ORIGINAL ARTICLE

Prevalence of Atrial Fibrillation in Pacemaker Patients

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Abstract

Background: Current pacemakers allow for the continuous recording of the occurrence of arrhythmic events. One of the most frequent arrhythmias after implantation of a device is atrial fibrillation (AF), an important risk factor for embolic events. The frequency of this arrhythmia in pacemaker patients has not been widely studied.

Objectives: This study aimed to evaluate the prevalence, incidence, and predictors of the occurrence of AF in patients with double-chamber pacemakers and without a history of atrial fibrillation prior to implantation.

Methods: A dynamic, retrospective, and prospective cohort study was carried out with 186 patients undergoing biannual follow-up of the double-chamber pacemaker, without previous AF, in a single service, between 2016 and 2018. Clinical data were collected from the medical records and the telemetry of the device and the prevalence, incidence rate, relative risk by univariate analysis (by chi-square), and risk ratio were calculated by multivariate analysis (by Cox regression); values of $p<0.05$ were considered significant.

Results: There was a prevalence of 25.3% FA, with an incidence of 5.64 cases / 100 persons-year. The median time for the development of arrhythmia was 27.5 months. Multivariate analysis identified 5 statistically significant predictors: male gender, OR: 2.54 [1.04–6.15]; coronary artery disease, OR: 2.98 [1.20–7.41]; hypothyroidism, OR: 3.63 [1.46–9.07]; prior heart surgery, OR: 2.67 [1.01–7]; and left atrial enlargement, OR: 2.72 [1.25–5.92].

Conclusion: The prevalence and incidence of AF in this population are high. Risk factors for AF were: male gender, coronary artery disease, hypothyroidism, prior heart surgery, and left atrial enlargement.

Keywords: Arrhythmias, Cardiac/complications; Atrial Fibrillation; Risk Factors; Hypertension; Embolism; Pacemaker, Artificial; Atrioventricular Node.

Introduction

The pacemaker is a device used to treat various changes in heart rate, whether they are dysfunctions in the sinus and atrioventricular nodes, or in the intraventricular fascicles, preventing mortality and the onset of symptoms.[1] The latest models are capable of performing a continuous monitoring of electrical activity, detecting and recording the occurrence of arrhythmic events, even if brief and asymptomatic, which allows for the adoption of specific treatment.[2]

One of the most frequently detected arrhythmias by these devices is atrial fibrillation (AF), which in the general population is related to an increased risk for cardiovascular outcomes, ischemic stroke, and early mortality. It was found that individuals with AF detected by the pacemaker have a two to three-fold higher risk of stroke or systemic embolism, in addition to more hospitalizations and heart failure.[2-4]

The relationship between non-physiological ventricular pacing in the VVI mode (single chamber) and the development of AF is already well established, due to atrioventricular dissociation. However, arrhythmia was also frequent in patients with double-chamber pacemakers, and its frequency in individuals, as well as the predictors of its occurrence, have not been widely studied, especially in Brazil.[4] Thus, the primary objective of the present study is to determine

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the prevalence and incidence of atrial fibrillation after double-chamber pacemaker implantation in patients without previous known events of arrhythmia. Previous studies have often included patients with a prior history of AF. We also intend to assess which demographic, clinical, and echocardiographic factors and device characteristics can be used as predictors of the risk of developing AF, in order to describe the clinical profile of these patients.

Materials and Methods

Study Design

This is an analytical, observational, cohort, dynamic, retrospective, and prospective study, which evaluated the measures of occurrence (incidence rate and prevalence) and the predictors associated with the analyzed outcome: development of atrial fibrillation detected by the pacemaker. This research project was carried out in accordance with the principles of the Declaration of Helsinki and was approved by the Research Ethics Committee of the State University of Ponta Grossa, under opinion number 1,472,025.

