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Reflections on CABANA Trial (Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation Trial)

Reflexões sobre o Estudo CABANA (*Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation Trial*)

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Atrial fibrillation has been consolidated in recent decades as a serious public health problem, considering its notorious increase in prevalence with aging combined with increased population survival. Data from the Framingham Heart Study indicate that, even in an optimal scenario of absence of classic risk factors for its occurrences, such as smoking, alcohol abuse, obesity, hypertension, diabetes, and heart disease, about 10% of individuals aged 80 or over and about 25% of those aged 90 or over will have atrial fibrillation[1]. These rates substantially increase when added to single or combined risk factors. Despite its already well-known association with the occurrence of thromboembolic stroke[2], the presence of atrial fibrillation has been identified as an independent mortality risk factor in large population studies[3].

In September 2005, the National Heart, Lung and Blood Institute of the United States, considering the epidemiological importance of atrial fibrillation and the increase in the number of patients submitted to treatment by percutaneous ablation, convened a task force responsible for evaluating the role of ablation in the treatment of this arrhythmia. As the role of ablation in maintaining sinus rhythm has been defined in several studies[4], this task force recommended a large study to establish its impact on mortality reduction.

After the implementation of a pilot study (CABANA Pilot Study) that in fact endorsed the superiority of ablation in maintaining sinus rhythm compared to pharmacological treatment, the National Institute for Health approved the funding of the Catheter Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation Trial (CABANA Trial), with the support of the catheter, devices and mapping systems industry. The results of this study were eagerly awaited by the community of atrial fibrillation researchers from all over the world, considering the types of outcomes evaluated and the reliability of results that would be brought by a potentially correct design under the methodological aspect. This reflection is essential since, over the years, several studies have been carried out on the subject, but most of them have a great weakness of scientific credibility, given

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their design characteristics, such as retrospective character, lack of comparison to control groups, small samples, endpoints based on so-called "soft" outcomes, etc.

In March 2019, the results of the CABANA Trial were finally published[5]. CABANA was a multicenter, prospective, randomized, open, intent-to-treat study, involving 126 centers in 10 countries, aiming to compare percutaneous ablation to conventional drug therapy in the occurrence of a composite outcome that included death, disabling stroke, major bleeding, and cardiac arrest. *Patients with paroxysmal or persistent atrial fibrillation, aged 65 years or older, were included in the study. Patients under 65 years of age could be included, as long as they presented one or more risk factors for thromboembolism.* All patients had to be potentially eligible for ablation or drug therapy, which could be by controlling the rhythm and/or heart rate. The use of oral anticoagulation was recommended in both groups of patients, according to the guidelines of the American Heart Association, American College of Cardiology and European Society of Cardiology. About 2,200 patients were included.

Concisely, the final results of the study after about four years of *follow-up could not demonstrate the superiority of ablation over drug therapy concerning the composite endpoint.* The number of patients in the randomized group for a drug therapy that was crossed for ablation was high (≅ 27%), in a *crossover* not considered for the evaluation of final results, *since it was an intent-to-treat study.*

The feeling of disappointment and nonconformity with the demonstrated results was generalized in the community of electrophysiologists. One of the basic principles of the scientific method that gives credibility to the study design is the intention to treat, which was criticized based on the assumption that, in a *per-protocol* evaluation, the results would favor the ablation treatment. The perception of the disguised desire for a change of method to achieve the desired effect, something incompatible with science, remained.

Randomized studies are designed to promote a balance of the participants' characteristics at the beginning, and the *intention-to-treat* principle is fundamental for the maintenance of this balance. The removal of patients from a group to be included in the comparison group potentially promotes a rupture of this balance and creates uncertainties that significantly compromise the reliability of the study results. However, the famous statement attributed to the astronomer Carl Sagan must always be kept in mind: "absence of evidence is not evidence of absence."

Many methodological variables are capable of interfering with the search for an evidence-based truth in a study, even though it is a randomized controlled trial. In a close look at the CABANA Trial design, some overlooked aspects are too intriguing. The initial hypothesis of the study was that percutaneous ablation *primarily* would reduce total mortality in comparison to conventional drug therapy. In 2013, an essential primary endpoint change was established: it went from a single endpoint (overall mortality) to a composite endpoint, which included death, disabling stroke, major bleeding, and cardiac arrest. This change was induced by a lower-than-expected rate of events and a slower inclusion of patients. In a thorough verification of the studied primary composite endpoint components, it is possible to identify an apparent plausibility of only one of the four established endpoints: stroke. In other words, it is rational to suppose that patients submitted to ablation for treatment of atrial fibrillation, when compared to those treated by medication, will have a lower rate of occurrence of strokes, as a result of a supposed superiority of ablation rhythm control. However, why assume that the highest bleeding rates would be lower in the ablation-treated group, considering the recommendation of permanent use of anticoagulant therapy in patients *of both groups* based on their higher risk chance?

Regarding the "cardiac arrest" component, why infer that this outcome is expected in patients with atrial fibrillation and, consequently, of a lower probability of occurrence in the group treated by ablation, which supposedly would have a more dynamic rhythm control? Is cardiac arrest relevant to atrial fibrillation patients? Finally, the composite outcome component *mortality* is no less problematic for valuation of importance in patients with atrial fibrillation.

Atrial fibrillation has been identified in population studies as an independent predictor of total mortality[3], as previously mentioned. However, it is important to emphasize that atrial fibrillation is an arrhythmia that

accompanies several different clinical conditions, each of them conferring its particularities under the aspect of prognostic significance. For example, a 66-year-old male patient, with paroxysmal atrial fibrillation, without other comorbidities, anticoagulated, would be eligible for CABANA Trial. Would we expect in this patient a significant mortality risk conferred by arrhythmia that could be modified by percutaneous ablation? Apparently not. On the other hand, a 66-year-old patient with ischemic heart disease, heart failure, and persistent atrial fibrillation, anticoagulated, would also be eligible for CABANA Trial. It is quite reasonable to infer that atrial fibrillation in this patient is an increasing risk factor for mortality, considering wall stress and increased myocardial oxygen consumption generated by arrhythmia in a heart with fibrosis and ischemia, and that the recovery and maintenance of a stable sinus rhythm have a significant prognostic impact in terms of hard outcomes.

It is, therefore, understandable that CASTLE-AF Trial (Catheter Ablation versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation Trial), which compared ablation and medication in patients with heart failure, has demonstrated a reduction in mortality provided by ablation, related to a higher chance of rhythm control determined by this therapy[6].

It is thus reasonable to deduce that CABANA Trial is a fragile study under the methodological aspect *primarily in its essence*, based on a debatable hypothesis, applied in a heterogeneous, broad, and nonspecific population. No results other than those found could be expected. It is back to square one. Doubts and dilemmas persist. Fundamental random criteria defined by Bradford Hill in the evaluation of this problem, such as the strength of association, biological gradient, biological plausibility, and experimental evidence[7] did not consistently support the construction of the CABANA Trial hypothesis. That is the biggest problem.

Since atrial fibrillation is such a multifaceted problem, the question to be formulated for structuring a study hypothesis that aims to evaluate mortality when talking about ablation should be: *which category of patients should be assessed in this study?*

REFERENCES

1. Staerk L, Wang B, Preis SR, Larson MG, Lubitz SA, Ellinor PT, McManus DD, Ko D, Weng L-C, Lunetta KL, Frost L, Benjamin EJ, Trinquart L. Lifetime risk of atrial fibrillation according to optimal, borderline, or elevated levels of risk factors: cohort study based on longitudinal data from the Framingham Heart Study. Brit Medic J. 2018;361:1-10 https://doi.org/10.1136/bmj.k1453

2. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: The Framingham Study. Strok. 1991;22(8):983-88. https://doi.org/10.1161/01.STR.22.8.983

3. Andersson T, Magnuson A, Bryngelsson IL, Frøbert O, Henriksson KM, Edvardsson N, et al. All-cause mortality in 272, 186 patients hospitalized with incident atrial fibrillation 1995–2008: A Swedish nationwide long-term case–control study. Eur Heart J. 2013;34(14):1061-67. https://doi.org/10.1093/eurheartj/ehs469

4. Packer DL, Mark DB, Robb RA, Monahan KH, Bahnson TD, Moretz K, et al. Catheter ablation versus antiarrhythmic drug therapy for atrial fibrillation (CABANA) trial: study rationale and design. Am Heart J. 2018;199:192-99. https://doi.org/10.1016/j.ahj.2018.02.015

5. Packer DL, Mark DB, Robb RA, Monahan KH, Bahnson TD, Poole JE, et al. Effect of catheter ablation vs antiarrhythmic drug therapy on mortality, stroke, bleeding, and cardiac arrest among patients with atrial fibrillation. CABANA Rand Clinic Trial. 2019;321(13):1261-274. https://doi.org/10.1001/jama.2019.0693

6. Marrouche NF, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L, et al. Catheter ablation for atrial fibrillation with heart failure (CASTLE-AF). N Engl J Med. 2018;378(5):417-27. https://doi.org/10.1056/NEJMoa1707855

7. Leong DP, Eikelboom JW, Healey JS, Connolly SJ. Atrial fibrillation is associated with increased mortality: causation or association? Europ Heart J. 2013;34(14):1027-30. https://doi.org/10.1093/eurheartj/eht044

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Importance of Postoperative Atrial Fibrillation Development in Heart Surgery: Intra-Hospital Outcomes in Santa Catarina Tertiary Cardiology Center

Importância do Desenvolvimento de Fibrilação Atrial no Pós-Operatório em Cirurgia Cardíaca: Desfechos Intra-Hospitalares em Centro Terciário de Cardiologia Catarinense

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ABSTRACT

Objective: To determine the incidence of postoperative atrial fibrillation (PAF) of cardiac surgery, its impact on morbimortality and duration of hospital stay in a tertiary cardiology center of the state of Santa Catarina, Brazil. **Methods:** Cohort study with 134 adult patients submitted to cardiac surgery. **Results:** the incidence was 32.8%. After multivariate analysis, patients who did not receive beta-blockers were associated with PAF with a relative risk odds ratio (RR) 10.73 (p <0.001). The highest rate of cardiovascular events (cerebrovascular accident, mortality, and acute coronary syndrome) was 25% in the PAF group. 10% (RR 3.21; p = 0.035) which, consequently, generated longer hospitalization time in these patients (19.1 vs. 12.5; p = 0.01). **Conclusion:** the incidence of PAF was high, caused a significant increase in morbimortality and duration of hospital stay, and consolidated the role of beta-blocker therapy in its prevention, and may serve as a basis for future prevention policies.

KEYWORDS: Atrial fibrillation; Postoperative care; Morbidity.

RESUMO

Objetivo: Determinar a incidência de fibrilação atrial no pós-operatório (FAPO) de cirurgia cardíaca, seu impacto sobre a morbimortalidade e o tempo de internação hospitalar em um centro terciário de cardiologia do estado de Santa Catarina, Brasil. **Métodos:** Estudo de coorte com 134 pacientes adultos submetidos à cirurgia cardíaca. **Resultados:** A incidência foi de 32,8%. Após análise multivariada, os pacientes que não receberam betabloqueador estiveram associados à FAPO com razão de chances risco relativo (RR) 10,73 (p < 0,001). A maior taxa de eventos cardiovasculares (*acidente vascular cerebral*, mortalidade e síndrome coronariana aguda) foi de 25% no grupo FAPO vs. 10% (RR 3,21; p = 0,035) o que, consequentemente, gerou tempo de internação maior nesses pacientes (19,1 vs. 12,5; p = 0,01). **Conclusão:** A incidência de FAPO foi elevada, ocasionou significativo aumento de morbimortalidade e tempo de internação hospitalar e consolidou o papel da terapia betabloqueadora na sua prevenção, podendo servir como base a futuras políticas de prevenção dessa intercorrência.

PALAVRAS-CHAVE: Fibrilação atrial; Cuidados pós-operatórios; Morbidade.

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INTRODUCTION

Postoperative atrial fibrillation (PAF) is the most prevalent complication after cardiac surgery[1,2]. In the postoperative period (PP) of cardiac surgery, the incidence of PAF varies between 25 and 62%, depending on the type of surgery[2,3]. PAF predisposes the patient to a higher incidence of thromboembolic events, hemodynamic instability, and increases the chance of a cerebrovascular accident (CVA) by 2.5 to 4.5 times[4,5]. The duration of hospital stay of patients with PAF is also longer, causing higher costs to the health[6].

The peak incidence of this arrhythmia is on the second to fourth postoperative day, and studies indicate that its risk may be reduced with the administration of specific perioperative drugs[7,8]. The identification of patients at high risk for developing PAF may be of great value for early intervention and preventive measures to reduce morbimortality[5]. Although some factors, such as advanced age and underlying comorbidities, are already established for the development of this tachyarrhythmia, the pathophysiological mechanisms are not yet fully elucidated, but activation of the sympathetic nervous system and the inflammatory process caused by surgery are the most accepted[1,9-11].

Although these tachyarrhythmias are considered transient and benign, in specific patient clinical profiles, they may have different outcomes[1,4]. Despite efforts to reduce its occurrence, the improvement of the surgical technique and anesthesia methods did not cause a significant reduction in this complication, and its prevention is still a challenge[3,4].

This study aims to evaluate the intra-hospital outcomes associated with the development of PAF. Besides, to determine the incidence and its associated factors in a tertiary cardiology center of Santa Catarina.

METHODS

A retrospective historical cohort study of 147 adult patients (age ≥ 18 years) who submitted to cardiac surgery (with or without extracorporeal circulation due to ischemic heart disease, and/or valve associated or not, another procedure) in 2015 at the Hans Dieter Schmidt Regional Hospital, in Joinville, State of Santa Catarina. Of these, 13 patients who were diagnosed with persistent or permanent, paroxysmal atrial fibrillation (AF) were excluded, leaving 135 patients for analysis. The outcomes studied were the occurrence of PAF, clinical [mortality, duration of stay, cardiovascular events - acute coronary syndrome (ACS), and CVA] and factors associated with the development of PAF.

According to the institutional protocol, all patients were submitted to continuous cardiac monitoring for 48 hours in an intensive care setting and daily electrocardiographic examinations until hospital discharge. Additional electrocardiograms were performed for cardiovascular symptoms and/or asymptomatic tachycardia.

AF was defined as supraventricular arrhythmia whose electrocardiographic tracing showed "f" waves of variable morphology and amplitude, with irregular ventricular rhythm. Episodes of AF lasting at least 30 seconds or requiring treatment due to symptomatology or hemodynamic instability were considered for work.

Echocardiographic parameters of left ventricular ejection fraction (LVEF) and left atrial diameter (LA) were collected by the most recent exam found in the records, which includes both transesophageal (TEE) and transthoracic (TTE) examinations. The ejection fraction was calculated using the Teicholz or Simpson methods, according to the presence of segmental dysfunction. Atrial diameters were assessed using the M mode.

The medical records were reviewed in order to record the clinical information necessary to complete the clinical protocol. These clinical diagnoses were defined according to the previous publications[12].

The strength of association of each factor for PAF was measured by relative risk (RR) estimates with 95% confidence intervals (95% CI). Data analysis was performed with the aid of the SPSS version 8.0 program. In multivariate analysis, binary logistic regression and the odds ratio (OR) were used as an association measure. In the model construction process, the importance of each component was verified by the likelihood ratio test. A value of -2log likelihood was used (deviance), measured to determine how well the model fits the data. Interval estimates were calculated with 95% CI. All variables with $p < 0.25$ (univariate analysis) were candidates to enter the model, according to the methodology of Hosmer and Lemeshow[13]. Only variables with $p < 0.05$ remained in the model.

The hospital's research ethics committee approved the study protocol (nº 1.779.036).

RESULTS

Of the 134 patients submitted to cardiac surgery, 32.8% developed PAF. This incidence is related to postoperative time and showed that about 80% occurred from the second to the fourth postoperative day, with a peak on the third day (40%).

Regarding the clinical profile of the patients, the only ones that showed significance in bivariate analysis were over 70 years (p = 0.003) and non-use of beta-blocker therapy in the perioperative period (p <0.001) (Table 1).

In Table 2, after multivariate analysis, the non-use of beta-blockers therapy remained statistically significant with an OR of 10.73 (95% CI 3.47-3.12; p <0.001).

The overall mortality in the sample was 17%, and there was a tendency for higher mortality in the PAF patients (0.19 ± 0.39 vs. 0.07 ± 0.25; p> 0.05) (Fig. 1), but when grouped into composite outcomes, cardiovascular events (CVA, mortality, and ACS) were observed with an incidence of 25% in the group that developed PAF. 10% [OR 3.21; 95% CI 1.08-11.58; p = 0.035] (Table 3).

The duration of stay was longer in patients with this complication (19.11 ± 15.87 vs. 12.58 ± 12, p = 0.01) (Fig. 2).

Table 1. Bivariate analysis of categorical variables and postoperative atrial fibrillation (PAF).

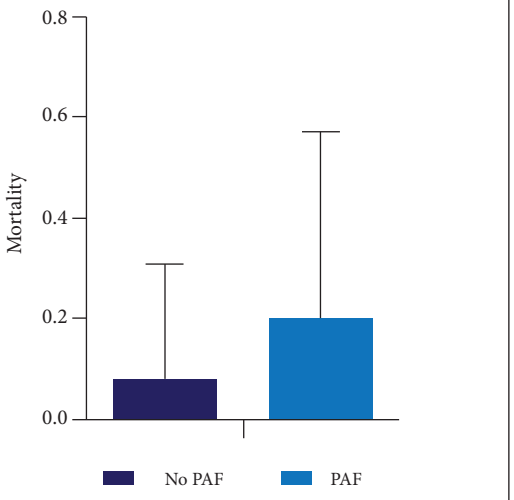
Period	Variable	PAF n = 44 (%)	No PAF n = 90 (%)	p-value
Preoperative	Male	28 (63.6)	56 (62.2)	0.874
	Age over 70 years	14 (31.8)	10 (11.1)	0.003†
	Chronic obstructive pulmonary disease	19 (43.2)	29 (32.2)	0.214
	Creatinine clearance < 50mg/dL	05 (11.4)	04 (4.40)	0.154*
	Extracardiac Arteriosclerosis	08 (18.2)	19 (21.1)	0.691
	Previous heart surgery	01 (2.30)	05 (5.60)	0.663*
	Endocarditis	03 (6.80)	03 (3.30)	0.394*
	Preoperative critical state	06 (13.6)	07 (7.80)	0.353*
	Rest Angina	02 (4.50)	06 (6.70)	1.000*
	Ejection fraction < 50%	15 (32.6)	29 (33.0)	0.968
	Recent acute heart attack	10 (22.7)	29 (32.2)	0.256
	Pulmonary arterial hypertension	06 (13.6)	04 (4.40)	0.080*
	Emergency surgery	03 (6.80)	04 (4.40)	0.683*
	Major Mitral Disease	05 (11.4)	10 (11.1)	1.000*
Intraoperative	Myocardial revascularization surgery	31 (70.5)	69 (76.7)	0.438
	Valve surgery	11 (25.0)	19 (18.9)	0.414
	Combined surgery	02 (4.50)	04 (4.40)	1.000*
Postoperative (PO)	Water balance > 1,500 mL within 48 hours PO	33 (75.0)	54 (60.0)	0.087
	Use of non-steroidal anti-inflammatory drugs	02 (4.50)	02 (2.20)	0.59*
	No pre and PO angiotensin-converting enzyme inhibitors	27 (61.4)	44 (48.9)	0.174
	No beta-blockers in pre and PO	40 (90.9)	46 (51.1)	0.000†

Statistical method employed: chi-square test and, when necessary, Fischer's exact test *. †p < 0.05 considered statistically significant.

Table 2. Variables associated with postoperative atrial fibrillation (PAF) in logistic regression (univariate and multivariate analysis with and without the PAF outcome).

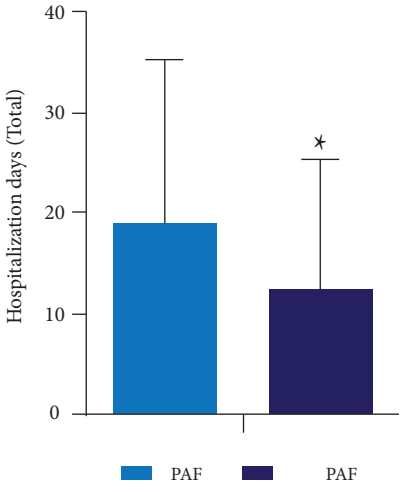
Variable	Gross OR (95% CI)	p-value	Adjusted OR (95%CI)	p-value
No beta-blockers pre and PO	8.445 (2.608-27.346)	0.000	10.735 (3.479-33.125)	0.000†
Age > 70 years	2.127 (0.775-5.837)	0.115	-	-

Statistical method employed: univariate and multivariate binary logistic regression; 95% CI = 95% confidence interval; PO = postoperative; RC = odds ratio.
† Variables that remained in the final model p < 0.05.



Statistical method employed: Student's t-test for independent samples.
*p < 0.05 considered statistically significant.

Figure 1. Mortality with and without postoperative atrial fibrillation (PAF).



Statistical method employed: Student's t-test for independent samples.
*p < 0.05 considered statistically significant.

Figure 2. Days of total hospitalization with and without postoperative atrial fibrillation (PAF).

Table 3. Analysis of cardiovascular events.

Variable	PAF n = 44 (%)	No PAF n = 90 (%)	Adjusted OR (95%CI)	p-value
Cardiovascular events	11 (25)	9 (10)	3.21 (1.08-11.58)	0.035†

PAF = postoperative atrial fibrillation; 95% CI = 95% confidence interval; RC = odds ratio. Statistical method employed: Chi-square test and, when necessary, Fischer's exact test; † p <0.05 considered statistically significant.

DISCUSSION

Despite the evolution of surgical techniques and PO management, PAF remains a very common complication[14-17]. An incidence of 32.8% was found, similar to the average reported in other published studies[18-20]. It is worth mentioning that continuous monitoring was used during intensive care and after intermittent electrocardiogram, which may have underestimated asymptomatic PAF. In some studies where continuous monitoring was used, rates reached[44] to 64%; however, this modality is adopted in a minority of published works[21,22]. Therefore, the data show a high incidence, stimulating the search for factors that contribute to PAF, thus being one of the objectives of this study.

The chronology was consistent with previously published data, in which most episodes occur until the fourth day of the postoperative period; in this study occurred in 80% of cases[23].

Before mentioning the factors associated with PAF, it is crucial to establish the multifactorial mechanisms associated with the development of arrhythmia[24]. Among them, perhaps the most easily approached by prophylactic measures is an autonomic imbalance, caused mainly by sympathetic hyperstimulation through the use of beta-blockers medications. In this study, it was indeed found that the non-use of this drug class had a more significant impact on the occurrence of arrhythmia. After multivariate analysis, a CR of 10.73 was obtained, reflecting the fundamental importance of the sympathetic nervous system block in this clinical context. Moreover, this is confirmed in the literature by a meta-analysis of 4.074 patients who found RR of 0.35 (95% CI 0.26-0.49) associated with this protective finding with therapy[25]. Importantly, the worst clinical scenario described would be the non-use of medication in pre and PO[25,26]. These results solidify this factor as fully modifiable through medical awareness of its use during this critical period. Also, they could be used as guidance or indicators for policies to prevent this complication.

Older age 70 years is an essential predictor of PAF in the literature. Mathew et al.[27] documented that, for each decade, there is a 75% increase in the chance

of arrhythmic occurrence. The researchers concluded that based on age alone, anyone over the age of 70 is considered at high risk for developing PAF[27]. In this study, there was an association in bivariate analysis, but after logistic regression age did not remain significantly statistical, most likely related to sampling size.

Regarding clinical outcomes, total mortality is associated with the development of PAF. When using the Society of Thoracic Surgeons (STS) database, reaching 49.264 patients, the group that developed PAF has twice the chance of mortality (RR 2.04, p <0.001)[28]. Confirming STS data, Almassi et al. [29], in an analysis of 3.855 patients submitted to cardiac surgery, found intra-hospital mortality of 6% in the group of patients with PAF vs. 3% in the group without arrhythmia. In this study, there was a tendency to increase with PAF, but without statistical significance, which could be explained by the association of sample size (reduced) and incidence of mortality (increased) when compared to studies already published.

PAF is associated with an increased incidence of major morbid events[29], such as increased thromboembolic risk[30] and myocardial ischemia, and this is particularly pronounced in increased CVA, as analyzed in the STS database between 2004 and 2005 of myocardial revascularization surgeries, where CVA prevalence increased (4 vs. 1.9%, p = 0.002)[6]. In this study, they grouped into a combined outcome of CVA and ACS mortality and reached a CR of 3.2 (p <0.05), which demonstrates the morbid potential of PAF.

Given the data found of higher morbidity associated with PAF, it is understandable to expect an increase in the duration of stay in days, as observed in our study (19.11 ± 15.87 vs. 12.58 ± 12; p = 0.01). Data from a Brazilian group showed similar results of a more extended hospital stay in days (16.9 ± 12.3 vs. 9.2 ± 4, p <0.001)[31].

Importantly, as the data source is from a clinical database, we have an estimation of the "real world" and data from the Brazilian public system. This consolidates future PAF prevention policies to minimize clinical and financial effects on health systems.

AUTHORS' CONTRIBUTION

Conceptualization, Silva R and Ronsoni R and Goldoni L; Methodology, Silva R and Ronsoni R and Scarduelli K, Investigation, Barreto ACC and Junqueira ACG; Writing - first version, Silva R and Barreto ACC and Junqueira ACG; Writing - Revision and Editing, Goldoni L and Ronsoni R; Supervision Ronsoni R and Scarduelli K.

REFERENCES

1. Shen J, Lall S, Zheng V, Buckley P, Damiano RJ, Schuessler RB. The persistent problem of new onset postoperative atrial fibrillation: a single institution experience over two decades. The J Thorac Cardiovasc Surgery. 2011;141(2):559-70. https://doi.org/10.1016/j.jtcvs.2010.03.011

2. Villareal RP, Hariharam R, Liu BC, Kar B, Lee VV, Elayda M, et al. Postoperative atrial fibrillation and mortality after coronary artery bypass surgery. J Am Coll Cardiol. 2004;43(5):742-8. https://doi.org/10.1016/j.jacc.2003.11.023

3. Ommen SR, Odell JA, Marshall S. Stanton. Atrial arrhythmias after cardiothoracic surgery. N Engl J Med. 1997;336(20):1429-34. https://doi.org/10.1056/NEJM199705153362006

4. Mariscalco G, Klersy C, Zanobini M, Banach M, Ferrarese S, Borsani P, et al. Atrial fibrillation after isolates coronary surgery affects late survival.Circulation. 2018;118(16):1612-8. https://doi.org/ 10.1161/CIRCULATIONAHA.108.777789

5. Geovanini GR, Alves RJ, Brito G de, Miguel GAS, Glauser VA, Nakiri K. Fibrilação atrial no pós-operatório de cirurgia cardíaca: quem deve receber quimioprofilaxia? Arq Bras Cardiol. 2009;92(4):326-30. https://doi.org/10.1590/S0066-782X2009000400013

6. Steinberg BA, Zhao Y, He X, Hernandez AF, Fullerton DA, Thomas KL, et al. Management of postoperative atrial fibrillation and subsequent outcomes in contemporary patients undergoing cardiac surgery: insights from the Society of Thoracic Surgeons CAPS-Care Atrial Fibrillation Registry. Clin Cardiol. 2014;37(1):7-13. https://doi.org/10.1002/clc.22230

7. Mahoney EM, Thompson TD, Veledar E, Williams J, Weintraub WS. Cost-effectiveness of targeting patients undergoing cardiac surgery for therapy with intravenous amiodarone to prevent atrial fibrillation. J Am Coll Cardiol. 2002;40(4):737-45. https://doi.org/10.1016/S0735-1097(02)02003-X

8. Silva RG da, Lima GG de, Guerra N, Bigolin AV, Petersen LC. Proposta de escore de risco para predição de fibrilação atrial após cirurgia cardíaca. Rev Bras Cir Cardiovasc. 2010;25(2):183-19. https://doi.org/10.1590/S0102-76382010000200009

9. Creswell LL, Schuessler RB, Rosenbloom M, Cox JL. Hazards of postoperative atrial arrhythmias. Ann Thoruc Surg. 1993;56(3):539-49. https://doi.org/10.1016/0003-4975(93)90894-n

10. Angelini P, Feldman MI, Lufschanowski R, Leachman RD. Cardiac arrhythmias during and after heart surgery: diagnosis and management. Prog Cardiovasc Dis. 1974;16(5):469-95. https://doi.org/10.1016/0033-0620(74)90007-3

11. Albahrani MJ, Swaminathan M, Phillips-Bute B, Smith PK, Newman MF, Mathew JP, et al. Postcardiac surgery complications: association of acute renal dysfunction and atrial fibrillation. Anesth Analg. 2003;96(3):637-43. https://doi.org/10.1213/01.ane.0000047886.81598.2c

12. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on atrial fibrillation. Chest. 2010;137(2):263-72. https://doi.org/10.1378/chest.09-1584

13. Hosmer DW, Lemeshow S. Applied logistic regression. New York: John Wiley; 1989.

14. Mathew JP, Parks R, Savino JS, Friedman AS, Koch C, Mangano DT, et al. Atrial fibrillation following coronary artery bypass graft surgery: predictors, outcomes, and resource utilization. MultiCenter Study of Perioperative Ischemia Research Group. JAMA. 276(4):300–6. https://doi.org/10.1001/jama.1996.03540040044031

15. Echahidi N, Mohty D, Pibarot P, Després J-P, O'Hara G, Champagne J, et al. Obesity and metabolic syndrome are independent risk factors for atrial fibrillation after coronary artery bypass graft surgery. Circulation. 2007;116(11 Suppl):I213-9. https://doi.org/10.1161/CIRCULATIONAHA.106.681304

16. Osranek M, Fatema K, Qaddoura F, Al-Saileek A, Barnes ME, Bailey KR, et al. Left atrial volume predicts the risk of atrial fibrillation after cardiac surgery: a prospective study. J Am Coll Cardiol. 2006;48(4):779-86. https://doi.org/10.1016/j.jacc.2006.03.054

17. Sabzi F, Zokaei AH, Moloudi AR. Predictors of atrial fibrillation following coronary artery bypass grafting. Clin Med Insights Cardiol. 2011;5:67-75. https://doi.org/10.4137%2FCMC.S7170

18. Echahidi N, Pibarot P, O'Hara G, Mathieu P. Mechanisms, prevention, and treatment of atrial fibrillation after cardiac surgery. J Am Coll Cardiol. 2008;51(8):793-801. https://doi.org/10.1016/j.jacc.2007.10.043.

19. Maisel WH, Rawn JD, Stevenson WG. Atrial fibrillation after cardiac surgery. Ann Intern Med. 2001;135(12):1061. https://doi.org/10.7326/0003-4819-135-12-200112180-00010

20. Nazeri A, Razavi M, Elayda MA, Lee V-V, Massumi A, Wilson JM, et al. Race/ethnicity and the incidence of new-onset atrial fibrillation after isolated coronary artery bypass surgery. Hear Rhythm. 2010;7(10):1458-63. https://doi.org/10.1016/j.hrthm.2010.06.037

21. Siebert J. Atrial fibrillation after coronary artery bypass grafting without cardiopulmonary bypass. Eur J Cardio-Thoracic Surg. 2000;17(5):520-3. https://doi.org/10.1016/S1010-7940(00)00368-7

22. Helgadottir S, Sigurdsson MI, Ingvarsdottir IL, Amar DO, Gudbjartsson T. Atrial fibrillation following cardiac surgery: risk analysis and long-term survival. J Cardiothorac Surg. 2012;7(1):87-93. https://doi.org/10.1186/1749-8090-7-87

23. Kannel WB, Abbott RD, Savage DD, McNamara PM. Epidemiologic features of chronic atrial fibrillation. N Engl J Med. 1982;306(17):1018-22. https://doi.org/10.1056/NEJM198204293061703

24. Yadava M, Hughey AB, Crawford TC. Postoperative atrial fibrillation: incidence, mechanisms, and clinical correlates. Cardiol Clin. 2014;32(4):627-36. https://doi.org/10.1016/j.ccl.2014.07.002

25. Crystal E, Garfinkle MS, Connolly SS, Ginger TT, Sleik K, Yusuf SS. Interventions for preventing post-operative atrial fibrillation in patients undergoing heart surgery. Cochrane Database Syst Rev. 2004;18(4):CD003611. https://doi.org/10.1002/14651858.CD003611.pub2

26. Andrews TC, Reimold SC, Berlin JA, Antman EM. Prevention of supraventricular arrhythmias after coronary artery bypass surgery. A meta-analysis of randomized control trials. Circulation. 1991;84(5 Suppl):III236-44.

