Cardiac Pacing in Hypertrophic Cardiomyopathy. A Cohort with 24 Years of Follow-Up

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Summary

Background: The benefits of heart stimulation in hypertrophic cardiomyopathy (HCM) patients have been questioned. Research work available in Brazil on those benefits is scarce.

Objective: To describe the indication, clinical response, complications and survival time related to pacemaker implant in HCM patients.

Methods: Thirty-nine hypertrophic cardiomyopathy patients were studied (41% males) and submitted to pacemaker implant from May, 1980 through November, 2003.

Results: Twenty-seven patients presented obstructive hypertrophic cardiomyopathy, and 12, non-obstructive. Mean age was 46.4 years of age (range 14 – 77), with follow-up of 6.4 ± 4.1 years. Major indications for implant were: spontaneous or induced atrioventricular block (54%), refractoriness to therapeutic conduct associated to high gradient (33%), support for drug therapy to treat bradychardia (8%), and atrial fibrillation prevention (5%). Functional class was shown to improve from 2.41±0.87 to 1.97±0.92 (p = 0.008), and symptoms referred were reduced. No change was made in drug therapy administration. No procedure-related deaths were reported. Although shown to be safe, the procedure was not free from complications (6 patients – 15.4%). Three deaths occurred in the follow-up period - the three of them were atrial fibrillation female patients, with evidence of functional deterioration. A close association was observed between clinical condition worsening and the onset of atrial fibrillation or flutter

Conclusions: Cardiac pacing in HCM patients was successful, with evidence of symptoms relief in obstructive HCM patients. No functional improvement was observed in non-obstructive patients.(Arq Bras Cardiol 2008;91(4):250-256)

Key words: Cardiac pacing, artificial; cardiomyopathy, hypertrophic; outcome assessment (health care); cohort studies.

Introduction

Hypertrophic cardiomyopathy (HCM) is inherited in an autosomal heart disease dominant fashion, with a high degree of clinical variability. Anatomically, it is characterized by ventricular hypertrophy in the absence of cardiac or systemic diseases that could justify it[1]. As the condition advances the following are to be pointed out: the development of ventricular and supraventricular arrhythmias (atrial fibrillation in particular), heart failure, cerebrovascular accidents and sudden death.

Deeper knowledge on HCM contributed for the development of more rational approaches – from genetic counseling to the use of invasive treatment methods, among them cardiac pacing.

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The use of a pacemaker in HCM patients is not circumscribed to the indications for symptoms refractoriness in high gradient patients. It also applies to conventional bradychardia support indications demanded by a number of etiologies, and include the non-rare associations between HCM and atrioventricular conduction disorders[2,3].

Data are scarce in regard to cardiac pacing in HCM patients in Brazil. Additionally, the progression of patients who had pacemaker implant is not known. The present study was conducted with the purpose to report the experience at the Clinics Hospital Heart Institute, University of São Paulo, at São Paulo, Brazil (HC-FMUSP - InCor). It describes the management and the follow-up of HCM patients submitted to pacemaker transplant in the last 24 years, and includes major indications, clinical response to implant, survival time, and complications related to the use of cardiac pacing.

Methods

A prospective and descriptive analysis cohort study, with 129 medical records reviewed from the Pacemaker Unit

data base; additional 613 HCM patients under follow-up at the Myocardiopathy Clinical Unit at the Heart Institute (HC-FMUSP). Thirty-nine patients were identified for HCM. Pacemaker implant was performed between May, 1980 and November, 2003. Data collection started in February, 2004 and was closed in September, 2004. No patients who had implantable cardioverter-defribillator (ICD) were included. Clinical follow-up time frame was 6.4±4.1 years.

Clinical, electrocardiographic, and echocardiographic data were obtained from medical records. All patients were reevaluated in 2004. Whenever death occurred, information was obtained from family members or death certificate. Two patients were lost to follow-up: one in 1997 - Functional Class I male, after a 17 year-follow-up, who had his pacemaker implanted due to post-myectomy total atrioventricular block (TAVB). The other patient was lost to follow-up in 199, after a 5-year follow-up. The female patient was Functional Class III, with indications of progression towards the dilated phase of heart failure.

