Associação entre anormalidades atriais eletrocardiográficas, dilatação atrial ecocardiográfica e prognóstico no AVC criptogênico

DISSERTAÇÃO DE MESTRADO

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SUMÁRIO

ABREVIATURAS

ACEI	Angiotensin-converting enzyme inhibitor
AE	Átrio esquerdo
AF	Atrial Fibrillation
ARB	Angiotensin receptor blocker
AVC	Acidente vascular cerebral
BMI	Body mass index
CI	Confidence interval
ECG	Electrocardiogram
HR	Hazard ratio
IQR	Interquartile range
LA	Left atrium
LAE	Left atrial enlargement
LAVI	Left atrial volume index
mRS	Modified Rankin scale
NCE	Non-cardioembolic stroke
OR	Odds ratio
PWTFV1	P-wave terminal force in lead V1
RR	Relative risk
SD	Standard deviation.

ARTIGO DE REVISÃO PARA PUBLICAÇÃO

TÍTULO COMPLETO EM PORTUGUÊS

Anormalidades atriais eletrocardiográficas, dilatação atrial ecocardiográfica e AVC criptogênico

TÍTULO COMPLETO EM INGLÊS

Electrocardiographic atrial abnormalities, echocardiographic atrial dilatation and cryptogenic stroke

TÍTULO RESUMIDO EM PORTUGUÊS

Cardiopatia atrial e AVC criptogênico

TÍTULO RESUMIDO EM INGLÊS

Atrial cardiopathy and cryptogenic stroke

PALAVRAS-CHAVE

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RESUMO

Acidente vascular cerebral (AVC) é uma importante causa de morbimortalidade e a maioria é de causa isquêmica. AVCs de causa indeterminada (AVC criptogênico) são responsáveis por 40% dos AVCs isquêmicos e a fibrilação atrial oculta é um possível mecanismo fisiopatológico relacionado a este subtipo. Como o subtipo cardioembólico é associado com o pior prognóstico comparado aos demais, é relevante reconhecer possíveis marcadores de fibrilação atrial, ou sinais de cardiopatia atrial nos AVCs criptogênicos. Nesse estudo nós revisamos índices de onda P no eletrocardiograma (força terminal da onda P em V1, duração da onda P e eixo da onda P), medidas de dilatação atrial no ecocardiograma (diâmetro atrial esquerdo e volume atrial esquerdo indexado) e a sua relação com os AVCs isquêmicos, particularmente com os criptogênicos.

ABSTRACT

Stroke is an important cause of death and disability, and most are due to ischemic cerebral infarction. Stroke of undetermined etiology (cryptogenic strokes) accounts for up to 40% of ischemic strokes and occult atrial fibrillation is a possible pathophysiologic mechanism related to this subtype. As the cardioembolic subtype is associated with the worst prognosis compared to the others, it becomes relevant to recognize possible markers of atrial fibrillation, or signs of atrial cardiopathy, in cryptogenic strokes. In this study we review electrocardiogram P-wave indices (P-wave terminal force in V1, P-wave duration and P-wave axis), echocardiogram measurements of atrial dilatation (left atrial diameter and left atrial volume index) and their relation with ischemic strokes, particularly cryptogenic strokes.

Introduction

Stroke remains as the second leading cause of death and disability around the world and 70-90% are due to ischemic cerebral infarction.[1] Stroke of undetermined etiology (cryptogenic strokes) accounts for up to 40% of ischemic strokes[2] and occult atrial fibrillation (AF) is a possible pathophysiologic mechanism related to this subtype.[3] As the cardioembolic subtype is associated with the worst prognosis compared to the others, it becomes relevant to recognize possible markers of AF, or signs of atrial cardiopathy, in cryptogenic strokes.[2]

Epidemiology

Prevalence

Worldwide, the incidence of ischemic stroke is 68%, while the incidence of hemorrhagic stroke (subarachnoid and intracerebral hemorrhage combined) is 32%, reflecting a higher proportion in low-income population.[4] In the United States, the annual incidence of new or recurrent stroke is approximately 795.000, of which 77% are first-ever strokes and 23% are recurrent strokes.[5]

In Brazil, stroke was responsible for 101.195 deaths which represents 8% of total deaths in 2017.[6] In Latin America, stroke incidence rates adjusted for age vary between 35 and 183 per 100.000 inhabitants, whereas, in Brazil, the rate is between 137 and 168 per 100.000.[6]

Population Characteristics

Women have a higher risk of stroke than men. The lifetime risk of stroke among those 55 to 75 years of age was 1 in 5 for women (95% CI, 20-21%) and 1 in 6 for men (95% CI, 14-17%).[7]

In the United States, blacks and Hispanics have an increased risk of stroke compared with whites. An increased incidence of stroke has also been found among Mexican American compared with non-Hispanic whites.[8]

In the United States, the incidence of small vessel strokes and cryptogenic strokes was twice higher among blacks. Large vessel strokes were 40% more frequent in blacks compared to whites. The

incidence of cardioembolic strokes was not significantly different in this population.[9] The age of subjects affected by cryptogenic stroke seems inconsistent. A meta-analysis suggested that young age (<50 years) is inversely associated with cryptogenic stroke (OR 0.6; 95% CI 0.4-1.0)[10], whereas other registries have found similar rates between younger and older age groups.[11]

Classification

The TOAST classification scheme for ischemic stroke attempts to classify them according to the major pathophysiologic mechanisms that are recognized as the etiology of most ischemic strokes. It assigns ischemic strokes to five subtypes according to clinical features and complementary exams, including brain imaging, cardiac tests, neurovascular evaluations and prothrombotic state laboratory evaluation. It is widely used and has good interobserver agreement.[12]

The five TOAST subtypes of ischemic stroke are: 1) Large artery atherosclerosis, 2) Cardioembolic, 3) Small vessel occlusion, 4) Stroke of other determined etiology and 5) Stroke of undetermined etiology.

