lead was implanted in the apical septum or the outlet septum.

In patients allocated into the LV Group, a *Medtronic 6228 CTH* deflectable catheter was introduced into the coronary sinus, serving as a guide for the introduction of a *Medtronic Attain 6227 DEF* deflectable guide catheter. When the latter was introduced into the coronary sinus, coronary sinus phlebography was performed in a left anterior oblique position at 30 degrees, with the aid of a *Medtronic Attain 6215* balloon catheter and non-ionic iodized contrast medium (*Iodixanol*, VisipaqueTM). When the radiological anatomy of the coronary sinus and its tributary veins was defined, a *Medtronic Attain StarFix® Model 4195 OTW* unipolar lead was introduced

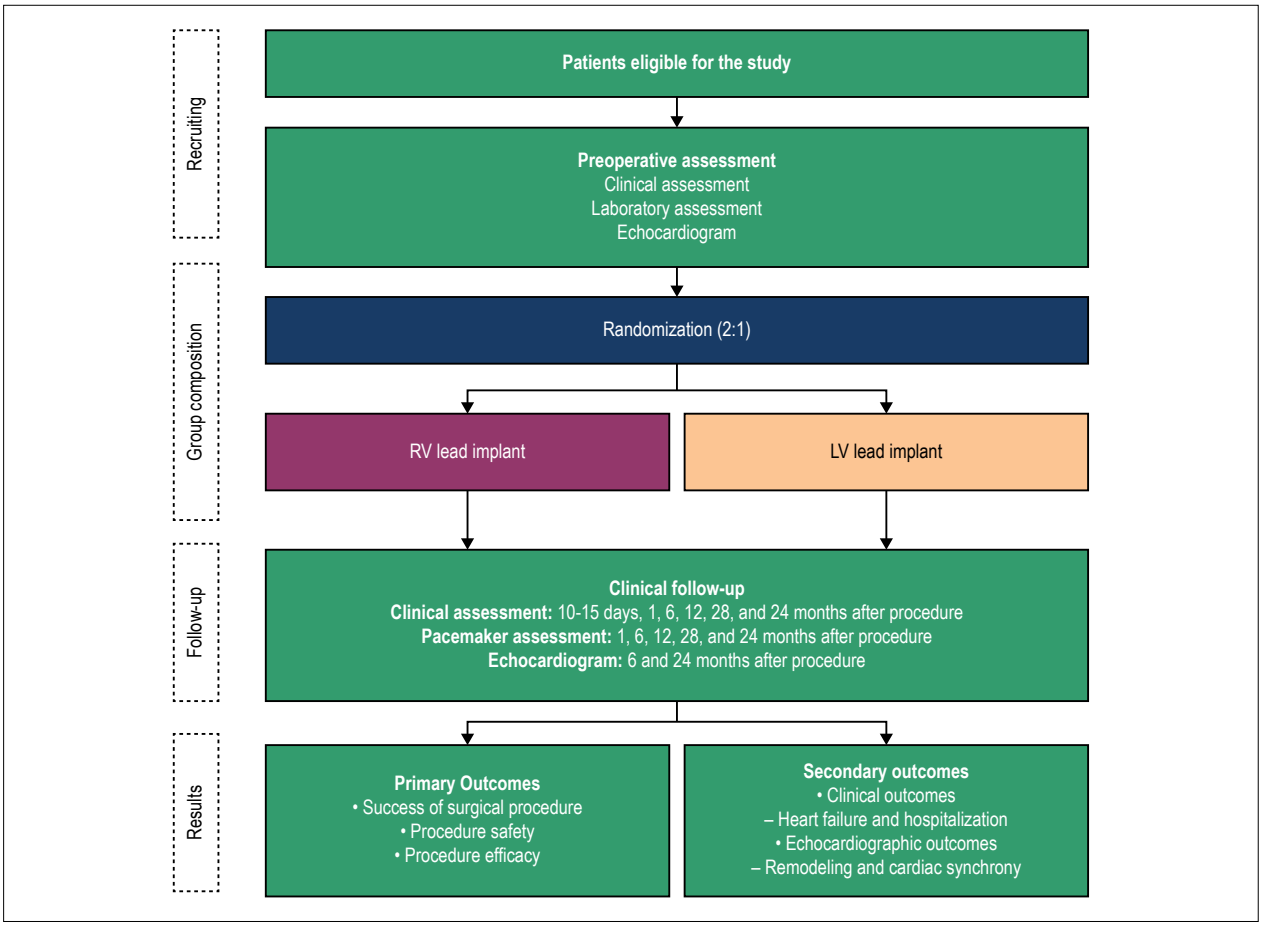

Figure 1 – *Diagram showing the main phases of the study. LV: left ventricle; RV: right ventricle.*

into one of the veins of the lateral or posterolateral wall (Figure 2). When it was not possible to use the veins of the lateral or posterolateral wall due to inadequate stimulation or sensitivity, phrenic stimulation, or lack of lead stability, the diagonal vein was used; placement in the anterior or posterior interventricular sulci was not permitted.