Sample and Data Collection

In a first step, 257 patients undergoing semiannual follow-up were included at the Cray da Costa Clinic, in Ponta Grossa, PR, Brazil, between 2016 and 2018. This study selected patients with double-chamber pacemakers who did not have a diagnosis of AF prior to device implantation. Seventy-one individuals were excluded due to a history of AF prior to implant surgery, unavailability of medical records or loss of follow-up prior to the first revision of the pacemaker. The inclusion took place after agreeing with the Informed Consent Form. Clinical data and complementary exams were obtained from medical records at the research site, while the occurrence of atrial arrhythmias and device characteristics were detected by pacemaker telemetry during the reviews. Participants had devices from four manufacturers: Biotronik, Boston Scientific, Medtronic and St. Jude Medical, enabled to detect arrhythmic events through the atrial electrode. All patients who presented AF were considered as having atrial fibrillation, regardless of the duration and number of events.

Statistical Analysis

The data were analyzed using the MedCalc Statistical software, version 14.8.1. The AF incidence rate was calculated based on the detection of a new arrhythmia in the device telemetry, taking into account the time elapsed since the pacemaker implantation procedure. The prevalence was calculated in the sample at the end of data collection. The quantitative variables were submitted to the Kolmogorov-Smirnov test to verify the normality of the distribution, while the Grubers test was used to identify outliers. The non-parametric Mann-Whitney test was used to compare measures of the central tendency of non-normally distributed variables from two groups, and the non-parametric Kruskal-Wallis test was used for the analysis of three or more groups. Results were represented by median (interquartile range). The assessment of risks associated with predictors was initially performed through univariate analysis, using the chi-square test. These data will be presented based on the relative risk (RR) [95% confidence interval (CI)]. For the multivariate analysis, the Cox proportional hazards model was used, which included five variables selected to present a statistically significant P value in the univariate analysis or for their clinical relevance. The risk will be presented through the odds ratio (OR) [95% CI]. For each statistically significant predictor in the model, the number needed to harm (NNH) was estimated, aiming to measure the effect size associated with each factor. The value from Cox regression was calculated based on the method of Altman and Andersen.[5] The determination of cutoff points was performed using the ROC curve. Categorical qualitative variables will be expressed in absolute numbers and percentages. Values of $p<0.05$ were considered significant.

Results

Among the patients studied, 186 had a double-chamber pacemaker and had no detection of AF prior to surgery. In the studied sample, 97 (52.2%) were women. The median age upon implantation was 67 years (IQR 56.75 – 76), and the median follow-up time to the last device revision was 52 months (IQR 19 – 101).

The main indications for pacemaker implantation in these patients were atrioventricular blocks (74.6%) and sinus node disease (20.3%). There was a slight predominance of women in the sample composition,

and the most prevalent diseases were hypertension, hypercholesterolemia, and heart failure. The other characteristics are shown in Table 1.

There was a prevalence of 47 patients (25.3%) with AF, calculated after the last follow-up. The incidence rate was 5.64 cases per 100 individuals in each year of follow-up. The median time to arrhythmia development was 27.5 months (IQR 9 – 56). Graph 1 shows the percentage of patients with AF according to the time between implant and detection, in relation to all who presented this arrhythmia.

Through univariate analysis (Table 2), the variables of interest for a multivariate analysis were defined: male gender, changes in thyroid function, and increase in left atrial diameter. Note that the history of previous heart surgery reached a level very close to significance, as did coronary artery disease. For all risk analysis related to heart surgery, myocardial revascularization procedures were disregarded, given their direct relationship with coronary artery disease.

There was no significant difference in age. In the group of patients with AF, the median was 68 years (60 – 76), similar to the group that did not develop arrhythmia, with a median of 67 years (55 – 75) (Mann-Whitney test, p=0.54).