The last subtype, also known as cryptogenic stroke, includes cases where an etiology of stroke cannot be determined with any degree of confidence, including those with two or more potential causes identified and those with a negative or an incomplete evaluation.

A related concept is embolic stroke of undetermined source (ESUS), which is defined as a nonlacunar brain infarct without proximal artery stenosis or cardioembolic sources. This concept implies that a full standard evaluation was done, whereas the traditional definition of cryptogenic stroke did not require full evaluation. Therefore, ESUS represents a subset of cryptogenic stroke.[13]

Electrocardiogram – P-wave Indices

Abnormalities in atrial activation measured through analysis of P-wave morphology have been associated with atrial remodeling[14], ischemic stroke[15] and increased risk of atrial fibrillation.[16] P-wave

indices include P-wave axis, P-wave duration, advanced interatrial block and P-wave terminal force in V1 (PWTFV1). Examples of P-wave indices are found on **Figure 1**.

P-wave terminal force in V1

It is a measure of left atrium activation. It is computed by multiplying the duration (ms) and the depth (μV) of the downward deflection of the P-wave in lead V1.[17]

The first study to show an association between ischemic stroke and P-wave terminal force in V1 was a case-control study, published in 2005. In this study, when analyzed as a categoric variable, a PWTFV1 >40ms.mm was associated with ischemic stroke after adjustment for other stroke risk factors (OD 2.32; 95% CI 1.29-4.18), although it had low sensitivity and specificity (54 and 62% respectively) and low positive and negative predictive values (51 and 64% respectively).[18] When analyzed as a continuous variable, a 2009 study demonstrated that PWTFV1 was a predictor for atrial fibrillation (OR 2.1; 95% CI 1.8-2.4) and for ischemic stroke (HR 2.60; 95% CI 2.05-3.29).[19] A systematic and meta-analysis review was published in 2017, reviewing 8 studies. When analyzed as a continuous variable PWTFV1 was associated with ischemic stroke (OR per 1 SD change, 1.18; 95% CI 1.12-1.25) and similar results were found when analyzed as a categorical variable (>40ms.mm, OR 1.59; 95% CI 1.10-2.28).[20]

A recent study failed to show an association between PWTFV1 and ischemic stroke, due to low interobserver and inter P-wave measurements (ICC 0.68, p <0.002), indicating significant under and overestimation of PWTFV1.[21] This parameter was not useful to detect paroxysmal atrial fibrillation after stroke in subjects without atrial fibrillation history.[22] In the context of cryptogenic stroke, there is no consensus data regarding the usefulness of PWTFV1. Although an association of increased PWTFV1 with incident cryptogenic or cardioembolic stroke independently of the presence of AF was demonstrated,[23] this association only applied to cardioembolic and non-ESUS cryptogenic stroke in younger patients.[24]

P-wave axis

It is a measure of the net direction of atrial depolarization and is determined by measuring the positive and negative P-wave deflections on all limb leads and calculating the direction of electrical activity. Abnormal P-wave is any value outside 0-75°.[25]

In a cohort study, abnormal P-wave axis was associated with increased risk of atrial fibrillation after adjustment for traditional cardiologic risk factors.[26] Moreover, this index was also independently associated with ischemic stroke and this association seemed stronger in cardioembolic strokes.[27] No studies have been published up to date showing an association between cryptogenic stroke and abnormal P-wave axis.

Recently, it has been proposed the inclusion of P-wave indices to improve ischemic stroke prediction in individuals with atrial fibrillation[28]. Of the P-wave indices considered (P-wave duration, PWTFV1, P-wave axis, advanced interatrial block), only abnormal P-wave axis was associated with ischemic stroke risk independent of CHA_2DS_2-VASc score. The $P_2CHA_2DS_2$-VASc improved the C-statistic (95% CI) from 0.60 (0.51–0.69) to 0.67 (0.60–0.75) in ARIC cohort[29] and 0.68 (0.52–0.84) to 0.75 (0.60–0.91) in MESA (validation cohort)[30].

P-wave duration

It is a reflection of the time required for left and right atrial depolarization. It is measured from the P-wave onset (conclusion of T-P segment) to return to baseline. Prolonged P-wave duration is defined as >120ms.[17]

Studies have failed to show an association between P-wave duration and ischemic stroke.[28,31] Increased P-wave duration was an independent predictor of atrial fibrillation in patients with cryptogenic stroke.[32]

Echocardiogram – Atrial Measurements

Enlargement of left atrium have been associated with atrial fibrillation, ischemic stroke and death in several studies (**Table 1**). Left atrial volume index is a more robust parameter of atrial dimension and superior to left atrial diameter and area in predicting cardiovascular outcomes in subjects with sinus rhythm. A study comparing left atrial diameter, left atrial area and left atrial volume index demonstrated that all three parameters were independently predictive of combined outcome of atrial fibrillation detection, transient ischemic accident, stroke, myocardial infarction, congestive heart failure or cardiovascular death. The overall performance for the prediction of cardiovascular events was greatest for LA volume (area under the receiver operator characteristic curve: indexed LA volume 0.71; LA area 0.64; LA diameter 0.59).[33]

After cryptogenic stroke, individuals with increased left atrial volume index and abnormal markers of coagulation and hemostatic activation had a good predictive ability for the composite outcome of atrial fibrillation, malignancy or recurrent stroke (area under curve 0.84).[34] Both left atrial diameter and left atrial volume index were independently associated with paroxysmal atrial fibrillation and flutter detection in patients following post cryptogenic stroke with implantable loop recorders.[35]

A small study suggests that subjects with embolic stroke of undetermined source have left atrial dysfunction and remodeling at rest and exercise in comparison to healthy, matched controls. ESUS subjects have larger left atrial end-diastolic volume at rest and with exercise, a lack of response to maximal exercise of left atrial ejection fraction and left atrial spherical remodeling assessed by 3D echocardiogram.[36]

Subtle abnormalities in left atrial function can be detected by myocardial strain analysis by speckle-tracking echocardiography. A retrospective case-control study analyzed left atrial reservoir strain in individuals with cryptogenic stroke. Left atrial strain was significantly lower in cryptogenic stroke subjects (30 ± 7.3% vs 34 ± 6.7%) and larger indexed left ventricular end-systolic volume (OR 1.04; 95% CI, 1.01-1.07) was independently associated with cryptogenic stroke.[37]

Future perspectives

It is unclear whether P-wave indices and left atrial dilatation assessed by echocardiography are useful parameters in identifying subjects at higher risk of cardioembolic events in cryptogenic stroke. If an association between abnormal P-wave indices, echocardiogram left atrial dilatation and worse neurologic prognosis in cryptogenic stroke is found, this may represent markers of higher risk of cardioembolic events. If those parameters, possible identifying patients with cardio atriopathy, might play a small role in selecting patients for specific therapy, such as anticoagulation, remains to be determined.