Exclusion of patients when implant through the coronary sinus was not feasible

This study excluded all patients allocated into the LV Group in whom it was not possible to implant the lead in coronary veins. After the surgical team determined that implantation in the LV was not possible, the *Medtronic Attain StarFix® Model 4195 OTW* lead was removed and a new *Medtronic CapSureFix Novus® 5076-58* was implanted in the RV. After the procedure, the patients were excluded from the study.

Study outcomes

This study's primary outcomes include: (1) The proposed procedure was successful, defined by coronary sinus catheterization with lead implant in the posterior or lateral LV wall; (2) Procedure safety, defined by the absence of surgical complications during the study period (24 months); (3) Procedure efficacy, defined by the maintenance of chronic stimulation thresholds at < 2.5 V with 0.4 ms during the study period (24 months).

Secondary outcomes were clinical evolutions and echocardiographic changes, such as: (1) Alteration of left ventricular function, defined by the reduction of at least 10% of the ejection fraction in the examination performed at the end of the study; (2) LV positive remodeling, defined by a 15% increase in the systolic diameter of the cardiac chamber. (3) Ventricular dyssynchrony, defined by the presence of intra-or interventricular electromechanical delay in the examination performed at the end of the study.

Sample size calculation

The calculation of this study's sample size was based on the average occurrence rate of the primary outcomes according to the description in the literature, considering an alpha error of 5% and a statistical power of 80%. With respect to operative outcomes, we found procedural success, efficacy, and safety rates in 99% and 91% of the patients who underwent lead implantation in the RV and the LV, respectively.[1,2,28] The sample size required for finding an equivalence between the two techniques was estimated at 188 patients in the LV Group and 94 in the RV Group, with a total of 282 cases.

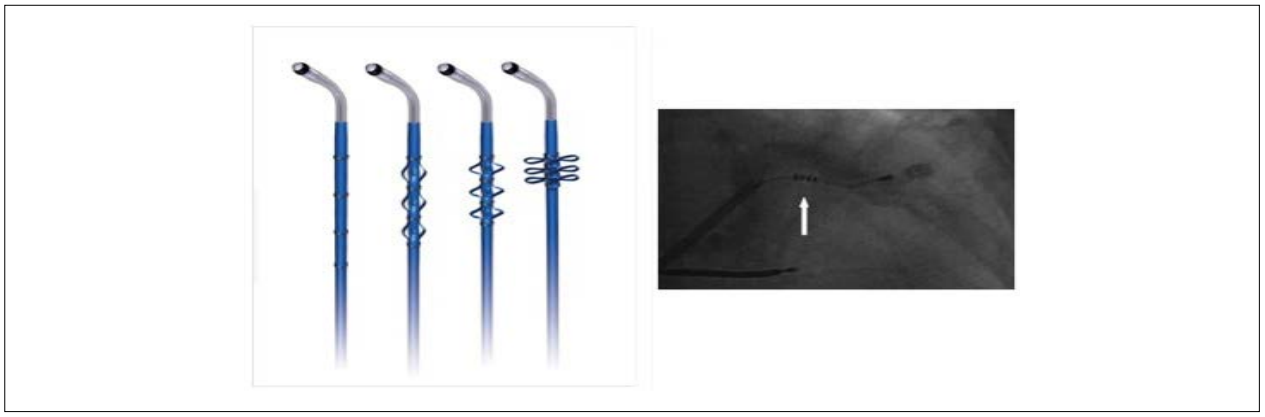

Figure 2 – *View of the active-fixation coronary sinus lead (Medtronic Attain StarFix® Model 4195 OTW).*

Electronic data collection and management

Demographic, clinical, surgical, and echocardiographic data were collected and stored in an electronic database developed in REDCap (*Research Electronic Data Capture*) System,[34,35] which is hosted on our institution's server.