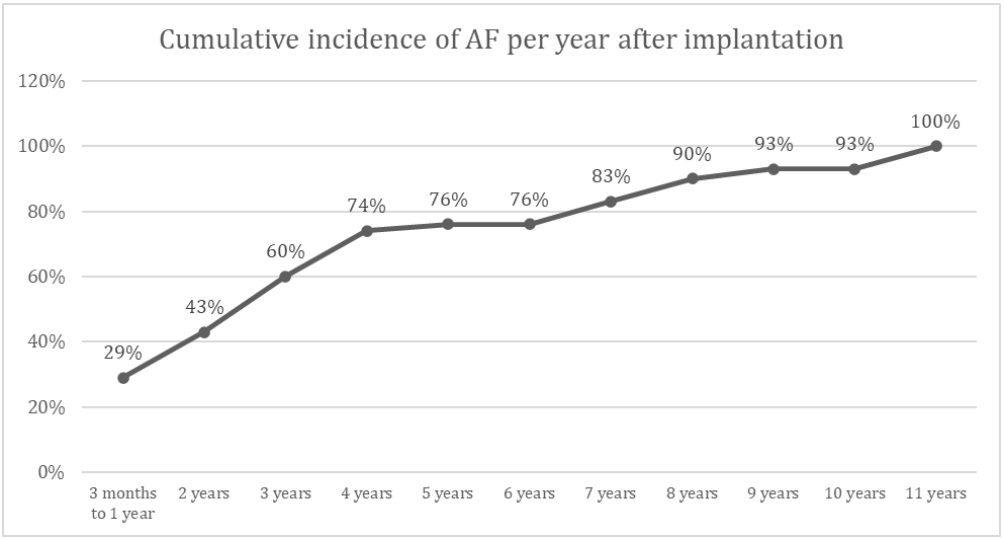
Cox's proportional hazards model demonstrated that the male gender, coronary artery disease, hypothyroidism, previous heart surgery, and enlarged left atrium are significant predictors of the development of atrial fibrillation (Table 2). In patients with AF, the median left atrial diameter was 46 mm (39.5 – 50), significantly greater than the median of patients without AF, 40 mm (37 – 45). The comparison is shown in Graph 2.

The cut-off value for the diameter of the left atrium was established as 45 mm using the ROC curve (area under the curve=0.68, Youden index=0.38), which is a reference that has also been adopted in other studies[2,4]. Values for NNH were calculated considering exposure to the factor for 4 years, a period in which approximately 75% of AF cases are detected. The results found are expressed in Graph 3.

Table 1 – Characteristics of the studied sample

Variables	Prevalence in the sample (%)
Women	52.2
Device manufacturer	
Biotronik	50.3
St. Jude Medical	47.0
Boston medical	1.6
Medtronic	1.1
Systemic Arterial Hypertension	83.4
Hypercholesterolemia	49.7
Heart failure	29.7
Coronary artery disease	22.8
Diabetes Mellitus	21.4
Hypothyroidism	16.7
Hyperthyroidism	4.1
Previous heart surgery, of which:	17.4
Coronary artery bypass graft	32%
valve replacement	64%
Others	4%

Source: the author.