27. Mathew JP, Fontes ML, Tudor IC, et al. A multicenter risk index for atrial fibrillation after cardiac surgery. JAMA. 2004;291(14):1720-9. https://doi.org/10.1001/jama.291.14.1720

28. LaPar DJ, Speir AM, Crosby IK, et al. Postoperative atrial fibrillation significantly increases mortality, hospital readmission, and hospital costs. Ann Thorac Surg. 2014;98(2):527-33; discussion 533. https://doi.org/10.1016/j.athoracsur.2014.03.039

29. Almassi GH, Schowalter T, Nicolosi AC, Aggarwal A, Moritz TE, Henderson WG, et al. Atrial fibrillation after cardiac surgery: a major morbid event? Ann Surg. 1997;226(4):501-11. https://doi.org/10.1097/00000658-199710000-00011

30. Fuller JA, Adams GG, Buxton B. Atrial fibrillation after coronary artery bypass grafting. Is it a disorder of the elderly? J Thorac Cardiovasc Surg. 1989;97(6):821-5.

31. Silva RG, Lima GG, Laranjeira A, Costa AR, Pereira E, Rodrigues R. Fatores de risco e morbimortalidade associados à fibrilação atrial no pós-operatório de cirurgia cardíaca. Arq Bras Cardiol. 2004;83:99-104. https://doi.org/10.1590/S0066-782X2004001400002

https://doi.org/10.24207/jca.v32n2.009_IN

Effects of Epicardial Fat Reduction on P-wave Duration of Morbidly Obese Patients Submitted to Bariatric Surgery: an Observational Study

Efeitos da Redução da Gordura Epicárdica na Duração da Onda P de Obesos Mórbidos Submetidos à Cirurgia Bariátrica: um Estudo Observacional

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ABSTRACT

Introduction: Epicardial fat (EF) is biologically active and, through its paracrine effect, interacts with the atrial myocardium and may be involved in the atrial remodeling observed in obese individuals. P-wave duration (PWD) is a non-invasive marker of atrial conduction time and reflects changes related to atrial remodeling. The effects of the reduction of EF induced by bariatric surgery on PWD have not yet been defined. **Methods:** We prospectively recruited 22 morbidly obese patients with no other comorbidities at the Unidade de Cirurgia Bariátrica (Bariatric Surgery Unit) of Unviversidade de São Paulo's Hospital das Clínicas. The patients were submitted to clinical and laboratorial evaluations, 12-lead eletrocardiography (ECG), two-dimensional echocardiogram and 24 h Holter. The same evaluation was performed 12 months after bariatric surgery. In order to make a comparison of the continuous variables, we used the paired and Wilcoxon T tests. To evaluate the association between independent variables, a regression model was used for repeated measures. **Results:** A total of 20 patients completed the protocol (age: 36.35 ± 10.26 years, 18 women). There was a significant reduction of PWD, body mass index (BMI) and EF after bariatric surgery ($p<0.05$). There was also an average reduction of 11.55 ± 8.49 ms in PWD. In the multiple regression analysis, an association was observed between the reduction of PWD and the reduction of EF and BMI. **Conclusions:** In morbidly obese patients with no other comorbidities, the reduction of EF after bariatric surgery was associated with an improvement in atrial remodeling indicated by a significant reduction in PWD.

KEYWORDS: P wave; Morbid obesity; Bariatric surgery.

RESUMO

Introdução: A gordura epicárdica (GE) é biologicamente ativa e, por meio de seu efeito parácrino, interage com o miocárdio atrial e pode estar envolvida no remodelamento atrial observado em obesos. A duração da onda P (DOP) é um marcador não invasivo do tempo de condução atrial e reflete alterações relacionadas ao remodelamento atrial. Os efeitos da redução da GE induzida pela cirurgia bariátrica sobre a DOP ainda não foram definidos. **Métodos:** Recrutamos prospectivamente 22 obesos mórbidos sem outras comorbidades na Unidade de Cirurgia Bariátrica do Hospital das Clínicas da Universidade de São Paulo. Os pacientes foram submetidos a avaliações clínica e laboratorial, além de eletrocardiograma (ECG) de 12 derivações, ecocardiograma bidimensional e Holter de 24 h. A mesma avaliação foi realizada 12 meses após a cirurgia bariátrica. A fim de que as variáveis contínuas fossem comparadas, foram utilizados os testes T pareado e de Wilcoxon. Já para avaliar a associação entre variáveis independentes foi utilizado um modelo de regressão para medidas repetidas. **Resultados:** Ao todo, 20 pacientes completaram o protocolo (idade: 36,35 ± 10,26 anos, 18 mulheres). Houve uma redução significativa da DOP, do índice de massa corporal (IMC) e da GE após cirurgia bariátrica ($p<0,05$). Houve também redução média de 11,55 ± 8,49 ms na DOP. Na análise de regressão múltipla, foi observada associação entre a redução da DOP e a redução da GE e do IMC. **Conclusões:** Em obesos mórbidos sem outras comorbidades, a redução da GE após cirurgia bariátrica foi associada a melhora do remodelamento atrial, indicada por uma redução significativa da DOP.

PALAVRAS-CHAVE: Onda P; Obesidade mórbida; Cirurgia bariátrica.

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INTRODUCTION

Epicardial fat (EF) is a layer of adipose tissue located between the surface of the myocardium and the visceral pericardium. It covers 80% of the cardiac surface and is responsible for 20% of total heart weight. EF is mainly found in the atrioventricular and interventricular sulci, around the atria and along the coronary arteries[1,2]. Under normal physiological conditions, it performs a cardioprotective function by releasing energy to the myocardium in situations of high metabolic demand. Also, it participates in thermoregulation, acts as a protection for ganglia and nerves and in the regulation of vasomotricity of the coronary circulation[3].

The thickness and volume of EF in obese individuals are recognizably greater[4]. Excess of EF in this population has been associated with the pathophysiology of some cardiovascular diseases, such as metabolic syndrome, coronary artery disease, and atrial fibrillation[5-7]. Since it is biologically active and presents ample interaction with the atrial myocardium, it is speculated that EF could produce a series of pro-inflammatory mediators capable of inducing the triggering of atrial fibrosis in obese individuals[8]. The duration of the P wave in electrocardiograms (ECG) is admittedly a marker of atrial remodeling and is associated with a higher risk of atrial fibrillation[9]. Recently, our group demonstrated that, in morbidly obese individuals, EF thickness was independently associated with a longer duration of the P wave, reinforcing the negative impact of EF on atrial remodeling[10]. The objective of the present study was to evaluate the effects of the reduction of EF on the P wave duration after weight loss induced by bariatric surgery.

METHODS

Population of the Study

Between March 2015 and February 2016, we consecutively recruited 22 morbidly obese patients at the Bariatric Surgery Unit of the Clinical Hospital of the University of São Paulo Medical School (HCFMUSP). In the week before bariatric surgery, the participants underwent anthropometric evaluation, clinical history, physical examination, laboratory tests, as well as 12-lead ECG, 24-hour Holter, and two-dimensional echocardiogram. The same evaluation, except for the 24-hour Holter, was repeated 12 months after the bariatric surgery. Patients with arterial hypertension, diabetes, dyslipidemia, presence of heart disease, branch blocks, history of fibrillation or atrial flutter, presence of significant arrhythmias in the 24-h Holter, anemia or thyroid dysfunction, and those who did not complete the evaluation protocol were excluded from the sample (Fig. 1). The ethics committee approved the study protocol, and all participants signed the informed consent form.

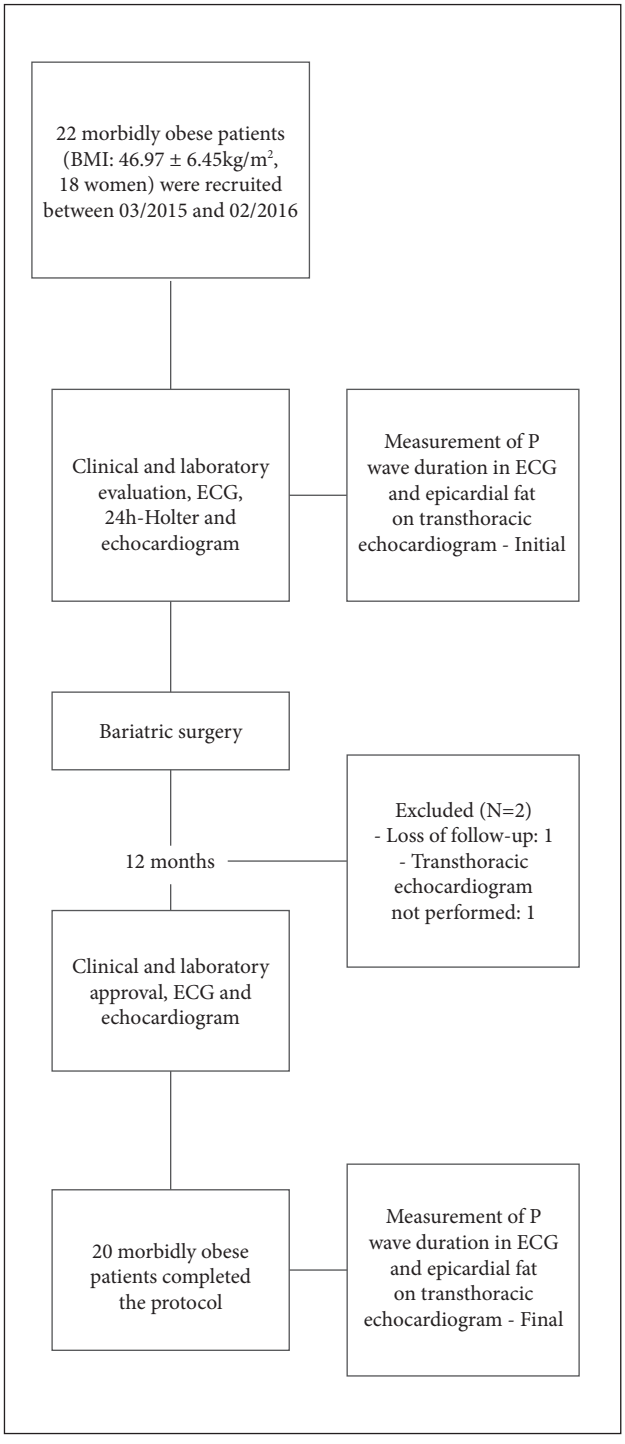

Figure 1. Study flowchart.

Echocardiogram Analysis

A two-dimensional echocardiogram (Artida®, Toshiba Medical Systems) was performed at rest by the same observer using a PST-25BT 1.8-4.2 MHz transducer in the preoperative period and 12 months after bariatric surgery. With the patients in left lateral decubitus position, through the parasternal long- and short-axes, and apical two- and four-chamber views, the following parameters were accessed: left atrial diameter, systolic and diastolic diameters of the left ventricle (LV), right ventricular cavity diameter, and thickness of the interventricular septum and the LV posterior wall. The LV ejection fraction was estimated by the Teichholz biplane method. To evaluate the diastolic function, the mitral flow velocities by pulsed Doppler were taken into consideration to determine the E and A waves. The E/A ratio was used to evaluate the diastolic function. Devereux's formula calculated the LV mass.

Evaluation of Epicardial Fat

The EF thickness was defined according to the method previously described and validated11. EF was obtained during three consecutive cardiac cycles in longitudinal and transversal parasternal views in the right ventricular (RV) free wall during the end of systole, using the interventricular septum and the aortic ring as anatomical references. The space between the myocardial surface and the visceral pericardium was considered EF. The mean of the measurements recorded in the two incidences was considered the final result of the EF thickness. To evaluate the reproducibility of the method, the images were transferred to a workstation, where a second observer, blind to the patients' clinical condition, reassessed the measurement of EF. Considering the total number of measurements performed pre- and postoperatively, 50% of the sample was randomly selected to perform the interobserver analysis. A good correlation between observers was demonstrated (g = 0.9; CI 95% [0.8 - 1.0]).

Evaluation of P Wave Duration In ECG

A 12-lead ECG with simultaneous recording was performed in the pattern 2*N* (recording speed of 50 mm/s and amplitude of 2 mV/cm) in all participants. All ECGs were obtained in the same device and in the same period (between 10 am and 12 pm) to avoid circadian variations of electrocardiographic intervals. The examination was repeated under the same conditions 12 months after bariatric surgery. The P wave duration analysis was performed by a single observer with experience in the method and blind to the clinical condition of the participants. At least nine leads in which the P wave was visible and measurable were necessary for the recording to be taken into account in the analysis. The measurement was manually performed with the aid of a 0.01 mm precision digital caliper and magnifying lenses, as previously described by other researchers[12]. The beginning and end of the P wave were defined by the junction between the isoelectric line of the ECG and the initial and final phases of the P wave. The mean of the sum of three consecutive measurements in the same lead was calculated in all ECG leads (Fig. 2). The longer duration of the P wave in the ECG was used for analysis. A P wave duration greater than or equal to 110 ms was considered increased.

Statistical Analysis

Continuous variables were expressed as mean and standard deviation, while categorical variables were presented as numbers or proportions. Kolmogorov-Smirnov test was used to test normality. On the other

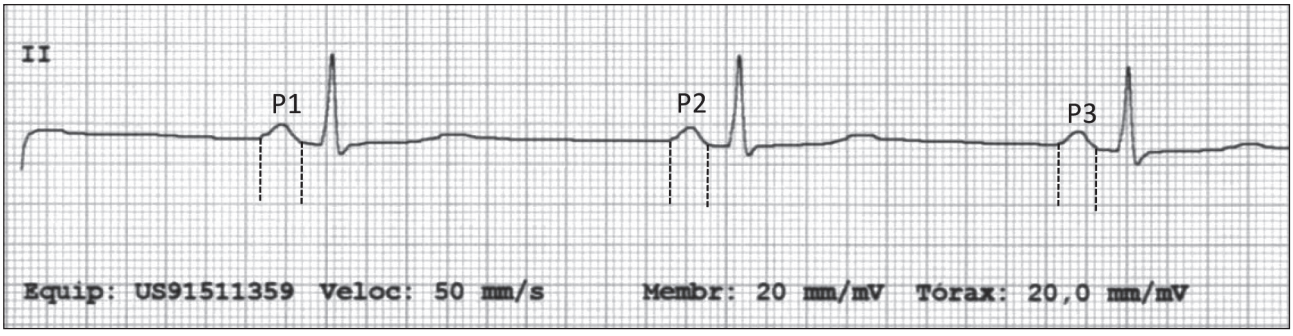

Figure 2. Analysis of the P wave duration in the ECG (lead II).

hand, to compare continuous variables, paired T and Wilcoxon tests were used, according to the distribution of the population regarding the normality curve. To evaluate the association between independent variables, a regression model for repeated measurements (Generalized Estimating Equation) was used. Finally, the gamma method was used to test interobserver variability. A p-value below 0.05 was considered statistically significant. The data were analyzed in the R software version 3.4.1 (R Core Team; Vienna, Austria, 2014).

RESULTS

In total, 20 patients completed the study protocol (age: 36.35 ± 10.26 years, 18 women), 17 performed the gastric bypass technique, and three were submitted to vertical gastrectomy by laparoscopy (see Fig. 1). No postoperative complications were observed among the participants. During follow-up, no clinical complications related to the surgery were observed.

Clinical and laboratory data are shown in Table 1. In the postoperative evaluation, a significant reduction in weight and body mass index (BMI) was observed ($p < 0.001$). There was a significant improvement in the glycemic and lipidic profile, as well as in the C-reactive protein (CRP) levels ($p < 0.05$). Creatinine levels remained unchanged.

Measurements of EF and P wave duration are shown in Table 2. There was a significant reduction in the EF thickness and in the P wave duration after bariatric surgery (7.72 ± 1.60 × 4.56 ± 1.40 and 109.55 ± 11.52 × 98.00 ± 1.49; $p < 0.001$), as well as a mean reduction of 11.55 ± 8.49 ms in the P wave duration, with a reduction above 10 ms in 11 study participants (55% of the sample). Before bariatric surgery, eight individuals (40% of the sample) presented increased P wave duration in ECG (≥ 110 ms), and only three remained with altered values after bariatric surgery (Fig. 3). In the multiple regression analysis, an association was observed between reductions in the EF thickness and BMI and reduction in the P wave duration in the ECG (Table 3).

Table 1. Clinical and laboratory characteristics of the study population.

Data	Before bariatric surgery	12 months after bariatric surgery	p-value
Weight (kg)	126.95 ± 16.38	89.47 ± 17.55	< 0.001
Body mass index (kg/m²)	47.19 ± 6.15	33.08 ± 6.91	< 0.001
Systolic blood pressure (mmHg)	110.10 ± 12.71	108.50 ± 7.96	0.224
Diastolic blood pressure (mmHg)	74.45 ± 6.80	74.45 ± 5.25	0.344
Glycemia (mg/dl)	88.10 ± 9.30	82.6 ± 4.36	0.019
Glycated hemoglobin (%)	5.45 ± 0.43	5.18 ± 0.40	0.003
Total cholesterol (mg/dl)	184.85 ± 23.30	151.60 ± 17.97	0.001
Triglycerides (mg/dl)	121.10 ± 50.24	76.80 ± 21.33	0.001
C-reactive protein (mg/dl)	11.79 ± 7.64	2.63 ± 2.14	0.001
Creatinine (mg/dl)	0.76 ± 0.13	0.74 ± 0.14	0.622

P1

Table 2. Data from measurements of P wave duration and echocardiography.

Data	Before bariatric surgery	12 months after bariatric surgery	p-value
P wave duration (ms)	109.55 ± 11.52	98.00 ± 10.49	0.001
Left atrial diameter (mm)	36.12 ± 3.46	37.06 ± 2.73	0.40
Left ventricular systolic diameter (mm)	30.30 ± 2.49	30.52 ± 1.51	0.742
Left ventricular diastolic diameter (mm)	46.20 ± 4.23	47.70 ± 2.11	0.137
Left ventricular ejection fraction (%)	63.15 ± 4.25	65.65 ± 2.85	0.016
Posterior wall (mm)	9.40 ± 0.99	9.26 ± 0.94	0.524
Septum (mm)	9.45 ± 1.0	9.61 ± 0.99	0.606
E/A (cm/s)	1.31 ± 0.39	1.60 ± 0.48	< 0.001
Left ventricular mass (g/m²)	151.10 ± 27.73	158.05 ± 22.35	0.391
Epicardial fat (mm)	7.72 ± 1.60	4.56 ± 1.40	< 0.001

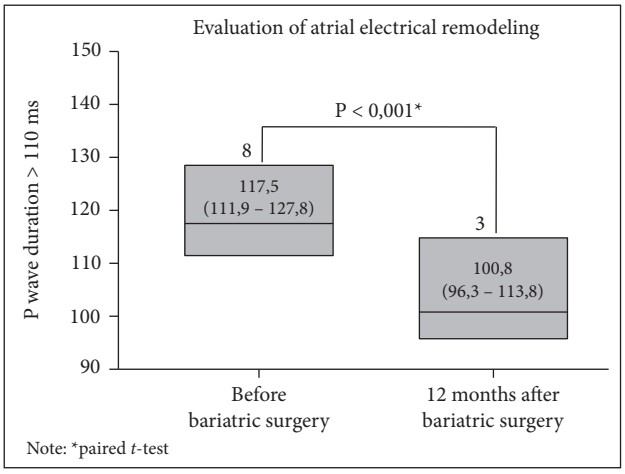

Figure 3. Evaluation of atrial electrical remodeling for obese patients with P wave duration above 110 ms.

Table 3. Multiple regression analysis.

		β	Dp	p-value
P wave duration	Epicardial fat	2.96	1.36	0.029
	Body mass index	0.47	0.22	0.038

DISCUSSION

In this study, we observed that EF reduction promoted by weight loss after bariatric surgery was associated with a significant decrease in the duration of the P wave. This finding involves cardiac visceral fat in the pathophysiological process of atrial remodeling in morbidly obese patients.

The impact of obesity and EF on the electrical and structural remodeling of atria has been tested in experimental studies. In an animal model, Abed et al. demonstrated that the progressive increase in obesity was able to promote an increase in volume, inflammation, and degree of interstitial fibrosis of the atria, as well as in accumulation of fat in the myocardium and expression of profibrotic atrial receptors[13]. In a study conducted by Lin et al., the incubation of the atrial cell by epicardial adipocytes was able to prolong the action potential, change the functionality of ionic channels and increase the induction of activity triggered when such cell is exposed to the effect of isoproterenol, demonstrating that the visceral fat can modulate the electrophysiological properties of the atrial cell and contribute to the electrical remodeling of the atria[14]. More recently, Mahajan et al. observed that electrophysiological changes in the posterior wall of obese sheep were exclusively attributed to EF infiltration, indicating that this localized phenomenon may contribute to the formation of an arrhythmogenic substrate in the atria[15].

The association between EF and atrial remodeling is also corroborated by evidence in population records and observational studies. According to the Framingham Heart Study, pericardial fat is associated with electrocardiographic measurements related to atrial conduction (P wave duration, PR interval, and P wave terminal force) even after adjustments for extracardiac fat deposits[16]. In a population similar to our study, Iacobellis et al. demonstrated a correlation between the dimensions of the left atrium (LA) measured by echocardiography and the EF thickness[17]. In analyses involving ECG and different imaging methods, the P wave duration was associated with the EF thickness and volume[10-18]. Together, all these analyses reinforce the hypothesis of cardiac visceral fat involvement in atrial remodeling.

The impact of weight reduction on cardiac remodeling is known and has already been analyzed after bariatric surgery[19]. Observational studies also indicate that weight reduction is capable of promoting a reduction in the duration and dispersion of the P wave[20]. However, the evidence that indicates the effects of the EF reduction on atrial remodeling is still scarce. In the study conducted by Monno et al., the reverse remodeling of the atria was evaluated in a group of patients submitted to catheter ablation and was inversely associated with greater thickness of EF and the presence of metabolic syndrome[21]. Although there was no weight reduction during follow-up, a significant reduction in EF was observed in the group that did not present recurrence of atrial fibrillation (AF) after ablation. In our study, the P wave reduction was associated with a reduction of BMI and EF. As they are interdependent conditions, the contribution of these variables in models that involve weight and obesity reduction should be considered together, because these variables are hardly dissociated.

Although the measurement of P wave duration indirectly reflects the size of the atria, and the normalization of this duration has occurred in 40% of obese patients, in this study we did not observe a reduction in the LA diameter after bariatric surgery. Technical issues related to image acquisition in patients with limited ultrasound window may have interfered with the results and cannot be disregarded. On the other hand, the observed changes may reflect more improvement in conduction than necessarily a reduction

in the atrial diameter. Evaluations of atrial remodeling by electroanatomic mapping demonstrated that, in areas of low voltage, the presence of fragmented potentials and slowing of atrial conduction were associated with regions of EF deposit in the atria of obese patients[22]. How modifiable are these alterations, due to lifestyle changes and interventions such as bariatric surgery, is a subject for further investigation.

The limitations of this study are mainly related to the size and restrictive nature of the sample. The inclusion of only obese patients without other comorbidities, although it reduces the external validation of the study, was essential to mitigate possible biases of confusion present in analyses involving the evaluation of atrial remodeling and obesity. Currently, the measurement of the EF volume is better estimated by tomography or magnetic resonance imaging, but the availability of these diagnostic methods for morbidly obese patients is limited. Measurement of the P wave by manually performed ECG may present limited accuracy when compared to other evaluation methods[23]. New studies are necessary to confirm our findings.

CONCLUSIONS

In a select group of morbidly obese patients submitted to bariatric surgery, the reduction in the EF thickness was associated with the reduction in the P wave duration and indicates that cardiac visceral fat and weight reduction may have an important role in the reverse electrical remodeling of the atria.

AUTHOR'S CONTRIBUTION

Conceptualization, Cardoso AF, Grindler J, Santo MA; Methodology, Cardoso AF, Furtado MS, Fonseca AJ, Pichara NL, Oliveira CR, Cleva R; Investigation, Cardoso AF, Furtado MS, Santo MA; Writing – Original Draft, Cardoso AF, Cleva R, Santo MA; Writing – Review and Editing, Cardoso AF, Santo MA; Supervision, Cardoso AF, Santo MA.

REFERENCES

1. Iacobellis G, Corradi D, Sharma AM. Epicardial adipose tissue: anatomic, biomolecular and clinical relationships with the heart. Nat Clin Pract Cardiovasc Med 2005 Oct;2(10):536-43. https://doi.org/10.1038/ncpcardio0319

2. Corradi D, Maestri R, Callegari S, Pastori P, Goldoni M, Luong TV, et al. The ventricular epicardial fat is related to the myocardial mass in normal, ischemic and hypertrophic hearts. Cardiovasc Pathol 2004 Nov;13(6):313-6. https://doi.org/10.1016/j.carpath.2004.08.005

3. Sacks HS, Fain JN. Human epicardial fat: what is new and what is missing? Clin Exp Pharmacol Physiol 2011 Dec 1;38(12):879-87. https://doi.org/10.1111/j.1440-1681.2011.05601.x

4. Cikim AS, Topal E, Harputluoglu M, Keskin L, Zengin Z, Cikim K, et al. Epicardial adipose tissue, hepatic steatosis and obesity. J Endocrinol Invest. Springer International Publishing 2007 Jun;30(6):459-64. https://doi.org/10.1007/BF03346328

5. Lyon CJ, Law RE, Hsueh WA. Minireview: adiposity, inflammation, and atherogenesis. Endocrinology 2003 Jun;144(6):2195-200. https://doi.org/10.1210/en.2003-0285

6. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet 2005 Apr;365(9468):1415-28. htpps://doi.org/10.1016/S0140-6736(05)66378-7

7. Bos D, Vernooij MW, Shahzad R, Kavousi M, Hofman A, van Walsum T, et al. Epicardial fat volume and the risk of atrial fibrillation in the general population free of cardiovascular disease. JACC Cardiovasc Imaging 2017 Nov;10(11):1405-7. https://doi.org/10.1016/j.jcmg.2016.12.005

8. Auer J. Fat: an emerging player in the field of atrial fibrillation. European heart journal 2017;38:62-5. https://doi.org/10.1093/eurheartj/ehw013

9. Hari KJ, Nguyen TP, Soliman EZ. Relationship between P-wave duration and risk of atrial fibrillation. Expert Rev Cardiovasc Ther2018 Nov;16(11):837-43. https://doi.org/10.1080/14779072.2018.1533814

10. Fernandes-Cardoso A, Santos-Furtado M, Grindler J, Ferreira LA, Andrade JL, Santo MA. Epicardial fat thickness correlates with P-wave duration, left atrial size and decreased left ventricular systolic function in morbid obesity. Nutr Metab Cardiovasc Dis 2017 Aug;27(8):731-8. https://doi.org/10.1016/j.numecd.2017.05.009

11. Iacobellis G, Willens HJ. Echocardiographic epicardial fat: a review of research and clinical applications. J Am Soc Echocardiogr 2009 Dec;22(12):1311-9;1417-8. https://doi.org/10.1016/j.echo.2009.10.013

12. Kosar F, Aksoy Y, Ari F, Keskin L, Sahin I. P Wave duration and dispersion in obese subjects. Ann Noninvas Electro 2008 Jan 1;13(1):3-7. https://doi.org/10.1111/j.1542-474X.2007.00194.x

13. Abed HS, Samuel CS, Lau DH, Kelly DJ, Royce SG, Alasady M, et al. Obesity results in progressive atrial structural and electrical remodeling: implications for atrial fibrillation. Heart Rhythm 2013 Jan;10(1):90-100. https://doi.org/10.1016/j.hrthm.2012.08.043

14. Lin YK, Chen YC, Chen JH, Chen SA, Chen YJ. Adipocytes modulate the electrophysiology of atrial myocytes: implications in obesity-induced atrial fibrillation. Basic Res Cardiol2012 Sep;107(5):293. https://doi.org/10.1007/s00395-012-0293-1

15. Mahajan R, Lau DH, Brooks AG, Shipp NJ, Manavis J, Wood JPM, et al. Electrophysiological, electroanatomical, and structural remodeling of the atria as consequences of sustained obesity. J Am Coll Cardiol 2015 Jul 7;66(1):1-11. https://doi.org/10.1016/j.jacc.2015.04.058

16. Friedman DJ, Wang N, Meigs JB, Hoffmann U, Massaro JM, Fox CS, et al. Pericardial fat is associated with atrial conduction: the Framingham Heart Study. J. Am. Heart Assoc 2014 Apr 22;3(2):e000477-7. https://doi.org/10.1161/JAHA.113.000477

17. Iacobellis G, Leonetti F, Singh N, Sharma AM. Relationship of epicardial adipose tissue with atrial dimensions and diastolic function in morbidly obese subjects. Int J Cardiol 2007 Feb;115(2):272-3. https://doi.org/10.1016/j.ijcard.2006.04.016

18. Jhuo SJ, Hsieh TJ, Tang WH, Tsai WC, Lee KT, Yen HW, et al. The association of the amount of epicardial fat, P wave duration, and PR interval in electrocardiogram. J Electrocardiol 2018 Jul-Aug;51(4):645-51. https://doi.org/10.1016/j.jelectrocard.2018.04.009

19. Tuluce K, Kara C, Tuluce SY, Cetin N, Topaloglu C, Bozkaya YT, et al. Early reverse cardiac remodeling effect of laparoscopic sleeve gastrectomy. Obes Surg 2017 Feb;27(2):364-75. https://doi.org/10.1007/s11695-016-2301-2

20. Falchi AG, Grecchi I, Muggia C, Tinelli C. Weight loss and P wave dispersion: a preliminary study. Obes Res Clin Pract 2014 Nov-Dec;8(6):e614-7. https://doi.org/10.1016/j.orcp.2014.08.005

21. Monno K, Okumura Y, Saito Y, Aizawa Y, Nagashima K, Arai M, et al. Effect of epicardial fat and metabolic syndrome on reverse atrial remodeling after ablation for atrial fibrillation. J Arrhythm 2018 Oct 13;34(6):607-16. https://doi.org/10.1002/joa3.12124

22. Mahajan R, Nelson A, Pathak RK, Middeldorp ME, Wong CX, Twomey DJ, et al. Electroanatomical remodeling of the atria in obesity: impact of adjacent epicardial fat. JACC Clin Electrophisiol 2018 Dec;4(12):1529-40. https://doi.org/10.1016/j.jacep.2018.08.014

23. Dilaveris P, Batchvarov V, Gialafos J, Malik M. Comparison of different methods for manual P wave duration measurement in 12-lead electrocardiograms. Pacing Clin Electrophysiol 1999 Oct;22(10):1532-8. https://doi.org/10.1111/j.1540-8159.1999.tb00358.x

https://doi.org/10.24207/jca.v32i2.008_IN

Management of Hemorrhage Related to Direct Action Oral Anticoagulant Medication

Manejo das Hemorragias Relacionadas aos Anticoagulantes Orais de Ação Direta

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ABSTRACT

Introduction: Direct Oral Anticoagulant – DOACs) are a new class of anticoagulant that directly inhibit the trombine (dabigatrane) or Xa factor (rivaroxabane, edoxabane and apixabane) in the coagulation cascade. These medications are being more frequently used for the treatment and prevention of thrombolytic events, mainly in patients with atrial fibrillation, in substitute to varfrine or other vitamin K antagonists (VKAs). Although the incidence of hemorrhage is higher in AVKs than in DOACs, these events may also occur in this group, even in the form of intracranial hemorrhage (ICH), with risk of death. Nowadays, DOACs indications have progressively enhanced and the availability of their specific reverse agents certainly will enhance the safety of their usage. Idarucizumab, reverse agent of dabigatrane, and alpha andexanet, reverse agent of Xa factor, have been approved by the Food and Drug Administration in the United States and ciraparantag may be approved in a near future. **Objective:** To review the literature on the manage of hemorrhage related to the use of DOACs. **Methods:** Review of literature that used articles from 1998 to 2017, from several platforms and journals. **Conclusion:** DOACs constitute a great advance in prophylaxis and treatment of thrombolytic diseases, which presents elevated morbidymortality, and hemorrhages are the main adverse events related to their usage, being rarely necessary the immediate reverse of the anticoagulation. However, the existence of DOACs specific reverse agents enhance the safety of patients, whose anticoagulation may be rapidly reversed if necessary.

KEYWORDS: Atrial fibrillation; Blood coagulation; Pharmaceuticals effects.