Statistical analysis

The data registered in the REDCap System were exported in the form of Excel spreadsheets (Microsoft Excel) and analyzed by the *Statistical Package for the Social Sciences* (SPSS), version 17.0.

All variables were initially analyzed descriptively. For quantitative variables, this analysis was done by observing the minimum and maximum values, the averages, and standard deviations. Absolute and relative frequencies were calculated for all qualitative variables.

We used unpaired Student's *t*-test to compare averages between groups; when the normality assumption of the data was rejected, the variable was evaluated by logarithmic transformation. The chi-squared test or Fisher's exact test was used to test homogeneity between proportions. We used Analysis of Variance with repeated measures to compare groups throughout the evaluations.

Data analysis was performed according to the intention-to-treat principle. The level of significance for statistical tests was set at 5%.

Results

Participants

In the period between June 2012 and January 2014, 417 patients were indicated for conventional PM implantation due to bradyarrhythmias and were, thus, potential candidates for participation in this study. Of these, 91 were included in the study (Figure 3).

Patient inclusion was prematurely interrupted by a consensual decision made by the study's monitoring committee due to problems related to safety of using the *Medtronic Attain StarFix® Model 4195 OTW* lead. Following this decision, no other participants were included. Nonetheless, clinical follow-up continued until the last patient, who was included in January 2014, had completed 24 months of postoperative follow-up. The premature interruption of this study occurred due to difficulties in obtaining adequate left ventricular pacing conditions with the operating technique defined in the research protocol, on the part of the study population.

Demographic and basic clinical characteristics

The population included in this study was composed of 71 individuals who participated in all phases of the study. There was a slight predominance of females (52.1%), as well as individuals who self-identified as white (69.0%). At the moment of inclusion, average age was 66.5 ± 11.2 years, varying from 24 to 85 years of age. Demographic and clinical characteristics were similar in both groups, except for the presence of Chagas disease, which was more common in the LV Group (Table 1).

Characteristics of the operation

Atrioventricular PM were implanted in 95.8% of individuals studied. Single-chamber ventricular pacing was indicated in 3 (4.2%) patients as a consequence of permanent atrial fibrillation. Details regarding surgical procedures performed on patients in the RV and LV Groups are shown in Table 2.

Data comparison related to the operations performed to implant the devices used in this study revealed significant differences between the groups. Time spent implanting left ventricular leads was, on average, 32.4 minutes greater than RV lead implant. Moreover, the total duration of the procedure was also longer, lasting, on average, 36.3 minutes more in patients in the LV Group.

The approach used to introduce the leads also differed significantly between the two groups. In patients allocated to the LV Group, cephalic vein dissection, either isolated or in association with one puncture in the subclavian vein, was more frequent. The analysis in Table 2 shows that two punctures of the subclavian vein was the preferred technique for the patients in the RV Group ($p = 0.002$).