Conclusion

Both electrocardiogram and echocardiogram parameters, particularly P-wave terminal force in V1 and left atrial volume index might be useful in identifying patients of higher risk of cardioembolic events following an ischemic stroke of undetermined etiology.

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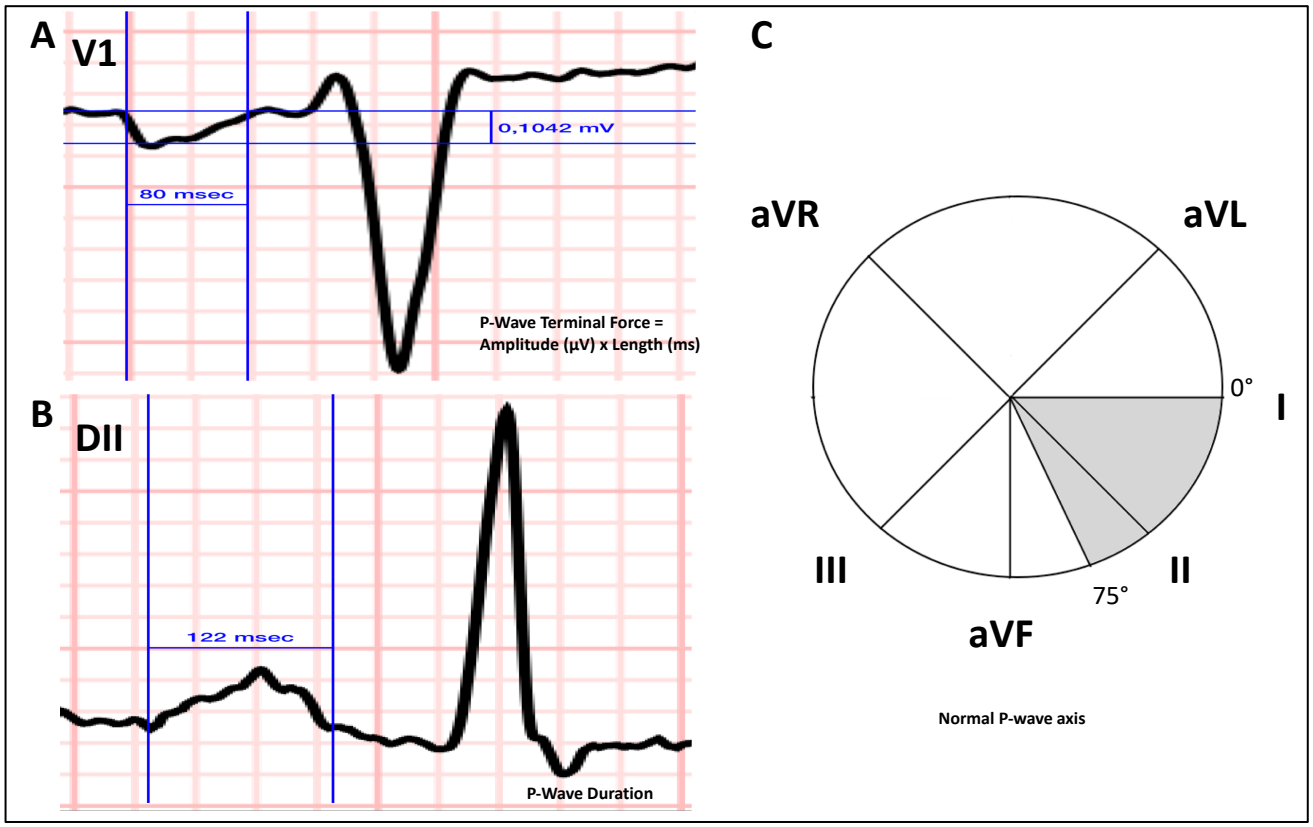
FIGURES AND TABLES

Table 1. Selected studies relating echocardiogram left atrium measurement with risk of ischemic stroke.

References	Echocardiogram measure	Outcome	Adjusted effect estimates
Benjamin et al.[38]	LA diameter	Ischemic stroke and death	Per 10mm increase in LA size: RR of stroke 2.4 in men (95% CI 1.6-3.7) and 1.4 in women (95% CI, 0.9-2.1)
Di Tullio et al.[39]	LA diameter index	Ischemic stroke	Per 10mm/1.7m^2 (adjusted OR 1.47, CI 95% 1.03-2.11). Association not present in women and age>60y
Yaghi et al.[40]	LA diameter	Recurrent stroke	Moderate-severe LAE was associated with recurrent cardioembolic or cryptogenic stroke (HR 2.83, CI 95% 1.03-7.81), but not total ischemic stroke (HR 1.06, CI 95% 0.48-2.30)
Yaghi et al.[41]	LA diameter	Prevalent brain infarct on MRI	Moderate- severe LAE was associated with prevalent infarcts (RR 1.22, 95% CI 1.04–1.44)
Barnes et al.[42]	LAVI	First ischemic stroke and death	Increased LAVI was predictor of ischemic stroke (HR 1.63, CI 95% 1.08-2.46) and mortality (HR 1.3, CI 95% 1.09-1.56)
Russo et al.[43]	LA volume	Silent brain infarct on MRI	Greater LA volume associated with subclinical cerebrovascular disease (OR per SD increase 1.37, CI 95% 1.04-1.80)
Jordan et al.[44]	LAVI	Recurrent cardioembolic stroke and AF	LAVI was greater in cardioembolic stroke versus NCE (OR per mL/m^2, 1.07; 95% CI, 1.05–1.09. AF detection in ESUS per mL/m^2 (OR 1.09; 95% CI, 1.02–1.15)

AF: atrial fibrillation; CI: confidence interval; HR: hazard ratio; LA: left atrium; LAE: left atrial enlargement; LAVI: left atrial volume index; NCE: non-cardioembolic stroke; OR: odds ratio; RR: relative risk; SD: standard deviation.