RESUMO

Introdução: Os anticoagulantes orais diretos (direct oral anticoagulant – DOACs) são uma nova classe de anticoagulantes que inibem diretamente a trombina (dabigatran) ou o fator Xa (rivaroxabana, edoxabana e apixabana) na cascata da coagulação. Esses estão sendo cada vez mais utilizados para tratamento e prevenção de eventos tromboembólicos, principalmente em pacientes com fibrilação atrial, em substituição à varfarina ou outros antagonistas de vitamina K (AVKs). Embora a incidência de hemorragias seja maior nos AVKs do que nos DOACs, elas também podem ocorrer nesse grupo, até mesmo na forma de hemorragia intracraniana (HIC) com risco de morte. Atualmente as indicações dos DOACs vêm aumentando progressivamente, e a disponibilização de seus agentes reversores específicos certamente aumentará a segurança e, consequentemente, sua utilização. O idarucizumab, reversor da dabigatrana, e o andexanet alfa, reversor dos inibidores do fator Xa, foram aprovados pelo Food and Drug Administration (FDA) dos Estados Unidos e o ciraparantag poderá ser aprovado em um futuro próximo. **Objetivo:** Revisar a literatura sobre o manejo da hemorragia relacionada ao uso dos DOACs. **Métodos:** Revisão da literatura que utilizou artigos de 1998 a 2017, de diversas plataformas e revistas. **Conclusão:** Os DOACs constituem um grande avanço na profilaxia e tratamento da doença tromboembólica, que cursa com elevada morbimortalidade, e as hemorragias são os principais eventos adversos relacionados ao seu uso, sendo raramente necessária a reversão imediata da anticoagulação. No entanto, a existência dos reversores específicos dos DOACs aumenta a segurança dos pacientes, que poderão ter sua anticoagulação revertida rapidamente, se necessário.

PALAVRAS-CHAVE: Fibrilação atrial; Coagulação sanguínea; Efeitos dos fármacos.

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INTRODUCTION

Oral anticoagulation is essential for the prevention and treatment of embolism and thrombosis. Only in the United States, over six million people use oral anticoagulant medication (OACs), which could be related to higher risk of bleeding and could also echo in morbidymortality of this group[1].

The incidence of diseases that require OACs have been progressively increasing and this is directly linked to the aging of the population. Atrial fibrillation (AF), the most prevalent arrhythmia in the world, presented an enhance of 13% regarding incidence in the last two decades, and age is a risk factor not only for the development of AF but also for the risk of cardio thrombolytic events. Cerebral Vascular Accident (CVA) is the main complication of FA and it is related to this arrhythmia in 20% of the cases[2.]

Direct Oral Anticoagulants (DOACs), represented by the direct suppressants of Xa factor (rivaroxaban, edoxaban and apixaban), and thrombin direct suppressant (dabigatran) are alternatives to the vitamin K antagonists (VKAs) for the profilaxys and treatment of thrombolytic events, greatly in part related to AF and present a series of clinical advantages when compared to VKAs, such as higher anticoagulant stability and less risk not only for intracranial hemorrhage but also bleeding[5].

Regarding hemorrhage complications, due to the short half-life of these medications, in most cases only the suspension, associated to clinical support actions, may be enough to stop the bleeding. The usage of prothrombic complex[4], haemodialysis and the use of activated carbon (AC) may be useful in reducing the action of DOACs; however, in cases of overdosage, massive bleeding, hemodynamic compromise or need of urgent surgical intervention, the reversion of the anticoagulant activity may be needed. To act in these more serious cases, DOACs specific reverse agents were developed, and the three main drugs are: idarucizumabe, andexanet and ciraparantag.

OBJECTIVE

To review the literature regarding hemorrhage management related to DOACs.

METHODS

This review of literature study used articles from 1998 to 2017, researched in the platforms PubMed, Medline, Cochrane Library, SciELO and UpToDate and in the scientific journals Journal of the American Medical Association, New England Journal of Medicine and Blood, using the following keywords: atrial fibrillation, anticoagulation, DOAC, alpha andexanet, idarucizumabe, ciraparantag.

DEVELOPMENT

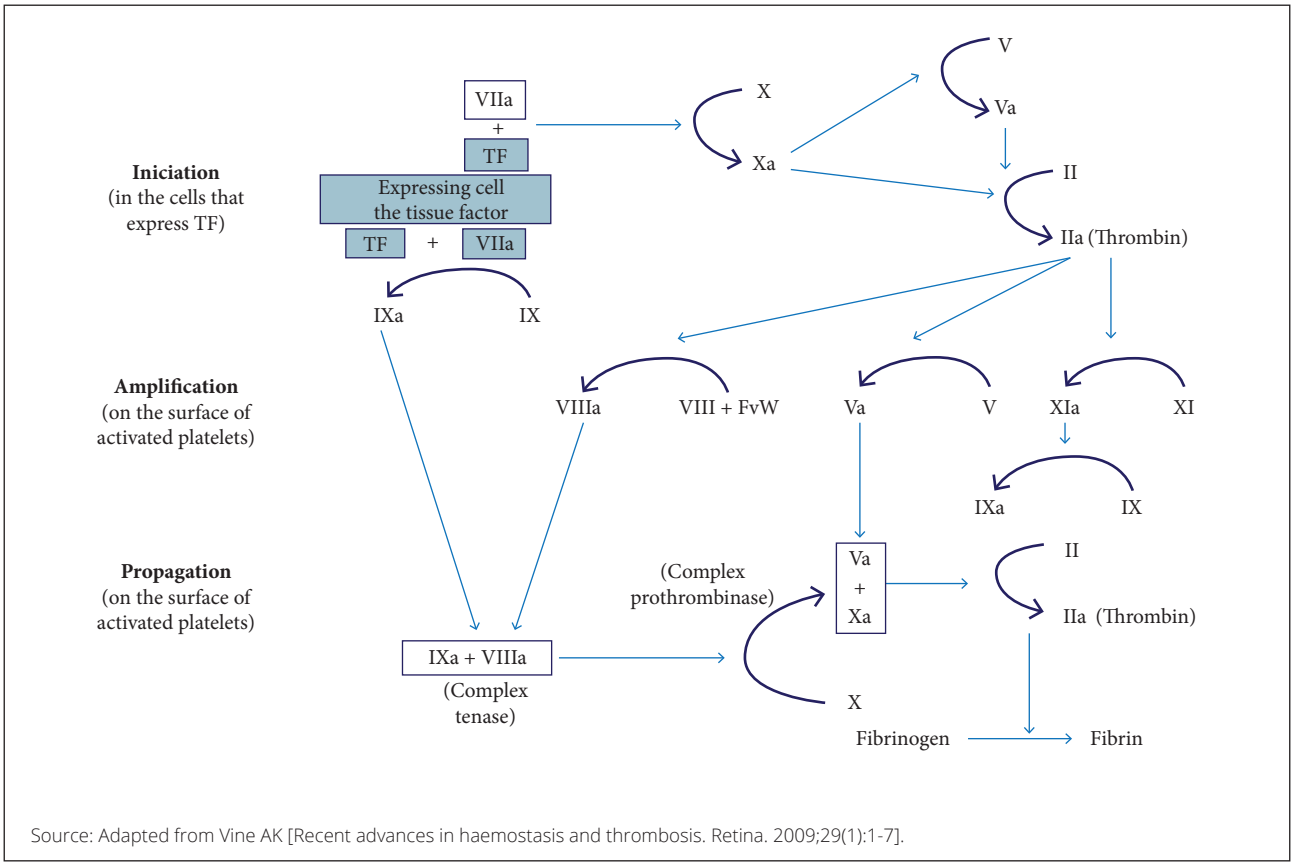
Homeostasis is a normal physiological answer from the body that prevents significant blood loss after vascular damage. Coagulation cascade is a complex series of reactions that guarantees the occurrence of homeostasis (Fig. 1).

Anticoagulant system, which works in parallel to the fibrinolytic system, guarantees that the formation of the thrombus is a controlled and balanced procedure, allowing the degradation of already formed thrombus. DOACs are divided into direct inhibitors of thrombin or direct inhibitors of Xa factor, and their characteristics are presented in Table 1.

Exetilate dabigatran is an oral pro-pharmaceutical that is converted in the liver into dabigatran, a direct, reversible, competitive inhibitor of thrombin[5]. There are tests of anticoagulant activity, such as the ecarin clotting time (ECT), thrombin time (TT) and partially activated thromboplastin (PATP) to detect the excessive activity of the dabigatran. TT is the most sensible in detecting low levels of dabigatran[6, 7].

The direct inhibitors of Xa factor (rivaroxaban, apixaban and edoxaban) directly linked themselves to the active sites of X factor in the circulation and, linked to the clot, block the interaction with its substrate. They are metabolized by the kidneys (25-35%) and liver (up to 75%) and patients with hepatic insufficiency may present this drug accumulation, but in spite of that, these medications do not seem to be toxic to the liver[8].

Rivaroxaban is a direct inhibitor, reversible and competitive of the Xa factor, orally administrated. It should not be use in patients with clearance <15 mL/min, as well as in patients with important



Source: Adapted from Vine AK [Recent advances in haemostasis and thrombosis. Retina. 2009;29(1):1-7].

Figure 1. Coagulation cascade [tissue factor (TF) activated].

liver illness (Child-Pugh B and C with coagulopathy)[9]. This medication has not been tested in people under 18 years of age[10].

Rivaroxaban interacts with CYP-3A4 and protein P suppressant drugs (such as ketoconazol, itraconazol, voriconazol, posaconazol and ritonavir) and its concomitant use with these drugs is not recommended[11]. It is not necessary to perform tests to monitor the coagulation during the treatment with rivaroxaban, except in patients that present bleeding, suspect of medication intoxication or need of emergency surgery[13].

Apixaban is a direct inhibitor, reversible and competitive of Xa factor, orally administrated, needing adjust of the dose according to the creatinine clearance. It is also recommended to reduce its dose in patients that use CYP-3A4 and protein P inhibitors[14].

Edoxaban is a direct inhibitor of Xa factor, selective and reversible[15,16]. Around 73% of the drug of the dose is eliminated unaltered in urine and faeces[17,18]. The recommended dose for the prevention of Cerebral Vascular Accident in patients with AF is of 60 mg once a day, reducing to 30 mg once a day in patients with creatinine clearance between 15-50 mL/min, weight <60kg or concomitant use of any protein P inhibitor (for ex., verapamil, quinidin, eritromicin and ketoconazol)[19]. This medication is not recommended for patients with terminal kidney failure, creatinine clearance ,15 mL/min or under hemodialysis.

The incidence of bleeding is 2-3% a year higher in patients using DOACs, being the incidence of CVA 1-0.5%[21].

DISCUSSION

Hemorrhage management related to the use of DOACs varies according to the gravity of the case. Light hemorrhages may be resolved only with the temporary suspension of the drug and, in the most severe cases, fluid reposition may be needed, as well as hemodynamic support, mechanical compression, surgical hemosthasis, and the use of blood derivatives. If all those measurements were not enough, one must use pro-coagulants, such as the prothrombic complex[21].

Table 1. Properties of DOACs.

	Dabigatran	Rivaroxaban	Apixaban	Endoxaban
Action mechanism	Thrombin direct inhibitor	Xa factor direct inhibitor	Xa factor direct inhibitor	Xa factor direct inhibitor
Time to achieve seriec level	1 to 2 h if swallowed with food	2 to 4 h	3 to 4 h	1 to 2 h
Half-life	12 to 17 h (young people); 14 to 17 h (eldery)	5 to 9 h (young people); 11 to 13 h (eldery)	12 h	10 to 14 h
Dose (fanv)	150 mg twice a day	20 mg once a day	5 mg twice a day	60 mg once a day
Metabolism by cyp3a4	No	Yes	Yes	Minimum
Elimination	80% kidney	70% liver 30% kidney	30% kidney	50% kidneyl

Source: Crit Care Res Pract. 2018. ID:4907164.

Other therapies include hemodialysis, capable of removing up to 60% of the circulant dabigatrana and AC, effective in reducing the absorption of anticoagulant in the first hours after the ingestion. In the cases of overdose, massive bleeding, need to restore hemostasis by hemodynamic compromise or need of urgent surgical intervention, the reserve of the anticoagulant activity may be needed, using DOACs reverse agents[21]. Their indications and characteristics are presented in Table 2 and Table 3.

Idarucizumabe, specific reserve agent of dabigatrana, was approved for clinical use in October and November 2015, in the United States and Europe, respectively and in Brazil, its liberation occurred in April 2017. Alpha andexanet, reverse of Xa factor inhibitors, was approved by the Food and Drug Administration (FDA) in an accelerated scheme, however in Brazil its usage has not been cleared yet. The most recent DOACs reverse agent, ciraparantag, is in initial phase of studies and it proposes the reverse of all types of DOACs.

Clinical Measurements

In case of greater bleeding, which occurs in critical location in association with hemodynamic instability or fall of ± 2 g/dL of hemoglobine, DOACs must be suspended, being their specific reverse agents indicated, as well as volume replacement and local hemostasis[22].

In case of external bleeding, local control measurements must be performed, preferentially with criastalloides (0.9% saline, Ringer or Lactate), aiming the volemic restauration and hemodynamic stability. Hypothermia as well as acidosis must be corrected and, in case of symptomatic anemia and/or active bleeding, red blood cells must be transfused, in order to maintain hemoglobin at ± 7 g/dL in general patients and at ± 8 g/dL in coronary patients[23].

Plaquets transfusion must be performed if there is less than 50.000[24] and if fibronogenius crioprecipitate is less than 100 mg/dL. Care must be taken when indication DOACs in patients with morbidity that enhances the risks of bleeding, mainly dabigatran, since liver dysfunction may lead to coagulopathy and reduce the metabolism of the anticoagulant, enhancing the risk of hemorrhages. When DOACs specific reserve actions or agents are unavailable, non-specific reverse measurements should be performed.

Prothrombic complex is a complex of factors derived from human plasma capable of reversing the anticoagulating action of VKA. In animal studies, prothrombic complex was also efficient in reversing the effects of dabigatran[25], with recommended dose of 50 U/kg (maximum of 4.000 U)[26]. There are no randomized studies evaluating the use of prothrombic complex in patients with higher bleeding due to the use of Xa factor inhibitors, therefore the dose is based on cases, series of cases and studies in pre-clinical phase, being the initial suggested dose of 50 U/kg[27]. AC may be used to remove the non-absorbed drug by the gastrointestinal

Table 2. Indications of the DOACs reserve agents.

Bleeding with risk of death: intracranial hemorrhage, symptomatic extradural hemorrhage or in expansion or uncontrollable hemorrhage
"Closed" bleeding or in critical organs: intraspinal, intraeye, pericardium, pulmonary, retroperitoneal or intramuscular or compartmental syndrome
More persistent bleeding in spite of al the measurement for local hemostasis or risk of recurrent bleeding
Surgery or emergency intervention in patients with risk risk of bleeding during the proceedure: neurosurgery, lumbar punction, cardiac surgery, vacular or hepathic surgery

Source: J Thromb Haemost. 2015;14:623-7.

Table 3. Properties of the specific reverse of DOACs.

	Idarucizumabe	Alpha Andexanete	Ciraparantag
Target	Dabigratan	Direct inhibitor do fator Xa, LMWH, fondaparinux	Direct inhibitor of Xa factor, low molecular weight heparin, fondaparinux, heparin, dabigratan
Compound	Human monoclonal antibody fragment	Recombinant molecule derived from human Xa factor	Bonding through the non-covalent hydrogen actions, diminishing the bonding to endogenous targets
Action mechanisms	Afinity of bonding to dabigatran 350 times higher than the affinity of dabigratan-trombin bonding	Alteration of the receptor of the Xa inhibitors with greater afinity of the bonding than "natural" Xa factor	100-400 mg intravenous administration
Dose	5 g (divided into two doses of 2.5 g intravenously adminstrated)	400-800 mg in bolus, followed by 4-8 mg/min in continuous infusion in 2h	Within 10 min
Start of the action	Immediate	Within de 5 min	Yes
Reservsion duration	12 h	1 to 2 h	24 h
Elimination	Renal	Indefinite	Indefinite
Clinical Study	Reverse-AD	Annexa-A and AnnexA-R	Ansell et al[37].
Development phase	III/approved	III	II
Adverse effects	Cutaneous reaction, bruises at the site of application and epistaxis	Urticaria, disgeusia, headaches and flushing	Disgeusia, headaches and flushing

LMWH: Low Molecular Weight Heparin
Source: Critical Care Research and Practice. 2018. ID: 4907164.

tract and should be performed in up to 2 to 4 hours after the ingestion[28].

Hemodyalisis is useful for bleeding related to dabigatran, due to low affinity to this molecule by plasmatic proteins, due to the excretion mostly by the kidneys[29]. On the other hand, Xa inhibitors cannot be dyalised, since present strong bonding to plasmatic proteins[21].

Antifibronilitc agents may be indicated to patients with greater bleeding caused by either Xa inibitors or dabigatran. Activated VII factor, fresh frozen plasma or cryoprecipitate must be avoided due to the lack of studies showing benefits and the associated high risks (for ex., transfusional reaction, volume overload)[21].

DOACs reverse agents are indicated in case of urgent reversion of the anticoagulant effect, such as in massive bleeding, in the presence of hemodynamic instability or when patient needs urgent/emergency surgery in the presence of the usage of such pharmaceuticals.

Idarucizumabe may be used to reverse the action of dabiatran. A fragment of the human monoclonal antibody produced in ovarium cels of hamsters from China connects to dabigatran with high afinity and specificity. The recognition and the bonding to dabigatran are due to the structural similarity to thrombin mediated by hydrophobic and hydrogen interactions and saline bridges. The dose adjustment is not necessary according to kidney and liver function, weight or age. The peak of idarucizumabe concentration is reached in a few minutes, followed by quick elimination[30].

When 5 g of idarucizumabe is administrated, 32.1% will be recovered in urine in the period of 6 hours and less than 1% in the next 18 hours. The remaining will be eliminated through protein catabolism, mainly through the kidneys. Transitory proteteinuria has been observed, which normally reaches its peak after 4 hours of administration and disappears between 12 to 24 hours. In the absence of dabiatran in the organism, idarucizumabe has no effect in the formation of thrombin or in the coagulation parameters (dTT, ECT, TT, PATP). In phase 1 studies, no statistically significant differences were demonstrated between the side effects found in patients that received placebo or idarucizumabe, neither relevant clinical findings or altered laboratory parameters, vital signs, eletrocardiogram or physical exams alterations were found[3]. Idarucizumabe dose selection for the use in clinical tests was based on targets to neutralize the dose of dabigatran used in patients with AF on RE-LY study (150 mg of dabigatran twice a day). The 5 mg dose was chosen to reverse the dose of the anticoagulant in patients with moderate kydney function. In the studies that involved patients of masculine and feminine gender of different agents and kidney functions, the administration of idarucizumabe, in the dose of 2.5 g every 12 hours, resulted in the satisfactory reversion of anticoagulation by dabigatran, being this dose selected for further studies. Idarucizumabe has shown to be effective and safe in the reversion of the anticoagulant effect of the dabigatran, in bleeding situations. The safety observed in the study gives support to the use in emergency situations, and the medication has already indications for the treatment of severe hemorrhages[31].

Alpha andexanet is a specific reserve agent of the Xa inhibitors criated by bioengenheering. It is a recombinant molecule with structure similar to the endogenous Xa factor, with high afinity to the Xa factor inhibitors, as well as the direct and indirect ones (rivaroxaban, edoxaban, apixaban, low molecular weight heparin and fondaparinux), but it does not have catalytic effect, so it does not performs the cleavage of the prothrombin to thrombin. The bonding site of Xa factor was substituted by alanine, which allows the bonding and removal of Xa factor inhibitors in the intravascular, restoring the activity of the endogenous Xa factor, with consequently reduction of the anticoagulant activity[32].

Andexanet alpha has instravenous administration, being the first dose in bolus, followed by a maintanance dose in the next 2 hours[33]. The start of the action is in 2 to 5 minutes after the drug infusion and its half-life is in 30 to 60 minutes. The Xa inhibitors anticoagulant levels rise after a few hours of andexanet administration, and the drug is not removed with the reverse agent, as it happens with dabigatran, when the antibody idarucizumabe is used 34,35. Dose adjustment is not necessary. In 2 minutes after the administration, alpha andexanet showed reversion of the anticoagulant effects of all Xa factor inhibitors, including the reduction of its activity and the restoration of thrombin generation and coagulation time. Endovenous administration in bolus, followed by continuous infusion of andexanet resulted in sustained reduction of the anti-Xa factor, which returned to the levels of the placebo group 2 hours after the stop of the infusion[34].

Ciaraparantag (PER977) is a small cathionic synthetic molecule, which bonds to the Xa inhibitor factor, thrombin direct inhibitors, non-fractioned heparin and low molecular weight heparin through non-covalent hydrogen bridges. Phase 2 studies investigating reversion of edoxaban and evaluating the doses of ciraparantag are in progress and plans for phase 3 studies have already been announced[36].

CONCLUSION

DOACs constitute a great advance in prophylaxis and treatment of thrombolytic disease, which presents elevated morbiditymortality. These drugs are of easy use, present high efficiency and safety and do not need of therapeutic dose adjustment by the coagulogram, which have been elevating their use. An important obstacle regarding DOACs use was the impossibility of reversion of their action in case of severe bleeding or emergency surgeries.

Although rarely necessary, in case of immediate reversion, the existence of reverse agents enhances the security of patients, which may lead to the enhancement of their usage. For this reason, it is very important the availability of DOACs specific reverse agents, even knowing that most cases regarding bleeding related to their use do not need any drastic intervention.

AUTHORS' CONTRIBUTION

Conceptualization, Ganem IRA; Martins LCB and Tomé CEM; Methodology, Ganem IRA and Tomé CEM; Investigation, Ganem IRA; Martins LCB and Tomé CEM; Writing – first version, Ganem IRA; Martins LCB and Tomé CEM; Writing – revision & editing, Ganem IRA; Martins LCB and Tomé CEM; Grant acquisition, Ganem IRA; Martins LCB and Tomé CEM; Resources, Ganem IRA; Martins LCB and Tomé CEM; Supervision, Martins LCB and Tomé CEM.

REFERENCES

1. Barnes GD, Lucas E, Alexander GC, Goldberger ZD. National trends in ambulatory oral anticoagulant use. Am J Med. 2015;128(12):1300-5.e2. https://doi.org/10.1016/j.amjmed.2015.05.044
2. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart disease and stroke statistics–2016 update: a report from American Heart Association. Circulation. 2016;133:e38-360. https://doi.org/10.1161/CIR.0000000000000350
3. Reilly PA, van Ryn J, Grottke O, Glund S, Stangier J. Idarucizumab, a specific reversal agent for Dabigatran: Mode of action, Pharmacokinetics and pharmacodynamics, and safety and efficacy in fase 1 subjects. The American Journal of Medicine. 2016. http://dx.doi.org/10.1016/J.amjmed.2016.06.007
4. Suryanarayan D, Schulman S. Potencial antidotos for reversal of old and new oral anticoagulants. Tirombaço Res. 2014;133(Suppl 2):S158-66. https://doi.org/10.1016/S0049-3848(14)50026-6
5. Marques SP. Velhos e novos anticoagulantes orais. Perspectiva farmacológica. Rev Port Cardiol. 2012;31(1):6-16. https://doi.org/10.1016/S0870-2551(12)70034-3
6. Dager WE, Gosselin RC, Kitchen S, Dwyre D. Dabigatran effects on the international normalized ratio, activated partial thromboplastin time, thrombin time, and fibrinogen: a multicenter, in vitro study. Ann Pharmacother. 2012;46:1627. https://doi.org/10.1345/aph.1R179
7. Reilly PA, Lehr T, Haertter S, Conolly SJ, Yusuf S, Eikelboom JW, et al. The effect of dabigatran plasma concentrations and patient characteristics on the frequency of ischemic stroke and major bleeding in atrial fibrillation patients: the RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulation Therapy). J Am Coll Cardiol. 2014;63:321-38. https://doi.org/10.1016/j.jacc.2013.07.104
8. Douros A, Azoulay L, Yin H, Suissa S, Renoux C. Non-vitamin K antagonist oral anticoagulants and risk of serious liver injury. J Am Coll Cardiol. 2018;71:1105. https://doi.org/10.1016/j.jacc.2018.01.009
9. Poulsen BK, Grove EL, Husted SE. New oral anticoagulants: a review of the literature with particular emphasis on patients with impaired renal function. Drugs. 2012;72:1739. https://doi.org/10.2165/11635730-000000000-00000
10. Turpie AG, Kreutz R, Llau J, Norrving B, Haas S. Management consensus guidance for the use of rivaroxaban – an oral, direct factor Xa inhibitor. Thromb Haemost. 2012;108:876. https://doi.org/10.1160/TH12-03-0209
11. Gulseth MP, Wittkowsky AK, Fanikos J, Spinler SA, Dager WE, Nutescu EA, et al. Dabigatran etexilate in clinical practice: confronting challenges to improve safety and effectiveness. Pharmacotherapy. 2011;31:1232. https://doi.org/10.1592/phco.31.12.1232
12. Nutescu E, Chuatrisorn I, Hellenbart E. Drug and dietary interactions of warfarin and novel oral anticoagulants: an update. J Thromb Thrombolysis. 2011;31:326. https://doi.org/10.1007/s11239-011-0561-1
13. Powell JR. Are new oral anticoagulant dosing recommendations optimal for all patients? JAMA. 2015;313:1013. https://doi.org/10.1001/jama.2015.59
14. Bristol-Myers Squibb Pharma Company. Highlights of prescribing information. Disponível em: http://packageinserts.bms.com/pi/pi_eliquis.pdf
15. Furugohri T, Isobe K, Honda Y, Kamisato-Matsumoto C, Sugiyama N, Nagahara T, et al. DU-176b, a potent and orally

active fator Xa inhibitor: in vitro and in vivo pharmacological profiles. Thromb Haemost. 2008;6(9):1542-9. https://doi.org/10.1111/j.1538-7836.2008.03064.x

16. Zafar MU, Vorchheimer DA, Gaztanaga J, Velez M, Yadegar D, Moreno PR, et al. Antithrombotic effects of factor Xa inhibition with DU-176b: Phase-1 study of an oral, direct factor Xa inhibitor using an ex-vivo flow chamber. Thromb Haemost. 2007;98(4):883-8. https://doi.org/10.1160/TH07-04-0312

17. Lixiana. Summary of product characteristics. (European Medicines Agency). Available at: http://www.ema.europa.eu/ema/index.jsp?curl=Pages/medicines/human/medicines/002629/human_med_001874.jsp&mid=WC0b01ac058001d124

18. Masumoto H, Yoshigae Y, Watanabe K, Takakusa H, Okazaki O, Izumi T, et al. In vitro metabolism of edoxaban and the enzymes involved in the oxidativo metabolism of edoxaban. AAPS J. 2010;12:1

19. Salazar DE, Mendell J, Kastrissios H, Green M, Carrothers TJ, Song S, et al. Modelling and simulation of edoxaban exposure and response relationships in patients with atrial fibrillation. Thromb Haemost 2012;107(5):925-36. https://doi.org/10.1160/TH11-08-0566

20. Ruff CT, Giugliano RP, Antman EM, Crugnale SE, Bocanegra T, Mercuri M, et al. Evaluation of the novel factor Xa inhibitor edoxaban compares with warfarin in patients with atrial fibrillation: design and rationale for the Effective aNticoaGulation with factor xA next GEneration in Atrial Fibrillation - Thrombolysis In Myocardial Infarction study 48 (ENGAGE AF-TIMI 48). Am Heart J. 2010;160(4):635-41. https://doi.org/10.1016/j.ahj.2010.06.042

21. Hylek EM, Held C, Alexander JH, et al. Major bleeding in patients with atrial fibrillation receiving apixaban or warfarin: The ARISTOTLE Trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation): Predictors, Characteristics, and Clinical Outcomes. J Am Coll Cardiol. 2014;63:2141. https://doi.org/10.1016/j.jacc.2014.02.549

22. Garcia DA, Crowther M. Management of bleeding in patients receiving direct oral anticoagulants. UpToDate.2018

23. Carson JL, Guyatt G, Heddle NM, Grossman BJ, Cohn CS, Fung MK, et al. Clinical practice guidelines from the AABB: red blood cell transfusion thresholds and storage. JAMA. 2016;316:2025-35. https://doi.org/10.1001/jama.2016.9185

24. Contreras M. Consensus conferenc on platelet transfusion. Final statement. Blood Rev. 1998;12:239-40. https://doi.org/10.1016/S0268-960X(98)90005-4

25. Tummala R, Kavtaradze A, Gupta A, Ghosh RK.Specific antidotes against direct oral anticoagulants- a comprehensive review of clinical trials data. Int J Cardiol. 2016;214:292-8. https://doi.org/10.1016/j.ijcard.2016.03.056

26. Wong H, Keeling D. Activate prothrombin complex concentrate for the prevention of dabigatran-associated bleeding. Br J Haematol. 2014;166:152-3. https://doi.org/10.1111/bjh.12831

27. Dibu JR, Weimer JM, Ahrens C, Manno E, Frontera JA.The role of FEIBA in reversing novel oral anticoagulants in intracerebral hemorrhage. Neurocrit Care. 2016;24:413-9. https://doi.org/10.1007/s12028-015-0213-y

28. Van Ryn J, Stangier J, Haertter S, Liesenfeld KH, Wienen W, Feuring M. Dabigatran etexilate-a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity. Thromb Haemost. 2010;103:1116-27. https://doi.org/10.1160/TH09-11-0758

29. Stangier J, Rathgen K, Stahle H, et al. Influence of renal impairment on the pharmacokinetics and pharmacodynamics of oral dabigatran etexilate. Clin Pharmaokinet. 2010;49:259-68. https://doi.org/10.2165/11318170-000000000-00000

30. Schiele F, van Ryn J, Canada K, Newsome C, Sepulveda E, Park J, Nar H, et al. A specific antidote for dabigatran, funcional and structural characterization. Blood. 2013;121:3554-62. https://doi.org/10.1182/blood-2012-11-468207

31. Glund S, Stangier J, Schmohl M, Ganser D, Norris S, van Ryn J, et al. Safety, tolerability, and efficacy of idarucizumab for the reversal of the anticoagulant effect of dabigatran in healthy male volunteers: a randomised, placebo-controlled, double-blind phase 1 trial. Lancet. 2015;386:680-90. https://doi.org/10.1016/S0140-6736(15)60732-2

32. Lu G, DeGuzman FR, Hollenbach SJ, Karbarz MJ, Abe K, Lee G, et al. A specific antidote for reversal of anticoagulation by direct and indirect inhibitors of coagulation factor Xa. Nat Med. 2013;19:446-51. https://doi.org/10.1038/nm.3102

33. Connolly SJ, Milling TJ, Eikelboom JW, Gibson CM, Gold A, Curnutte JT, et al. Andexanet alfa for acute major bleeding associated with factor Xa inhibitors. N Engl J Med. 2016;375(12):1131-41. https://doi.org/10.1056/NEJMoa1607887

34. Siegal DM, Curnutte JT, Connolly SJ, Lu G, Conley PB, Wiens BL, et al. Andexanet alfa for the reversal of factor Xa inhibitor activity. N Engl J Med. 2015;373(25):2413-24. https://doi.org/10.1056/NEJMoa1510991

35. Quintard H, Viard D, Drici MD, Ruetsch C, Samama CM, Ichai C. Idarucizumab administration for reversing dabigatran effect in na acute kidney injured patient with bleeding. Thromb Haemost. 2017;117(1):196-7. https://doi.org/10.1160/TH16-06-0445

36. Ansell JE, Bakhru SH, Laulicht BE, Steiner SS, Grosso M, Brown K, Dishy V, et al. Use of PER977 to reverse the anticoagulants effect of edoxaban. N Engl J Med 2014; 371: 2141-2

37. J. E. Ansell, S. H. Bakhru, B. E. Laulicht et al., "Use of PER977 to reverse the anticoagulant effect of edoxaban," New England Journal of Medicine, vol. 371, no. 22, pp. 2141-2142, 2014

https://doi.org/10.24207/jca.v32i2.988_IN

What is the Diagnosis?

CASE PRESENTATION

A female 82-year-old Caucasian patient with a history of paroxysmal atrial fibrillation (AF) for several years, with palpitation crises of varying duration between a few minutes and several hours, without clinical control, using beta-blockers and diltiazem. The patient presented complaints of fatigue on moderate efforts, without precordial pain or syncope, with progressive asthenia and indisposition. She informed three previous hospitalizations for chemical cardioversion of AF.