Statistical analysis

Statistical analysis was carried out through SPSS for Windows® Version 13.0. Mann-Whitney U test was used for non-related samples analysis (comparison with obstructive HCM [OHCM] patients versus non-obstructive [NOHCM] patients. Student t test was used for related sample analysis quantitative data whenever variables distribution were assumed to be normal. Wilcoxon test was used whenever pre-requisites could not be assumed to be normal. For qualitative data analysis, in addition to frequency distribution comparisons before and after implant were carried out through chi-square distribution (Mcnemar's non-parametric test). Statistic significance (p value) was reached whenever alpha value was ≤ 0.05.

Results

Patients' mean age at the time of implant was 46±15 years of age (14 – 76 range). Sixteen patients (41%) were males. From all patients, 20 (51%) presented Functional Class III or IV heart failure (New York Heart Association – NYHA classification) and 16 (41%) presented atrial fibrillation at early follow-up. Variables analysis included gender, age, functional class, reason for implant and stimulation mode, echocardiographic data, symptoms (syncope and pre-syncope group, dyspnea, palpitations and precordial pain), time of follow-up, clinical response, complications and implant-related survival period.

Table 1 summarizes population data and compares patients' profiles in the presence or absence of gradient in left ventricle outflow tract.

Thirty-nine HCM patients were submitted to pacemaker implant in 24 years of follow-up. Female patients

Table 1 - Clinical and electroechocardiographic data in the presence or absence of gradient in left ventricle outflow tract.*

Data	Total (n = 39)	Obstructive (n = 27)	Non-obstructive (n = 12)	p
Clinical Follow-up - years	6.4±4.1	6.3±4.3	6.5±3.9	0.81*
Males n (%)	16 (41)	11 (41)	5 (42)	0.96*
Age at Implant – Years of age	46 (14-77)	49 (14-76)	40 (25 – 52)	0.08*
Symptoms				
Dyspnea	32 (82)	24 (89)	8 (67)	0.04*
Palpitations	23 (59)	13 (48)	10 (83)	0.05*
Precordial pain	20 (51)	13 (48)	7 (58)	0.64*
Pre-syncope	6 (16)	3 (11)	3 (25)	0.30*
Syncope	12 (31)	8 (30)	4 (33)	0.88*
Atrial Fibrillation – no. (%)	16 (41)	8 (30)	8 (64)	0.03*
Functional Class (NYHA)				
I (%)	7 (18)	4 (15)	3 (25)	NA
II (%)	12 (31)	7 (26)	5 (42)	NA
III/IV (%)	20 (51)	16 (59)	4 (33)	NA
Echocardiogram Data				
Gradient – mmHg	62±52	88±41	6±9	NA
Septum (mm)	19.5±4	20.5±4	17.6±3	0.13*
Posterior Wall -mm	10.6±2	11.2±2.2	9.4±2	0.48*
Left Atrium - mm	46.9±9	46.3±7	47.8±12	0.81*

± Stand for Mean ± Standard Deviation; P - Mann-Whitney U Test; NA – Not Applicable*

Table 2 - Indications for pacemaker implant in the presence of absence of obstruction at LV outflow tract.

		Total	%	Obstructive	%	Non-obstructive	%
Atrioventricular Block	Post-surgery TAVB	6	15.4	5	18.5	1	8.3
	Spontaneous TAVB	6	15.4	2	7.4	4	33.3
	AV Post-Ablation TAVB	9	23.1	3	11.1	6	50.0
Refractory	Precordial pain	3	7.7	3	11.1	0	-
	Syncope	7	17.9	7	25.9	0	-
	Dyspnea	3	7.7	3	11.1	0	-
Support	Bradychardia	3	7.7	3	11.1	0	-
AF Prevention	AF Prevention	2	5.1	1	3.7	1	8.3
	Total	39	100	27	100	12	100

predominated, with a total of 59% of total population. Out of the 39 patients 27 (69%) presented OHCM and 12 (31%) NOHCM.

As shown in Table 1, 82% of patients were classified in Functional Class II or higher (NYHA). Over 50% of patients were Functional Class III or IV.

Despite optimized therapy, dyspnea (82%), palpitations (59%) and precordial pain (51%) were the most commonly found symptoms. Syncope and pre-syncope were referred by 18 patients (45%) and were the reason for pacemaker implant indication whenever associated to high gradient in 7 patients (26%).

Echocardiographic data showed 19.5±4 mm mid-portion septal hypertrophy. Those patients were also observed to present increased left atrium at the time the study started (average size 46.9±9 mm). Mean gradient found in OHCM patients was 88.4±41mmHg.