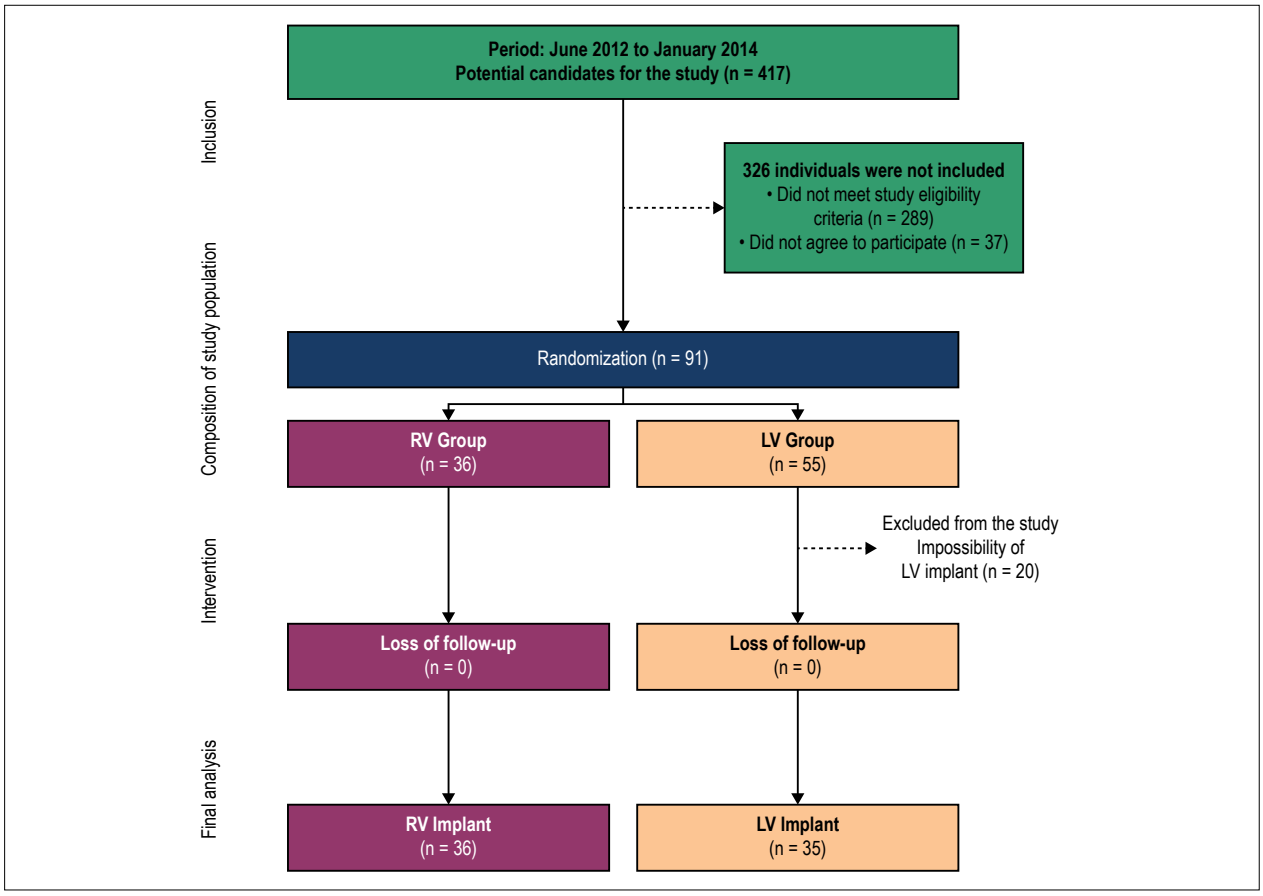

Figure 3 – *Composition of the study population. LV: left ventricle; RV: right ventricle.*

Primary study outcomes

Success of the proposed surgical procedure

In all patients in the RV Group, PM implantation was successfully performed without any intercurrences. In the LV Group, on the other hand, it was not possible to implant the lead in coronary veins in 20 (36.4%) of the of the 55 patients initially allocated.

The most frequent cause of failure to implant the LV lead was undesired phrenic nerve stimulation in regions that could be stimulated through the LV free wall. This problem occurred in 12 patients, representing 60% of all causes of LV implant failure. Coronary sinus cannulation difficulties (n = 3), inability to access coronary veins (n = 5), and unstable positioning (n = 2) prevented the use of left ventricular pacing in the other cases of failure to use the coronary sinus.

Surgical procedure safety

Postoperative complications were detected only in the LV Group. The most frequent complication was phrenic stimulation, observed in 9 (25.7%) patients.

During the clinical follow-up period, 4 (11.4%) patients in the LV Group underwent reoperation. There were 1 case of LV lead fracture (358 days after the initial implant) and 3 (8.6%) cases of phrenic stimulation which could not be resolved by reprogramming (42, 55, and 70 days after the initial procedure). In all 4 cases, the surgical procedure was performed successfully and without complications. The surgical team, however, decided to perform new lead implants in the RV, leading to a crossover of patients from the LV Group to the RV Group.

Surgical procedure efficacy

Once the previously mentioned complications were corrected, stimulation and sensitivity were considered adequate in all phases of the study in 100% of the patients in the RV Group and 31 (88.6%) patients in the LV Group (Table 3). Of the 4 patients who presented ventricular stimulation thresholds above those considered adequate in this study, 2 cases occurred intraoperatively (acute phase); 1 patient presented alterations in the stimulation threshold during months 6, 12, 18, and 24 of clinical follow-up and 1 presented alterations in months 18 and 24 of clinical follow-up.

Secondary study outcomes

Clinical outcomes

There were two deaths in the study, both in patients in the RV Group. The declared causes were acute myocardial infarction, 13.2 months after implantation, and septic shock due to pneumonia, 20.9 months after implantation.