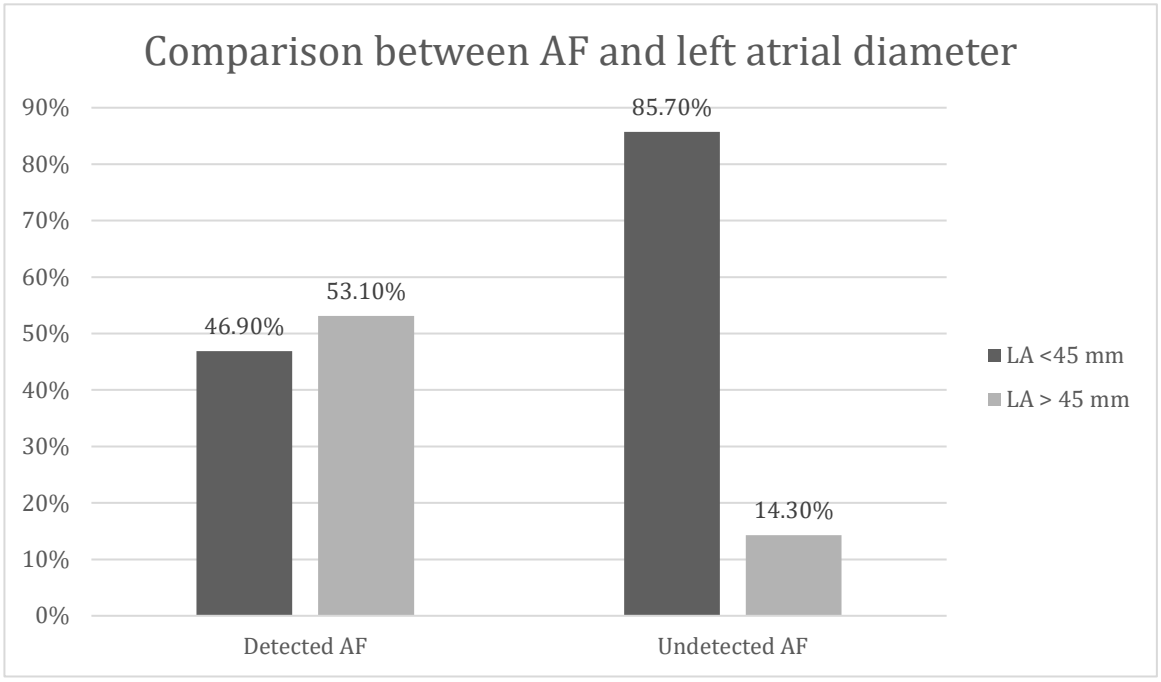


Graph 1 – Cumulative incidence of atrial fibrillation in relation to the total number of patients with this outcome. There is a rapid increase in the initial 4 years, with less occurrence of new cases after this period.
Source: the author.

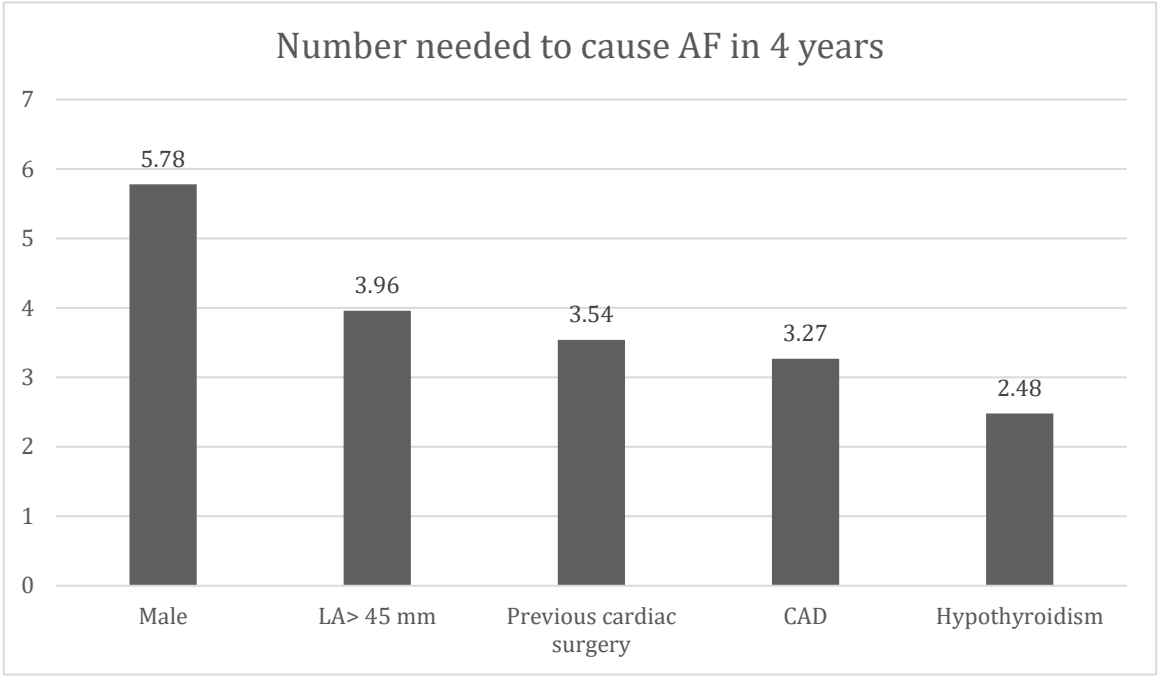
Table 2 – Analysis of predictors for the development of atrial fibrillation