Figure 1. Examples of P-wave indices measurements, **A.** P-wave terminal force in V1. **B.** P-wave duration. **C.** P-wave axis.



RACIONAL PARA O ESTUDO

A alta prevalência e morbimortalidade do AVC criptogênico torna necessário o reconhecimento de marcadores relacionados a sua fisiopatologia, indicando indivíduos de maior risco cardioembólico. Anormalidades atriais, tanto eletrocardiográficas, quanto ecocardiográficas estão associadas a AVCs isquêmicos, porém o seu papel no subtipo criptogênico ainda não é definido. O presente trabalho pretende estudar uma associação entre parâmetros eletrocardiográficos da onda P (força terminal em V1, eixo e duração), parâmetros ecocardiográficos de dilatação atrial (diâmetro e volume atrial indexado) e pior prognóstico neurológico em pacientes com AVC criptogênico, medido pela escala de Rankin. **(Figura 2)**

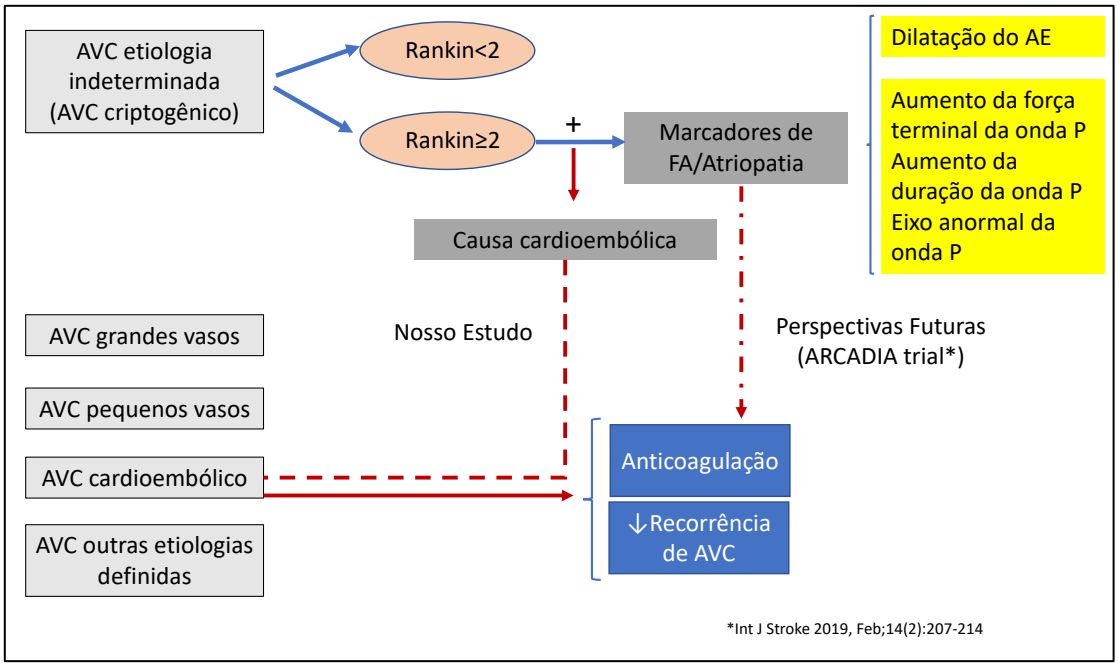


Figura 2: Esquema conceitual da associação entre marcadores eletrocardiográficos e ecocardiográficos de atriopatia e fisiopatologia no AVC isquêmico.

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Full title of the manuscript

Association of electrocardiographic atrial abnormalities, echocardiographic atrial dilatation and prognosis in cryptogenic stroke

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A shortened version of the title to be used as a running title

Increased left atrium and cryptogenic stroke

Abstract

Background and Purpose: It is unknown whether electrocardiogram P-wave abnormalities and echocardiography left atrial dilatation are useful to identify more disabling cryptogenic strokes. We evaluated the association between electrocardiographic P-wave abnormalities and echocardiographic left atrial measures with neurological disability in patients with cryptogenic stroke.

Methods: A retrospective cohort study included 143 hospitalized patients with cryptogenic stroke. Patients were classified according to modified Rankin scale at hospital discharge and in 3 months. Electrocardiographic P-wave abnormalities analyzed were P-wave terminal force, axis and left atrial enlargement. Echocardiogram left atrial measurements analyzed were diameter and volume index.

Results: The study population had a mean age of 63.4 ± 14.2 years and 53% were female. According to the modified Rankin scale, 70 patients were classified as Rankin score < 2 and 73 patients as Rankin score ≥ 2. Among the P-wave electrocardiogram parameters, there was a higher proportion of patients with left atrial enlargement assessed by downward deflection criteria in Rankin ≥ 2 in 3 months (5.1% in Rankin < 2 vs. 17.2% in Rankin ≥ 2, p=0.02). Considering the echocardiogram parameters, the proportion of abnormal left atrial volume index was higher in Rankin ≥ 2 group than Rankin < 2 (25% in Rankin < 2 vs 48% in Rankin ≥ 2, p=0.01). This difference remained significant after adjustment for age and gender (p=0.02) and this trend was also shown when analyzed as a continuous variable. At 3 months following hospital discharge, similar results were found with higher proportion of abnormal left atrial volume index in Rankin ≥ 2 group (22% in Rankin < 2 vs 36% in Rankin ≥ 2, p=0.02).