When OHCM patients were compared to NOHCM patients both populations had quite similar characteristics, with differences being functional class III/IV (59% OHCM versus 33% NOHCM), and atrial fibrillation, with NOHCM patients predominating (30% - OHCM versus 64% - NOHCM, $p = 0.032$). The difference is due to special indications for NOHCM, as discussed later.

Clinical treatment was based on beta-blockers and calcium channels blockers, either isolatedly or in association, for 72% of the population. Compliance was high. The same conduct was kept along follow-up time associated to the use of an anti-arrhythmic whenever required. It should be mentioned that oral anticoagulants were more often used due to atrial fibrillation. Diuretics were also seen to be used more often, in particular for non-obstructive patients.

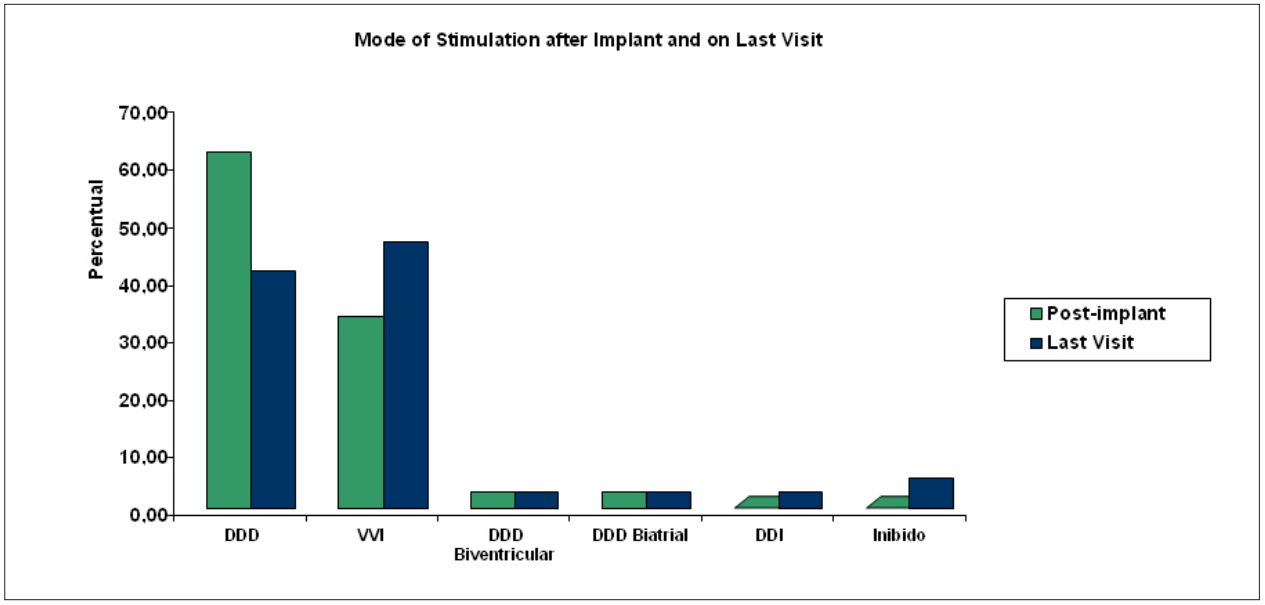

Figure 1 - Mode of Stimulation Post-Implant and on the Day of Last Visit

Table 3 - Distribution of patients following their functional class along time

Functional Class	Pre-Implant	Post-Implant	Last Visit
I	18%	49%	36%
II	31%	38%	33%
III or IV	51%	13%	31%

Indications for pacemaker implant

Table 2 shows the indications for pacemaker implant. They have been organized in 4 groups:

- Atrioventricular conduction block disorders (Total atrioventricular block - TAVB) - 21 patients (spontaneous or acquired);
- Gradient-related refractory symptoms - 13 patients;
- Drug support due to bradychardia - 3 patients;
- Atrial fibrillation prevention - 2 patients.

Stimulation mode

After implant, 24 patients (62%) were under sequence atrioventricular stimulation (DDD) pacing mode. Thirteen patients (33%) were under unichamber ventricular mode (VVI), and one patient (3%) under biatrial stimulation (Biatrial DDD) (Figure 1).

All OHCM patients whose indication was symptoms refractoriness (13 patients) had a prospective follow-up period and their pacemaker program for short AV interval (approximately 100ms), with ECG and ECHO adjusted programming in order to ensure maximum ventricular stimulation.