The patient had a history of systemic arterial hypertension, hypothyroidism, and atherosclerotic heart disease, and underwent coronary angioplasty in 2014 with the placement of a nonpharmacological stent, without a prior heart attack. She was on regular use of irbesartan 300 mg, clopidogrel 75 mg, and levothyroxine 75 mcg. Over the past eight months, there has been a worsening of AF crises, and she started to take propafenone in increasing doses, initially 150 mg BID, without improvement of symptoms, then 300 mg BID and currently 750 mg/day (300 – 150 – 300 mg 8/8 hours), without control of palpitations and with feeling of discomfort and weakness.

On physical examination, the patient was in good general condition, with no significant abnormalities. Her blood pressure was at 135/80 mmHg, with a heart rate of 72 bpm, irregular rhythm due to the presence of extrasystoles, normophonetic sounds in two times and mild systolic murmur at a mitral focus.

Laboratory tests were within normal limits. The patient presented Doppler echocardiography with left ventricle (LV) with standard segmental dimensions and contractility, ejection fraction of 68%, slight concentric LV hypertrophy, left atrium with slight increase (44 mm), alteration in LV distensibility, presence of mild mitral valve insufficiency and absence of pulmonary arterial hypertension or dilatation of right chambers. A 24-hour Holter performed one month before the examination showed the presence of sinus rhythm, mimic frequency of 49, maximum of 86, with a mean of 64 bpm, presence of rare atrial ectopias (29 isolated, 1 episode of atrial tachycardia with 5 beats and atrial frequency of 108 bpm), rare ventricular ectopias (78 isolated, without pairs or ventricular tachycardias) with first-degree AV block during sleep, QRS with duration at the maximum limit of normality (0.12 s) and nonischemic changes of ventricular repolarization.

Her electrocardiogram (Figure 1) showed the presence of sinus rhythm, mild interatrial conduction disorder (P wave duration of 125 ms), AV interval at the upper limit of normality (0.20 s), QRS with 125 ms duration and presence of isolated ventricular extrasystoles. The presence of alterations in ventricular repolarization, with ST-segment elevation in V1 and V2 derivations, with descending "saddle-back" concavity, and T waves inversion drew considerable attention. These alterations seemed very suggestive of the corresponding pattern of Brugada syndrome (SBr).

On this occasion, we opted for the suspension of propafenone and the introduction of amiodarone. This decision was based both on the inefficiency of the drug in controlling AF crises and on the interpretation that propafenone could have some role in the electrocardiographic pattern of SBr (see discussion below). Also, the prevention of thromboembolic accidents was optimized, with the replacement of clopidogrel by oral anticoagulants. The patient did not accept the suggestion of treating AF by catheter ablation.

Fifteen days after changing the antiarrhythmic medication, the patient returned to the clinic, and a new electrocardiogram was performed, shown in Fig. 2, with an evident disappearance of the SBr pattern.

The patient presented significant clinical improvement, remaining for more than two years without clinical recurrence of AF, with control by serial Holter without significant changes, keeping the electrocardiographic pattern free of the SBr pattern.

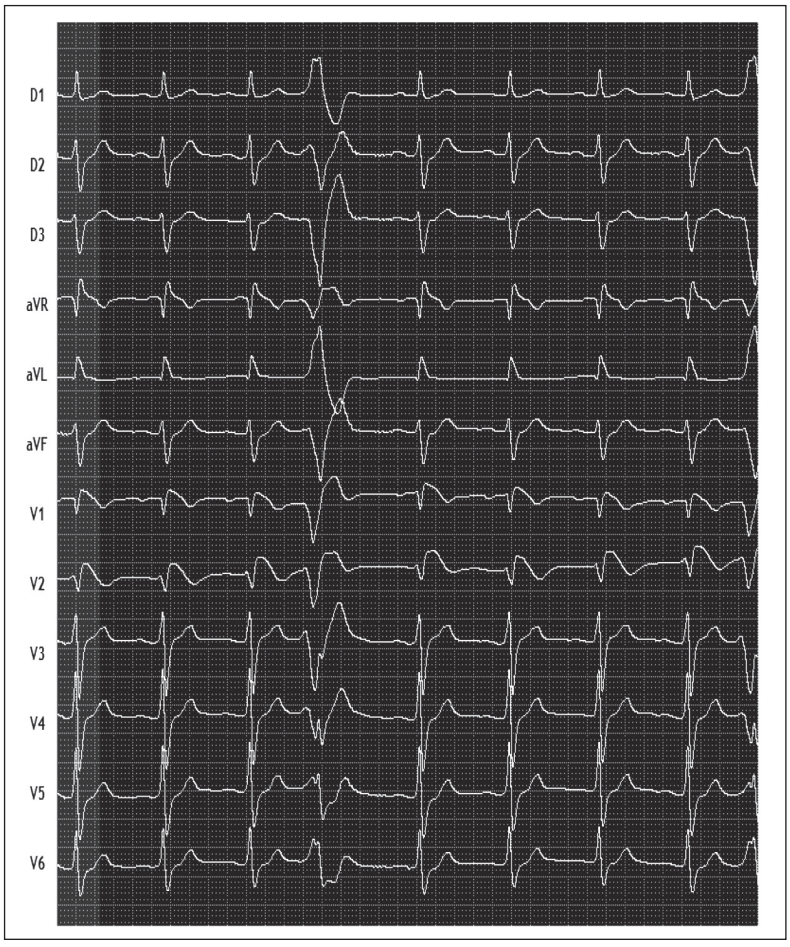


Figure 1. 12-lead electrocardiogram tracing in the first ambulatory visit, using propafenone 750 mg/day.

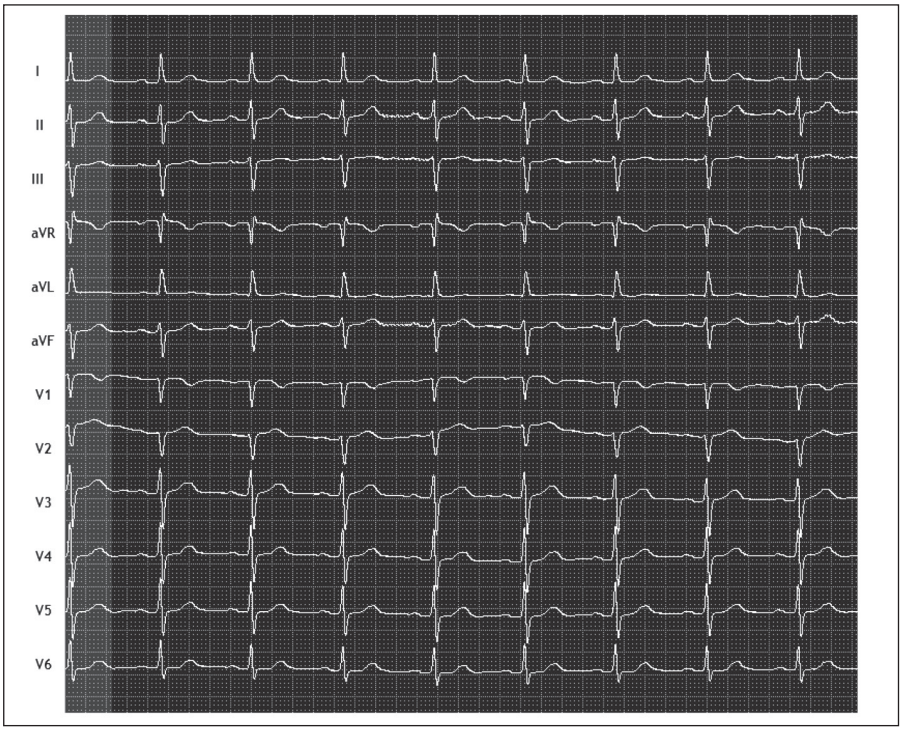


Figure 2. 12-lead electrocardiogram tracing obtained 15 days after the suspension of propafenone, replaced by amiodarone.

DISCUSSION

Brugada syndrome (SBr) is a clinical entity characterized by the presence of a pattern of right bundle-branch conduction disorder, ST-segment elevation in right precordial derivations, risk of severe ventricular tachyarrhythmias and sudden cardiac death in patients with a structurally normal heart[1,2]. In its pathophysiology, there is a clear understanding of the presence of a genetically determined disease, involving genes responsible for the transport of sodium, potassium, and calcium ions through the cardiomyocytes' cell membrane[2]. Thirty percent of patients with SBr have a mutation in the *SCN5A* gene, responsible for the alpha subunit of sodium channels, and more than 20 other mutations may be involved in its phenotypic manifestation.

Typical electrocardiogram alterations in SBr may suffer dynamic alterations dependent on several factors, such as autonomic balance, fever, or use of medication.

The classical electrocardiographic manifestations of SBr may present spontaneously or be revealed by intravenous administration of class I antiarrhythmic drugs, such as ajmaline, procainamide, flecainide or pilsicainide. When the electrocardiographic pattern of SBr is inconclusive in baseline conditions (SBr types 2 and 3) and becomes typical after chemical sensitization (SBr type 1), we classify it as "drug-induced SBr type 1". This maneuver is routinely used in electrophysiology laboratories for diagnosis and risk stratification of SBr.

However, the development of the electrocardiographic pattern of "drug-induced SBr" as a consequence of the adverse effect of the medication is much less known and discussed[5]. Several reports in the literature have shown that in the same way that some medications can prolong the QT interval and generate the so-called "acquired long QT syndrome", some drugs can cause clinical and electrocardiographic manifestations compatible with SBr type 1[3-5]. Among the pharmaceuticals involved in the occurrence of the phenotypic pattern of "drug-induced SBr" there are class IC antiarrhythmic drugs (propafenone, flecainide and pilsicainide, but in Brazil only propafenone is commercialized), tricyclic and tetracyclic antidepressants, anesthetic/analgesic agents (bupivacaine, propofol, procaine), antipsychotics (lithium), antiemetics (metoclopramide). Cocaine and alcohol are also among the drugs that can induce the SBr pattern. A complete list of drugs potentially involved in "drug-induced SBr" can be found at www.brugadadrugs.org.

Some authors discuss the clinical importance of "drug-induced SBr", with interpretations that these cases represent "phenocopy" of the clinical pattern of spontaneous SBr type 1, that is, the drug-induced electrocardiographic manifestation did not have the same clinical significance. However, most authors prefer to be cautious until the real clinical role of these cases is defined, preferring the term "drug-induced SBr"[3-6]. There are reports that after an aborted cardiac arrest, both the presence of spontaneous and drug-induced SBr may have similar clinical meanings[7].

The practical importance of understanding the so-called "drug-induced SBr" is that many patients with channelopathies such as SBr (manifest or latent), short QT syndrome, J wave syndrome, among others, may develop it with atrial fibrillation and be treated with propafenone, manifesting an increased risk of potentially severe ventricular arrhythmias[6,8]. There is still no consensus if all manifestations of "drug-induced SBr" present the same prognostic significance, with reports that different drugs at different doses may present different risks of development of ventricular arrhythmias[9].

ANSWER

Currently, we believe that patients with a clinical or electrocardiographic pattern compatible with SBr should be investigated about the possible use of medication that may be responsible for the condition and, if this information is positive, suspend the use of such drug. This was the case with the patient analyzed in this article, diagnosed as "drug-induced SBr", which was reversed after the suspension of propafenone.

Patients with a confirmed or suspected diagnosis of SBr should be advised that various drugs may cause serious clinical problems. The dissemination of *websites* such as www.brugadadrugs.org may help in the prevention of serious complications. Knowing the potential risk of the so-called "drug-induced SBr" makes us believe that it is mandatory to perform a 12-lead electrocardiogram in patients who initiate the use of drugs suspected of revealing latent cases of this type of canalopathy, in the same way as we do with drugs with the power to prolong the QT interval. In cardiological practice, taking this precaution when prescribing propafenone, one of the most common drugs used in the treatment of AF[10], becomes, in our opinion, a more than recommended, but necessary precaution.

REFERENCES

1. Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: A distinct clinical and electrocardiographic syndrome. A multicenter report. J Am Coll Cardiol. 1992;20(6):1391-6. https://doi.org/10.1016/0735-1097(92)90253-J

2. Priori SG, Wilde AA, Horie M, Cho Y, Behr ER, Berul C, et al. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. Heart Rhythm. 2013;10(12):1932-63. https://doi.org/10.1016/j.hrthm.2013.05.014

3. Antzelevitch C, Yan GX, Ackerman MJ, Borggrefe M, Corrado D, Guoe J. et al. J-Wave syndromes expert consensus conference report: emerging concepts and gaps in knowledge: endorsed by the Asia Pacific Heart Rhythm Society (APHRS), the European Heart Rhythm Association (EHRA), the Heart Rhythm Society (HRS), and the Latin American Society of Cardiac Pacing and Electrophysiology (Sociedad Latino-Americana de Estimulación Cardíaca y Electrofisiología [SOLAECE]). Europace 2017;19(4):665-94. https://doi.org/10.1016/j.joa.2016.07.002

4. Priori SG, Wilde AA, Horie M, Cho Y, Behr ER, Berul C, et al. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. Heart Rhythm. 2013;10(12):1932-63. https://doi.org/10.1016/j.hrthm.2013.05.014

5. Ramalho DD, Freitas J. Drug-induced life-threatening arrhythmias and sudden cardiac death: A clinical perspective of long QT, short QT and Brugada syndromes. Rev Port Cardiol. 2018;37(5):435-46. https://doi.org/10.1016/j.repc.2017.07.010

6. Nagayama T, Nagase S, Kamakura T, Wada M, Ishibashi K, Inoue YY, et al. Clinical and Electrocardiographic Differences in Brugada Syndrome with Spontaneous or Drug-Induced Type 1 Electrocardiogram. Circ J. 2019;83(3):532-9. https://doi.org/10.1253/circj.CJ-18-0643

7. Turker I, Ai T, Itoh H, Horie M. Drug-induced fatal arrhythmias: Acquired long QT and Brugada syndromes. Pharmacol Ther. 2017;176:48-59. https://doi.org/10.1016/j.pharmthera.2017.05.001

8. Li L, Ruan Y, Liu N, Zhao O, Zhang M, Li X, et al. "Pill-in-the-Pocket" Treatment of Propafenone Unmasks ECG Brugada Pattern in an Atrial Fibrillation Patient with a Common SCN5A R1193Q Polymorphism. Front Physiol. 2019;10(356):1-8. https://doi.org/10.3389/fphys.2019.00353

9. Delise P, Allocca G, Sitta N, Migliore F, Dagradi F, Spazzolini C, et al. Cardiac arrest and Brugada syndrome: Is drug-induced type 1 ECG pattern always a marker of low risk? Int J Cardiol. 2018;254:142-145. https://doi.org/10.1016/j.ijcard.2017.10.118

10. Magalhães LP, Figueiredo MJO, Cintra FD, Saad EB, Kuniyishi RR, Teixeira RA, et al. II Diretrizes Brasileiras de Fibrilação Atrial. Arq Bras Cardiol. 2016;106(4):1-22.

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ARTIFICIAL HEART STIMULATION
Orginal Article

Comparison of Two Transvenous Temporary Pacemaker Fixation Methods: FIX-IT Trial

Comparação entre 2 Métodos de Fixação de Marca-passo Provisório Transvenoso: FIX-IT Trial

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ABSTRACT

Introduction: the necessity for temporary pacemaker (TP) goes through several scenarios. Some patients require the device to complete an infection treatment, regain the pace after myocardial infarction, or while awaiting the release of the definitive device by the health care provider. Regardless of the TP passage technique, good electrode fixation is essential, avoiding dislocation and the necessity for repositioning, among other complications. **Objective:** to compare two forms of TP fixation, one under direct fixation to the skin and the other keeping the venous introducer connected to the plastic protection through the pacemaker electrode lead. **Methods:** Forty patients were randomized, 20 in each group. Data regarding the procedure time, electrode lead position, command thresholds, sensitivity, and complications were recorded. The primary outcome considered was the necessity for repositioning or exchange of transvenous TP and secondary any complication without the necessity to reposition it. **Results:** There were no significant differences in the total duration of the procedure between the groups in the initial position of the electrode and the access route used. The group with plastic protection had a higher primary outcome (60%) than the direct fixation group (20%; p = 0.0098). There were no differences regarding the secondary outcome (p = 1.0). The group with plastic protection also had more total complications compared to the other group (p = 0.0262). **Conclusion:** Direct fixation of the pacemaker electrode lead was safer concerning the fixation with plastic protection, reducing complications such as electrode dislocation requiring repositioning or replacement without increasing the procedure time.

KEYWORDS: Artificial pacemaker; Artificial heart stimulation; Sutures.

RESUMO

Introdução: A necessidade de marca-passo provisório (MPP) transita por diversos cenários. Alguns pacientes necessitam do dispositivo para completar um tratamento de infecção, recuperar o ritmo após infarto do miocárdio ou enquanto aguardam liberação do dispositivo definitivo pela operadora de saúde. Independentemente da técnica de passagem do MPP, a boa fixação do eletrodo é fundamental, evitando-se deslocamentos e necessidade de reposicionamento, entre outras complicações. **Objetivo:** Comparar duas formas de fixação de MPP, uma sob fixação direta na pele e outra mantendo-se o introdutor venoso conectado à proteção plástica por todo cabo-eletrodo do marca-passo. **Métodos:** Randomizaram-se 40 pacientes, 20 em cada grupo. Registraram-se dados referentes ao tempo do procedimento, posição do cabo-eletrodo, limiares de comando, sensibilidade e complicações. Consideraram-se como desfecho primário a necessidade de reposicionamento ou troca do MPP transvenoso e secundário qualquer complicação sem a necessidade de reposicioná-lo. **Resultados:** Não houve diferenças significativas na duração total do procedimento entre os grupos na posição inicial do eletrodo e na via de acesso utilizada. O grupo com a proteção plástica apresentou desfecho primário maior (60%) em relação ao grupo de fixação direta (20%; p = 0,0098). Não houve diferenças em relação ao desfecho secundário (p = 1,0). O grupo com proteção plástica também apresentou mais complicações totais em relação ao outro grupo (p = 0,0262). **Conclusão:** A fixação direta do cabo-eletrodo do marca-passo se mostrou mais segura em relação à fixação com proteção plástica, reduzindo complicações como deslocamentos do cabo-eletrodo que necessitem de reposicionamento ou troca desse, sem aumento no tempo do procedimento.

PALAVRAS-CHAVE: Marcapasso artificial; Estimulação cardíaca artificial; Suturas.

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INTRODUCTION

The necessity for a definitive pacemaker goes through several scenarios, and some patients need to remain under the use of a temporary pacemaker (TP) either to complete an infection treatment, regain the pace after myocardial infarction or even awaiting the release of the definitive device by the health care provider.

The rate of pacemaker implantation per million inhabitants in Brazil is substantially lower than in neighboring countries, despite the progressive increase in total implantation of these devices in the last decade[1]. Population aging and the consequent degenerative diseases of the heart excito-conductor system will increase the demand for implantation of these devices shortly. The current economic crisis and chronic underfunding of the Unified Health System (UHS), in contrast, will hinder meeting this growing demand. This scenario will culminate in a more significant number of patients admitted to emergency services awaiting electronic heart device implantation. Many of these patients stay in the hospital for days, weeks, and even months, mostly on transvenous TP. Therefore, implantation techniques of these systems in a practical way, ensuring safe ventricular stimulation and avoiding future complications, are essential.

Several techniques for implantation of TTPs have been described: (i) under direct vision, with the aid of radioscopy; (ii) with the aid of intracavitary electrogram; (iii) blind, with electrode lead under stimulation with maximum energy[2,3]. Temporary pacemaker implantation is described using active fixation electrode and connected to a permanent external pacemaker generator to the skin; however, the material required for this implant modality is not available in the vast majority of emergency services[4,5].

There is no definition on the best implantation form. There is little material in the literature comparing the techniques[6,7], It is up to the doctor to choose, according to his experience, not only the way of passage, but also the way of fixing the electrode lead. On the other hand, it is essential to minimize possible complications related to the procedure, such as those related to venepuncture, infections, myocardial perforations, arrhythmias, electrode displacement, among others[2].

In this study, it will compare two TP electrode lead clamping techniques, evaluating several variables, including displacement and loss of command.

METHODS

A unicentric randomized study was performed, dividing 40 patients who required urgent TTP implantation into two groups, 20 in each branch. Patients were randomized as soon as they agreed and signed the consent form. Before randomization, the project was submitted and approved by the institution's ethics committee (CAAE: 57695016.4.0000.5483, Opinion Number: 1.754.718).

Group 1 was submitted to the direct fixation of the electrode lead over the skin, without the aid of an introducer, or a plastic protective cover (Fig. 1). In group 2, the electrode lead was maintained with the vascular introducer connected to the respective plastic protective cover of the TP passage material (Fig. 2).

The electrode lead fixation of group 1 was made with 3.0 nylon wire. After the electrode was positioned in the heart, the venous introducer was removed and then the initial fixation was performed on the insertion of the electrode lead in the skin with a U-point followed by three common bailarinas (without to suture the skin) interspersed with

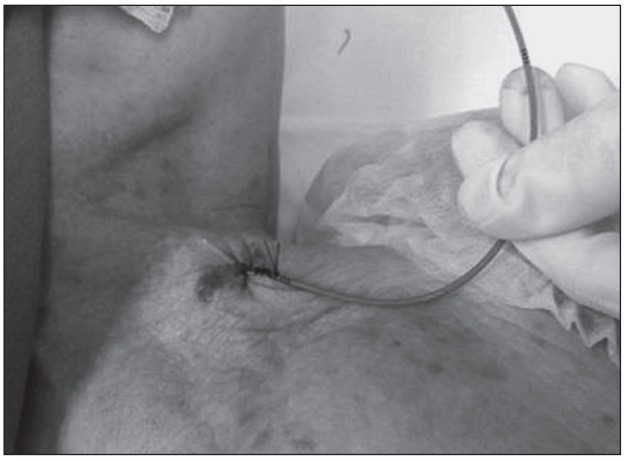

Figure 1. Direct fixation

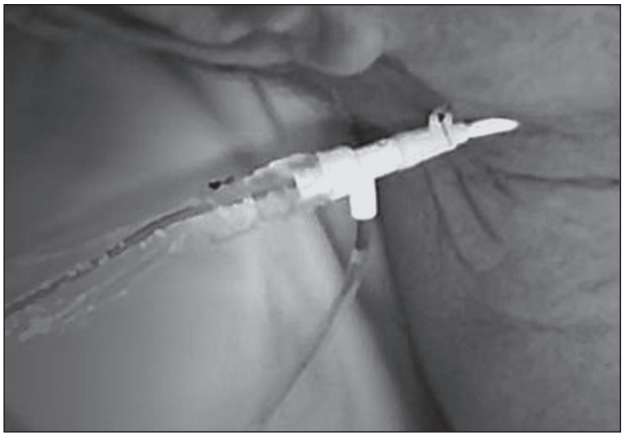

Figure 2. Fixing with plastic protection

another three with a stitch on the skin, where the needle end of the wire was crossed giving a small spot on the skin under the electrode. At the end of each bailarina, as well as at the initial U-point, a double knot was made followed by two other single knots. The distance from the electrode-wire insertion to the last bailarina was always less than 2 centimeters.

The patients in group 2 did not have their electrode leads fixed directly to the skin, but kept with the respective vascular introducer present in the material available for passage, and this was connected with the plastic protection around the electrode lead, fixing the set (electrode lead and plastic protection) through a lock at its opposite end to the introducer. Only one point remained in fixing the introducer with the skin. There was no suture of the electrode lead directly to the skin, involving plastic protection.

The material used up to the 20th randomized patient was a 6F temporary bipolar stimulation catheter of Dispomedica® (Hamburg, Germany) without active myocardial fixation, with a non-valved vascular introducer. From the 21st patient, an update of the same material was used, which was then disposed of a vascular valve introducer. Importantly, in both groups, the final dressing was performed by keeping the outer portion of the electrode lead coiled and attached with adhesive material (micropore, adhesive tape, etc.) so as to avoid direct accidental traction on the insertion point on the skin (group 1) or about the introducer (group 2).

Three techniques of TP passage were used: the first through direct vision by radioscopy in a hemodynamic laboratory, the second by the bedside with the aid of intracavitary electrograms and the third by the bedside, but blindly, without the assistance of electrograms. TP passthrough mode was not randomized. Preference was given to the passage of TP with the aid of radioscopy in a hemodynamic laboratory. However, at the discretion of the team and depending on the urgency and/or severity of the case, the bedside passage was performed with or without the aid of intracavitary electrograms.

Information was collected regarding patient age, paying source, days of hospitalization until randomization, the provenance of another service, previous TP use, previous antibiotic use, the reason for TP implantation, passage mode, the access route, the electrode end position and the procedure time. At the end of the passage, the initial assessment was performed for sensitivity and command threshold. This evaluation was repeated twice a day for all days when the patient was using this device. The deadline for the use of TP was set at 15 days. After this period, if the patient still needed temporary stimulation, a new TP would be implanted in place of the previous one, and the patient's follow-up in the study would be terminated (Fig. 3). All patients submitted to TP implantation were referred to the intensive care unit (ICU) of the same hospital and remained there under standardized care while in need of temporary stimulation. Chest radiograph was performed daily to control electrode placement with EKG.

The primary outcome was defined as any complication requiring pacemaker electrode replacement or repositioning. A secondary outcome was defined as any complications in which there was no need to change or reposition.

The collected data were submitted to statistical analysis with a professional of the area. Statistical analyses were performed using the chi-square test and the nonparametric Mann-Whitney U test, and those with p-values less than 0.05 were defined as statistically significant results.

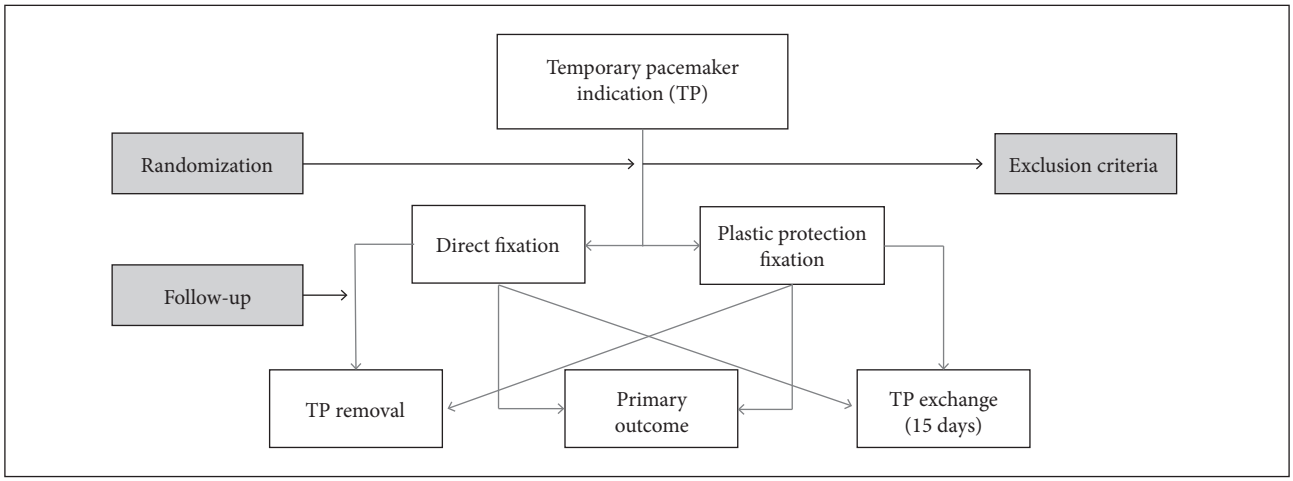

Figure 3. Study Design

RESULTS

Forty patients were randomized between October 2016 and July 2017 in a single service, dividing 20 patients in each branch (group 1: direct fixation: group 2: fixation with plastic protection). Randomization was performed as soon as TP passage was indicated, immediately after patients' informed consent. No statistically significant differences were observed between the groups regarding age, gender, paying source, length of hospital stay before randomization, the provenance of another service, previous TP use, previous antibiotic use and escape rate (Table 1). Even having the preference for passing TP under direct hemodynamic view, there were no significant differences between the groups regarding the mode of TP passage. Only one case of bedside blind passage was observed in group 2 after the patient presented cardiopulmonary arrest due to hypoxia and progressed to asystole after cardiopulmonary resuscitation.

The most commonly used access route was the right subclavian vein, a service preference, in order to keep the left side free for implantation of the definitive device. However, the left subclavian veins and the right and left internal jugular veins were also used, depending on the clinical condition of the patient and the access route available at the time of implantation. Nevertheless, no significant differences were observed regarding the access route used between the groups (Table 1).

The initial position of the electrode was also evaluated; In cases of bedside implanted TP, this evaluation was performed with chest radiograph in three incidences. Although the predominant initial position in group 1 was the right ventricle (RV) apex and in group 2 the subtricuspid region, there were no statistically significant differences between groups concerning the TP electrodeposition (Table 1).

All implantation was performed by at least two team members, one with experience in the procedure. Although the total time of the procedure was slightly longer in group 1,

Table 1. Baseline of patients.

	Direct fixation (group 1)	Fixing plastic protection (group 2)	P-value
Age (years)	71.55 (53-90)	74.65 (64-84)	0.34
Gender	75% (15) male 25% (5) female	70% (14) male 30% (6) female	0.7233
Paying Source	55% UHS. 35% supplementary health. 5% private, 5% partner	70% UHS. 25% supplementary health, 5% Partner	0.7411
Length of stay to randomization (days)	3.3 (0-39)	2.45 (0-15)	0.966
Provision of another service	8 patients (40%)	13 patients (65%)	0.1134
Previous TP	8 patients (40%)	7 patients (35%)	0.744
Time with TP (days)	11.33 (2-35)	12 (2-22)	0.52
Previous ATB	7 patients (35%)	6 patients (30%)	0.7357
Prior ATB Time (days)	5.71 (0-20)	6.17 (0-13)	0.774
TP Pass Indication	55% TAB, 20% AB 2ºG, 15% SND, 5% asystole, 5% Others	70% TAB, 15% AB 2ºG, 5% SND, 5% preoperative, 5% others	0.7743
TP Pass Mode	70% scopy, 30% IE	60% scopy, 35% IE, 5% blind	0.7411
Access vein	60% RSV, 30% LVSC, 10% RIJV	75% RSV, 15% LVSC, 5% RIJV, 5% LIJV	0.5013
Electrode position	40% apex RV, 30% subtricuspid, 15% low septum, 10% average septum, 5% RV sidewall	40% subtricuspid, 25% apex RV. 10% VSRV, 10% low septum. 5% average septum, 5% RV sidewall, 5% without information	0.7257
Procedure Time (min)	30% 16-30 min, 30% 31-45 min. 15% 46-60 min, 15% 1-15 min. 10% +60 min	35% 16-30 min, 30% 31-45 min, 25% 1-15 min, 10% +60 min.	0.5376

ATB = antibiotic; AB 2ºD = 2nd degree atrioventricular block; TAB = total atrioventricular block; SND = sinus node disease; IE = intracardiac echocardiogram; TP = provisional pacemaker; UHS = Unified Health System; RV = right ventricle; RIJV = right internal jugular vein; LIJV = left internal jugular vein; RSV = right subclavian vein; LVSC = left subclavian vein; VSRV = RV output path.

justified by the time required for direct attachment of the electrode to the skin, there were no significant differences regarding the total duration of the procedure between groups (Fig. 4, Table 1).

The mean of TP initial command values was also analyzed. The value was slightly lower in group 2 compared to group 1: 0.93V vs. 1.53V (p = 0.01) (Fig. 5). The initial sensitivity analysis was hampered by the peculiarities between each patient and the fact that some did not have an escape heart rate susceptible to sensitivity analysis, so this variable was not considered in the study.

The primary outcome, that is, any complication that led to electrode lead replacement or repositioning was significantly higher in group 2 than in group 1 (p = 0.0098) (Fig. 6). In all patients who presented the primary outcome, there was displacement of the electrode with loss of ventricular capture at maximum energy. One patient from group 2 presented, besides the displacement of the electrode lead with loss of ventricular command, low energy phrenic stimulation, motivating the repositioning of the TP (Fig. 7). No significant differences were observed between groups regarding the number of device implantation days until the primary outcome.

Still, regarding the primary outcome, the result was analyzed after the material update from the 21st patient, coincidentally leaving 10 patients in each group to be randomized. Despite the higher number of patients who reached the primary outcome in group 2 compared to group 1 (70 vs. 30%), no statistically significant difference was observed in this subgroup (p = 0.074) (Fig. 8).