Conclusion: Our study demonstrated an association between increased left atrial volume index and more disabling cryptogenic stroke, whereas the only electrocardiogram P-wave

abnormality to show this association was left atrial enlargement assessed by downward deflection criteria.

Introduction

Stroke remains as a prevalent cause of death and disability around the world and 70-90% are due to ischemic cerebral infarction.[1] Stroke of undetermined etiology (cryptogenic strokes) accounts for up to 40% of ischemic strokes[2] and occult atrial fibrillation (AF) is a possible pathophysiologic mechanism related to this subtype.[3] As the cardioembolic subtype is associated with the worst prognosis compared to the others, become relevant to recognize possible markers of AF, or signs of atrial cardiopathy, in cryptogenic strokes.[2]

Atrial cardiopathy, characterized by morphologic and physiologic changes in the atria, may increase the risk of paroxysmal AF, thrombus formation and embolization.[4] P-wave abnormalities in electrocardiogram, particularly P-wave terminal force in lead V_1 ($PWTFV_1$), are useful markers that can be used to stratify the risk of incident ischemic stroke.[5] Left atrial dilatation, assessed by left atrial volume index (LAVI), in transthoracic echocardiography, independently predicted AF after stroke in patients without prior AF history.[6]

Modified Rankin scale (mRS) is the primary outcome scale used in most acute stroke trials to identify more disabling stroke.[7] This scale includes the entire range of functional outcomes from no symptoms to death, it has strong correlation with measures of stroke infarct volumes, and its use has demarcated effective and ineffective acute stroke therapies in trials, as even a single-point change on the mRS is clinically relevant.[8]

It is unclear whether electrocardiogram P-wave abnormalities and echocardiography left atrial dilatation are useful to identify more disabling cryptogenic strokes. We test the hypothesis that abnormal P-wave axis, increased P-wave terminal force and left atrial enlargement obtained by electrocardiogram, and increased LA size

by echocardiogram, possibly linked to cardioembolic phenomenon, are associated with worse neurologic functionality in patients with cryptogenic stroke, assessed by mRS.

Methods

Study Population

This retrospective cohort study included all patients aged ≥ 18 years who were hospitalized for ischemic stroke and classified as TOAST of undetermined etiology (cryptogenic stroke), at Hospital de Clínicas de Porto Alegre, a tertiary teaching hospital in Southern Brazil, from January 2012 to April 2015. Only patients with an available digitalized electrocardiogram (ECG) were enrolled. We excluded patients with atrial fibrillation and atrial flutter history. Of the 210 patients with cryptogenic stroke, 143 patients were included in this study (**Figure 1**). This study was conducted in accordance with the standards set out in the Declaration of Helsinki, and its protocol was approved by the institutional Research Ethics Committee. The data that support the results of this study are available from the corresponding author on request.

Patients were classified according the degree of disability at hospital discharge and in 3 months following hospital discharge, using a modified Rankin scale applied by a neurologist. Patients that missed the 3 month's medical appointment were considered to have the same Rankin scale at hospital discharge. Stroke subtype was categorized according to TOAST classification after physical examination, laboratorial tests, electrocardiogram, echocardiogram and neuroimaging. Comparisons were made between patients with a non-disabling stroke (Rankin score < 2) and patients with disabling stroke (Rankin score ≥ 2).[9]

Electrocardiogram and echocardiogram analysis

The ECGs were saved as a pdf file and analyzed by a single investigator (EGP) using EP Calipers software, version 1.17. Heart rhythm, P-wave axis, P-wave's duration and amplitude in DII lead, and P-wave terminal force in V1 lead were measured **(Figure 2)**. Abnormal P-wave axis was considered when ≥ 75º or ≤ 0º[10]. Increased P-wave terminal force was defined as ≥ 4000μV·ms.[11] Left atrial enlargement was defined as a P-wave duration ≥ 120ms in DII lead (length criteria) or a downward deflection of the P-wave in lead V1 ≥ 0,1mV (downward amplitude criteria)[12]. Sinus rhythm was defined as positive in leads I, II and aVF and negative in lead aVR[12]. Intraobserver variability for P-wave terminal force was assessed in 20 select studies. The intraclass correlation coefficient was 0.995 (95% CI, 0.992-0.999) and the coefficient of variation was 4%.

Echocardiogram images were obtained using Aplio 300 (Toshiba Medical Systems, Tokyo, Japan), Philips iE33 (Philips, Bothell, Washington), Vivid 7 (General Electric, Milwaukee, Wisconsin, USA) ultrasound systems, equipped with 4 to 2 MHz sectorial transducers. 2-Dimensional cine loops and static images were recorded according to a specific protocol. Images were read off-line in a dedicated workstation (ComPACS, Medimatic Srl, Italy), by a single observer (EGP). Left atrial diameter was measured on parasternal longitudinal bidimensional image and left atrial volume was measured at the end-ventricular systole from apical 4-chamber and apical 2-chamber views, just before the mitral valve opening, utilizing the Simpson's method.[13] All measurements and definition of cut-offs were performed using an average of 3 consecutive cardiac cycles, according to recommendations from the American Society of Echocardiography.[14] Left atrial volume was indexed by body surface area utilizing Du Bois formula.[15] Abnormal left atrial volume index defined as greater than 34mL/m^2, abnormal left atrial diameter defined as greater than 4cm and abnormal left atrial diameter index defined as greater than 27mm/m^2.[14] Intraobserver variability for LAVI was

assessed in 20 select studies. The intraclass correlation coefficient was 0.98 (95% CI 0.96-0.99) and the coefficient of variation was 7.8%.

