



## Research Brief

# Atrial thrombi in elective patients considered for atrial fibrillation rhythm control: Risk factors and prognostic value



Marcella Cabral Caires<sup>a, b</sup>, Roberto Muniz Ferreira<sup>a, b, \*</sup>, Thaís Fonseca Rodrigues<sup>a</sup>, David Hong Kang<sup>a</sup>, Lúcia Helena Alvares Salis<sup>a</sup>, Nelson Albuquerque de Souza e Silva<sup>a</sup>

<sup>a</sup> Federal University of Rio de Janeiro, Edson Saad Heart Institute, Rua Rodolpho Paulo Rocco 255, Ilha Do Fundão, Rio de Janeiro, RJ, 21941-913, Brazil

<sup>b</sup> Samaritano Hospital, Cardiology Department, Rua Bambina 98, Botafogo, Rio de Janeiro, RJ, 22251-050, Brazil

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## ABSTRACT

The prognostic value of atrial thrombi (AT) among elective patients with atrial fibrillation (AF) referred for a rhythm control strategy is unclear. In this study, clinical variables were correlated with the presence of AT and long term survival among 205 patients submitted to transesophageal echocardiography before elective AF cardioversion or ablation. Atrial thrombi were present in 7.8% of cases and were significantly associated with reduced survival. Obesity was the only independent clinical predictor of AT [OR 4.27 (1.15–15.79),  $p = 0.03$ ]. In patients with AF, AT appear to be associated with adverse outcomes, possibly indicating more advanced atrial cardiomyopathy.

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## 1. Introduction

Atrial fibrillation (AF) affects approximately 37.6 million individuals worldwide and is associated with up to 30% of all strokes, primarily due to an increased risk of left atrial thrombus (LAT) formation.<sup>1</sup> In patients considered for rhythm control, exclusion of LAT is essential for the prevention of periprocedural thromboembolism. Transesophageal echocardiography (TOE) has an important role in this context, considering LAT has been identified in up to 5.5% of anticoagulated patients referred for cardioversion.<sup>2</sup> Although LAT is a recognized risk factor for thromboembolic events, a paucity of data remains regarding the association of this finding with subsequent mortality.<sup>3</sup> The purpose of this study was to determine the prevalence, risk factors and prognostic value of atrial thrombi (AT) in elective patients with AF considered for rhythm control.

## 2. Methods

Consecutive patients with AF or atrial flutter submitted to TOE before elective cardioversion or catheter ablation between January 2013 and December 2017 were analyzed. Clinical variables were retrospectively collected from medical charts and correlated with the presence of right or left AT and long-term survival. Patients with previous occlusion of the left atrial appendage, myocardial infarction in the preceding 7 days, cerebrovascular event in the previous 4 weeks, sepsis or active cancer were excluded. Subcutaneous low molecular weight heparin was given before the index procedure to those not already on oral anticoagulation. In those submitted to multiple TOE, the first echocardiogram or the first exam with AT was considered for the analysis, if such diagnosis was present.

Categorical variables were analyzed with Pearson's  $\chi^2$  and Fisher's exact tests. Continuous normally distributed variables were expressed as mean  $\pm$  standard deviation and assessed by 2-sample  $t$  tests. Non-normal distributions were represented by the median associated with the 25th to 75th percentile interquartile range, and analyzed by the Wilcoxon-Mann-Whitney test. Logistic regression and a Cox proportional hazards model were used to identify predictors of AT and survival, respectively. Survival curves were constructed from Kaplan Meier estimates and differences were analyzed using the logrank test, with follow-up being censored at 40 months. A  $p$  value  $<0.05$  was considered significant. The study

\* Corresponding author. Federal University of Rio de Janeiro, Edson Saad Heart Institute, Rua Rodolpho Paulo Rocco 255, Ilha do Fundão, Rio de Janeiro, RJ, 21941-913, Brazil.

E-mail address: [betomf@terra.com.br](mailto:betomf@terra.com.br) (R.M. Ferreira).

was performed in accordance with the Declaration of Helsinki and under the terms of local legislation.

### 3. Results

A total of 502 exams were screened for inclusion, of which 244 were excluded according to the prespecified criteria. Among the remaining 258 procedures, 26 patients underwent 2 exams, 9 were submitted to 3 procedures and 4 echocardiograms were performed in 3 individuals. The final analysis was performed considering one procedure from 205 individual patients.