Table 1 – Demographic and clinical characteristic of study participants

Characteristics	Total (n = 71)	LV Group (n = 35)	RV Group (n= 36)	p
Female sex, n (%)	37 (52.1)	19 (54.3)	18 (50.0)	0.717(1)
Age (years), average ± SD	66.5 ± 11.2	68.4 ± 9.2	64.8 ± 12.8	0.179(2)
White race, n (%)	49 (69.0)	24 (68.6)	25 (69.4)	0.936(1)
Functional Class (NYHA), n (%)				
I	22 (31.0)	12 (34.3)	10 (27.8)	
II	33 (46.5)	15 (42.9)	18 (50.0)	0.544(1)
III	14 (19.7)	8 (22.9)	6 (16.7)	
IV	2 (2.8)	-	2 (5.6)	
Structural cardiac disease, n (%)				
None	52 (73.2)	25 (71.4)	27 (75.0)	
Chagas disease	12 (16.9)	9 (25.7)	3 (8.3)	0.063(3)
Ischemic heart disease	6 (8.5)	1 (2.9)	5 (13.9)	
Hypertrophic cardiomyopathy	1 (1.4)	-	1 (2.8)	
Associated comorbidities				
None	2 (2.8)	1 (2.9)	1 (2.8)	1.000(3)
Hypertension	59 (83.1)	28 (80.0)	31 (86.2)	0.492(1)
Chagas disease	8 (11.3)	5 (14.3)	3 (8.3)	0.710(3)
Diabetes	19 (26.8)	10 (28.6)	9 (25.0)	0.734(1)
Dyslipidemia	23 (32.4)	10 (28.6)	13 (36.1)	0.497(1)
Cardiovascular medications, n (%)				
None	4 (5.6)	2 (5.7)	2 (5.6)	1.000(3)
ACEI/ARB	52 (73.2)	28 (80.0)	24 (66.7)	0.204(1)
Diuretics	29 (40.8)	12 (34.3)	17 (47.2)	0.267(1)
Betablockers	8 (11.3)	6 (17.1)	2 (8.3)	0.151(3)
QRS duration prior to implant > 120 ms, n (%)	53 (74.6)	26 (74.3)	27 (75.0)	0.944(1)
LV ejection fraction, average ± SD	59.9 ± 6.8	61.1 ± 4.4	58.1 ± 8.4	0.069(2)
LV final systolic volume, average ± SD	42.1 ± 16.1	39.5 ± 15.4	44.8 ± 16.5	0.168(2)
LV final diastolic volume, average ± SD	100.7 ± 24.7	97.1 ± 27.2	104.3 ±21.7	0.223(2)
BNP, average ± SD	83.2 ± 111.8	72.3 ± 77.6	93.8 ±137.6	0.482(2)
TNF alpha, average ± SD	50.7 ± 186.6	74.9 ± 265.1	27.2 ± 13.5	0.388(2)
IL6, average ± SD	11.3 ± 16.0	9.1 ± 12.4	13.4 ± 18.8	0.092(2)

ACEI: angiotensin converting enzyme inhibitors; ARB: angiotensin receptor blockers; LV: left ventricle; NYHA: New York Heart Association; RV: right ventricle; SD: standard devition. (1) Chi-squared test; (2) Unpaired Student's t-test; (3) Fisher's exact test.

There were no hospitalizations due to heart failure during the study's follow-up period. At the end of the first month of observation, 100% of the patients in the RV Group and 97.1% in the LV Group were oligosymptomatic, being classified as in functional class (FC) I or II. The analysis of Figure 4 shows that there was no difference in behavior between the groups throughout the follow-up period. Few patients presented symptoms with minor exertion and were classified as FC III. No cases were classified as FC IV.

Echocardiographic results

The echocardiographic studies performed at the baseline and at month 24 of follow-up showed that there was left ventricular remodeling and changes in ejection fraction over time in both groups. They also showed the presence of differences in the mechanics of the two ventricles resulting from right or left ventricular pacing.

The analysis in Table 3 makes it possible to observe that: (1) a reduction of more than 10% in LV ejection fraction was observed in 23.5% of the patients in the RV group and in 20.6% of the LV Group (p = 0.767); (2) an increase of more than 15% in final systolic volume was observed in 27.3% of the individuals in the RV Group and 29.4% in the LV Group (p = 0.846), and that both outcomes occurred at the same time in 32.3% of the RV Group and 35.3% of the LV Group (p = 0.798).