Statistical Analysis

All normally distributed data were displayed as mean and standard deviation, and non-normally distributed data were displayed as median and interquartile range. Shapiro-Wilk's test was performed to evaluate the normality of distribution of each variable. Categorical data were shown as a total number and proportion. We compared demographic, clinical characteristics and left atrium (LA) morphology data (at hospital discharge and in 3 months following hospital discharge) between groups using two-sample t-test with unequal variance or Wilcoxon rank-sum and χ^2. Multivariate logistic regression analysis was performed to adjust for demographic characteristics (age and gender). All statistical analyses were performed with IBM SPSS Statistics version 23. P-values < 0.05 were considered statistically significant.

Results

Of the 1077 patients hospitalized for ischemic stroke in this period, 19% (n=210) had cryptogenic stroke and of that, 143 patients had available ECG and were in sinus rhythm. The study population (n=143) had a mean age of 63.4 ± 14.2 years and 53% were female. According to the modified Rankin scale applied at hospital discharge, 70 patients were classified as Rankin score < 2 and 73 patients as Rankin score ≥ 2. Baseline characteristics of this study population are described in Table 1. Overall, patients with a Rankin score ≥ 2 were elderly and mostly women (62%) than Rankin < 2, with similar for most clinical parameter beyond the expected difference in the CHA_2DS_2-VASc score and NIHSS at admission.

Hospital Discharge

Most of the P-wave electrocardiogram abnormalities (left atrial enlargement length criteria, P-wave terminal force and axis) were no different between groups at hospital discharge. Although it was not statistically significant, there was a higher proportion in left atrial enlargement assessed by downward deflection in patients with Rankin > 2 (6% in Rankin < 2 vs. 15% in Rankin ≥2, p=0.07) (**Table 2**). Considering the echocardiogram parameters, left atrial diameter did not differ between groups (3.8 ± 0.5 cm in Rankin < 2 vs 3.9 ± 0.6 cm in Rankin ≥ 2, p=0.61), even when we compared only the proportional of patients with abnormal LA diameter (**Table 2**). This difference remained significant after adjustment for age and gender (p=0.02). And, this trend was also shown when left atrial volume index was analyzed as a continuous variable **(Figure 3)**.

3 Months Follow Up

At 3 months following hospital discharge, 143 individuals were analyzed. There were 8 deaths and 14 individuals who lost follow-up. Considering P-wave electrocardiogram abnormalities, only the proportion of patients with left atrial enlargement assessed by downward deflection criteria was higher in Rankin ≥ 2 group (5.1% in Rankin < 2 vs. 17.2% in Rankin ≥ 2, p=0.02). Similar echocardiographic results were found, with higher proportion of abnormal LA volume index in Rankin ≥ 2 group (22% in Rankin < 2 vs 36% in Rankin ≥ 2, p=0.02) (**Table 3)**, even after adjustment for age and gender (p=0.03).

Discussion

To our knowledge, this is the first study to suggest an association between left atrial dilatation, left atrial enlargement assessed by downward and more disabling cryptogenic stroke. Besides that, we did not find any differences among the other P-wave abnormalities or left atrial diameter between groups with different degree of neurologic disability. These findings suggest that left atrial volume index could be a marker in identifying patients with more disabling cryptogenic stroke.

Previous studies have described the association between several abnormal P-wave parameters, identified by ECG, and ischemic stroke, as markers of atrial cardiopathy.[16] However, in our population with cryptogenic stroke, most P-wave abnormalities analyzed (abnormal P-wave terminal force and axis) were not associated with more disabling cryptogenic stroke. Even that studies have shown that abnormal P-wave terminal force could be used as a predictor of stroke,[5] this parameter was not useful to detect paroxysmal atrial fibrillation after stroke in subjects without atrial fibrillation history[6] and have poor inter-observer reliability.[17] In the context of cryptogenic stroke, there is no consensus data regards the usefulness of $PWTFV_1$. Although an association of increased $PWTFV_1$ with incident cryptogenic or cardioembolic stroke independently of the presence of AF was demonstrated,[18] this association only applied to cardioembolic and non-ESUS cryptogenic stroke in younger patients.[19] Therefore, $PWTFV_1$ could not recognize the complex cardioembolic phenomenon *per se* and other parameters should be used to assess the risk of AF and cardioembolic events in these individuals. Left atrial enlargement assessed by ECG was an independent predictor of one month stroke outcome in an African population[20]. A thorough search of the relevant literature yielded no articles associating left atrial enlargement parameters and cryptogenic stroke. Left atrial enlargement downward deflection in V_1 criteria is more specific than length criteria to

detect left atrial dilatation compared to echocardiogram (93% vs. 88%)[21] and this difference may explain the findings in our study.

Left atrial volume index is a more robust parameter of atrial dimension and superior to left atrial diameter and area in predicting cardiovascular outcomes in subjects with sinus rhythm.[22] An association between LAVI and cardioembolic stroke as well as atrial fibrillation detection in patients with embolic stroke of undetermined source was described in a recent study.[23] Our study showed that patients with abnormal LAVI had more disabling cryptogenic strokes, and a possible explanation to this phenomenon is that LAVI is a marker of atrial cardiopathy and may itself represent an independent risk for cardioembolic strokes and have a higher chance of undetected atrial fibrillation. Even the previous randomized trials did not show any benefit for secondary prevention with anticoagulants after cryptogenic stroke,[24,25] maybe this benefit could be demonstrated in a subgroup with atrial cardiopathy, as shown in a post hoc analysis of one of these trial. However, this hypothesis needs to be tested and one currently underway trial can help us on this discussion.[26]

Limitations

Several limitations should be noted. We used a single-center database of a tertiary hospital which limits the external validation of our study. Moreover, our sample size might not be big enough to show small differences between groups. Finally, the retrospective cohort design indicates an association between LAVI and more disabling cryptogenic stroke and precludes drawing conclusions about causality.

Conclusion

Our study demonstrated an association between increased left atrial volume index, left atrial enlargement downward deflection criteria and more disabling cryptogenic strokes. Prospective larger studies are necessary to confirm if these findings can identify patients who could benefit more of any diagnostic test or specific therapy.