Predictors		univariate analysis		Multivariate analysis	
		RR [95% CI]	p	OR [95% CI]	p
Male gender		1.92 [1.14 - 3.23]	0.01*	2.54 [1.04 - 6.15]	0.04*
Recommendation	SND	1.21 [0.65 - 2.27]	0.53		
	AVB	0.65 [0.37 - 1.13]	0.12		
SAH		0.86 [0.46 - 1.63]	0.65		
Hypercholesterolemia		0.66 [0.39 –1.11]	0.12		
Hypertriglyceridemia		0.73 [0.21 - 2.57]	0.63		
Heart failure		1.55 [0.94 - 2.55]	0.08		
CAD		1.47 [0.87 - 2.48]	0.14	2.98 [1.20 - 7.41]	0.02*
DM		1.26 [0.72-2.21]	0.41		
Hypothyroidism		2.17 [1.34 - 3.50]	0.001*	3.63 [1.46 - 9.07]	0.006*
Hyperthyroidism		2.38 [1.27 - 4.44]	0.007*		
Heart surgery†		1.72 [0.96 - 3.07]	0.06	2.67 [1.01 - 7]	0.04*
LA > 45 mm		3.01 [1.77 - 5.10]	0.001*	2.72 [1.25 - 5.92]	0.012*
ACEi		1.23 [0.68 - 2.23]	0.49		
ARB		0.68 [0.39 - 1.16]	0.16		
CCB		0.55 [0.24 - 1.26]	0.16		
Aldosterone antagonist		1.59 [0.94 - 2.70]	0.08		

ACEi: angiotensin-converting enzyme inhibitor; ARB: Angiotensin II Receptor Blockers; AVB: Atrioventricular block; CAD: Coronary Artery Disease; CCB: Calcium channel blockers; DM: Diabetes mellitus; LA: Left atrium (diameter); SAH: Systemic arterial hypertension; SND: Sinus node disease.
** (p<0.05). †Previous heart surgery, excluding Coronary artery bypass graft.*
Source: the author.



Graph 2 – Comparison between the detection of AF and the proportion of patients with a left atrial diameter greater than 45 mm.
Source: the author.



Graph 3 – Necessary number of patients exposed to the predictor factor to trigger a case of AF after 4 years of exposure.
Source: the author.

Discussion

Atrial fibrillation is the most frequent arrhythmia in clinical practice, and is present in approximately 0.4% of the general population.[6] In patients with dual-chamber pacemakers (DDD), these values are notably higher, although lower than those recorded in populations with a single-chamber device.[7]

The prevalence reported in studies referring to the DDD pacemaker ranges between 16% and 55%, depending on the methodology used.[2,7] When there is inclusion of patients who had a history of AF prior to device implantation, higher prevalence values were found, while those who exclusively selected patients with no prior history resulted in a lower frequency.

The present study fits into the second case, with a prevalence of 25.3%, a result compatible with data available in the literature. It should also be considered that, in the country, more than 20 thousand devices are implanted annually, making AF a cause of considerable morbidity in this group of individuals.[8]

The calculation of the annual incidence rate showed that, at each year of follow-up, in a population of 100 pacemaker patients, approximately five will develop this arrhythmia. The progression of cases occurs quickly and linearly up to the fourth year after implantation, a period in which 75% of cases develop.

In the incidence study conducted by Campos et al., a minimum period of two months was established as an inclusion criterion, thus avoiding cases of previous asymptomatic AF detected after implantation.[9] As shown in Graph 1, all arrhythmic events were detected after an interval of three months after the implant procedure, which runs in line with the current literature.

It is well-known that the risk of AF in the general population is associated with increasing age;[5] however, this factor did not prove to be statistically significant as a predictor of AF in the evaluated sample. A possible explanation for this result is the fact that the study participants were predominantly elderly, and age would not, therefore, represent a relevant variable in this context.

The correlation between arterial hypertension and AF in individuals without pacemakers has been recognized since the Framingham study, although the associated increased risk is not as prominent.[10] Among the device carriers included in the present study, there was no significant difference in the occurrence of atrial fibrillation, and the reason that led to this result is not clear, probably related to sampling issues.