Table 2 – Operation data of study participants

Characteristics	Total (n = 71)	LV Group (n = 35)	RV Group (n= 36)	p
Pacemaker type, n (%)				
Single-chamber	3 (4.2)	2 (5.7)	1 (2.8)	0.614(3)
Dual-chamber	68 (95.8)	33 (94.3)	35 (97.2)	
Lead implant access				
Subclavian vein puncture	44 (62.0)	16 (45.7)	28 (77.8)	
Cephalic vein dissection	6 (8.5)	2 (5.7)	4 (11.1)	0.002(3)
Both	21 (29.6)	17 (48.6)	4 (11.1)	
Duration of ventricular lead positioning				
Average ± SD (minutes)	22.2 ± 21.4	38.5 ± 19.8	6.4 ± 3.6	< 0.001(2)
Variation (minutes)	2 - 119	8 - 119	2 - 15	
Total procedure duration				
Average ± SD (minutes)	84.8 ± 29.9	103.3 ± 27.9	66.9 ± 19.0	< 0.001(2)
Variation (minutes)	34 - 167	45 - 167	34 - 113	
RV pacing site, n (%)				
Apex	-	-	4 (11.1)	
Septum	-	-	32 (88.9)	NA
LV pacing site, n (%)				
Anterolateral	-	6 (17.1)	-	
Lateral	-	26 (74.3)	-	NA
Posterolateral	-	3 (8.6)	-	

LV: left ventricle; NA: not applicable; RV: right ventricle; SD: standard deviation. (2) Unpaired Student's t-test; (3) Fisher's exact test.

Table 3 – Echocardiographic outcomes, derived from the comparison between the baseline echocardiogram and the echocardiogram performed at the 24-month follow-up visit

Echocardiographic outcomes	LV Group (n = 34)	RV Group (n = 34)	p
LVEF			
10% reduction	7 (20.6%)	8 (23.5%)	0.767(1)
Without 10% reduction	27 (79.4%)	26 (76.5%)	
FSVLV			
15% increase	10 (29.4%)	9 (27.3%)	0.846(1)
Without 15% increase	24 (70.6%)	24 (72.7%)	
Alteration of LVEF and/or FSVLV			
Present	12 (35.3%)	11 (32.3%)	0.798(1)
Absent	22 (64.7%)	23 (67.7%)	
Intraventricular dyssynchrony			
Delay ≥ 65 ms	14 (43.7%)	19 (55.9%)	0.324(1)
Delay < 65 ms	18 (56.3%)	15 (44.1%)	
Interventricular dyssynchrony			
Delay ≥ 100 ms	22 (68.7%)	31 (91.2%)	0.022(1)
Delay < 100 ms	10 (31.3%)	3 (8.8%)	

LVESV: left ventricular end-systolic volume; LV: left ventricle; LVEF: left ventricle ejection fraction; RV: right ventricle. (1) Chi-squared test.