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Conflicts of Interest

None declared.

Figure and Table Legends

Table 1. Population characteristics.

Data expressed as number (%), mean ± standard deviation and median [interquartile range]. T-Student test was performed to compare means and Wilcoxon rank-sum test was performed to compare medians. χ^2 test was performed to compare categorical variables. ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; BMI: body mass index.

Table 2. Comparison of P-wave and atrial echocardiogram parameters between Rankin groups at hospital discharge.

χ^2 test was performed to compare categorical variables. LAE: downward criteria defined as a downward deflection of the p wave in lead V1 greater than 1 mV. LAE: length criteria defined as a duration of the p wave greater than 120ms in lead II. Abnormal P-wave axis defined as $\geq$ 75º or $\leq$ 0º. Abnormal P-wave terminal force defined as greater than 4000μV·ms. Abnormal left atrial volume index defined as greater than 34mL/m^2. Abnormal left atrial diameter defined as greater than 4cm. Abnormal left atrial diameter index defined as greater than 27mm/m^2. LAE: left atrial enlargement.

Table 3. Comparison of P-wave and atrial echocardiogram parameters between Rankin groups at 3 months.

χ^2 test was performed to compare categorical variables. LAE: downward criteria defined as a downward deflection of the p wave in lead V1 greater than 1 mV. LAE: length criteria defined as a duration of the p wave greater than 120ms in lead II. Abnormal P-wave axis defined as $\geq$ 75º or $\leq$ 0º. Abnormal P-wave terminal force defined as greater than 4000μV·ms. Abnormal left atrial volume index defined as greater than 34mL/m^2. Abnormal left atrial diameter defined as greater than 4cm. LAE: left atrial enlargement.

Figure 1. Flowchart of the study.
ECG: Eletrocardiogram.

Figure 2. A: Eletrocardiogram measurement of P-wave terminal force in lead V1.
B: Echocardiogram measurement of atrial volume in apical 4 chambers view.
C: Echocardiogram measurement of atrial volume in apical 2 chambers view.

Figure 3. Rank-sum comparison of left atrial volume index between Rankin groups at hospital discharge.
Data expressed as median [interquartile range].

Table 1.

	All (n=143)	Rankin < 2 (n=70)	Rankin ≥ 2 (n=73)	p-value
Age, years (mean ± SD)	63.4 ± 14.2	60.6 ± 13.8	66 ± 14.2	0.02
Female sex	76 (53%)	31 (44%)	45 (62%)	0.04
BMI, kg/m² (median ± IQR)	28.2 [24.4-30.8]	28.7 [25.9-31.1]	27.1 [23.4-30.8]	0.11
Co-morbidities				
Hypertension	116 (81%)	53 (76%)	63 (86%)	0.11
Diabetes	45 (32%)	21 (30%)	24 (33%)	0.71
Cigarette smoking	53 (37%)	25 (36%)	28 (38%)	0.74
Obesity	13 (9%)	8 (11%)	5 (7%)	0.34
Heart failure	5 (4%)	3 (4%)	2 (3%)	0.61
Ischemic heart disease	16 (11%)	7 (10%)	9 (12%)	0.66
Previous stroke	32 (22%)	14 (20%)	18 (25%)	0.5
Chronic kidney disease	9 (6%)	4 (6%)	5 (7%)	0.78
Cancer	7 (5%)	5 (7%)	2 (3%)	0.22
Prosthetic heart valve	4 (3%)	2 (3%)	2 (3%)	0.97
Thrombolitic therapy	25 (18%)	12 (17%)	13 (18%)	0.92
NIHSS at admission	3 [0-7]	1 [0-4]	6 [2-10]	0.01
CHA_2DS_2-VASc (median ± IQR)	2.9 [2.0-4.0]	2.0 [1.0-4.0]	3.0 [2.0-4.8]	0.004
Left atrium echocardiogram characteristics				
Diameter, cm (mean ± SD)	3.85 ± 0.54	3.83 ± 0.54	3.89 ± 0.54	0.61
Diameter index, cm/m^2 (mean ± SD)	2.2 ± 0.34	2.1± 0.3	2.3 ± 0.4	0.02
Volume, mL (mean ± SD)	57.2 ± 21	55.9 ± 22.1	60.2 ± 18.2	0.34
Volume index, mL/m^2 (mean ± SD)	31.3 ± 10.8	29.9 ± 10.4	34.2 ± 11,1	0.051
Medications in use				
Acetylsalicylic acid	49 (34%)	23 (33%)	26 (36%)	0.73
Clopidogrel	5 (4%)	1 (1%)	4 (6%)	0.19
Warfarin	3 (2%)	1 (1%)	2 (3%)	0.58
Diuretic	45 (32%)	22 (31%)	23 (32%)	0.99
Statin	43 (30%)	19 (27%)	24 (33%)	0.46
Beta-blocker	35 (25%)	12 (17%)	23 (32%)	0.05
ACEI / ARB	85 (59%)	38 (54%)	47 (64%)	0.22
Amiodarone	2 (1%)	1 (1%)	1 (1%)	0.98
Calcium channel blocker	20 (14%)	8 (11%)	12 (16%)	0.39
Digoxin	2 (1%)	1 (1%)	1 (1%)	0.98

Table 2.

Eletrocardiogram parameters	All (n=143)	Rankin < 2 (n=70)	Rankin ≥ 2 (n=73)	p-value
LAE: downward amplitude criteria	15 (11%)	4 (6%)	11 (15%)	0.07
LAE: length criteria	48 (34%)	23 (33%)	25 (34%)	0.86
Abnormal P-wave terminal force	46 (32%)	22 (31%)	24 (33%)	0.85
Abnormal P-wave axis	19 (13%)	8 (11%)	11 (15%)	0.52
Echocardiogram parameters				
Abnormal left atrial volume index	42 (36%)	15 (25%)	27 (48%)	0.01
Abnormal left atrial diameter	68 (48%)	31 (44%)	37 (51%)	0.44

Table 3.