Regarding the secondary outcome, there were no significant differences between the groups (p = 1.0) (Fig. 9). However, there were differences in the cause that led to the outcome: while in group 1 there were two patients with electrode lead displacement requiring inversion of stimulation polarity, a pneumothorax, and a puncture site hematoma, in group 2 there was electrode displacement in two patients, one with high energy phrenic stimulation and the other with persistent ventricular arrhythmias due to the presence of the electrode. Summing up all the complications that led to the primary and secondary outcomes, it is clear that electrode lead displacement appears as the most frequent complication (p = 0.0262)

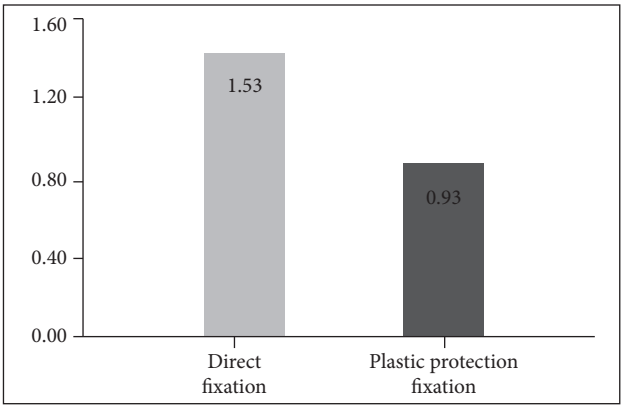

Figure 5. Initial Command Threshold Average (p = 0.01).

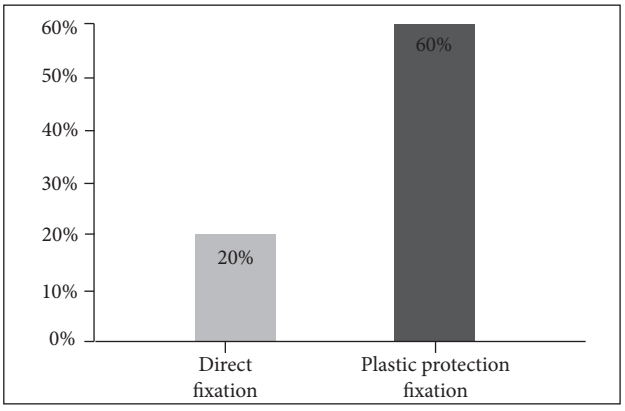

Figure 6. Primary outcome (p = 0.0098).

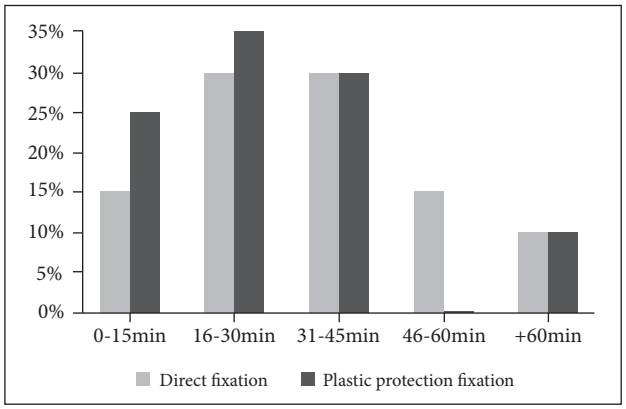

Figure 4. Procedure time (p = 0.5673).

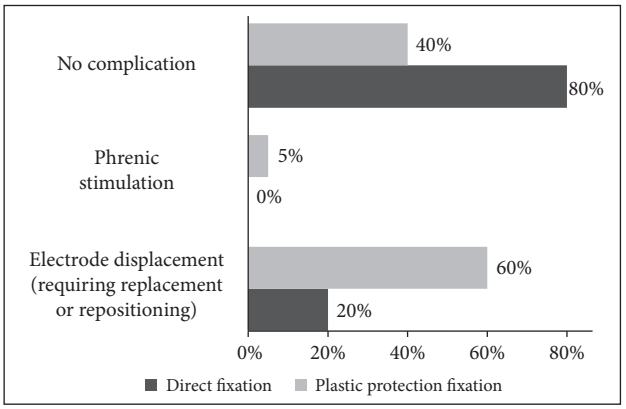

Figure 7. Complications primary outcome (p = 0.0225).

(Fig. 10). There were no patients with hemothorax, cardiac tamponade, venous thrombosis, or temporary stimulation system infection in the present study.

There were a total of four deaths during patient follow-up, two in each group. None of the deaths was directly related to the TP implantation procedure, nor problems related to temporary artificial cardiac stimulation. In group 2, both deaths were due to septic shock secondary to nosocomial pneumonia, as was one of group 1 deaths. The other death in this group was due to complications from cardiogenic shock.

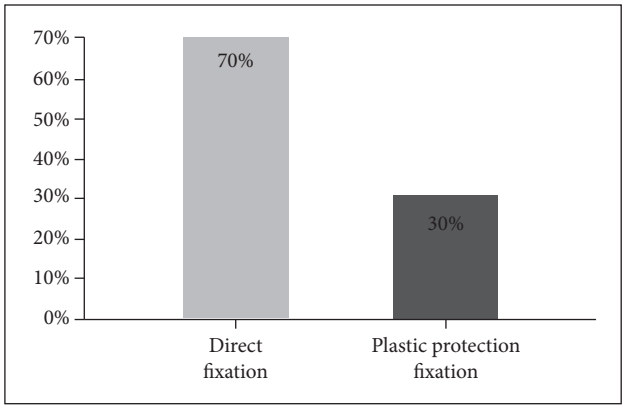

Figure. 8. Primary outcome after 20th patient (p = 0.074).

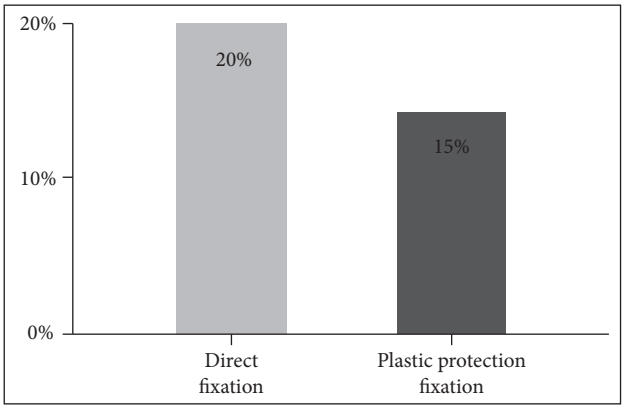

Figure 9. Secondary outcome (p = 1.0).

DISCUSSION

The present study revealed that patients who had TP fixed directly to the skin had a lower primary outcome, that is, any complication that resulted in the replacement or repositioning of the electrode lead compared to the group that had TP fixed with the plastic protection set and vascular introducer. There is a much more substantial amount of electrode dislocations in group 2 compared to group 1, proving that the TP fixation method with only the plastic protection and the vascular introducer increase the risk for displacements. Importantly, all patients who reached the primary outcome had electrode displacement, which makes this complication the most common in the TP setting. As previously described, after the 20th randomized patient, there was an update of the material used, with a new valved vascular introducer that, in theory, would help stabilize the TP electrode lead due to its friction with the valve rubber (especially in patients with group 2). The result of the analysis of this subgroup showed that, despite the greater tendency of dislocations and, consequently, primary outcome in group 2 after updating the material used, there was no statistically significant difference between the groups. However, it should be noted that in this subgroup, only a sample of 10 patients was used in each branch of the study, which loses its statistical power in the analysis.

It was decided not to use active fixation electrode leads in this study since these electrodes are not available in most services, but a passive fixation electrode of a brand very present in the national market. Thus, we tried to portray the reality available in the vast majority of intensive care and emergency services.

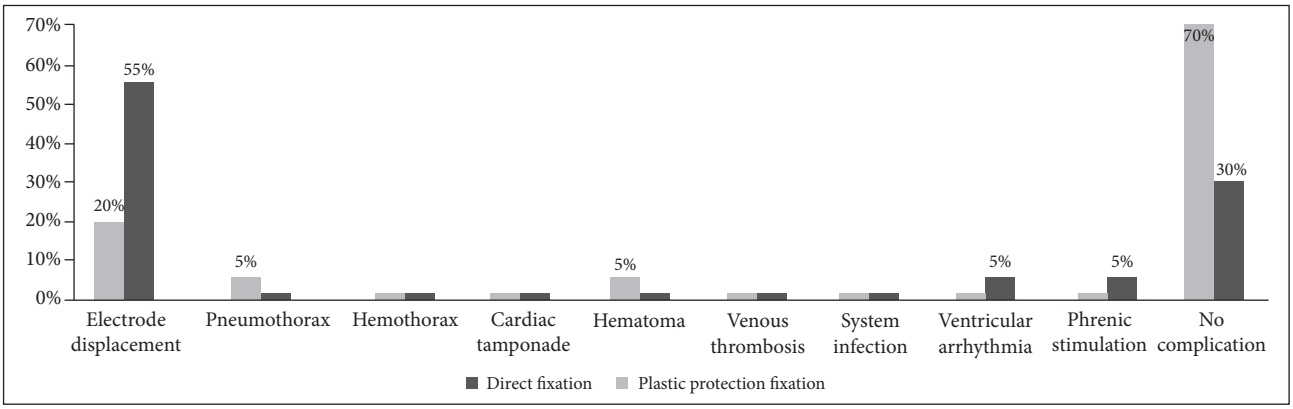

Figure 10. Combination primary and secondary outcome (p = 0.0262).

Analysis of total TP implantation time between groups was also relevant. The initial hypothesis was that the removal of the vascular introducer followed by the points used for fixation in group 1 patients would imply a longer procedure time compared to group 2; However, the results show that there was no statistically significant difference between the groups regarding the total procedure time (Table 2, Fig. 4). In this case, it should be noted that TP implantation was performed by a minimum of two people, at least one with extensive experience in this procedure, which may have contributed to this similarity between the groups.

Regarding the initial command threshold, despite the difference between the groups in their mean (Fig. 5), it is essential to consider that the values did not determine the outcome of the primary outcome analysis, mainly because the mean value group 2 was lower than group 1.

If, on the one hand, unicentric work limits the number of randomized patients in the study, on the other hand, they submit them to standardized ICU care of the service, thus minimizing any differences in care with TP in the follow-up.

CONCLUSION

This is the first work that determines the best TP fixation methodology when comparing two widely used fixation techniques. It is concluded that, due to the necessity to use TTP, the direct fixation of the electrode lead to the skin after endocavitary implantation results in a significantly lower rate of complications, such as electrode lead dislocation, avoiding the necessity for repositioning or replacement of the device. It is noteworthy that, for higher statistical power in the analysis of groups (and subgroups), a more significant number of randomized patients is required.

REFERENCES

1. Pachón-Mateos JC, Pereira WL, Batista Junior WD, Mateos JCP, Mateo EIP, Vargas RNA, et al. Registro brasileiro de marcapassos, ressincronizadores e desfibriladores. Relampa. 2013;26(1):39-49
2. Pachón-Mateos JC. Marcapasso cardíaco provisório: indicações e procedimentos empregados no controle de doentes graves. Rev Bras Marcapasso e Arritmia. 1990;3(3):94-9
3. Shah B, Awan ZA. Temporary pacemakers implantation: do we need fluoroscopy? J Ayub Med Coll Abbottabad. 2015;27(2):284-6
4. Maciąg A, Syska P, Oręziak A, Przybylski A, Broy B, Kołsut P, et al. Long-term temporary pacing with an active fixation lead. Kardiol Pol. 2015;73(12):1304-9. https://doi.org/ 10.5603/KP.a2015.0093
5. Kawata H, Pretorius V, Phan H, Mulpuru S, Gadiyaram V, Patel J, Steltzner D, et al. Utility and safety of temporary pacing using active fixation leads and externalized re-usable permanent pacemakers after lead extraction. Europace. 2013;15(9):1287-91. https://doi.org/10.1093/europace/eut045
6. Purohit M, Kaarne M. Sutureless fixation of temporary pacing wire. Asian Cardiovasc Thorac Ann. 2004;12(3):270-1. https://doi.org/10.1177/021849230401200321
7. Pinneri F, Frea S, Najd K, Panella S, Franco E, Conti V, et al. Echocardiography-guided versus fluoroscopy-guided temporary pacing in the emergency setting: an observational study. J Cardiovasc Med. 2013;14(3):242-6. https://doi.org/10.2459/JCM.0b013e32834eecbf

https://doi.org/10.24207/jca.v32n2.001_IN

Modulation of Heart Contractility

Modulação da Contratilidade Cardíaca

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ABSTRACT

Patients with heart failure (HF) are being benefited by electric therapy through conventional pacemakers when associated to bradycardia and cardiac resynchronization therapy or with low ejection fraction and presence of QRS longer than 150 ms, mainly in the presence of left branch block. Other groups of patients with HF present limitations regarding electrotherapy. However, an old concept has gained space in the treatment of patients who are outside the national and international guidelines for electrotherapy in HF: the modulation of heart contractility. This article has the purpose of presenting a review of already produced scientific evidence regarding this new modality for HF treatment.

KEYWORDS: Heart failure; Artificial pacemaker; Electric stimulation therapy.

RESUMO

Pacientes com insuficiência cardíaca (IC) vêm se beneficiando da terapia elétrica por meio de marcapassos convencionais quando associada à bradicardia e à terapia de ressincronização cardíaca ou com fração de ejeção rebaixada e presença de QRS maior que 150 ms, principalmente na presença de bloqueio de ramo esquerdo. Outros grupos de pacientes com IC apresentam limitações ao tratamento com eletroterapia. No entanto, um conceito antigo tem tomado espaço no tratamento de um grupo de pacientes que fica fora das diretrizes nacionais e internacionais para eletroterapia na IC: a modulação da contração cardíaca. Este artigo tem como objetivo apresentar a revisão das evidências científicas já produzidas e publicadas acerca dessa nova modalidade de tratamento da IC.

PALAVRAS-CHAVE: Insuficiência cardíaca; Marcapasso artificial; Terapia por estimulação elétrica.

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INTRODUCTION

Electrotherapy has been helping patients with heart failure (HF) since 1990 and has solidified as an option in the therapeutic arsenal for these patients. In the last decade, important studies showed the benefits in life quality, morbidity, and mortality rate of cardiac resynchronization therapy (CRT) and in the reduction of mortality by using an implantable cardiac defibrillator (ICDs)[1,2].

Regarding the improvement in the quality of life and clinical, laboratory and hemodynamic parameters, CRT remains as the only therapeutic option to be used in most patients, when there is an indication to implant an artificial device of cardiac stimulation.

However, lately only a minimal group of patients are being benefited from this therapy: those with dilated myocardiopathy with severe dysfunction of the left ventricle (LV), QRS with duration longer than 130 ms (mainly longer than 150 ms) and symptoms associated to HF[2].

Modulation of heart contractility (MHC) through an implant of artificial heart stimulation has been presenting benefits in life quality, six-minutes walking test and hemodynamic parameters in group of patients for which CRT does not have conventional indication, such as those with disabling symptoms, with QRS with duration less than 130 ms and ejection fraction (EF) between 25 to 45%[3].

DEVICE DESIGNED FOR THE MODULATION OF CONTRACTILITY

It is a device with a similar structure of conventional cardiac pacemakers. There are three connections, one for the atrial electrode lead and two for the ventricular electrode leads to be implanted in the interventricular septum of the right ventricle (RV). The electrode leads have the same conventional heart stimulation. The device has an external battery charger used to recharge the battery at least once every three or four weeks and a specific programmer (Fig. 1)[3].

The device implantation is very similar to a conventional pacemaker, with atrial electrode leads being implanted on the atrial appendix or lateral wall, and ventricular electrode leads in the medium-septum region of the interventricular septum, with a minimum distance of 2 cm between the ends of these leads. The performed tests are the same as the ones performed for the evaluation of conventional electrode leads, in which it is searched as the best parameter, a functional sensitivity of ventricular signal[3] (Figs. 2 and 3).

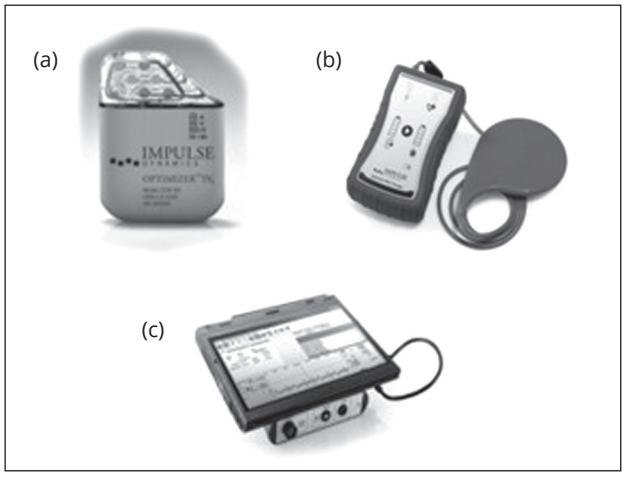

Figure 1. (a) pulse generator Optimizer IVs; (b) External charger used for recharging the battery and (c) device programmer.

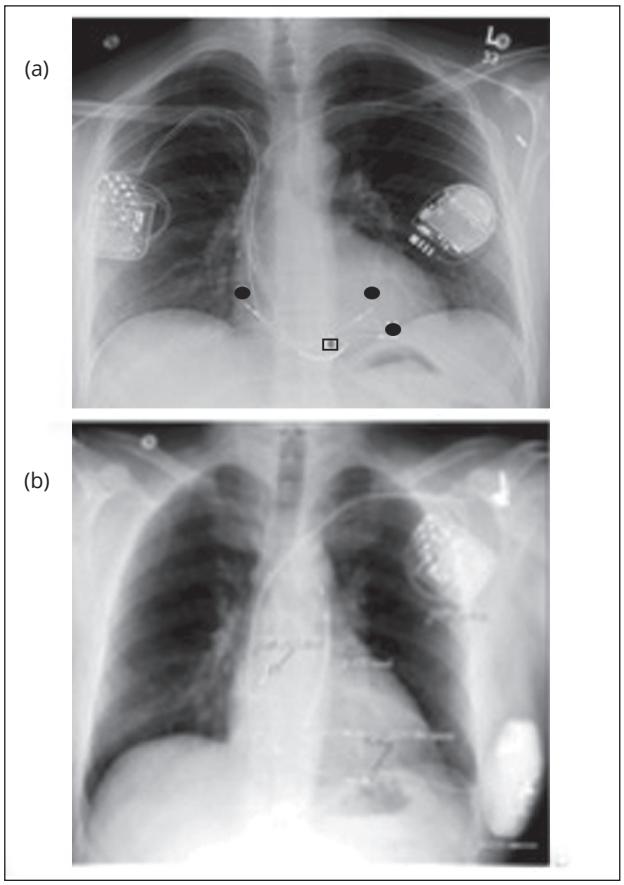

Figure 2. (a) Post-implant radiography of a patient with unicameral ICD implanted on the left and MHC implanted on the right (black circles showing the leads of the MHC lead wires and black square showing the lead of the ICD lead). (b) radiography after implantation of subcutaneous ICD and MHC, both in left hemithorax.

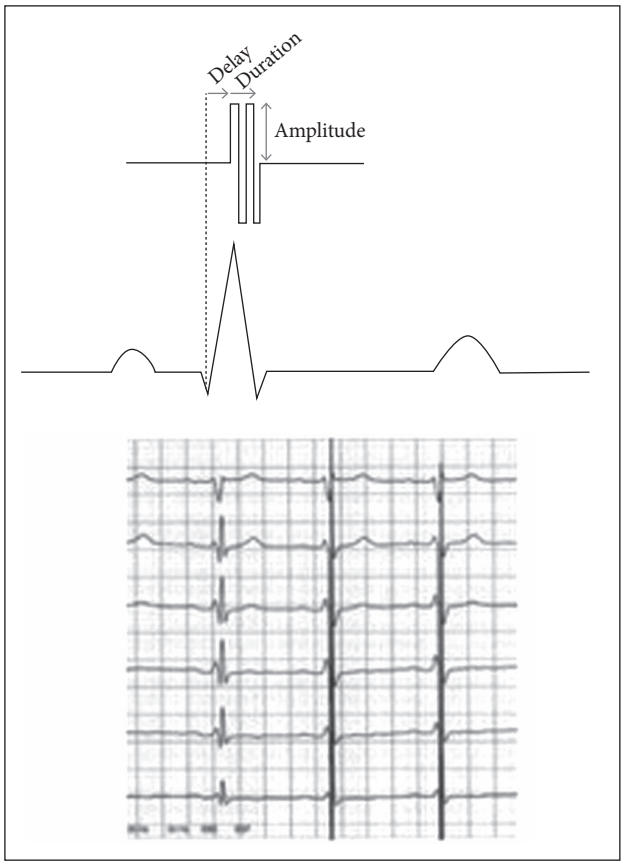

Figure 3. (a) Drawing showing the biphasic signals released by the MHC after a pre-set delay to trigger during the ventricular refractory period and thus do not cause ventricular excitation. (b) Surface ECG showing one beat before the onset of MHC and then 2 beats after application.

MHC is performed through the liberation of a dual-phase high voltage signal of 7.5 v with 22 ms of duration during the absolute refractory period[3].

CALCIUM PHYSIOLOGY IN THE HEART CONTRACTILITY- RELAXATION CYCLE

To comprehend the mechanism of action of this new device, it is essential to remember the role of the calcium cycle in the excitation-contraction coupling of the heart muscle. This is very important in the acute and sub-acute phase of MHC.

Calcium has a leading role in the regulation of contraction and relaxation phases of the heart muscle. The association between calcium flow and the connection of the contractility with the excitation wave (excitation-contraction on coupling) is relatively well understood. The central hypothesis is related to the liberation of calcium from the sarcoplasmic reticulum (SR)[4,5].

Small amounts of calcium come and go from the cardiomyocyte each cardiac cycle through the sarcoplasmic membrane, and a higher quantity of calcium arrives at the cell cytoplasm coming from the SR (Fig. 4).

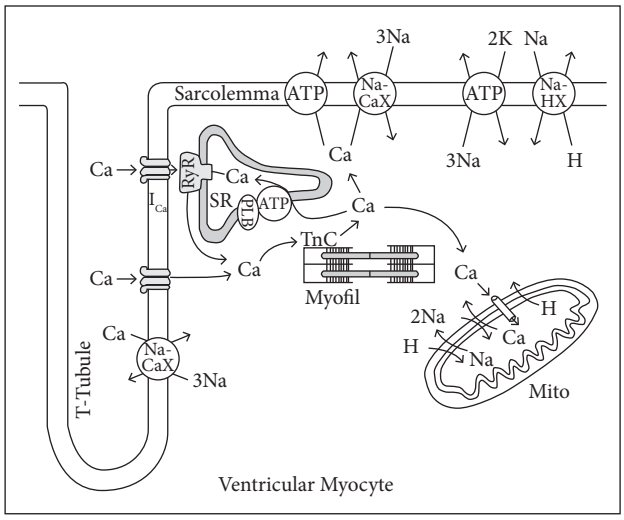

Figure 4. Schematic diagram of calcium flows within the myocyte during the cardiac cycle.

Each wave of cardiac depolarization that goes through the myocytes by the T tubules opens the L-type calcium channels from the cytoplasmic membrane, near the SR, activating, this way, the channels of calcium release, called ryanodine receptors. Therefore, the myocyte depolarization releases a great amount of calcium in the cytosol as a response to the small entrance in the cardiomyocyte from depolarization. This process elevates in up to 10 times the concentration of calcium ion in the cytosol. The result in the enhance of calcium ion interaction with troponin C to initiate the process of contractility.[4,5].

CHANNELS OF CALCIUM LIBERATION FROM SR

Ryanodine Receptors

Each L-type calcium channel from the sarcolemma controls a group of six to 20 channels of liberation from SR to anatomic proximity from T tubules calcium channels with channels located in the SR[4].

Ryanodine receptors have two functions: 1) to control calcium release channels from the SR; and 2) to act together with the support that has a series of key regulating proteins for the junctional complex. These proteins include the ones that respond to the phosphorylation of the A-kinase protein (KAP) and its anchorage protein AKAP[4].

The inactivation of calcium release by the SR after its increase in the cytosol is not well understood, and there are several hypotheses for this phenomenon: 1) increase in the calcium concentration in the cytosol inhibits the process of more calcium release; 2) the increase of calcium concentration in the cytosol may activate a calcium uptake pump by the SR; 3) the SR has less calcium; and 4) ryanodine receptor becomes inactivated, making it resistant to calcium concentration. Regardless of the way it happens, the decreased calcium concentration in cytosol provokes the beginning of the diastole[4].

CALCIUM UPTAKE BY THE SR THROUGH CALCIUM ATPase

Calcium ions are uptaken to the interior of the SR through a calcium pump called SERCA, that has many isomorphic shapes, being predominant in the heart the SERCA2a[4,5]. For each hydrolyzed ATP by this enzyme, two calcium ions are uptaken to the interior of the SR. The source of energy comes from the generation of ATP from cytosol through glycolysis. Meaningful connections between SERCA and heart contractility are found. For instance, in HF, the activity of SERCA is diminished[4,5].

Phospholamban is the name given for "phosphate receptors," and their activity is guided by a state of phosphorylation, a process that alters the molecular configuration of SERCA to promote their activity. Two more significant kinase proteins are involved in this process: one is activated through PKA in response to beta-adrenergic stimulation and cyclic AMP, and the other is activated through calcium and calmodulin, which acts in two different phosphorylation sites. When phospholamban responds to the beta-adrenergic stimulation of the cardiomyocyte by gaining calcium uptake through SERCA within SR, improving the relaxation rate, the higher activation is the phosphorylation of the PKA site. Additionally, the higher calcium content within SR corresponds to the more significant calcium release by ryanodine receptor; the answer, subsequently to the depolarization wave, generates higher frequency and force of contraction[4].

Calcium, uptaken within SR by the calcium re-uptake pump, stays stored there until the next release. Calcequestrin, a protein that stores calcium in the SR, stays in the region of SR next to T tubules. Calcium storage by calsequestrin makes it available for the releasing process as soon as it loads calcium inside the entrance of its releasing channel. This process exchanges calcium ions released from the external entrance to the cytosol interior. Calreticulin is another protein that stores calcium with structure and similar functions to calsequestrin[4-6].

SARCOLEMA CONTROL OF CALCIUM AND SODIUM IONS

Calcium Channels

The beginning of the excitation-contraction process occurs by the opening of the L-type calcium channels in the sarcoplasmic membrane. This channel is highly calcium-selective and allows its transfer to the cytosol interior in its open state when the depolarization of the membrane occurs[4].

Once it is activated (open) by membrane depolarization, the calcium channel is inactivated (closed) by: 1) increase of voltage during depolarization due to a more positive potential than negative during activation; and 2) increasing of internal calcium concentration, especially calcium flux from ryanodine receptor that pushes its concentration, present in the subsarcolemmal internal space, to near the entrance of L channels of the T tubules to help terminate the current flow[4,5].

Ion Pumps and Ion Switchers

To counterbalance the calcium entrance within the cardiac cell in each cycle, the same quantity must leave in any of these two processes: 1) calcium may be switched by sodium through the calcium-sodium exchange; e 2) through the calcium pump by ATP use that transfers it to the outside of the cell against a concentration gradient[4].

In HF, the changes in the calcium cycle are fundamental to the worsening of the heart muscle contractility. Calcium storage in the SR is severally affected due to the combination of adverse effects: 1) less SERCA activity; and 2) calcium escape in the diastolic phase associated to the hyperphosphorylation and abnormal function of the ryanodine receptor. These alterations provoke decrease of calcium in the SR, decrease of liberation in the SR, diastolic escape of calcium and increase of its concentration in the cytosol. Besides that, the action of the L-type channels is down-regulated[4].

ACTION MECHANISM OF THE MHC

The action mechanism of the MHC is related to the management of the calcium cycle in the acute phase. Chronically, the improvement of the heart contractility occurs due to the increase of phosphorylation of the regulatory paths of calcium keys, which enhances contractility and restores usual standards, which is the profile of the fetal gene of HF[3].

Acute Increase of Contractility

Studies in eye muscle tissues in rabbits and dogs with HF produced by coronary embolization and trabecular muscle in patients with HF have shown an increase in contractility and EF with the beginning of the stimulation with a modulator of heart contractilit[7,8].

Among the benefits of the calcium cycle provoked by MHC are the up-regulation of L-type calcium channels and improvement of calcium uptake within SR, provoking improvement of the extracellular influx during contractility after the begging of the modulation and calcium release from this reticulum[3] (Fig. 5).

CHRONIC EFFECTS IN HF

Modulation has shown improvement of EF, in the systolic volume, dP/dT from LF VE and delay of enhancing the diastolic volume and final systolic from LV and RV[9].

HF produces changes in the cardiomyocyte phenotype to a more juvenile pattern via reversion to a program of a fetal gene. This way, there is an increase in the expression of BNP (*brain natriuretic peptide*) and the calcium-sodium exchanger, with decreasing the expression of SERCA2A, alpha-MHC (*major histocompatibility complex*) and phospholamban. Chronic use of MHC in animals with HF causes reverse remodeling of the fetal gene in direction, again, to the regular adult program[10,11]. This way, the calcium cycle within the cardiomyocyte is improved.

The up-regulation of SERCA and the higher phosphorylation of phospholamban increase calcium uptake by SR, resulting in higher release in beating subsequently and, therefore, increasing cardiac contractility.

Studies have shown that these actions in changing the expression of genes in calcium regulation in cardiomyocytes are seen two hours after the beginning of the stimulation, locally, in cardiomyocytes near the tip of the electrode leads [14]. However, after three months of MHC, distant sites have also shown the same benefits. This represents a general reversion of the physiopathology in the expression of the fetal gene in HF[11,12].

Clinical Studies

Over 3.000 patients all around the world have received the implant of the MHC devices. Several clinical

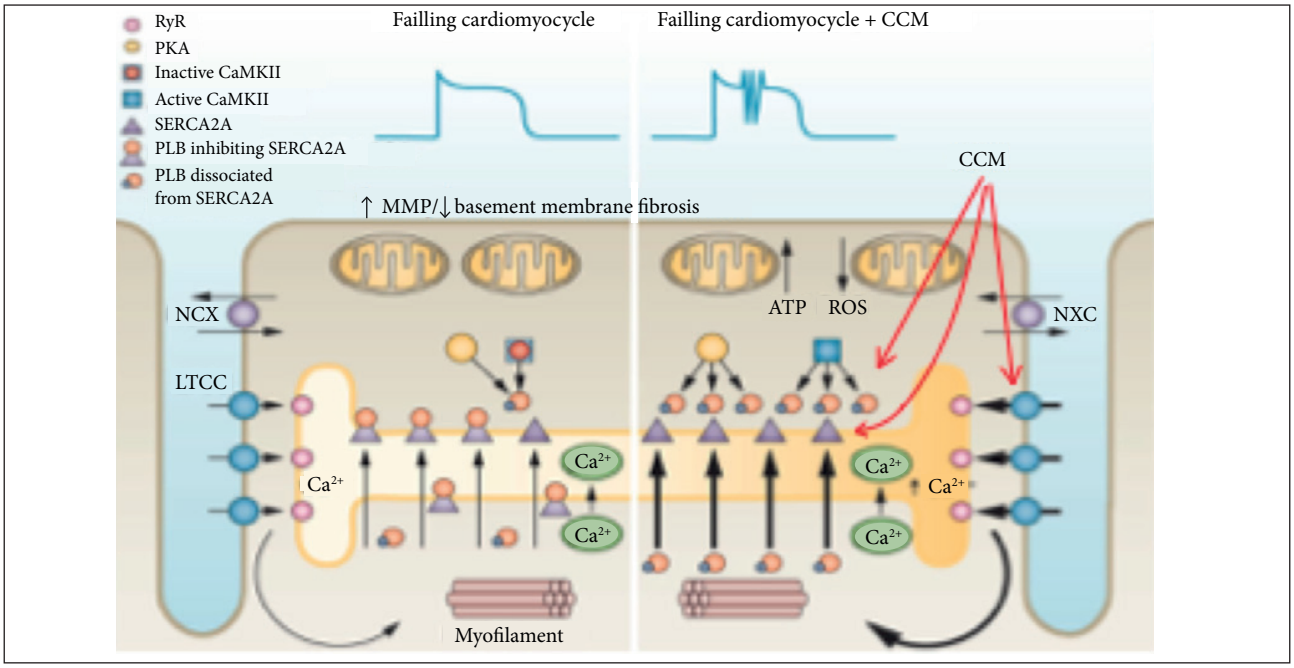

Figure 5. Schematic diagram of calcium flow in the diseased myocardium (right) and mechanism of action of MHC (left).

studies have confirmed good results in pre-clinical studies, pointing in the direction that MHC can bring benefits beyond medical therapy optimized for HF[3].