Regarding pathophysiological mechanisms, it can be assumed that hypertension causes changes in left ventricular compliance, leading to myocyte distension and left atrium dilation. Atrial electrical alterations may be present even before the existence of detectable ventricular morphological alterations on echocardiography. There is a delay in atrial conduction associated with the loss of normal tissue refractoriness, producing a reentry mechanism that is predisposed to arrhythmias.[11]

There are proposals for approaches aimed at reducing atrial changes that culminate in AF. It is well-known that the renin-angiotensin-aldosterone system participates in cardiac remodeling processes, and some randomized trials have sought to reduce the incidence of this arrhythmia in patients with pacemakers through angiotensin-converting enzyme inhibitors and angiotensin receptor blockers II, presenting controversial results.[12]

Zhang et al.,[13] used olmesartan for 24 months in order to prevent the occurrence of AF in patients with a DDD pacemaker implanted by atrioventricular block, reducing the risk by more than 50%[13]. From another perspective, a European retrospective study showed a trend towards a lower incidence of AF in the group that received ACEI or ARB, although it did not reach statistical significance.[14]

This last research exposes a similar situation to the results on the use of ARB in the present study, as shown in Table 2. As these are observational studies, the indications for use were not uniform between the groups and the dosages varied according to the case, affecting the quality of the assessment.

According to data from the Framingham study,[10] cholesterol levels did not correlate with the development of AF, a result similar to that obtained in the current sample, in which the relative risk was 0.66 with a wide confidence interval, without statistical significance.

Approximately 40% of individuals who developed AF had heart failure, which is considerably higher when compared to 25% of patients without fibrillation. In the general population with AF, the prevalence is also lower, approximately 19%.[6] Despite the apparent difference between groups, heart failure did not result in a statistically significant predictor by univariate analysis.

Another analyzed disease was diabetes mellitus, frequent in the population and identified by the Framingham study as a risk factor for AF.[10] On the other

hand, studies of patients with pacemakers were not able to demonstrate such a correlation, a fact also observed in the selected sample.[2,4,7,12]

In the present study, the Cox proportional hazards model was used to assess a set of variables in relation to the time between implant and outcome. The five variables considered most relevant were selected in order to avoid the occurrence of overfitting in the model, which would impair the applicability of the analysis in a broader context.

The first predictor found was the male gender, with a hazard ratio of 2.54, which is also a known risk factor for atrial fibrillation in the general population. However, if on the one hand women have a lower incidence, it is important to note that the literature describes a greater impact on the quality of life and mortality in this group.[6]

This is an unmodifiable characteristic, and the issues involved in triggering arrhythmia are not clear. Hormone replacement is also an object of study for the prevention of this and other cardiovascular events. Among the variables analyzed in Cox regression, this was the factor with the highest number needed to trigger AF, that is, approximately 6 men with a pacemaker are needed for a case of atrial arrhythmia to occur in a period of 4 years.

Most of the studies found do not include the previous history of heart surgery in the analysis of risk for AF. In the included participants who had previously undergone surgery (17.4% of the sample), the most frequently performed procedure was valve replacement, in 64% of the patients, followed by myocardial revascularization, in 32% of the patients, which was compatible with the profile described in the Brazilian population.[15]

A Korean study with 649 patients found no significant risk difference between those with a history of heart surgery (approximately 15% of the sample) and those who did not undergo any procedure.[4] However, our study excluded from the calculation the patients who underwent coronary artery bypass graft surgeries, as they have a direct correlation with coronary artery disease, another investigated factor, and the resulting collinearity would affect the multivariate analysis.