Although 2 patients were sent for pacemaker implant under biatrial stimulation, that mode could be applied to one of them only. One patient (3%) was submitted to atriobiventricular pacemaker implant (Biventricular DDD) after myectomy surgery due to the onset of TAVB and heart failure immediately after surgery.

As a result of an increase in atrial fibrillation cases, only 16 patients (41%) were under DDD pacing on their last visit. Eighteen patients (46%) were under ventricular unichamber pacing, and one (3%) under biatrial atrioventricular pacing. Two patients (5%) presented pacemaker inhibition (one did not show evidence of objective improvement at stimulation; the other presented atrial flutter with high ventricular response). One patient had his pacemaker programmed for DDI stimulation mode (double chamber, no ventricular stimulation via atrium) due to atrial fibrillation paroxysms.

Clinical response to treatment

Table 3 presents functional state before and after implant, as well as on the day of last visit (in average, post-implant data refer to the first 3 to 6 months after surgery).

Total population was observed to show functional class improvement. The relevance of such difference is due to the change in class that could be observed for OHCM patients (Table 4), and may be directly related to post-implant gradient reduction (reduction from 88.4 mmHg down to 34 mmHg).

Functional class improvement after pacemaker implant - kept to last visit day - was reflected directly on symptoms relief. The reduction was statistically significant at all components under analysis, as shown in Table 5.

Before pacemaker implant, 41% of the population under analysis presented atrial fibrillation or flutter. At the end of the follow-up, 59%. From those, approximately 30% of the OHCM patients presented atrial fibrillation/flutter atrial in the pre-implant period. The number of patients presenting those arrhythmias practically doubled, along the course of observation, reaching 59%.

Among NOHCM patients, approximately 67% presented those arrhythmias. Such high prevalence, however, was basically due to the specific indication of the pacemaker. Although the role played by ablation or "modification" in the atrioventricular node associated to pacemaker implant as a treatment conduct for refractory HCM is not yet fully understood, it has been suggested in the literature[4-6]. Fifty percent of patients was referred for atrioventricular node ablation and pacemaker implant due to symptomatic, refractory AF/flutter.

Complications associated to pacemaker

Six complications were observed (15%). One patient presented frenic stimulation that was corrected through programming; one patient presented electrode dislocation, and surgery correction was required; a third patient developed chronic pain at pacemaker site, which was

Table 4 - Functional Class Variation in Total Population and in Obstructive and Non-obstructive HCM.

	Functional Class			
	Pre-Implant	Post-Implant	Last Visit	p*
Total	2.41±0.87	1.65±0.74	1.97±0.92	0.008
Obstructive	2.52±0.84	1.69±0.72	1.94±0.89	0.003
Non-obstructive	2.17±0.94	1.58±0.79	2.04±1.01	0.687

** p value for differences between functional class at pre-implant and on last visit.*

Table 5 - Comparison of symptoms reported before pacemaker implant and on the day of last visit.

Total			
	Pre-Implant	Last Visit	P*
Dyspnea	32(82.1%)	23(59%)	0.004
Palpitations	23(59%)	16(41%)	0.039
Precordial pain	20(51.3%)	6(15.4%)	0.0001
Pre-syncope	6(15.8%)	0(0%)	0.031
Syncope	12(30.8%)	4(10.3%)	0.008

** p value calculated by Mcnemar's test*

corrected with drug administration. Pacemaker syndrome was observed in one patient, resulting in atrial electrode implant and change in stimulation mode. Bundle of His ablation and unichamber pacemaker implant were performed in one patient, who needed a new surgery for the implant of a prosthesis with a frequency sensor to correct chronotropic deficit. The major complication was associated to generator change due to manufacturer's recall. The patient had to be submitted to a number of new surgeries to change the generator, to withdraw the system through generator extrusion and for system reimplantation.

Post-implant survival

Three deaths occurred in the post-implant survival period. In the 20-40-year-old range, the female patients presented AF/flutter and were in the dilated phase of the disease. Two of them were NOHCM patients - one due to heart failure (cardiogenic shock) and the other due to pulmonary embolus. The third patient presented OHCM, and had the indication for pacemaker implant due to gradient, refractoriness and recurring syncope. The same patient developed atrial flutter, had been on oral anticoagulant, and the cause of death was hemorrhagic cerebrovascular accident.