In the first major clinical study in humans, the FIX-HF-3, published in 2004, 25 patients, with mean age of 62 years, submitted themselves to the implant of the modulator of heart contractility, with HF from functional class from *New York Heart Association* (CF NYHA) III, refractory to the optimized medicament therapy. Still, regarding inclusion criteria, patients with EF under 35% and QRS lower or equal to 130 ms were selected. Twelve patients had idiopathic myocardiopathy disease as base disease and 13 coronary illness. The dP/dT gave the acute evaluation. After the implant, the generator was activated for three hours a day for eight weeks[13].

In 23 of 25 patients, the device was implanted successfully. There was a significant improvement of CF NYHA from III to II in 15 patients and for I in 4 patients. EF rose from 22 to 28%, and the score in quality of life for patients with HF in the *Minnesota* Living with Heart Failure Questionnaire (*MLHFQ*) improved from 43 points to 25 points. The 6-minute walking test rose from 411 m to 465 m[13].

Regarding adverse effects, nine patients have presented some discomfort intermittent with the stimulation. There were two deaths not related to the device. Schmidinger et al.[16], with these results, have concluded that MHC is a promising technique to improve the systolic function and symptoms in patients with refractory HF regarding optimized medicament treatment[13].

These results have stimulated the conduction of a more significant clinical study, the FIX-HF-4, published in 2008. Patients with symptomatic HF (CF NYHA higher or equal to II), of idiopathic or ischemic origin, EF < 35% and oxygen peak uptake (VO_{2max}) between 10 and 20 mL 0_2/min/Kg were included in the study. Patients were using maximum tolerated medication for HF. Patients with an indication of conventional CRT, atrial fibrillation, acute myocardium attack in three months prior randomization, other modalities of coronary disease, excessive HF, and frequent ventricular arrhythmia were excluded from the study[14].

A total of 164 patients were randomized in two groups (1 and 2) during two periods (phase 1 and 2) for 12 weeks each phase[14].

At the end of each phase, the following protocol was performed: cardiopulmonary stress test (with VO_{2max}), MLHFQ, six-minute walking test, and evaluation of CF NYHA[17].

The primary endpoints were the measures of VO_{2max} and the MLHFQ at the end of every phase in every group. Secondary endpoints were the changes in CF and six-minute walking test[14].

Group 1 was composed of 80 patients who initially received the device turned on, while in group 2, 84 patients received the device turned off. In phase 2, the groups received the opposite treatment regarding the initial situation[14].

During the first phase, VO_{2max} enhanced similarly in both groups; however, in the second phase, VO_{2max} continued enhancing in the group with the active treatment and diminished in the group where the device was turned off initially[14].

MLHFQ improved in both groups in the first phase, being better in the group with active treatment, and continued improving after cross-over in the group where the device was turned on, while it got worse in the group where the device was turned off[14].

The walking test had similar behavior to the VO_{2max} result, and the evaluation of CF improved in both groups during the two phases[14] (Fig. 6).

The authors concluded that there was consistent improvement regarding tolerant to exercise and quality of life with MHC.

The FIX-HF-5 study was the most important study performed to evaluate the security and effectiveness of MHC. It was performed in 50 centers in the USA and included 428 patients with CF NYHA III/IV, with narrow QRS and EF ≤ to 35%, which were randomized to receive optimized medical treatment (OMT) (213 patients) versus OMT+MHC (215 patients). The primary endpoint regarding effectiveness was the anaerobic ventilation limit, and the secondary was VO_{2max} and MLHFQ after six months. The primary safety endpoint was the test of non-inferiority between the groups in 12 months for all causes of deaths and hospitalization[15].

Regarding the security endpoint, the OMT group presented 103 events in 213 patients (48.4%) and the OMT+MHC group 112 events in 215 patients (52.1%). This difference was within the preestablished limited, presenting, therefore, security endpoint for the treatment with MHC[15].

Regarding effectiveness results, anaerobic ventilation limit (primary endpoint of effectiveness) diminished in both groups in 0.14 mL/kg.min after 24 weeks. VO_{2max}

increased in the group OMT + MHC and diminished in the group OMT, with a significant statistical difference. MLHFQ and NYHA improved significantly more in the OMT+ MHC group than in the OMT group. There was also non-significant improvement in the 6-minute walking test in the group OMT + MHC[15].

This study has managed to find the primary security endpoint, however, did not reach primary effectiveness endpoint, which was the improvement of the anaerobic ventilation limit. However, there was an improvement in VO_{2max} and in MLHFQ, as well as in CF of NYHA. The two last findings were similar to the ones

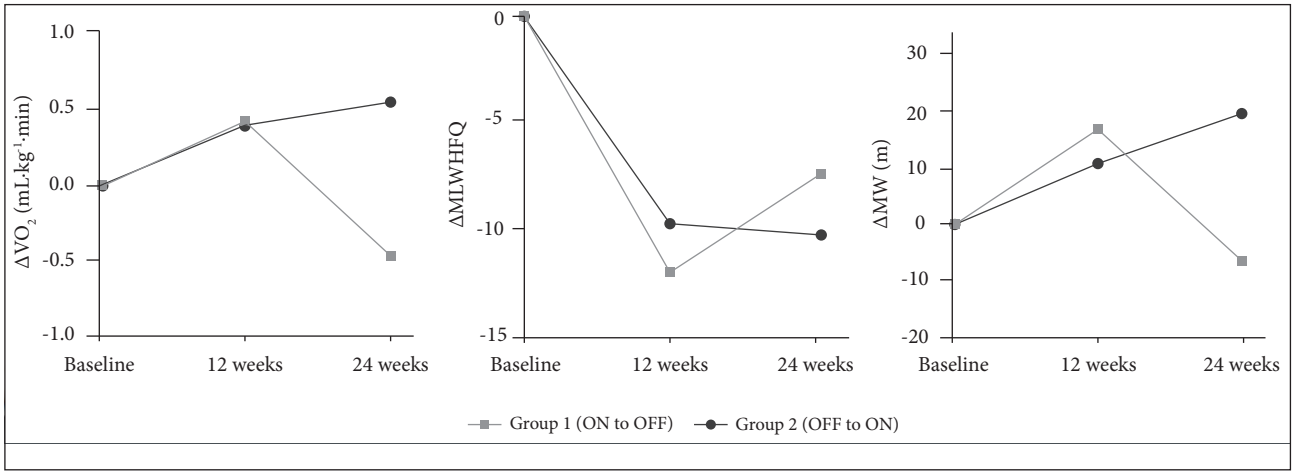

Figure 6. (a) VO_{2max} changes in each group compared to their respective baseline values. Results presented for cases with complete data; These results substantially agree with those based on multiple assignments. (b) Minnesota Living with Heart Failure Questionnaire changes in each group compared to their respective baseline values. Results presented for full data cases; these results substantially agree with those based on multiple assignments. (c) Changes in the 6-minute walk test in each group compared to their respective baseline values[17].

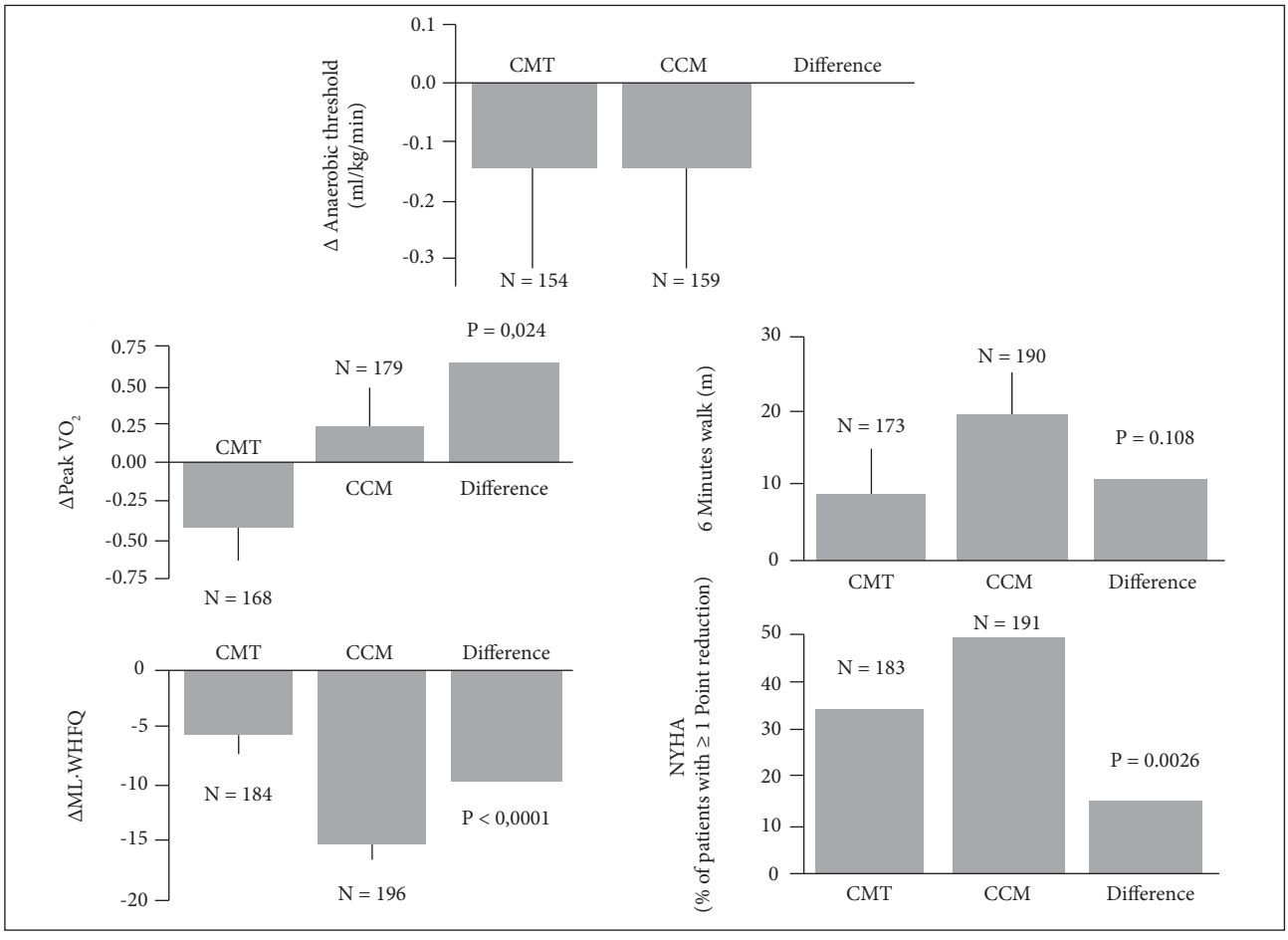

Figure 7. Graphs with summary results of the FUX-HF-5 study.

found in a study that validated the use of the devices in CRT[15].

In the subgroup analysis, it was noticed that NYHA III and EF above 25% obtained the best results [18] (Fig. 7).

The use of this primary *endpoint* (anaerobic ventilation limit) for this study was required by the Food and Drug Administration (FDA), since it was about a not blind study and measures such as quality of life and exercise tolerance is subjective parameters, susceptible to the placebo effect[15].

The authors criticized, among other aspects, this fact and affirmed that, although the anaerobic ventilation limit is an objective parameter of evaluation, it has not been validated as an *endpoint* in HF studies[15].

Two meta-analyses about the theme have been published. In 2012, Cheuk-Man et al[19]. published a meta-analysis regarding the controlled studies registered in Cochrane, MEDLINE, and EMBASE, comparing MHC and OMT or *sham* treatment. The results of interest were all the causes of mortality, all the causes of hospitalization and adverse effects. Three studies randomized 641 patients and the analysis of this population has shown that compared to the control, MHC has not significant statistically diminished mortality, hospitalization. However, it did not enhance the risks of adverse effects[16].

Another meta-analysis, published in 2014 by Giallauria et al.[17], having as a database the same population of the previous publication, used primary VO_{2max}, *endpoints*, six-minute walking test and quality of life in the MLHFQ questionnaire. This analysis concluded that compared to standard treatment for HF, MHC has significant improved VO_{2max}, the walked distance in the six-minute test and the quality of life in the MLHFQ questionnaire (Fig. 8).

Long Term Results

Four publications presented long term results in the mortality of patients treated with MHC. Schau et al.[18] evaluated retrospectively 54 patients submitted to MHC implant between 2003 to 2010. Patients presented moderate to severe ventricular dysfunction, NYHA III/IV, and mean EF of 23%. Following three years, 24 patients died (18.4% by year). The mortality was equivalent to the expected prevision by the prediction model of mortality for HF from the Seattle Heart Failure Model (*SHFM*).

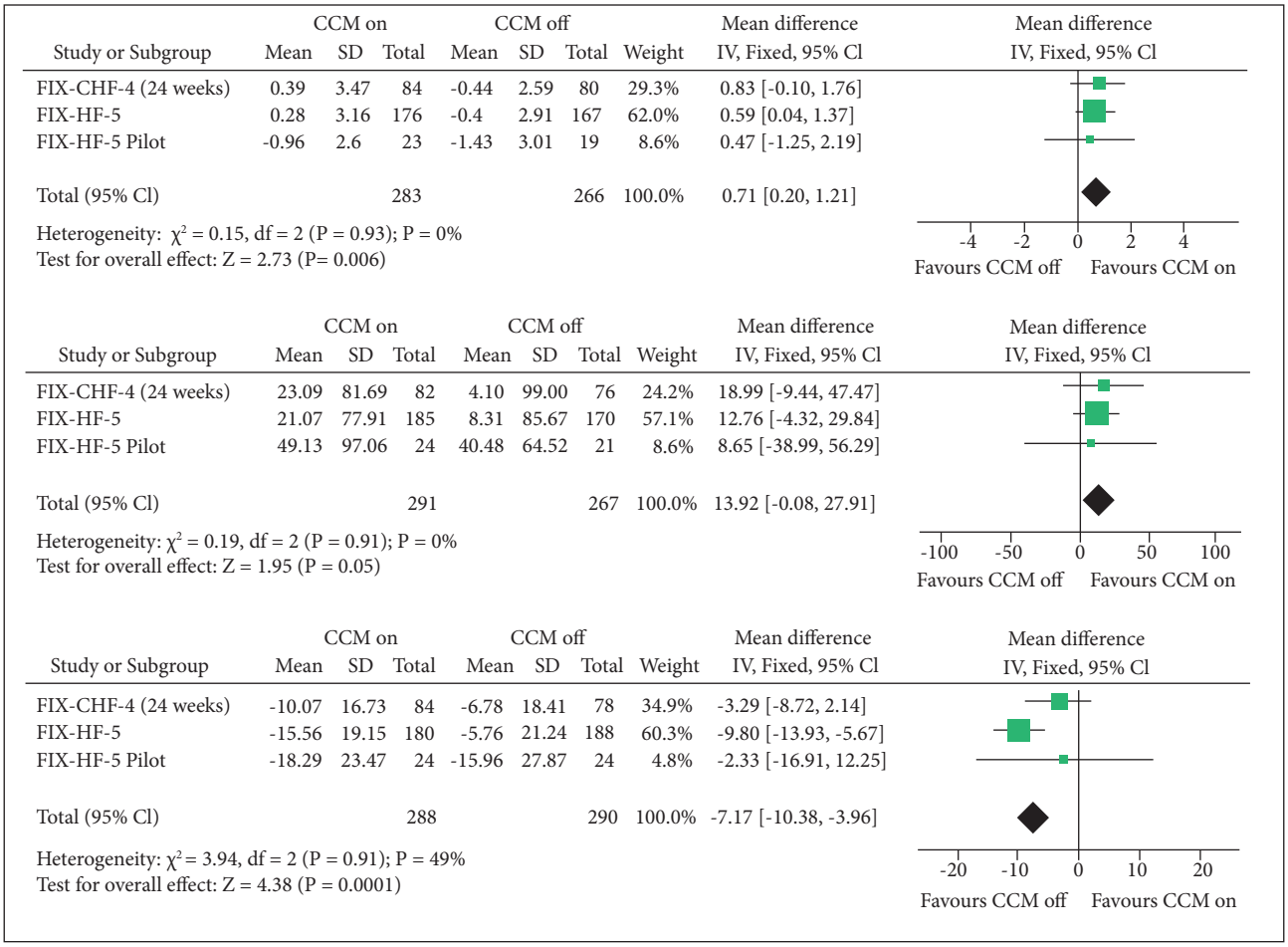

Figure 8. VO_{2max} change results tables (top table).

In another study, published by Kuschyk et al.[19] conducted by only once center, 81 patients were followed up for three years, between 2004 and 2012. This population had a mean EF of 23%, and the majority presented NYHA III/IV. The authors found long term improvement in the quality of life, NYHA, EF, and pro-BNP measures in the follow-up of these patients. The survival curve presented significant diminishing in the mortality when compared to the prediction model of mortality of HF from *Meta-analysis Global Group in Chronic Heart Failure* (MAGGIC) – 13.1% *versus* 18.4% in the first year and 32.1% *versus* 40% in the third year.

A recent study, conducted by Liu et al.[20], evaluated the effects of this therapy in 41 patients with EF < 40%. The follow up was of six years, and the cases were compared 1:1 with control, with similar age, EF, medication, and cause of HF. The primary *endpoints* were all causes of mortality, and the secondary *endpoints* included hospitalization for HF and death by cardiovascular disease. EF was of 28%, and all the causes of mortality were inferior in the MHC group. When stratified by EF, patients with below 25% did not show significant improvement in mortality. However, in population with EF between 25 to 40%, the diminishing in mortality was expressive in MHC. Similar improvement was found in secondary endpoints.

Kloppe et al.[21] have followed up for 4.5 years 68 patients submitted to MHC implant and with mean EF of 26% in two centers in Germany. This study showed a diminishing in the mortality in year 1, 2, and 5 in group MHC comparing to the prediction model of mortality from *SHFM*.

Future Perspectives

Nonetheless, the great potential regarding this new therapy, a series of challenges still must be overcome so it can be included in the therapeutic arsenal for HF.

A significant part of the patients with an indication for MHC is based on current European guidelines[22] and clinical studies, and it is already with cardiac devices such as CRT and ICD. This means that these people already have one, two, three, or more electrode leads within the heart. With this therapy, in the current state of the art, demands the implant of at least three electrode leads, which means that many of the problems regarding the excess of leads, such as thrombosis, higher risk for infections, may appear. There are studies regarding the upgrade of this therapy, for example, with the coupling of a cardio defibrillator to the same device of MHC.

Another current limitation is the need for detection of the P wave for the liberation of impulse by the MHC, which prevents patients with atrial fibrillation and frequent ectopies to be candidates to use this device. Improvements in the algorithm, avoiding the need for synchronization with a P wave, would allow these patients also to make use of this therapy, as well as would avoid the use of an electrode lead in the atrium.

Although the improvement in the quality of life parameter and functional capacity is essential, there remains to show, with large randomized, double-blind and multicenter studies, the impact on survival and improvement in mortality of these patients, in order to change paradigms regarding this new therapy.

Currently, the European guidelines for the treatment of HF patients consider those with ventricular dysfunction, CF II-III and QRS <120 ms possible candidates to the use of this new technology[22].

AUTHORS' CONTRIBUTION

Conceptualization, Salgado C; Investigation, Silvestrini TL; Writing, Silvestrini TL; Revision, Ronsoni; Supervision, Salgado C.

REFERENCES

1. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NAM, Freedman RA, Gettes LS, et al. ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmic Devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. J Am Coll Cardiol. 2008;51(21):e1-62. https://doi.org/10.1016/j.jacc.2008.02.032

2. Wilcox JE, Fonarow GC, Zhang Y, Albert NM, Curtis AB, Yancy CW et al. Clinical effectiveness of cardiac resynchronization and implantable cardioverter-defibrillator therapy in men and women with heart failure: findings from IMPROVE HF. Circ Heart Fail. 2014;7(1):146-53. https://doi.org/10.1161/CIRCHEARTFAILURE.113.000789

3. Abi-Samar F, Gutterman D. Cardiac contractility modulation: a novel approach for the treatment of heart failure. Heart Fail Rev. 2016;21(6):645-60. https://doi.org/10.1007%2Fs10741-016-9571-6

4. Braunwald E, Zipes DP, Libby P, Bonow RO. Braunwald's hearth disease: a text book of cardiovascular medicine. 7a ed. 2015.

5. Dibb KM, Graham HK, Venetucci LA, Eisner DA, Trafford AW. Analysis of cellular calcium fluxes in cardiac muscle to understand calcium homeostasis in the heart. Cell Calcium. 2007;42(4-5):503-512. https://doi.org/10.1016/j.ceca.2007.04.002

6. Bears DM. Cardiac excitation-contraction coupling. Nature. 2002;415(6868):198-205. https://doi.org/10.1038/415198a

7. Burkhoff D, Shemer I, Felzen B, Shimizu J, Mika Y, Dickstein M, et al. Electric currents applied during the refractory period can modulate cardiac contractility in vitro and in vivo. Heart Fail Rev. 2001;6(1):27-34.

8. Morita H, Suzuki G, Haddad W, Mika Y, Tanhehco EJ, Sharov VG, et al. Cardiac contractility modulation with nonexcitatory electric signals improves left ventricular function in dogs with chronic heart failure. J Card Fail. 2003;9(1):69-75. https://doi.org/10.1054/jcaf.2003.8

9. Morita H, Suzuki G, Haddad W, Mika Y, Tanhehco EJ, Goldstein S, et al. Long-term effects of non-excitatory cardiac contractility modulation electric signals on the progression of heart failure in dogs. Eur J Heart Fail. 2004;6(2):145-150 https://doi.org/10.1016/j.ejheart.2003.11.001

10. Butter C, Rastogi S, Minden HH, Meyhofer J, Burkhoff D, Sabbah HN. Cardiac contractility modulation electrical signals improve myocardial gene expression in patients with heart failure. J Am Coll Cardiol. 2008;51(18):1784-9. https://doi.org/10.1016/j.jacc.2008.01.036

11. Imai M, Rastogi S, Gupta RC, Mishra S, Sharov VG, Stanley WC, et al. Therapy with cardiac contractility modulation electrical signals improves left ventricular function and remodeling in dogs with chronic heart failure. J Am Coll Cardiol. 2007;49(21):2120-8. https://doi.org/10.1016/j.jacc.2006.10.082

12. Lyon AR, Samara MA, Feldman DS. Cardiac contractility modulation therapy in advanced systolic heart failure. Nat Rev Cardiol. 2013;10(10):584-98. https://doi.org/10.1038/nrcardio.2013.114

13. Stix G, Borggrefe M, Wolpert C, Hindricks G, Kottkamp H, Bocker D, et al. Chronic electrical stimulation during the absolute refractory period of the myocardium improves severe heart failure. Eur Heart J. 2004;25(8):650-5. https://doi.org/10.1016/j.ehj.2004.02.027

14. Borggrefe MM, Lawo T, Butter C, Schmidinger H, Lunati M, Pieske B, et al. Randomized, double blind study of non-excitatory, cardiac contractility modulation electrical impulses for symptomatic heart failure. Eur Heart J. 2008;29(8):1019-28. https://doi.org/10.1093/eurheartj/ehn020

15. Kadish A, Nademanee K, Volosin K, Krueger S, Neelagaru S, Raval N, et al. A randomized controlled trial evaluating the safety and efficacy of cardiac contractility modulation in advanced heart failure. Am Heart J. 2011;161(2):329-37. https://doi.org/10.1016/j.ahj.2010.10.025

16. Kwong JS, Sanderson JE, Yu CM. Cardiac contractility modulation for heart failure: a meta-analysis of randomized controlled trials. Pacing Clin electrophysio. l. 2012;35(9):1111-8. https://doi.org/10.1111/j.1540-8159.2012.03449.x

17. Giallauria F, Vigorito C, Piepoli MF, Stewart Coats AJ. Effects of cardiac contractility modulation by non-excitatory electrical stimulation on exercise capacity and quality of life: an individual patient's data meta-analysis of randomized controlled trials. Int J Cardiol. 2014;175(2):352-7. https://doi.org/10.1016/j.ijcard.2014.06.005

18. Schau T, Seifert M, Meyhofer J, Neuss M, Butter C. Long-term outcome of cardiac contractility modulation in patients with severe congestive heart failure. Europace. 2011;13(10):1436-44. https://doi.org/10.1093/europace/eur153

19. Kuschyk J, Roeger S, Schneider R, Streitner F, Stach K, Rudic B, et al. Efficacy and survival in patients with cardiac contractility modulation: long-term single center experience in 81 patients. Int J Cardiol. 2015;183(15):76-81. https://doi.org/10.1016/j.ijcard.2014.12.178

20. Liu M, Fang F, Luo XX, Shlomo BH, Burkhoff D, Chan JY, et al. Improvement of long-term survival by cardiac contractility modulation in heart failure patients: a case-control study. Int J Cardiol. 2016;206(1):122-6. https://doi.org/10.1016/j.ijcard.2016.01.071

21. Kloppe A, Lawo T, Mijic D, Schiedat F, Muegge A, Lemke B. Long-term survival with cardiac contractility modulation in patients with NYHA II or III. Int J Cardiol. 2016; 209 (15):291-295 https://doi.org/10.1016/j.ijcard.2016.02.001

22. Ponikowiski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Eur Heart J. 2016;37(27):2129-2200. https://doi.org/10.1093/eurheartj/ehw128

https://doi.org/10.24207/jca.v32i2.006_IN

Sudden Death by Catecholaminergic Polymorphic Ventricular Tachycardia in Children

Morte Súbita por Taquicardia Ventricular Polimórfica Catecolaminérgica em Criança

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ABSTRACT

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) is a severe cardiac arrhythmogenic hereditary illness, which affects children and young adults with a structurally healthy heart. Its prevalence is of one case in 10 thousand inhabitants. It is a potentially fatal illness, part of the differential diagnosis of syncope in children. The present study has the purpose of relating the case of a child that, during the investigation of convulsive syncope, presented sudden death aborted due to CPVT and to describe the diagnosis difficulties of the case, comparing with data from the literature.

KEYWORDS: Ventricular tachycardia; Cardiac sudden death; Tachycardia.

RESUMO

A taquicardia ventricular polimórfica catecolaminérgica (TVPC) é uma doença cardíaca arritmogênica grave, hereditária, que acomete crianças e adultos jovens com coração estruturalmente normal. Sua prevalência é de um caso em 10 mil habitantes. É uma doença potencialmente fatal, que faz parte dos diagnósticos diferenciais de síncope em criança. O presente trabalho tem como objetivo relatar o caso de uma criança que, durante investigação de síncope convulsiva, apresentou morte súbita abortada devido à TVPC e abordar as dificuldades diagnósticas do caso, comparando com dados da literatura.

PALAVRAS-CHAVE: Taquicardia ventricular; Morte súbita cardíaca; Taquicardia.

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INTRODUCTION

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) is a severe cardiac arrhythmogenic hereditary illness that affects children and young adults with a structurally healthy heart. It presents clinically as syncope, convulsive syncope or, in up to 30% of the cases, sudden death, in situations of physical distress or high emotions [1,2].

The possibility of CPVT must be taken into consideration when there is polymorphic adrenally-induced ventricular tachycardia, in the absence of any other cardiac structural or electric anormality[3,4]. Exams such as holter and, mainly, an ergometric test may consolidate the diagnosis hypothesis, since, when performing physical effort or going through situations of emotional distress the electrocardiogram may show polymorphic ventricular extra-systoles or even evoke ventricular tachycardia [5,6].

The diagnosis confirmation is done according to a genetic profile. The main gene involved is the dominant *RyR2*, a receptor of cardiac ryanodine, in approximately 60% of the cases[3,6-8]. However, other genes, such as autosomal recessive *CASQ2*, which codifies the cardiac calsequestrineque, among other less frequent, have already been confirmed as causers of the desease[4].

The prevalence of CPVT is of one case in every 10 thousand inhabitants and, although it is not so rare, it is an under-diagnosed illness due to a series of factors[4]. One of the causes of under-diagnosis is its presentation as syncope or convulsive syncope, which leads, many times, to a wrong primary diagnosis of vasovagal syncope or epilepsy[8]; another cause of under-diagnosis is due to the structurally healthy heart that, adding to the lack of knowledge of the disease, makes the cardiac pathology be discarded at the beginning of the investigation. Still, the genetic profile study for the confirmation of the diagnosis is not always accessible [3].

CPVT treatment is performed with behavioral measures, such as restraining intense physical activities and avoiding situations of strong emotions, in association to medicament therapy with beta-blockers as the first choice of pharmaceutical treatment, with the control of the disease in two thirds of the cases[2,4], and flecainide, antiarrhythmic from I-C class, not commercially available in Brazil, for the non-responders or intolerant to betablocking[9]. For refractory patients to the medicament therapy, there is still the option of left sympathetic denervation to diminish the CPVT and implantable cardiac defibrillators for the prevention of sudden death [5].

With that said, the purpose of this article was to contribute to the medical literature when presenting a case of sudden death aborted by CPVT in a child, with the diagnosis being difficult since exams of higher diagnostic accuracy were standard, aiming at a better understanding of the theme.

CASE REPORT

Patient GNA, male gender, Caucasian, brought by his mother for the first consultation four years ago, when presenting nine years of age, complaining of convulsive syncope in high emotional distress, physical exercises or pain. He had already been examined by a neuro pediatrician that, after the investigation, referred him to Cardiology. No other complains or comorbidity was mentioned, and no positive data on the family history was brought up.

For the initial investigation of the case, the following exams were performed: electrocardiogram, 24h holter, tilt-table-test, and maximum ergometric test. All the exams were within normal; however, the patient continued symptomatic. Then, the patient was submitted to the placement of an implantable looper, which showed an episode of sinusal pause during syncope, in a stressful situation due to traumatic pain.

The initial diagnosis was of vasovagal syncope, although the tilt-table-test was normal. It was chosen to maintain the implantable looper due to the exuberant clinical situation of the patient, which showed respiratory failure and cardiac arrest while performing physical activity. It was performed CPR, with the reversion of sudden death and the implantable looper identified polymorphic ventricular tachycardia.

Then, an invasive electrophysiological study was performed with endovenous isoprenaline and progressive ventricular stimulation; however, no tachyarrhythmia was induced. After this episode, as secondary prevention against sudden death, an implantable unicameral ventricular cardio defibrillator (ICD) was placed.

The genetic profile study was performed, which showed a mutation in the *RyR2* gene, confirming the diagnosis, starting the clinical treatment of beta-blocker, 40 mg of propranolol twice a day, not tolerating higher doses due to symptomatic hypotension.

Due to the intense anxiety of the patient, he performed many episodes of CPVT, followed by appropriate shocks of ICD, even with the use of beta-blocker. Reviewing

the literature, it was possible to notice that some cases of CPVT are refractory regarding the use of beta-blocker, indicating associating flecainide for the control of the disease. However, this antiarrhythmic medication is not commercialized in Brazil and, after judicial litigation, the patient started using 50 mg of flecainide twice a day and the propranolol was suspended, having clinical control of the appropriate therapies of ICD, remaining nowadays for 24 months without episodes of CPVT.

DISCUSSION

The CPVT is an arrhythmogenic hereditary potentially fatal illness, with mortality rate from 30% to 50% until 30 years of age in non-treated patients, highlighting the need of early diagnosis[1,3,5,10]. Due to the advanced age of its presentation, generally between seven and 12 years of age, and due to the patients having hearts without structural alterations, many receive the wrong diagnosis of orthostatic dysregulation or epilepsy, delaying, this way, the treatment for CPVT[5,11,12].

After the clinical suspicion of CPVT, non-invasive exams are performed by confirming the diagnosis hypothesis. The resting electrocardiogram is normal, just like the echocardiogram. In most cases, during the Holter test or, mainly, with effort during the ergometric test, polymorphic or bidirectional ventricular tachycardia is highlighted, when the patient goes through physical or emotional distress, ratifying the hypothesis diagnosis of CPVT When the effort test is stopped, the arrhythmias gradually disappear[5,10,11,13].

In the majority of the cases in which the non-invasive exams showed no alterations, the invasive electrophysiological exam may be performed in order to complement diagnosis, which highlights ventricular tachycardia with isoproterenol stimulation, sympathomimetic medication with mainly acts as beta-agonist, in 30 to 75% of the cases [11].

Diagnostic confirmation is performed through genetic study. Mutations in the gene that codifies the cardiac receptor of ryanodine, *RyR2*, are the most common alterations in CPVT, being present in approximately 60% of the cases. These mutations enhance the spontaneous diastolic liberation of calcium from the sarcoplasmic reticulum, mainly the presence of catecholamines, predisposing, therefore, ventricular tachycardia. In physiological situations, calcium should be removed from the intracellular medium in diastole by the exchange of calcium through the adenosine triphosphate (ATP) pump [2-4,6-8,13].