The prevalence of right and left AT was 1.46% and 6.83%, respectively. Any atrial thrombus was present in 7.8% of patients, and 95.6% were discharged in sinus rhythm (10.2% had spontaneous conversion). Left atrial spontaneous echo contrast (SEC) was identified in 29.8% of patients. No post-cardioversion thromboembolic events occurred. Clinical characteristics and their association with the presence of AT are listed in Table 1. In the multivariate analysis, obesity (body mass index  $\geq 30$  kg/m<sup>2</sup>) [OR 4.27 (1.15–15.79),  $p = 0.03$ ] and SEC [OR 8.94 (2.49–32.08),  $p = 0.001$ ] were independently associated with AT, even when the components of the CHA<sub>2</sub>DS<sub>2</sub>-VASC score were considered. A positive relationship between body mass index (BMI) and AT was also identified (Fig. 1A).

Mean follow up was 40.1 months (SD  $\pm 18.8$ ) and AT were associated with reduced survival in the multivariate analysis [OR 11.5 (4.48–29.49),  $p < 0.001$ ] (Fig. 1B). Other independent predictors of mortality were the CHA<sub>2</sub>DS<sub>2</sub>-VASC score [OR 1.55 (1.19–2.02),  $p = 0.001$ ], creatinine  $\geq 1.5$  mg/dl [OR 3.64 (1.18–11.21),  $p = 0.024$ ] and moderate to severe mitral regurgitation [OR 3.3 (1.29–8.4),  $p = 0.012$ ]. Oral anticoagulant use on admission was associated with improved outcomes [OR 0.33 (0.11–1.00),  $p = 0.05$ ]. Left atrial SEC was not predictive of subsequent mortality [OR 1.61 (0.66–3.94),  $p = 0.3$ ].

**Table 1**

Clinical and laboratory characteristics according to the presence of atrial thrombi on transesophageal echocardiography. CAD – coronary artery disease; Cr – creatinine; HGB – hemoglobin; IQR – interquartile range; LA – left atrial; LVD – left ventricular dysfunction; MI – myocardial infarction; MR – mitral regurgitation; MS – mitral stenosis; SD – standard deviation; <sup>1</sup>medication usage on hospital admission; <sup>2</sup>warfarin or direct oral anticoagulants; <sup>3</sup>amiodarone, sotalol or propafenone; <sup>4</sup>oral medications or insulin. Bold values are  $<0.05$ .

Patient characteristics	Total $n = 205$ (%)	AT present (%)		$p$ value
		No, $n = 189$	Yes, $n = 16$	
Mean age, yrs (SD $\pm$ )	72.1 (13.4)	71.8 (13.3)	75.1 (14.3)	0.189
Male gender	71.7	70.9	81.3	0.565
Hypertension	68.8	68.3	75	0.78
Diabetes	19.5	19.1	25	0.522
Hyperlipidemia	43.4	42.9	50	0.58
Obesity	21.5	19.6	43.8	<b>0.024</b>
Heart Failure or LVD	16.1	14.3	37.5	<b>0.015</b>
Prior MI or symptomatic CAD	26.8	24.3	56.3	<b>0.006</b>
Prior stroke	4.9	4.8	6.3	0.565
Moderate or severe MR	12.7	13.2	6.3	0.67
Moderate or severe MS	1.0	1.1	0	1.0
Prior valvular heart surgery	5.9	5.8	6.3	1.0
Median CHA <sub>2</sub> DS <sub>2</sub> -VASC score (IQR)	3 (2–4)	3 (2–4)	3 (2.5–4.5)	0.088
Mean baseline HGB, mg/dl (SD $\pm$ )	13.0 (1.9)	13.0 (1.9)	13.0 (2.1)	0.849
Median baseline Cr, mg/dl (IQR)	1.06 (0.95–1.13)	1.06 (0.95–1.13)	1.08 (0.97–1.26)	0.265
LA spontaneous echo contrast	29.8	25.9	75	<b>&lt;0.001</b>
Pre-procedural medications <sup>1</sup>				
Antiplatelets	27.8	26.5	43.8	0.138
Oral anticoagulants <sup>2</sup>	39.5	40.2	31.3	0.599
$\geq 3$ weeks	19.5	20.1	12.5	0.743
Beta blockers	27.8	27	37.5	0.367
Antiarrhythmics <sup>3</sup>	44.4	46	25	0.122
Statins	42.4	41.8	50	0.524
Antidiabetics <sup>4</sup>	18.1	17.5	25	0.497