Figure 2 shows a survival curve comparison when follow-up time was considered among both OHCM and NOHCM patients. Although this paper does not have enough data to perform an analysis of those patients' survival time, a gap between survival curves can be observed. No difference was observed for the risk of death in the different groups in the period under analysis (p=0.225).

Discussion

To our days, pacemaker implant has been the indication for the management of OHCM patients who are kept symptomatic despite optimized therapeutics[5,7],even considering the placebo effect body of evidence[8,9].

The therapeutic benefits of pacemakers on non-obstructive patients have been less extensively investigated due to strong evidence of the absence of improvement, or even of increased risk of functional deterioration[10], although some authors recommend cardiac pacing for this group of patients[11]. The mechanisms involved in the electrophysiologic and hemodynamic changes in pacemaker therapeutics are not the scope of the present article and may be found in the literature available[12-16].

A high rate of atrioventricular conduction system disorders was observed, with the need of pacemaker implant due to spontaneous TAVB in over 15% of cases. Conduction system disorders may be explained by the profile of patients under study and by applied therapeutics, in addition to the carefully screened population presenting potentially more serious progression of the condition.

Approximately 31% of patients (n=12) presented pre-implant syncope. Only 10% (n=4) in the post-implant follow-up – a significant reduction (p=0.008). For OHCM patients, syncope was the indication for pacemaker implant in 26% (n=7) of patients. From those, only three had repeated syncope after implant, which suggests the therapy may be effective in this subgroup (high gradient + syncope).

From the non-obstructive patients who presented syncope pre-implant, in their turn (n=4), only one patient had repeated

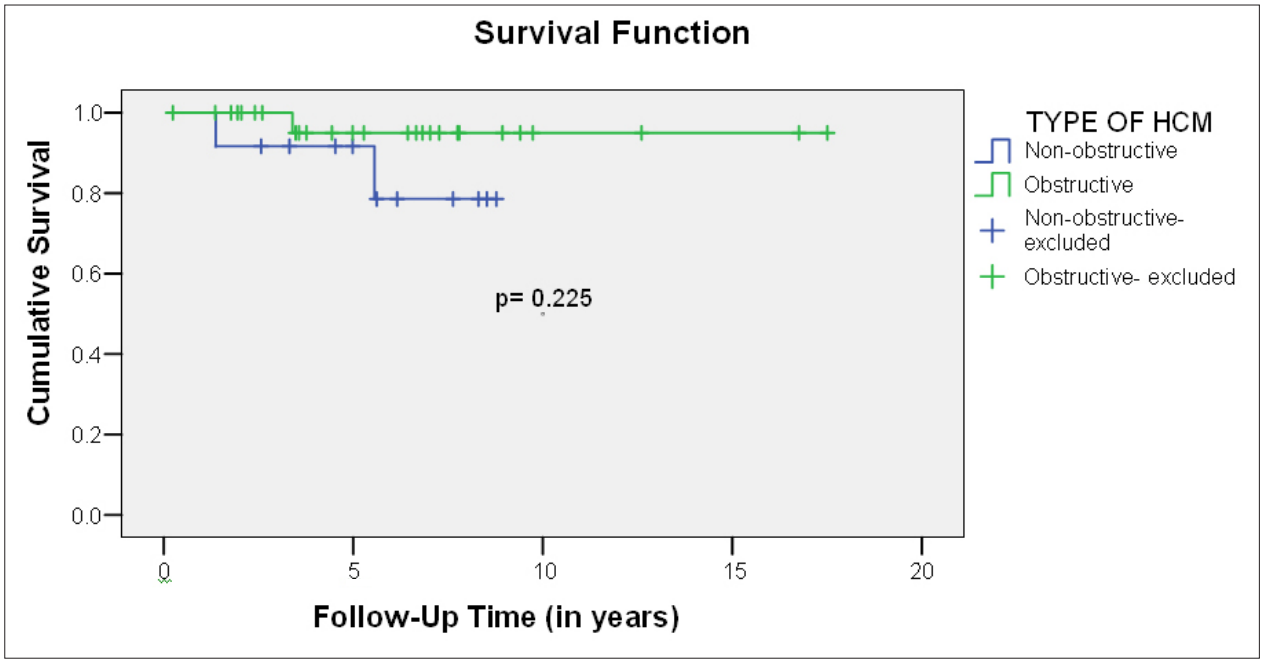

Figure 2 - p value calculated by Breslow test (Generalized Wilcoxon); Survival Curve in Years (Kaplan-Meier) after First Pacemaker Implant

syncope, which was associated to a new-onset atrial flutter.