Besides the alteration in the dominant autossomic gene *RyR2*, the CPVT may also have a rarer genetic mutation, as in the case of *CASQ2* gene, which codifies the cardiac casequestrine and is of autossomic recessive inheritance. It is the second genetic variant of the disease, responsible for less than 5% of the cases. *CASQ2* gene is responsible for the calcium recaptation for the sarcoplasmic reticulum during diastole. Mutations in the gene diminish the calcium recaptation, mainly under adrenergic stress, which predetermines CPVT. Rare cases of CPVT may also be sporadic [1,4,6,9].

Initial treatment of CPVT consists of behavioral measurements, such as restraining intense physical activities and situations which may generate great emotional distress, and pharmaceutical therapy with the use of beta-blockers in the maximum tolerated dose, since, when blocking beta receptors, there is inhibition of the sympathetic stimulation, with good response to treatment in two thirds of the cases [1,3-6,9,12].

For one third of the refractory or intolerant patients to beta-blockers and that continue to present arrhythmic cardiac events, a beta-blocker by flecainide may be associated or substituted, which is an antiarrhythmic agent from class IC that, besides blocking sodium cardiac channels, directly inhibits *RyR2* gene, diminishing even more the percentage of patients that maintain symptoms and arrhythmic events[1-6].

For refractory patients to the maximum pharmaceutical treatment, there are still other therapeutic choices, such as ICD implant, indicated for all as secondary prevention against sudden death and also for those with very symptomatic CPVT, despite the pharmacotherapy. There is also the option of left cardiac sympathetic denervation for patients who habitually present syncope or polymorphic ventricular tachycardia[1,4,9,11].

The patient in this study presented classical clinical case, with starting convulsive syncopes at nine years of age, in situations of physical or emotional distress. However, the diagnosis was difficult, since all the non invasive exams presented usual, being the diagnosis of CPVT confirmed only after an aborted sudden death episode, situation in which the implantable looper demonstrated polymorphic ventricular tachycardia and the patient was

then submitted to genetic profile study that showed typical alteration of the disease, the mutation in the *RyR2* gene.

The patient's treatment was also tricky since due to intense symptomatology, the patient suffered bullying at school, worsening the emotional distress and, therefore, the convulsive syncopes. Also, he presented intolerance to first choice pharmaceutical therapy, the beta-blocker, for presenting symptomatic hypotension. Then, the following adversity was to obtain the flecainide, since the drug is not commercially available in Brazil, demanding judicial litigation for its liberation.

However, after the use of flecainide, the patient showed a completely positive response to the treatment, remaining asymptomatic for 24 months, without the need for additional therapies. He still uses ICD as secondary prevention against sudden death but does not do any additional therapy since the introduction of flecainide.

AUTHORS' CONTRIBUTION

Conceptualization, Milan I.J., and Porto F.M.; Methodology, Milan I.J.; Investigation, Filho H.C, Neto A.B.L, Lima J.M.N.; Writing– First version, Milan I.J.; Writing – Revision & Editing, Milan I.J. and Porto F.M.; Supervision, Porto F.M.

REFERENCES

1. Atik SU, Alp FE, Dedeoğlu R, Koka A, Öztunç F, Eroğlu AG. A rare cause of sudden cardiac arrest: catecholaminergic polymorphic ventricular tachycardia. Turk Pediatri Ars. 2018;53(2):124-8. https://doi.org/10.5152/TurkPediatriArs.2017.3899.

2. Pérez FW, Afonso JSH, Marco MVG, Dorta EC, Acosta LA, Larrea OC, et al. Flecainide reduces ventricular arrhythmias in patients with genotype RyR2-positive catecholaminergic polymorphic ventricular tachycardia. Rev Esp Cardiol. 2018;71(3):185-91. https://doi.org/10.1016/j.rec.2017.04.032

3. Duan H, Lu Y, Qiao L, Hua Y, Li Y, Zhou K, et al. A delayed diagnosis of catecholaminergic polymorphic ventricular tachycardia with a mutant of RYR2 at c.7580T>G for 6 years in a 9-year-old child. Medicine. 2018;97(16):1-5. https://doi.org/10.1097/MD.0000000000010368

4. Velcea AE, Siliste C, Vinereanu D. Catecholaminergic polymorphic ventricular tachycardia – Looking to the future. Maedica (Buchar). 2017;12(4):306-10.

5. Napolitano C, Priori SG, Bloise R. Catecholaminergic polymorphic ventricular tachycardia. Gene Reviews. 2004; 633-39. https://doi.org/10.1016/B0-7216-0323-8/50071-3

6. Pölönen RP, Penttinen K, Swan H, Aalto-Setälä K. Antiarrhythmic effects of carvedilol and flecainide in cardiomyocytes derived from catecholaminergic polymorphic ventricular tachycardia patients. Stem Cells Int. 2018; https://doi.org/10.1155/2018/9109503

7. Lieve KVV, Verhagen JMA, Wei J, Bos JM, Werd C, Noguer FR, et al. Linking the heart and the brain: neurodevelopmental disorders in patients with catecholaminergic polymorphic ventricular tachycardia. Heart Rhythm. 2018;32(18):30826-9. https://doi.org/10.1016/j.hrthm.2018.08.025

8. Pan X, Phillippen L, Lahiri SK, Lee C, Park SH, Word TA, et al. In vivo Ryr2 editing corrects catecholaminergic polymorphic ventricular tachycardia. Circ Res. 2018;123(8):953-63. https://doi.org/10.1161/CIRCRESAHA.118.313369

9. Seidlmayer LK, Riediger F, Pagonas N, Nordbeck P, Ritter O, Sasko B. Description of a novel RyR2 mutation in a juvenile patient with symptomatic catecholaminergic polymorphic ventricular tachycardia in sleep and during exercise: a case report. J Med Case Rep. 2018;12(1). https://doi.org/10.1186/s13256-018-1825-6

10. Ylänen K, Poutanen T, Hiippala A, Swan H, Korppi M. Catecholaminergic polymorphic ventricular tachycardia. Eur J Pediatr. 2010;169(5):535-42. https://doi.org/10.1007/s00431-010-1154-2

11. Velasco A. Taquicardia ventricular polimórfica catecolaminérgica Rev Colom Cardiol. 2009;16(2):71-5.

12. Fujita S, Nishida K, Nakagawa R, Futatani T, Igarashi N, Usuda K, et al. Catecholaminergic polymorphic ventricular tachycardia managed as orthostatic dysregulation and epilepsy in 11- and 15-year-old sisters. Pediatr Int. 2018;60(11):998-1001. https://doi.org/10.1111/ped.13688

13. Domingo, AM. Genética de la taquicardia ventricular polimorfa catecolaminérgica; conceptos básicos. Arch Cardiol Méx. 2008;79(2):13-7.

14. Leite LR, Pereira KRP, Alessi SRB, Paola AAV. Taquicardia ventricular polimórfica catecolaminérgica. um importante diagnóstico em crianças com síncope e coração estruturalmente normal. Arq Bras Cardiol. 2001;76(1):63-8.

15. Oliveira ARF, Santiago GSL, Júnior EFX, Moser LRDN, Mourato FA, Mattos SS. Taquicardia ventricular polimórfica catecolaminérgica com morte súbita abortada. Rev Bras Cardiol. 2014;27(5):382-4.

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Guidelines for Performing Nuclear Magnetic Resonance Imaging Examinations in Patients with Cardiac Electronic Devices

Orientações para Realização de Exames de Ressonância Magnética Nuclear em Pacientes com Dispositivos Eletrônicos Cardíacos

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INTRODUCTION

It is estimated that up to 75% of patients with cardiac implantable electronic devices (CIEDs) will have an indication for nuclear magnetic resonance imaging (MRI) throughout their lives. This population has been historically excluded from the list of patients considered eligible for this examination due to the characteristics of the devices.

A CIED consists of electrode leads and a generator. Each electrode lead is a multifilament metal spiral connector that connects the generator to the heart muscle. The generator, in turn, consists of battery, circuits and connector for the electrode leads. The function of the electrode leads is to conduct electrical impulses with minimum energy sufficient to initiate a cardiac electrical impulse (P or QRS wave). Another essential function of the leads is to transmit electrical information acquired in the myocardium (intracavitary electrogram) to the generator, i.e., to feel the patient's native electrical rhythm, avoiding unnecessary stimulation.

The generator is usually located in the right or left infraclavicular space (or less frequently in the lateral region of the chest or abdomen). It has the function of interpreting stimuli coming from the electrode leads and generate electrical impulse by electric current between the myocardium and the generator (using the electrode leads as conductors). It contains the battery necessary for the impulse (with durability ranging from 7 to 15 years in general) and programmable circuits, that allow minimum frequency, increase in movement-dependent frequency, integration between the electrode leads located in several heart chambers, etc. In exceptional cases, such as in children, the generator can be positioned in the abdomen, and the electrode leads are usually transvenous and, eventually, epimyocardial. Systems with the generator directly implanted into the heart (leadless pacemaker) or with subcutaneous implantable cardioverter-defibrillator (ICD) are available for use in selected cases. The magnetic field generated by MRI can be interpreted by the CIED as abnormal cardiac electrical signal (QRS or P wave) and create interference that would cause one of the following behaviors:

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- Trigger artificial heart stimuli at high frequency;
- Inhibit stimuli of the heart;
- Damage the electrode leads, generator or heating of the system;
- Modification of forced stimulation parameters (reset);
- Trigger inappropriate shocks (in the case of internal cardioverter-defibrillator).

Despite the initial concern, the movement of the device and the torsion of the electrode leads were not evident due to the adherence of the tissues to the subcutaneous.

The heating of the system (causing damage to components and injury to the myocardium around the electrode lead) was proven for nonconditional electrodes. This may lead to an increase in the threshold necessary for myocardial stimulation and patient discomfort.

All CIEDs to be submitted to MRI shall be reprogrammed before and after the examination. Some newer devices are capable to detect the magnetic field of the MRI when activated for a predetermined period, which makes programming appropriate when the patient is inside the scanning room (zone 4). Most of them, however, should be reprogrammed to asynchronous or appropriate mode as late as possible and returned to the original setting after the end of the examination in the shortest period considered appropriate by the physician responsible for monitoring the patient with CIED. This orientation is based on the potential risk of asynchronous stimulation competing with the patient's own pace and being potentially arrhythmogenic in pacemakers. Patients with cardioverter-defibrillators should not leave a supervised environment without adequate protection from antitachycardia therapies.

DEFINITION OF DEVICES

- Pacemaker: device that has the function of stimulation and sensitivity. The pacemaker allows to guarantee the minimum stimulation frequency of the patient. Programming is described by letters (Table 1).
- Resynchronizers: also called multisite pacemaker, they are devices that allow simultaneous stimulation of the left ventricle (LV) by an electrode lead positioned in a epicardial tributary vein of the venous coronary sinus. They may or may not be associated with defibrillator function and, if so, it is called multisite defibrillator. Patients with cardiac resynchronizers have significant structural heart disease and compromised LV ejection fraction (usually less than 35%). The LV electrode lead is positioned in a epicardial tributary vein of the venous coronary sinus. Eventually the LV electrode lead can be implanted by epimyocardial access.
- Cardioverter-defibrillators (ICDs): CIEDs with stimulation function identical to the pacemakers'. They also have a capacitor that allows the device to release shocks with high energy. Their function is to control ventricular tachycardia or ventricular fibrillation, and they are usually implanted in patients with different degrees of ventricular dysfunction or with higher risk of cardiorespiratory arrest.
- Event monitors: Subcutaneous devices from 3 to 6 cm positioned in the anterior thorax. Their function is the prolonged monitoring of cardiac arrhythmias. All currently available event monitors are MRI compatible. It is recommended, at the physician's discretion, the evaluation of the data before the examination, due to the risk of loss of the information collected so far or even their suppression by the acquisition of magnetic field artifacts.
- Conditional devices: CIEDs for which exposure to magnetic field presents no risk to the patient. They are DCEIs that contain only electrode leads described by the manufacturer as conditional, connected to generators also described by the manufacturer as conditional and that do not meet the exclusion criteria. Electrode leads and generators must be from the same manufacturer. The use of electrode leads and generators from different manufacturers may not be guaranteed in case of damage to the system.
- Nonconditional devices: those that have not been extensively tested and/or are not guaranteed by the manufacturer against potential damage caused by the MRI environment (Table 2).

Table 1. Pacemaker programming modes for performing nuclear magnetic resonance.

Simulated chamber	Sensed chamber	Response to the sensed event	Adaptive frequency
O = None A = Atrium V = Ventricle D = Atrium and ventricle	O = None A = Atrium V = Ventricle D = Atrium and ventricle	O = None I = Inhibited T = Triggered D = Both	R = Connected frequency responde

Table 2. Checklist for performing magnetic resonance imaging (MRI) in patients with cardiac electronic devices.

Before the examination
Authorization from the surgeon informing (verification by the staff responsible for the MRI is necessary): • If the device is conditional; • If the autodetect or similar functions are programmed; • If the programming will be performed by a member of the electrophysiologist team/member of the radiology service immediately before the MRI and after the end of the examination; • If the patient is able to perform the procedure without reprogramming. • If it complies with the institutional protocols: • Check if there is a professional locally available for reprogramming the device when necessary (nonconditional or nonprogrammed); • Check if there is staff capable of attending cardiorespiratory arrest (CRA); • Check if there is material available for CRA care.
During the examination
• Check if there is effective rhythm and saturation monitoring. • After the examination: • Check the patient's vital signs; • Check if the device has been reprogrammed with the approval of the physician responsible for the procedure; • Confirm with the responsible physician the safety of the patient's discharge.

MINIMUM SAFETY PARAMETERS

The minimum safety parameters for patients with CIED in the MRI room are:

1. Monitoring of cardiac rhythm (preferably by electrocardiogram) and real-time saturation during the entire examination;
2. Presence of a physician and staff capable of attending cardiorespiratory arrest (CRA) in the radiology section (immediately outside zone 4, also known as the MRI room);
3. Availability of CRA material immediately outside zone 4, according to the current guidelines of the Advanced Cardiovascular Life Support (ACLS);
4. It is suggested to perform these procedures in a hospital or clinic that has parameters 1, 2 and 3 and the ability to safely remove the patient to the intensive care unit in case of need;
5. Have an institutional standard operating protocol that is easily accessible to all laboratory members.

SPECIFIC GUIDELINES FOR THE DIFFERENT DEVICES

Conditional Stimulators

Conditional implantable devices arrived in Brazil in 2012. The manufacturers initially developed electrode leads and generators that allow the performance of magnetic resonance exams with exclusion zone (avoiding thorax, cervical region and upper abdomen), subsequently developing authorized devices for the whole body. Other models were developed with similar technologies.

The patient pacemaker identification card contains the model of his electrode leads and generator with information about compatibility with resonance imaging. The complete updated list of electrode leads and conditional generators is available on the website of the Brazilian Association of Arrhythmia, Electrophysiology and Artificial Heart Stimulation (ABEC) (https://abecdeca.org.br/medico).

However, CIEDs must be reprogrammed prior to exposure to the magnetic field. The objective of this reprogramming is to make the CIED indifferent to the magnetic field (asynchronous mode) and to perform other modifications, such as increasing the stimulation energy. Reprogramming should also evaluate command thresholds and remaining battery charge to assess the safety of the patient's exposure to the magnetic field. Ideally, the battery should not be less than 30% of its capacity and the control thresholds should not be raised prior to the test, although they are not absolute contraindications to the procedure.

Parameters of 1.5 T, gradient slew rate < or = at 200 T/m/s and maximum SAR < or = at 2 W/kg allow safety in all conditional devices regardless of region of interest. Some devices already allow 3 T and this can be verified if it is in the interest of the patient and the physician responsible for imaging.

Conditional Cardioverter-Defibrillators

Conditional cardioverter-defibrillators also demonstrate proven safety to the patient's exposure to magnetic environment. They also need to be reprogrammed before the examination and return to the original parameters after its completion. In addition to indifference to the magnetic field (asynchronous mode), reprogramming aims to inhibit its inappropriate detection and its interpretation as tachycardia or ventricular arrhythmia.

This removes the antitachycardia protection inherent in the device during specific programming for resonance. Inhibition of tachycardia detection prevents the patient from receiving shocks during the examination.

Thus, in this context, if the patient spontaneously presents sustained ventricular tachycardia, treatment should be identical to that of patients who do not have an ICD, according to the current ACLS guidelines.

Nonconditional Devices

There is extensive literature on case series of patients with nonconditional CIED submitted to MRI without adverse events. Several studies are being conducted to validate the routine use of MRI in these devices.

Whenever MRI is the essential diagnostic method not replaceable or necessary on an emergency basis, the examination shall not be prevented by the presence of the CIED. Ideally, it should be carried out in an environment that meets the minimum conditions suggested in this document. Most devices submitted to MRI with 1.5 T tolerated the procedure, as well as exams lasting less than 40 minutes. Despite the absence of randomized studies, it is suggested the maintenance of safety parameters with short-term examinations and a field equal to or less than 1.5 T.

Reprogramming of nonconditional CIED functionality to "resonance compatible" parameters may be performed on any CIED, even if the manufacturer does not ensure the safety of the components in case of damage, such as: reduction or suppression of cardiac stimulation, sudden mode change, heating of circuits and electrode leads, and failure to capture during or after the procedure.

If necessary to perform MRI in nonconditional CIED, it is suggested the presence of a physician able to evaluate the functioning and reprogramming of the device in the radiology environment, with reassessment of the CIED functionality at the end of the procedure and before discharge from the supervised environment. The need for temporary cardiac stimulation in case of device dysfunction should also be foreseen.

EXCLUSION CRITERIA

Exclusion criteria should be considered and discussed with the attending physician. In case of patients with absolute need for the examination in the presence of exclusion criteria, the risk of potentially fatal events should be discussed with

the attending physician and the patient. The CIED shall be considered nonconditional and treated as such when there is (see description on nonconditional devices):

- Presence of abandoned or nonconditional electrode leads;
- Presence of epicardial electrode leads;
- Implant less than six weeks ago;
- Nonthoracic implants;
- Children.

SUGGESTED ADDITIONAL LITERATURE

Indik JH, Gimbel JR, Abe H, et al. HRS expert consensus statement on magnetic resonance imaging and radiation exposure in patients with cardiovascular implantable electronic devices Heart Rhythm. 2017;14(7):e97-e153. https://doi.org/10.1016/j.hrthm.2017.04.025

Mayo Foundation for Medical Education and Research. New protocols allow for MRI in selected patients with pacemakers [Internet]. Mayo Clinic; Disponível em: https://www.mayoclinic.org/medical-professionals/clinical-updates/cardiovascular/new-protocols-allow-mri-selected-pacemaker-patients

Mattei E, Gentili G, Censi F, et al. Impact of capped and uncapped abandoned leads on the heating of an MR-conditional pacemaker implant. Magn Reson Med. 2015;73(1):390-400. https://doi.org/10.1002/mrm.25106

Boilson BA, Wokhlu A, Acker NG, et al. Safety of magnetic resonance imaging in patients with permanent pacemakers: a collaborative clinical approach. J Interv Card Electrophysiol. 2012;33(1):59-67. https://doi.org/10.1007/s10840-011-9615-8

Burke PT, Ghanbari H, Alexander PB, et al. A protocol for patients with cardiovascular implantable devices undergoing magnetic resonance imaging (MRI): should defibrillation threshold testing be performed post-(MRI). J Interv Card Electrophysiol. 2010;28(1):59-66. https://doi.org/10.1007/s10840-009-9463-y

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What is the Diagnosis?

CASE PRESENTATION

Patient OG, 62 years, with arrhythmogenic cardiomyopathy in the right ventricle and low-tolerated sustained tachycardia, user of an implantable ventricular single-chamber cardiovascular defibrillator (ICD), returned asymptomatic for routine evaluation. There was no registry of sustained arrhythmia, and the limits of stimulation and sensitivity were checked and were appropriate (Fig. 1). However, facing the device's telemetry, it was detected lack of sensitivity in a ventricular extra-systole (Fig. 2).

This way, facing the possibility that this flaw could generate failure of detection of a slow ventricular tachycardia (Fig. 3), the level of sensitivity regarding ICD was improved, with the correction of the failure in the extra-systole intermittent sensitivity.

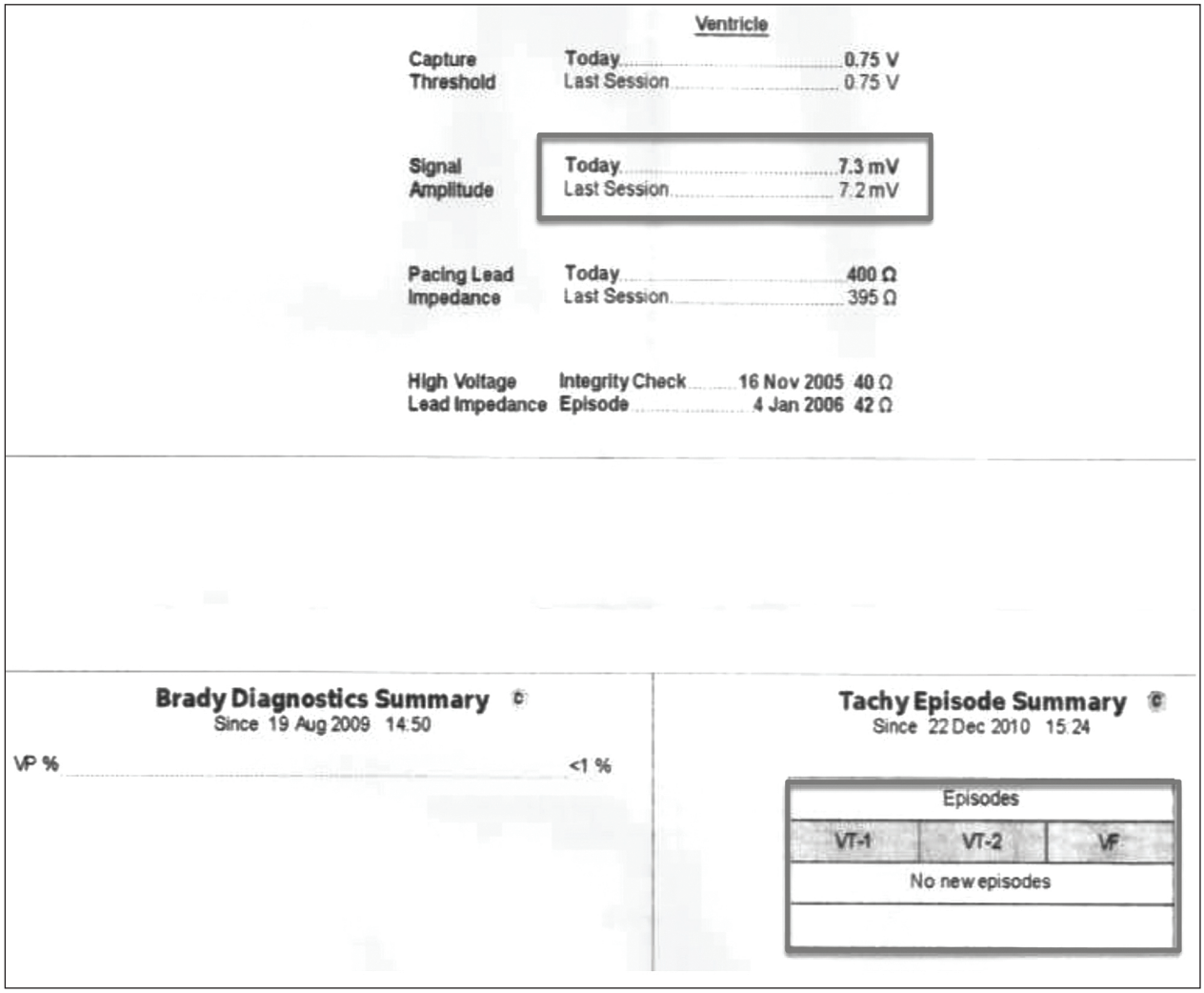

Figure 1. Electrophysiological measurements of the cardioverter defibrillator in the initial assessment and absence of documented ventricular arrhythmias.

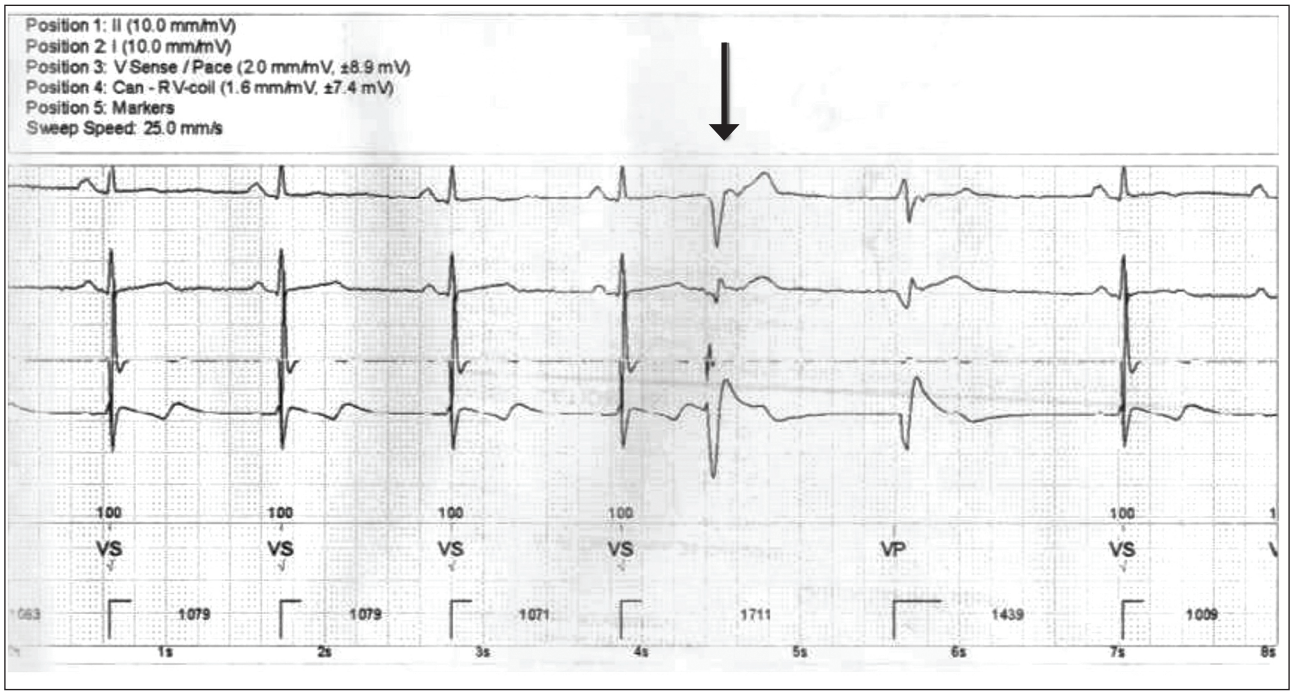

Figure 2. Ventricular extrasystole sensitivity failure during telemetry.

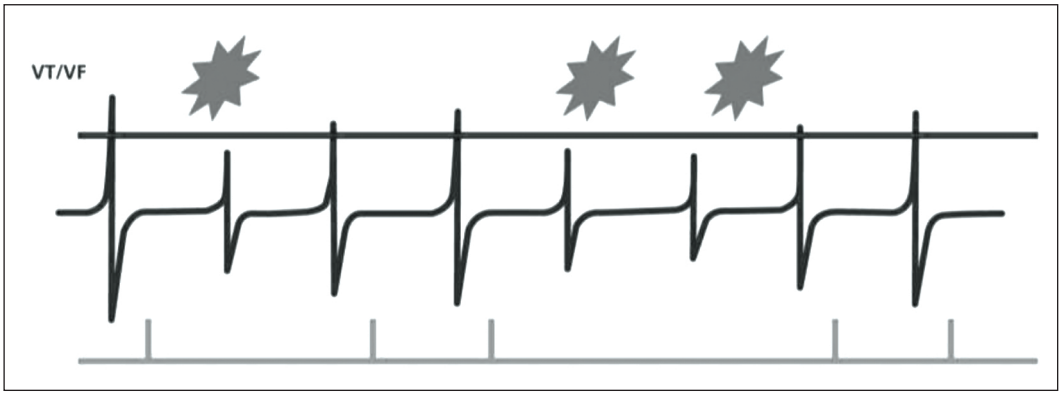

Figure 3. Possible detection failure of a slow ventricular tachycardia if the identified sensitivity failure was not corrected.

DISCUSSION

The ICDs, differently from pacemakers that posse fixed programming, present a sensitivity gain, called SenseAbility™ (Fig. 4) in the Abbott generators, whose purpose is to avoid failure of the sensitivity of quick and low amplitude ventricular events. The beginning of this sensitivity curve improves, called decay delay (Fig. 5) in the Abbott generators, and the speed of the sensitivity improvement, called threshold start (Fig. 6) in the Abbott generators, have a goal to avoid excessive sensitivity in T-waves, which would promote an inappropriate detection of a fake ventricular tachycardia. However, specifically, in this case, the programmed sensitivity improvement was promoting a failure of the ventricular sensitivity, which was corrected with the modification in the threshold start to 50% and the decay delay to 0 ms (Fig. 7).

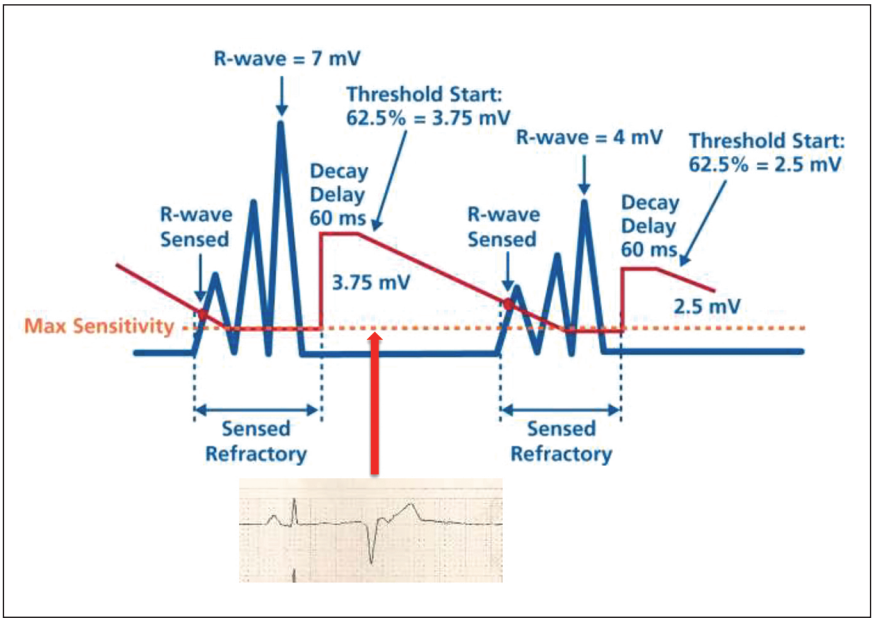

Figure 4. Abbot – St Jude Medical (Sense*Ability*™) cardioverter-defibrillator self-sensitivity gain and the moment when the patient's extrasystole was occurring, explaining its non-detection

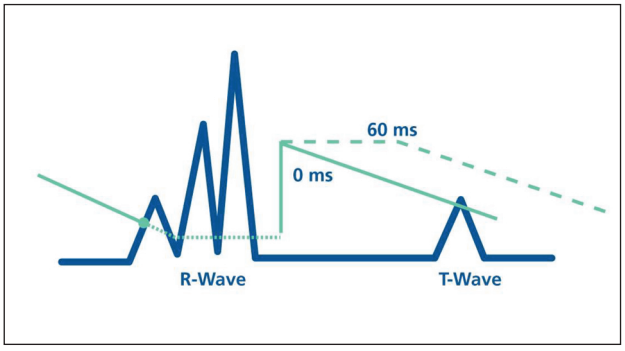

Figure 5. Abbot – St Jude Medical (Sense*Ability*™) ICD Sensitivity: "Decay Delay"; Moment after the sensed or stimulated QRS complex in which the auto-gain of sensitivity begins

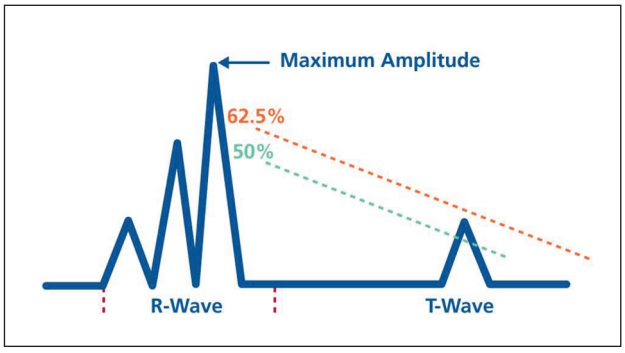

Figura 6. Abbot – St Jude Medical (Sense*Ability*™) ICD Sensitivity: "Threshold Start"; Amplitude after the sensed or stimulated QRS complex at which auto sensitivity gain begins.