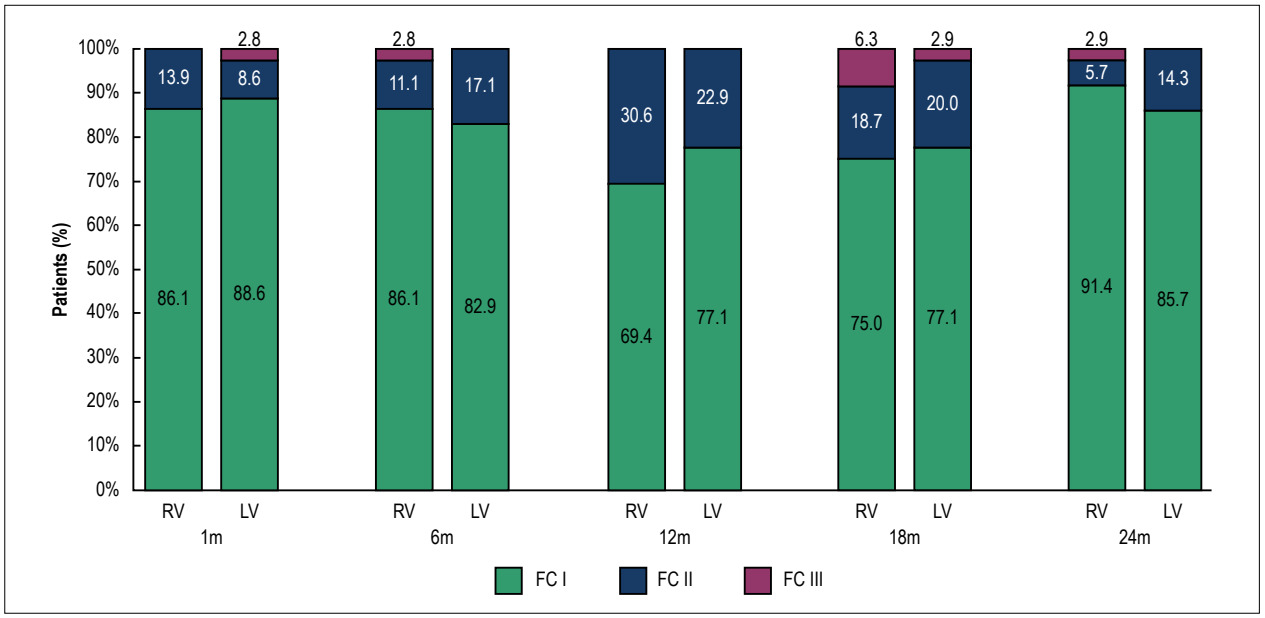

Figure 4 – *Behavior of Functional Classification of Heart Failure (NYHA) during assessment in the clinical follow-up phase. FC: functional class; LV: left ventricle; RV: right ventricle.*

According to the criteria defined for the present study, tissue Doppler analysis showed that 55.9% of the individuals in the RV Group and 43.7% of those in the LV Group had left ventricular intraventricular dyssynchrony (p = 0.324). This method also detected that 91.2% and 68.7% of patients in the RV and LV groups, respectively, had interventricular dyssynchrony (p = 0.022).

Discussion

The present study was the first designed with the specific purpose of comparing the clinical and functional effects of left ventricular pacing to those of right ventricular pacing in patients with advanced atrioventricular conduction block, as well as evaluating the feasibility of using coronary sinus as a safe alternative for the artificial pacemaker dependent patients on this type of therapy.

Considering the evidence that there are deleterious effects related to right ventricular pacing in patients with advanced atrioventricular blocks who have preserved ventricular function at the time of first PM implantation[7-14] and the fact that new transvenous techniques for implanting leads in the LV are being developed, we judge that it is important to evaluate whether there are clinical and functional differences that justify changing from the classic form of endocardial right ventricular pacing to LV pacing, as well as whether the routine use of left ventricular pacing through the coronary sinus is technically feasible in patients with atrioventricular blocks.

There were difficulties in patient inclusion in the study, mainly due to the high rate of chronic renal dysfunction in individuals with acquired atrioventricular block and due to the urgency of treating bradycardia, which made it difficult to perform fundamental tests for selection and inclusion of patients into the study. The main reason why only 91 patients were included was the monitoring committee's decision to interrupt the study, owing to problems related to the safety of the *Medtronic Attain StarFix® Model 4195 OTW* lead in the present study project. In more than a third of individuals allocated for LV implant, it was not possible to obtain safe conditions for artificial pacing of patients who were dependent on this type of therapy. In this manner, in 20 of the 55 patients allocated into the LV Group, after unsuccessfully attempting the left ventricular implant through the coronary sinus, the surgical team decided to perform the implant in the RV. Despite the fact that, at the end of the operation, these 20 patients received the lead in the RV, they were excluded from the phase which compared results regarding pacing effectiveness and clinical and functional effects. On the other hand, regarding safety analysis, the failure to obtain safe conditions for LV pacing in 36.4% of cases was decisive to the conclusion that the *Medtronic Attain StarFix® Model 4195 OTW* lead, notwithstanding its utility in patients undergoing biventricular implantation for cardiac resynchronization, is not an adequate option for unifocal ventricular pacing in patients dependent on PM.

The most frequent reason that left ventricular pacing failed in the patients of the present study was phrenic nerve stimulation. Although this complication is reported in 2–37% of patients with severe left ventricular dysfunction,[31-33,36] in the present study it occurred in 12 patients, which represents the main cause of failure to implant in the LV. Nevertheless, 25.7% of patients presented phrenic nerve stimulation in the postoperative period. We believe that the small epicardial surface of the LV lateral wall, in patients with preserved ventricular function, when compared to the epicardial area of patients with severe dysfunction, caused the regions where the left ventricular lead was implanted to be very close to the phrenic nerve. The association of this condition with the unipolar configuration of the *StarFix.* lead implicated an absence of alternatives for correcting the

phrenic nerve stimulation, with the exception of reducing the stimulation energy. Reducing the stimulation energy, in turn, prevented an adequate safety margin from being maintained in patients pacemaker dependent patients.