Thus, the results predominantly refer to valve replacements, indicating that the relationship with heart surgery may be indirect and the causal factor associated with valve damage. In this sample, approximately three patients need to undergo heart surgery for one of them to present the outcome. In fact, there is an association between valvular heart disease and AF in the general population, probably mediated by the overload of the left chambers followed by electrical and morphological alterations.[6,10]

As discussed above, several clinical entities result in left atrial dilation, triggering the electrical mechanisms that result in atrial fibrillation. This study investigated this relationship in patients with pacemakers and its impact on the incidence of atrial arrhythmias, finding a significantly larger median diameter of the left atrium in individuals with AF, a fact already well defined in other studies.[2,4,12,13]

The 45 mm cutoff value used herein achieved the best statistical performance in the ROC curve for the sample, which was above the echocardiographic measurements considered normal for the Brazilian population, 40 mm for women and 42 mm for men.[16] Patients with this increase had an almost 3-fold higher risk than other individuals for developing atrial fibrillation.

Several studies indicate the existence of coronary artery disease (CAD) in samples of patients with pacemakers with AF.[2,4,12,17] Despite this, among the publications available in the Pubmed and Scielo databases on the subject, it was not possible to find any work that demonstrated the risk of AF associated with CAD in these patients.

Thus, the use of CAD as part of the proportional hazards model, as well as the positive association found, are important results obtained through this study. In the analyzed sample, the NNH was approximately three individuals exposed to the occurrence of an outcome, a considerable effect as a risk for the occurrence of AF. Another reason that makes this result clinically relevant is the possibility of preventing ischemic processes that act on the pathophysiology of atrial fibrillation.[18]

The association of AF with hyperthyroidism is well established; however, evidence on the effects of low levels of thyroid hormones on arrhythmias has only been gathered more recently.[19] In patients with pacemakers, the diagnosis of hypothyroidism was associated with a higher risk of AF among the analyzed predictors, with an OR of 3.63, as shown in table 2. An NNH of 2.48 was also obtained from the regression, indicating that the number of individuals who develop AF from exposure is high.

The relationship between TSH values, prescribed levothyroxine dosage and arrhythmic events was not within the scope of this study; therefore, a thorough analysis of the possible causal link involved is not possible based on the obtained data.

Based on the existing literature, it can be suggested that an excessive dose of levothyroxine triggers subclinical hyperthyroidism, especially in elderly patients, leading to atrial fibrillation.[20] Thus, the importance of the involvement of thyroid dysfunctions in the incidence of AF is noted, being a topic open to further investigation to define clinical approaches capable of preventing the occurrence of arrhythmia.

Some important information can be obtained through this study. First of all, the epidemiological importance of atrial fibrillation in patients with double-chamber pacemakers should be researched so that its main factors could be better understood and addressed. In this sense, it was shown that some of the factors present in the general population also apply in cases detected by the device, such as gender and enlargement of the left atrium. In other situations, such as in coronary artery disease, in the history of heart surgery and hypothyroidism, there were no risk studies in patients with pacemakers.

Some results were not compatible with existing information in the literature, such as the risk in cases of arterial hypertension, heart failure, and age, the main factor in the general population. This is due to the characteristic of the studied sample, which is predominantly elderly, suggesting that this factor does not imply such a large risk variation in this group.

In addition, this study has its limitations due to information bias, the selection of individuals with devices from different manufacturers and configurations, and the lack of uniformity between the medications used by patients. This is a possible reason why the analyzed drugs do not reach statistical significance in relation to their benefit in the prevention of AF, requiring randomized clinical trials to adequately investigate these effects.

Conclusion

The prevalence of atrial fibrillation in patients with pacemakers was 25.3%, and the incidence rate was 5.64 cases per 100 people per year of follow-up. The significant risk factors for AF onset in univariate analysis were: the male gender, hypothyroidism, hyperthyroidism, and left atrial enlargement, and in the multivariate analysis: the male gender, left atrial enlargement, a history of heart surgery, and coronary artery disease.

Author contributions

Conception and design of the research: Costa MAC. Acquisition of data: Costa MAC, Santos JFLP. Analysis and interpretation of the data: Costa MAC, Santos JFLP. Statistical analysis: Santos JFLP, Schafranski MD. Writing of the manuscript: Costa MAC, Santos JFLP. Critical revision of the manuscript for intellectual content: Costa MAC.

Potential Conflict of Interest

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

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the *Universidade Estadual de Ponta Grossa* under the protocol number CAAE: 50811115.0.0000.0105. 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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