Although unichamber ventricular stimulation in right ventricle apex is associated to functional class improvement in OHCM patients, optimized effect from stimulation is obtained through sequence atrioventricular stimulation, which can only be performed in approximately 2/3 of patients. It was actually seen in less than 50% of patients on last evaluation day (44%) due to atrial fibrillation high incidence. It seems clear that maximum benefit from heart stimulation, as desired, was not reached. The general scenario suggests benefits from the method when symptoms relief and functional class improvement are evaluated (Tables 3-5). A more detailed analysis reports that in the immediate post-implant period there is substantial functional class improvement. In the long run such improvement loses strength, and statistical significance is kept for total population ($p=0.008$).

Clinical follow-up of NOHCM patients showed that symptom relief observed immediately post-implant could not be kept in the long term (Table 4). The reasons-why involved in clinical improvement in the first months post-implant were not evaluated. The placebo effect seems to be the first assumption. Functional class improvement among OHCM patients was observed to reflect on clinical improvement level. Should placebo effect be the only reason for improvement, then this population would probably have presented functional deterioration along time, or would have reverted to previous functional classes (as occurred among NOHCM patients), which was not observed. Those two findings confirm data previously observed in the literature, where beneficial effects from heart stimulation for the symptomatic, refractory OHCM condition, and clealy shows the absence of long-term improvement among patients who do not present obstruction.

Studies such as PIC Study have shown the association between sequence AV stimulation and symptom relief, as well as patients' preference for this stimulation mode with subsequent living standard improvement.[17] Although this was not specifically evaluated in the present study, in addition to investigating a group with diverse clinical characteristics, the cohort presented significant functional class improvement as well as significant symptom relief, which ultimately reflects on better living standards.

Whether the improvement observed in the OHCM group was associated to other factors rather than specifically gradient-related hemodynamic indication could be questioned, but such scenario could not be the object of study. What could be proven was that drug therapy based on beta-blockers and calcium channel blockers was practically unchanged. Symptomatic relief of OHCM patients may not be related to pacemaker stimulation only. Other factors may coexist and therefore interfere in a more favorable condition course for those patients. For those patients whose pacemaker was associated to myectomy no change was observed in functional class in pre-implant when compared to last visit evaluation. Therefore, clinical improvement may not be attributable to co-intervention, as the absence of improvement cannot be excluded as a result of co-intervention.

In the Trial M-pathy, the most classical study in demonstrating the placebo effect evidence of stimulation as a treatment mode for OHCM refractory patients, the occurrence of adverse events associated to pacemaker implant was observed in 35% of patients – quite a high percentage for complications[9]. However, the analysis of types and frequency of pacemaker implant related complications among HCM patients in our study (approximately 15%), matches literature findings in that definitive pacemaker implant is not risk free. However, the risks observed – differently from what was observed in the M-pathy – did not differ from those observed in the general population[18]. Therefore, pacemaker implant should not be avoided under the argument of higher risk of complication for the general population.

Cerebrovascular accident was present in approximately 12% of the study population –a high percentage when population age is taken into account, but explainable for the type of condition, associated comorbidities, and the anticoagulation therapy that was chosen.

At no point in time was heart stimulation associated to the causal effect of death occurrences. Deaths were actually associated to functional deterioration.

Another issue is whether death could be avoided through implant or the use of a defibrillator. Although those are high risk patients for arrythmogenic sudden death, other causes led to death, and they were well documented, not resulting from ventricular arrhythmia. Therefore, the implantable cardioverter-defribillator (ICD) most likely did not interfere in the death outcome.

Study limitations

Major limitations in the present work were related to the availability of medical records as well as the impossibility of carrying out comparative analyses on patients' perception of symptom improvement or the lack of it, with objective evaluation parameters for functional capacity evaluation. Since this is a retrospective, descriptive analysis, the symptom relief and functional class change outcomes may have been affected by other variables rather than heart stimulation. It is understood, however, that such limitations have not interfered in the major objective of the present work.

Conclusion

Although facing restrictions, our study results suggest the beneficial effects of heart stimulation for symptomatic, drug treatment refractory OHCM. It also clearly shows the absence of long-term improvement for non-obstructive patients.

Cardiac pacing may be used safely in HCM patients in need of chronotropic support, as well as OHCM patients who are shown to keep refractory to drug therapy.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any graduation.

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