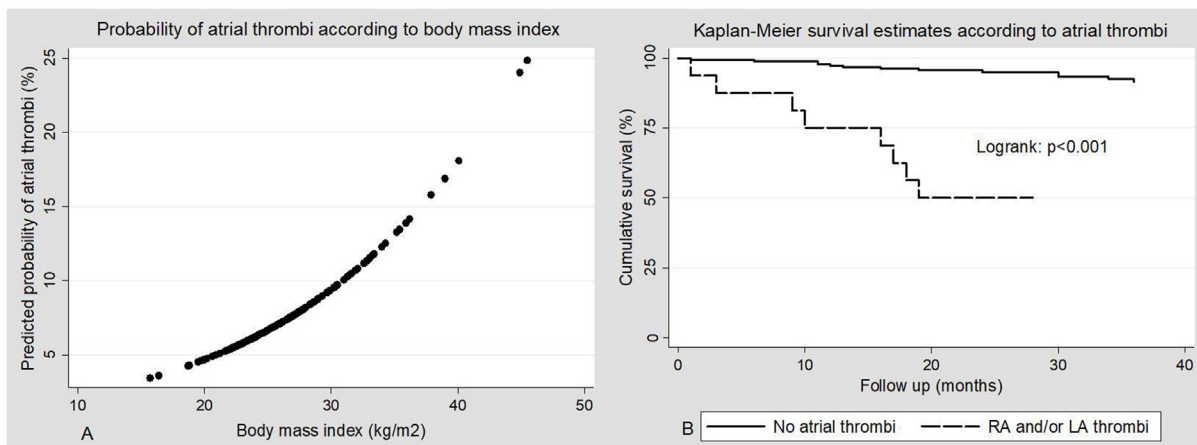
### 4. Discussion

Atrial fibrillation is associated with a higher risk of multiple complications including stroke, peripheral embolism, heart failure, cognitive decline, impaired quality of life and death.<sup>2</sup> However, the lack of a clear temporal relationship between AF and cerebrovascular events in previous studies supports the concept of an underlying atrial cardiomyopathy (AC). Since thromboembolic events may occur independently of AF burden, the identification of AT in this setting may suggest a more advanced stage of AC.<sup>4</sup>

The prevalence of AT was lower than what was reported in the ACUTE trial (13.8%), possibly because of the lower frequency of oral anticoagulation in the latter (39.5% vs 33%).<sup>5</sup> Nevertheless, these results underscore the importance of considering TOE before cardioversion even in anticoagulated patients.<sup>2</sup> In the current study, the presence of AT was the most significant predictor of reduced survival, suggesting that appropriate management of thromboembolic risk remains a fundamental component of treatment.

Although the relationship between obesity and thrombogenicity remains unclear, an increased risk of LAT in patients with AF and BMI  $>27$  kg/m<sup>2</sup> has been previously reported, similarly to the current results.<sup>6,7</sup> It is unclear whether the clinically approved dosages of direct oral anticoagulants for patients with AF have the same clinical efficacy in obese patients. Whether insufficient anticoagulation or an increased underlying thrombotic risk are both responsible remains to be confirmed.<sup>8</sup> In addition, the reduced survival of those with creatinine  $\geq 1.5$  mg/dl highlights the difficulties in managing the complications associated with chronic kidney disease and oral anticoagulation. Atrial fibrillation is not only predictive of mortality in this setting, but also of more advanced underlying cardiovascular complications and subsequent end stage renal disease.<sup>9</sup>

This study has limitations that have to be acknowledged. The findings are not applicable to patients with prosthetic heart valves or mitral stenosis. Baseline oral anticoagulation was lower than



**Fig. 1.** A - Body mass index (kg/m<sup>2</sup>) and probability of atrial thrombi on transesophageal echocardiography. B -Kaplan Meier curves for survival according to the presence of atrial thrombi on transesophageal echocardiography. LA – left atrial; RA – right atrial.

expected when compared to previous studies and post-discharge medications were unavailable.<sup>10</sup> Data regarding non-fatal thromboembolic events was also not recorded. Finally, the retrospective and single center design warrants further confirmation in larger studies.

## 5. Conclusions

In patients with AF, AT appear to be predictive of reduced survival, possibly by indicating more advanced AC. When a rhythm control strategy is chosen, TOE should be considered in high risk patients regardless of previous anticoagulation. Until additional aspects of AC and AF are revealed, antithrombotic therapy should continue to be the mainstay of treatment.

## Declaration of competing interest

All authors have approved the final article and agree to its contents, which has not been previously published or simultaneously sent to any other journal for publication. None of the authors have any conflicts of interest to declare.

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