Notwithstanding the premature interruption of the study, the results observed regarding ventricular pacing safety and effectiveness assessments were sufficient to reach strong conclusions.

Analysis of the intraoperative parameters of ventricular leads showed that the stimulation threshold, impedance, and sensitivity for QRS complexes showed significant differences between the groups. With the exception of two cases in the LV Group, the values obtained for both RV and LV stimulation were within the range considered ideal for safe ventricular pacing.

Even though the postoperative complication rate was expressively higher in the LV Group, undesired phrenic nerve stimulation was the most common complication, occurring in 9 of the 35 patients in this group. Of these, 3 cases required surgical correction due to the impossibility of resolving the problem by reprogramming the energy. A fourth patient required reoperation due to a fracture of the *StarFix* lead conductor. In these 4 cases, the medical team decided to implant a new lead in the RV, which resulted in 4 cases of crossover in the study.

Based on the criteria established in the study, efficacy, stimulation and sensitivity parameters were considered adequate in all evaluations perfomed for all patients of the RV group. In the LV Group, however, only 31 of the 35 patients studied presented adequate ventricular pacing conditions in all phases of the study. In 2 patients, the parameters did not meet the conditions established as adequate by the study during the intraoperative phase, but there was improvement in the stimulation conditions during the postoperative period. In 2 other cases, failure began to occur in month from the 6th and 18th months of follow-up.

The premature interruption of the study compromised the analysis of secondary results, as the sample size calculation had defined that 282 research subjects would be included in the study, 188 patients in the LV Group and 94 in the RV Group.

During the study's follow-up period, there were no hospitalizations owing to heart failure. On the other hand, we observed the occurrence of left ventricular remodeling and reduction of left ventricular ejection fraction when comparing the echocardiogram performed at the baseline with that obtained at month 24 of follow-up. Although the rate of patients whose LV ejection fraction worsened was higher in patients in the RV Group (23.5% vs. 20.6%), the number of individuals included in the study did not allow the sample to be analyzed regarding this result. The rate of ventricular remodeling was slightly higher in patients in the LV Group (29.4% vs. 27.3%).

Analysis of cardiac synchrony showed that there was an important difference between LV wall activation time in patients in the RV Group more frequently than in the LV Group (55.9% vs. 43.8%). Similarly, patients in the RV Group more frequently showed delays in activation between the RV and LV (91.2% vs. 68.8%). Notwithstanding the small number of patients evaluated, the difference in the occurrence rate of interventricular dyssynchrony between groups was statistically significant ($p = 0.022$).

Study limitations

Although the study met its primary objectives, there are some inevitable limitations. The main limitation is related to the premature interruption of the study which made it impossible to reach the sample size necessary for evaluating clinical and echocardiographic outcomes. Additionally, a small number of individuals with LV ejection fraction between 0.40 and 0.50 were included; these individuals would possibly have had greater chances of suffering the deleterious effects of RV pacing. This notwithstanding, the safety and efficacy results refer exclusively to the use of unipolar leads, which no longer represent state-of-the-art LV pacing through the coronary sinus, given that the last 3 years have seen the development of quadripolar leads that facilitate positioning with ideal stimulation in a location far from the phrenic nerve.[36,37]

Regardless of the methodological problems occurred, it was possible to observe that interventricular synchrony was shown to be significantly better in patients with LV pacing. This perspective opens doors for future studies to be conducted using quadripolar leads with the aim of preventing the deleterious effects of conventional ventricular pacing.

Conclusions

The routine use of isolated left ventricular pacing pacemaker dependent patients with the use of a *Medtronic Attain StarFix® Model 4195 OTW* lead through the coronary sinus was shown to be impractical given the low rates of procedural success, safety, and efficacy.

The comparison of the clinical and echocardiographic effects of left ventricular pacing with those of right ventricular pacing was not possible owing to the low level of cases studied, even though interventricular synchrony was shown to be significantly better in patients with LV pacing.

Author contributions

Conception and design of the research, analysis and interpretation of the data and writing of the manuscript: Crevelari ES, da Silva KR, Costa R; acquisition of data: Crevelari ES, Albertini CMM, Vieira MLC; obtaining funding: Costa R; critical revision of the manuscript for intellectual content: Crevelari ES, da Silva KR, Albertini CMM, Vieira MLC, Martinelli Filho M, Costa R.

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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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Análise de Projetos de Pesquisa (CAPPesq) do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo under the protocol number 00610412,2,0000,0068 (Plataforma Brasil CAAE). All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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