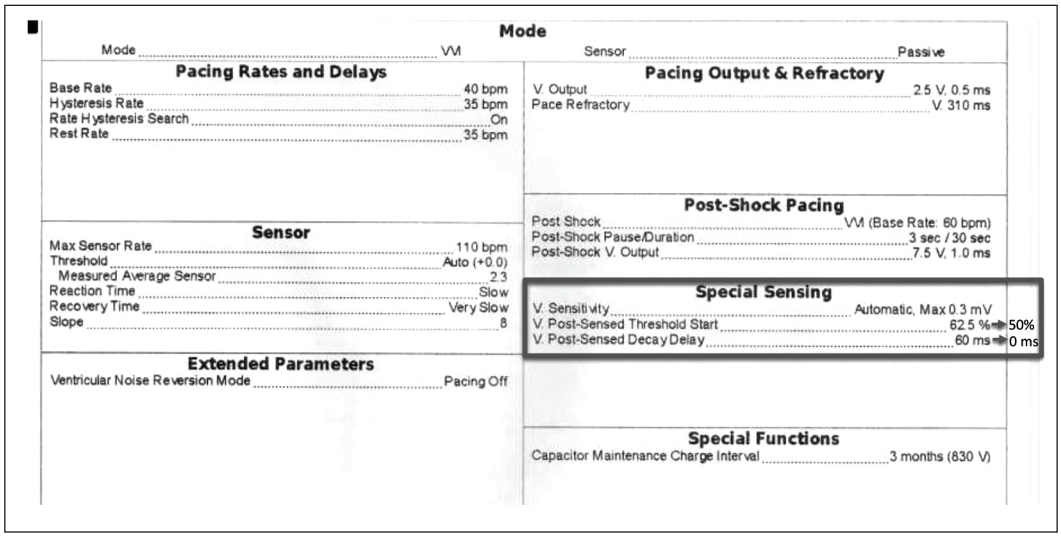

Figure 7. Parameters related to auto sensitivity gain programming in this cardioverter-defibrillator and modifications made to correct the sensitivity failure identified in routine evaluation.

ANSWER

The programming of ICDs sensitivity is fundamental, since, if one ventricular arrhythmia is not detected, it will not be treated. Whenever the parameters of an ICD are modified to promote higher sensitivity, it must be evaluated the possibility of excessive sensitivity of T-wave or non-cardiac events (such as miopotential of the diaphragm muscle in integrated bipolar electrodes, cross-sensitivity of P-waves). Whenever the parameters of the ICD are modified to promote less sensitivity, it must be evaluated the possibility of induction of clinical arrhythmia of the patient, in order to verify if there is appropriate detection of the event.

REFERENCES

1. Ellenbogen KA, Wilkoff BL, Kay GN, Lau CP, Auricchio A. Clinical cardiac pacing defibrillation, and resynchronization therapy. 5a ed. Philadelphia: Elsevier; 2017. https://doi.org/10.1016/c2014-0-01314-7

2. Barold SS, Stroobandt X, Sinnaeve AF. Cardiac pacemakers step by step. Chichester: Wiley-Blackwell; 2004.

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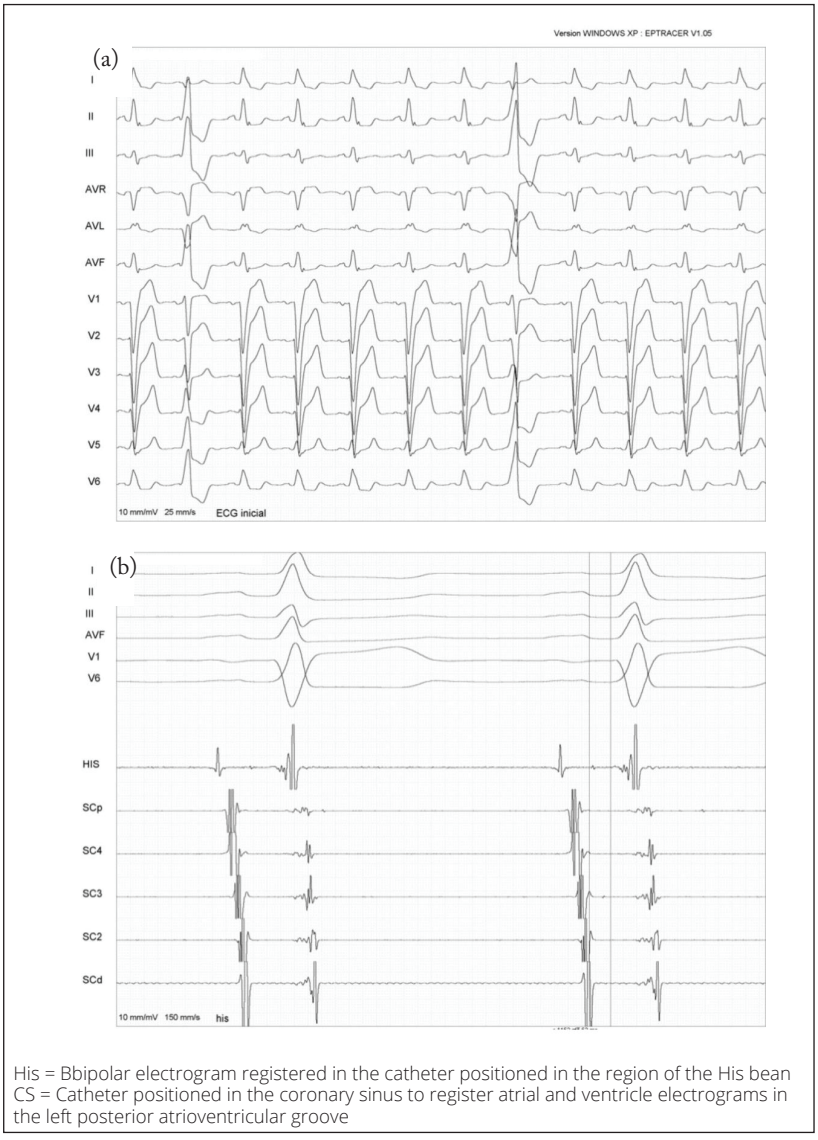
What is the Diagnosis?

CASE PRESENTATION

Patient from male gender, 60 years of age, referred for ablation for symptomatic ventricular arrhythmia despite treatment with amiodarone. Patient with chronic dilated cardiomyopathy post-myocarditis with optimized therapy and functional class II. A previous electrophysiological study showed sinus rhythm with a pattern of left branch block (LBB) (QRS = 150 ms), an interval of 50 ms and absence of ventricular tachyarrhythmia Through ventricle extra-systoles (20% 24h Holter), the patient was submitted to ablation. The initial entry in the electrocardiogram (ECG) and the HV interval are shown in Fig. 1. During the screening, it was noticed the finding presented in Fig. 2. How is that explainable?



His = Bbipolar electrogram registered in the catheter positioned in the region of the His bean
CS = Catheter positioned in the coronary sinus to register atrial and ventricle electrograms in the left posterior atrioventricular groove

Figure 1. Electrocardiogram initial of sinus rhythm entry, LBB, and isolated ventricle extra-systoles. In the inferior image (b), it is possible to see the intracavitary entry of the His bean with HV interval of 50 ms.

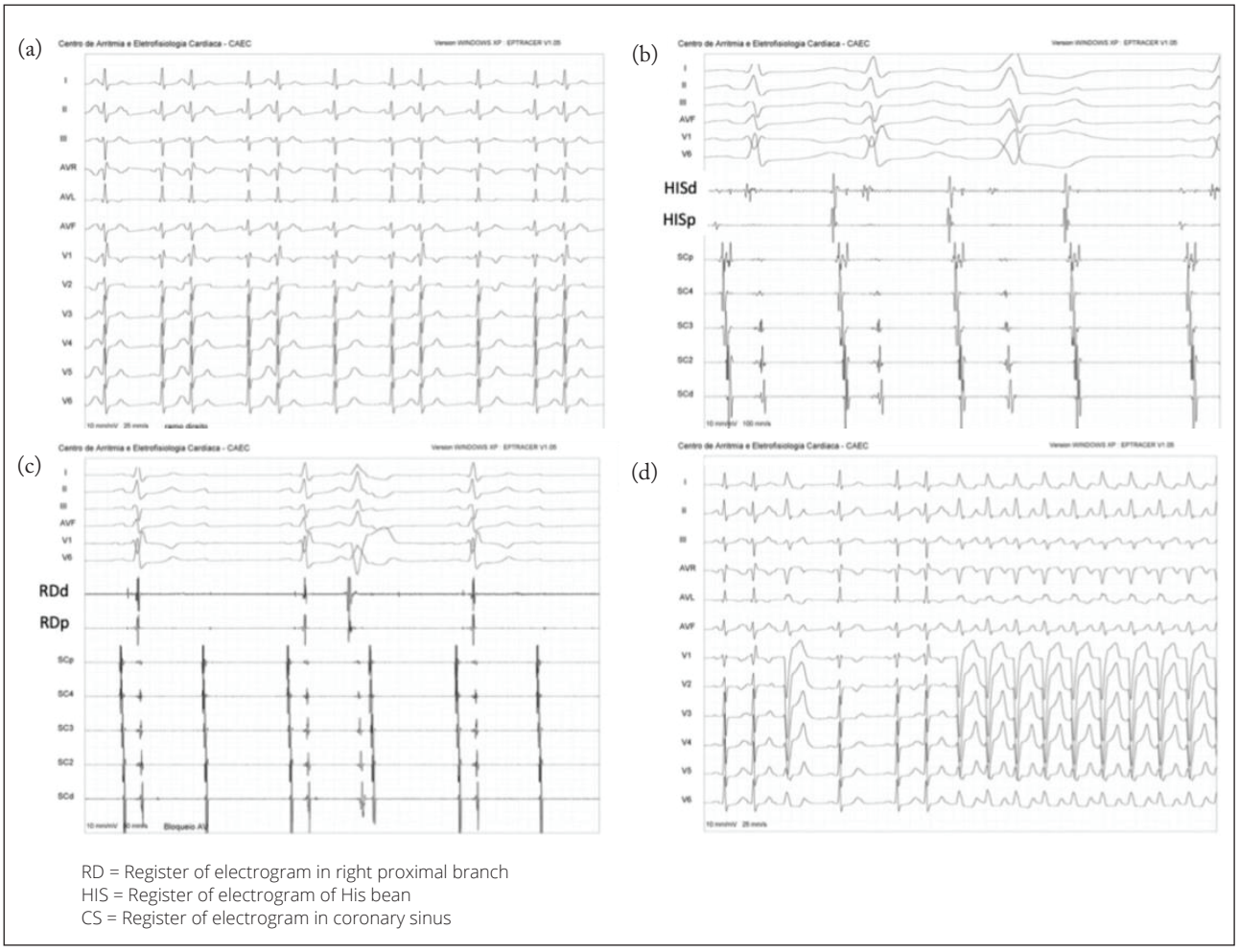


Figure 2. Second-degree atrioventricular block.

ANSWER

During sinus rhythm, there was the appearance of several degrees and blocks in the atrioventricular conduction (Fig. 2). It is essential to mention that the patient from this case already presented LBB and HV interval within normal (Fig. 1). In Figure 2a, it is possible to notice sinus rhythm with an atrioventricular block (AVB) of the second degree. Analyzing the ECG, it is noticed frequency in the atrioventricular conduction before the block (3:2 pattern), suggesting a diagnosis of second-degree AVB Wenckenbach type. Such block is expected at a nodal level. However, two points suggest that it might be not happening in the atrioventricular knot (AVN): 1) fixed PR interval; and 2) different degrees of RBB. After the analysis of the electrogram from His bean, it was verified an enhance in the HV interval before the infra-hissiane block happens, which makes the diagnosis of the Wenckenbach phenomenon in the conduction through the right branch. In Figs. 2c and 2d, it is noticed several degrees of conduction through the right branch, as already described, which is associated with slowing conduction through the previously affected left branch. Fig. 2b registers 2:1 infra-hissiane second-degree AVB, with ventricle isolated extra-systole, retrogressively conducting through the right branch and AVK, as well as promoting the subsequent enhancement of the AH interval.

The following diagram presents explanations for the electrophysiological traces (Fig. 3), which lead to the following conclusions: occurrence of 1) preexistent LBB with intermittent anterograde conduction; 2) infra-hissiane second degree; 3) Wenckenbach block in the right branch, and 4) occult nodal conduction after VES.

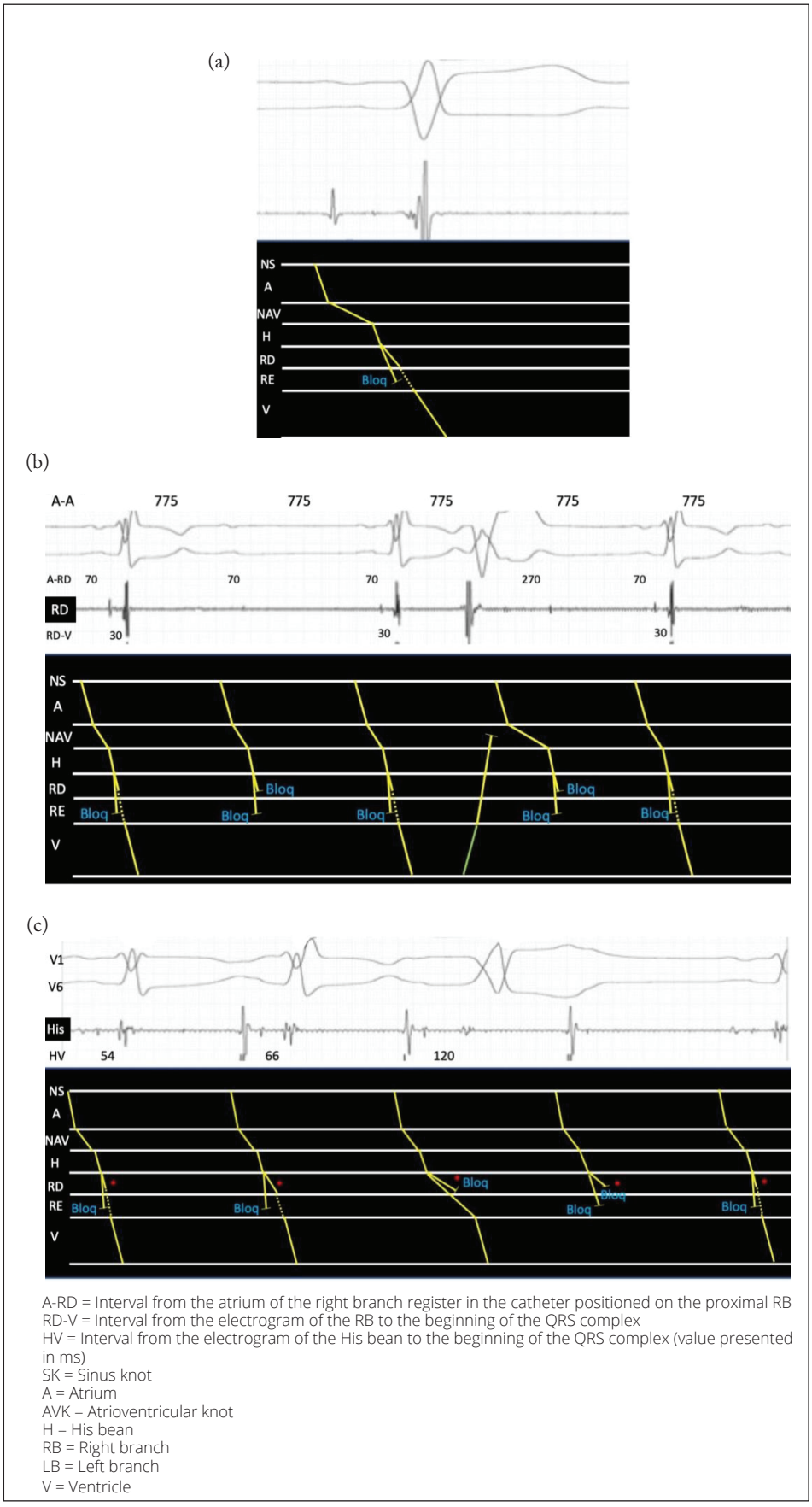


Figure 3. Diagram explaining the conduction disorders. (a) Basal atrioventricular conduction with LBB pattern. (b) 2:1 infra-hissiane second-degree AVB and nodal conduction promoted by VES, retrograde conduction to AVK. (c) Wenckebach phenomenon (in red) through RB with partial conduction through LB (LBB pattern) before the AV block.

REFERENCES

1. Josephson ME. Josephson's clinical cardiac electrophysiology: techniques and interpretations. 5th ed. Philadelphia, PA: Wolters Kluwer; 2016.
2. Issa ZF, Miller JM, Zipes DP. Clinical arrhythmology and electrophysiology: a companion to Braunwald's heart disease. 3rd ed. Philadelphia, PA: Elsevier; 2019. https://doi.org.10.1016/B978-1-4160-5998-1.X0001-8

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Synopsis of Most Relevant Articles on Cardiac Arrhythmias

Sinopse de Artigos Mais Relevantes em Arritmias Cardíacas

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Diurnal, Seasonal and Monthly Variations of Ventricular Arrhythmias in Patients with Implantable Cardiac Defibrillators*

Evolutionarily, the understanding of the incidence of therapies and, mainly, the damaging effects of short and long term shocks in patients with implantable cardiac defibrillators (ICD) has improved. Although changes in the programming of the devices have improved the outcomes, it is necessary an understanding of when tachyarrhythmia events occur, to optimize the programming of the devices and avoid unnecessary and inappropriate therapies. Six prospective studies were grouped to evaluate the frequency of ventricular arrhythmias (VA): PainFree Rx II, EMPIRIC, WAVE, EnTrust, MVP, and OMNI. All the episodes of VA ≤ 500 ms were included. The VA distribution in function of time, day, month, the season was evaluated through the construction of four negative bionominal models, for each model the outcome was the number of VA episodes in a given period. A total of 3.969 matters were included in the analysis, the mean age of the patients was of 65 ± 12.5 years, and the mean ejection fraction was of 28 ± 10.2%. The occurrence of VA was higher in the spring than in the summer (0.86% vs. 0.70%; p = 0.009), but not significantly different in the autumn (0.74%; p = 0.069) or in the winter (0.84%; p = 0,732). The estimated probability of occurring at least one VA episode in each block of one hour during the period of eight in the morning to ten at night in 365 days (0.10% to 0.12%) was higher (35% estimated to 63% higher) than in the period of mid-night to one in the morning (0.07%), not being found significant statistical differences according to days of the week or individual months throughout the year. The authors discuss that there should be variations in the autonomic tonus, adrenergic stimulation, or other modulating factors by the circadian cycle. It is also possible that factors such as air pollution, barometric pressure or humidity that differ throughout the seasons of the year may have either direct or indirect role in the occurring of ventricular ectopias. The results were similar to the TEMPEST (*temperature-related Incidence of Electrical Storm*) study, in which most episodes occurred in association to temperature rise compared to the previous month. In conclusion, there are periods of VA occurrence, and additional studies should be performed in order to understand the real reasons for that, as well as enabling better programming of the devices.

*Maan A, Sherfesee L, Lexcen D, Heist EK, Cheng A. Diurnal, seasonal, and monthly variations in ventricular arrhythmias in patients with implantable cardioverter-defibrillators. J Am Coll Cardiol EP. 2019;5(8):979-86. https://doi.org/10.1016/j.jacep.2019.05.014

"Omission" of Ergometric Test Loses and Delays the Diagnosis of Polymorphic Ventricular Tachycardia in Young Survivors of Sudden Cardiac Death*

Polymorphic Catecholaminergic Ventricular Tachycardia (PCVT) is a hereditary illness that affects 1 in 10.000 individuals and manifests itself clinically as syncope. Without treatment, the general mortality varies from 30 to 50% at 35 years of age. Unfortunately, the diagnosis may not be identified through a resting electrocardiogram, echocardiogram, or invasive electrophysiologic study. Therefore, the ergometric test (ET), or the provocative catecholaminergic test (CPT) is critical in the diagnosis of PCVT. The purpose of this study was to determine the number of diagnoses lost/delayed of PCVT in a coorte of young survivors of sudden cardiac death (CSD). After the analysis of 3.194 consecutive patients and the appropriate exclusions (congenital cardiopathy, coronary disease, myocarditis, etc.) a retrospective review of 101 survivors of (< 35 years of age at the moment of CSD) with structurally normal heart was used to identify those with lost or delayed diagnosis due to the neglected evidence or lack of ET/CPT. Among the 101 survivors , 41/101 (41%), experienced a CDS related to exercise or emotion (EECSD), being significantly (16.6 ± 8.2 years vs. 20.4 ± 11,0 years; p = 0.02) and had more events in pubic (34/41; 83% vs. 26/60.43%; p < 0001). The PCVT diagnosis was more common in EECSD survivors (8/41; 20% vs. 2/60; 3.3%; p = 0.01). Collectively, 15/101 patients (15%) presented a diagnosis of PCVT, the genetic diagnosis was the more common (13/41, 32%), and was lost/delayed in a third (5/15, 33%) the diagnostic time of the survivors with PCVT (mean delay of 15.8 ± 16.6 months). In conclusion, among the 15 patients diagnosed with PCVT, one third had a delay in the diagnosis by not performing an ET, being that an important exam to become standardized in the investigation of CSD in young people, especially if CSD occurring during exercise/emotion.

*Giudicessi JR, Ackerman MJ. Exercise testing oversights underlie missed and delayed diagnosis of catecholaminergic polymorphic ventricular tachycardia in young sudden cardiac arrest survivors. Heart Rhythm 2019;16(8):1232-239. https://doi.org/10.1016/j.hrthm.2019.02.012

Electronic Implantable Cardiac Devices in Elderly Population*

The number of electronic implantable cardiac devices (EICD) has increased, being added to higher longevity/life expectancy. However, most studies include few elderly patients (> 80 years), being the results extrapolated to this age group. The purpose of the revision was to analyze the different types of EICD and discuss approaches for the population > 75 years, besides the guidelines recommendations. Elderly patients have a higher chance of syncope by bradyarrhythmia, which could manifest by falls. The implant of *a loop recorder* may act in this profile of the patient for a possible electric diagnosis related to syncope. Around 80% of pacemakers (PM) are implanted in elderly patients, which are more susceptible to complications, mainly pneumothorax, and electrode displacement, implying in higher morbidity due to prolonged hospitalization. In fragile elderly patients with a total atrioventricular block (TAVB), the implant of a mono chamber PM may seem reasonable. The evidence of an implantable cardiac defibrillator (ICD) in elderly patients is not right in the main studies from the device since the mean age was of 63 years. Besides, this profile of patients presents a higher incidence of non-arrhythmic deaths, and the studies counted with 252 elderly patients (≥ 75 years). In the elderly population, a rational approach is to discuss together with the patient and family members, the device may modify the type of death, from sudden to long and more stressful, not impacting on the quality of life. Cardiac resynchronization therapy with (CRTD) or without (CRT) defibrillator is well-established in patients with heart failure; its use in elderly patients is rising, with implants in 40% of patients > 80 years Most studies have included mainly young patients, being the results in elderly not representative. Martens et al. investigated the impact in this population, with the improvement of functional class and ejection fraction compared to young. However, the use of ICD does not bring additional benefits to the

elderly population. The authors concluded that guidelines should not separately drive the implant of devices in the elderly population; these patients have complex comorbidities and personal desires, being fundamental a discussion regarding the offered therapy so that the purposes of both parties can be achieved.

*Lim W-Y, Prabhu S, Schilling RJ. Implantable Cardiac Electronic Devices in the Elderly Population. Arrhythm Electrophysiol Rev. 2019;8(2):143-46. https://doi.org/10.15420/aer.2019.3.4

Incidence and Predictors of Clinically Essential and Dangerous Arrhythmias During Effort Test in Pediatric Patients with Congenital Heart Disease*

Effort test (ET) is a crucial modality commonly used by pediatric heart centers to evaluate the functional capacity and effort-induced arrhythmias to guide the safe participation in physical activities and to help the decisions of handling medicament therapy. Data of EF in young and adult population with congenital heart disease (CHD) are limited and extrapolated in the adult population with cardiovascular disease. In a review of a single-center, the incidence of clinically essential arrhythmias was of 3%. The purpose of the present study was to quantify the incidence of arrhythmias in the pediatric population during EF and identify patients at risk. This was a retrospective study from *Boston Children's Institutional Research Board* from January 2013 to December 2015. A total of 5.307 EF, with a mean age of 16 years (variation of 13 to 24 years), is 20% with CHD.were analyzed. The exams were interrupted if there was the development of symptomatic supraventricular tachycardia, hemodynamic instability, pre-syncope or syncope, chest pain with progression, ventricular ectopias or elevation of the ST segment (> 2 mm) with chest pain or history of ischemia. The presence of CHD was of 49%, being Fallot's tetralogy the most prevalent (555 tests; 10%) were considered, according to the study, some high-risk criteria. The most common criteria were the presence of implantable cardio defibrillator (ICD) in 198 tests and cardiomyopathy in 186 tests. Some arrhythmias, classified in different degrees, were identified (46%), but only 33 events (0.6%) needed interruption of the exam. The absence of high risk criteria had 99.7% of negative predictive value (NPV) for an arrhythmia that needed interruption of the exam (95% confidence interval from 99.5% to 99.8%) and 99.96% of NPV to arrhythmia that needed intervention beyond to the exam interruption (95% confidence interval: 99.85% to 9999%). The authors pointed out that the incidence of arrhythmias in EF in the pediatric population, even with CHD, is low; using pre-defined criteria such as high risk, it was able to identify the patients with more adverse events (class IV or who needed electric external or internal cardioversion by the ICD). In conclusion, these data allowed better options in terms of supervising performed exams.

*Barry OM, Gauvreau K, Rhodes J, Reichman JR, Bourette L, Curran T, O'Neill J, Pymm JL, Alexander ME. Incidence and Predictors of Clinically Important and Dangerous Arrhythmias During Exercise Tests in Pediatric and Congenital Heart Disease Patients. J Am Coll Cardiol EP. 2018;4(10):1319-327. https://doi.org/10.1016/j.jacep.2018.05.018

Periodic Dynamic Repolarization as a Risk Factor After a Myocardium Heart Attack: Prospective Validation Study*

Patients after a myocardium heart attack (HA) present higher cardiovascular risk, including malignant arrhythmia, cardiac insufficiency, recurrent HA, thromboembolism, and death, being necessary the risk stratification. Periodic dynamic repolarization (PDR) is a new electrocardiographic phenomenon related to sympathetic activity associated to low-frequency oscillations (≤ 0,1 Hz) in repolarization and, therefore, promotes important notions

over the sympathetic regulation level in the left ventricular myocardium. Analysis of the studies ART (*Autonomic Regulation Trial*) and MADIT-II (*Multicenter Automatic Defibrillator Implantation Trial II*) showed an increase of PDR after HA strongly predicts subsequent death, but there was a limitation due to retrospective data. The study in question proposes analysis the results in prospective form patients under medicament therapy after HA. A total of 455 surviving patients of HA (≤ 80 years of age) in sinus rhythm were included. The primary and secondary outcomes were total and cardiovascular mortality after three years. In all patients, a high-resolution digital electrocardiogram was performed (2,048 Hz) during 20 minutes, in the morning period and upright position. According to mathematics calculation, the final step was the calculus of the PDR as mean of the wave coefficient corresponding to frequencies ≤ 0,1 Hz^3 after the transformation of the sign; the cut value was of ≥ 5,75 deg^2. A total of 754 patients were analyzed with the inclusion of 455 patients; during mean follow up of 27.25 months, 47 patients died, being 23 classified as cardiovascular. The increase in the PDR was significantly associated to both outcomes, with areas below the ROC curve of 69.3% (60.2-77.8%) and 79.1% (69.7-86.7%) to total and cardiovascular mortality, respectively. Patients with PDR ≥ 5,75 deg^2 presented total and cardiovascular mortality of 22.9 and 14.85%, respectively when compared to 6.82 and 0.87% in patients with PDR ≤ 5,75 deg^2. Multivary analysis showed that PDR ≥ 5,75 deg^2 was the independent risk factor, including score GRACE > 140, ejection fraction ≤ 35%, and the presence of diabetes mellitus. Higher PDR, however, indicated risk 2.2 and 9.5 times higher for total and cardiovascular mortality ($p = 0.024$ and $p = 0.003$, respectively). The exact mechanisms still need to be clarified, but previous data suggest that PDR reflects the dynamic effects of sympathetic activation in cardiac repolarization; it is known that sympathetic activity occurs in the range of low frequency and that in normal conditions the sympathetic activation causes differential effects in cellular layers of the ventricular myocardium, shortening the duration fo the potential of action. This could lead to the appearance of transmural dispersion of repolarization after sympathetic outbreaks, which could be captured by PDR. Sympathetic denervation, induced ischemia, and sympathetic hyperinervation after HA contribute to the increasing of transmural dispersion, resulting in higher PDR. The authors concluded that PDR promotes additional information as a non-invasive methodology over the sympathetic tonus, and that also has a great prognostic impact.

*Rizas KD, Doller JA, Hamm W, Vdovin N, Stuelpnagel LV, Zuern CS, Bauer A. Periodic repolarization dynamics as risk predictor after myocardial infarction: prospective validation study. Heart Rhythm 2019;16(8):123-231. https://doi.org/10.1016/j.hrthm.2019.02.024

Therapy with Subcutaneous Versus Transvenous Implantable Defibrillator: a Meta-analysis of Case-Control Studies*

Therapy with implantable cardio defibrillator (ICD) is effective for the primary and secondary prevention of sudden cardiac death; its use is associated, however, to short and long term complications, providing morbidity and mortality. Transvenous devices are vulnerable to fracture, and the infection rate of the device itself varies from 0.67 a 1.49%. Subcutaneous ICD (S-ICD) is a recent technology designed to overcome the complications related to transvenous ICD (T-ICD); it presents, however, limitations such as lack of stimulation capacity, not allowing *anti-tachycardia pacing* (ATP). The purpose of the study was, therefore, promote a meta-analysis to summarize and compare the outcomes between S-ICD and T-ICD, including complications regarding the electrode, inappropriate therapies, and appropriate shocks. A study database from PubMed and Embase since the year 2000 was reviewed, identifying six studies for the revision of texts, excluding one study due to the inclusion of the teenage population. The populations were similar regarding age, gender, indications for ICD (primary *versus* secondary prevention), and the proportion of patients with ischemic heart illness, hypertrophy cardiomyopathy (ischemic, non-ischemic and dilated) or hypertrophy cardiomyopathy. The complications with electrode were significant smaller in the Group S-ICD (OR: 0.13; 95% IC:

0.05 to 0.38); the total degree of infection was of 0.35% (8 in 2.269) in S-ICD, similar to T-ICD (OR: 0.75; 95% IC: 0.30 to 1.89). The prevalence of inappropriate therapy (*oversensing* of T-wave, supraventricular tachycardia or inappropriate sensitivity) was similar between the groups (OR: 0.87; 95% IC: 0.51 to 1.49); however, the nature of the therapies was different among them. In the T-ICD group, there was a bigger number of inappropriate therapies due to supraventricular tachycardia; meanwhile, in the S-ICD group, the *oversensing* episodes (sensitivity of noise and T-wave) were more frequent. Only two studies showed data on appropriate shocks, with 17% in S-ICD (95% IC: 6.3% to 26.4%) and 21.3% in T-ICD (95% IC: 12.6% to 27.3%). A study in progress, PRAETORIAN (*Prospective, RAndomizEd comparison of subcutaneous and tRansvenous. ImplANtable cardioverter-defibrillator therapy*), is the most recent randomized, controlled, and multi-centered study, comparing advantages and disadvantages of S-ICD. The current study did not show differences between the infection rate among the two types of device. The authors concluded that the choice of the device, the risk com complications *versus* the rate of inappropriate therapies, as well as the limitations of S-ICD must be individually considered and that S-ICD is safe and effective in properly chosen patients.

*Ray IB-S, Liu J, Jia X, Gold M, Ellenbogen K, Nicolantonio JD, Komócsi A, Vorobcsuk A, Kim J, Afshar H, Lam W, Mathuria N, Razavi M, Rasekh A, Saeed M. Subcutaneous versus transvenous implantable defibrillator therapy: a meta-analysis of case-control studies. JACC: Clinical Electrophysiology 2017;3(13):1475-483. https://doi.org/10.1016/j.jacep.2017.07.017