Eletrocardiogram parameters	All (n=143)	Rankin < 2 (n=79)	Rankin ≥ 2 (n=64)	p-value
LAE: downward amplitude criteria	15 (11%)	4 (5.1%)	11 (17.2%)	0.02
LAE: length criteria	48 (34%)	30 (38%)	18 (28.1%)	0.21
Abnormal P-wave terminal force	46 (32%)	23 (29.1%)	23 (35.9%)	0.39
Abnormal P-wave axis	19 (13%)	9 (11.4%)	10 (15.6%)	0.46
Echocardiogram parameters				
Abnormal left atrial volume index	42 (36%)	17 (25.4%)	25 (52.1%)	0.03
Abnormal left atrial diameter	68 (48%)	36 (45.6%)	32 (50%)	0.59

Figure 1.

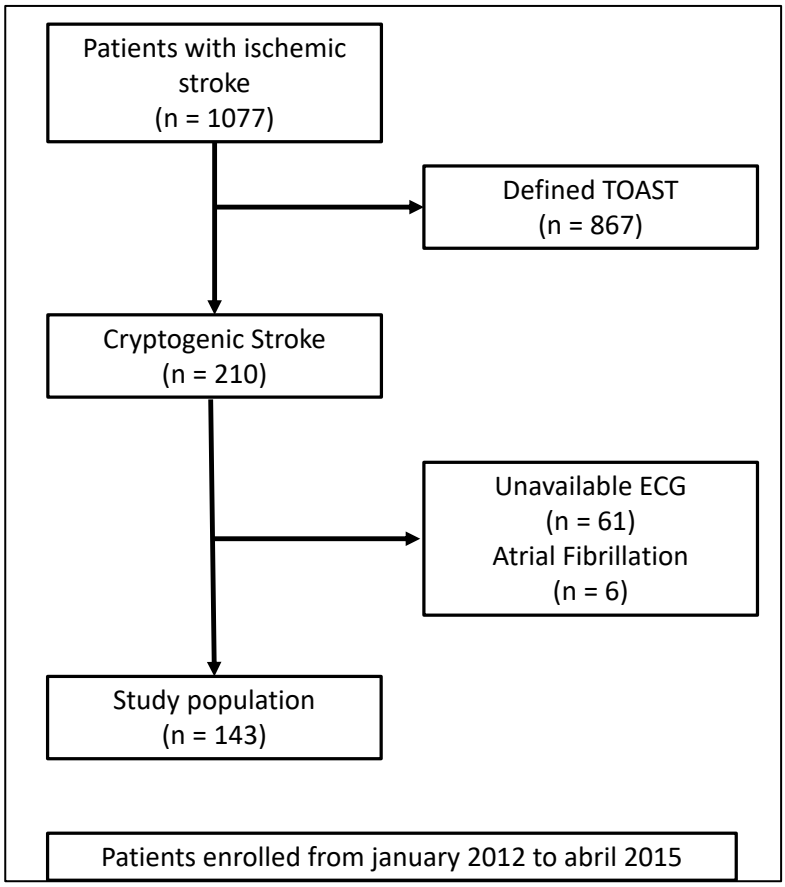

Patients with ischemic stroke
(n = 1077)
Defined TOAST
(n = 867)
Cryptogenic Stroke
(n = 210)
Unavailable ECG
(n = 61)
Atrial Fibrillation
(n = 6)
Study population
(n = 143)
Patients enrolled from january 2012 to abril 2015

Figure 2.

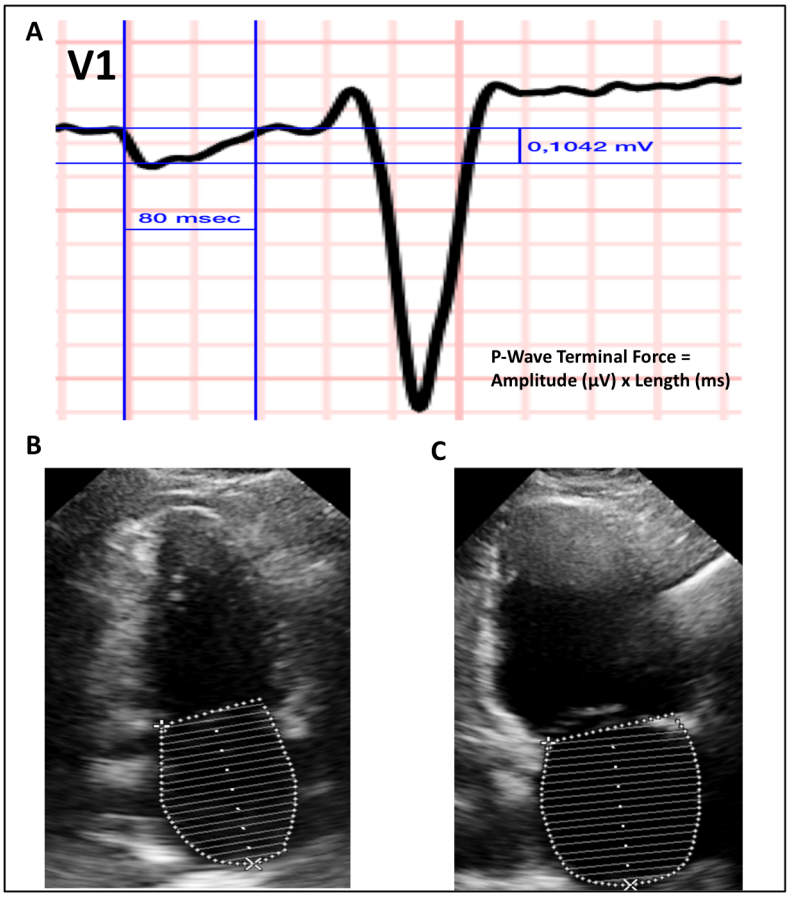
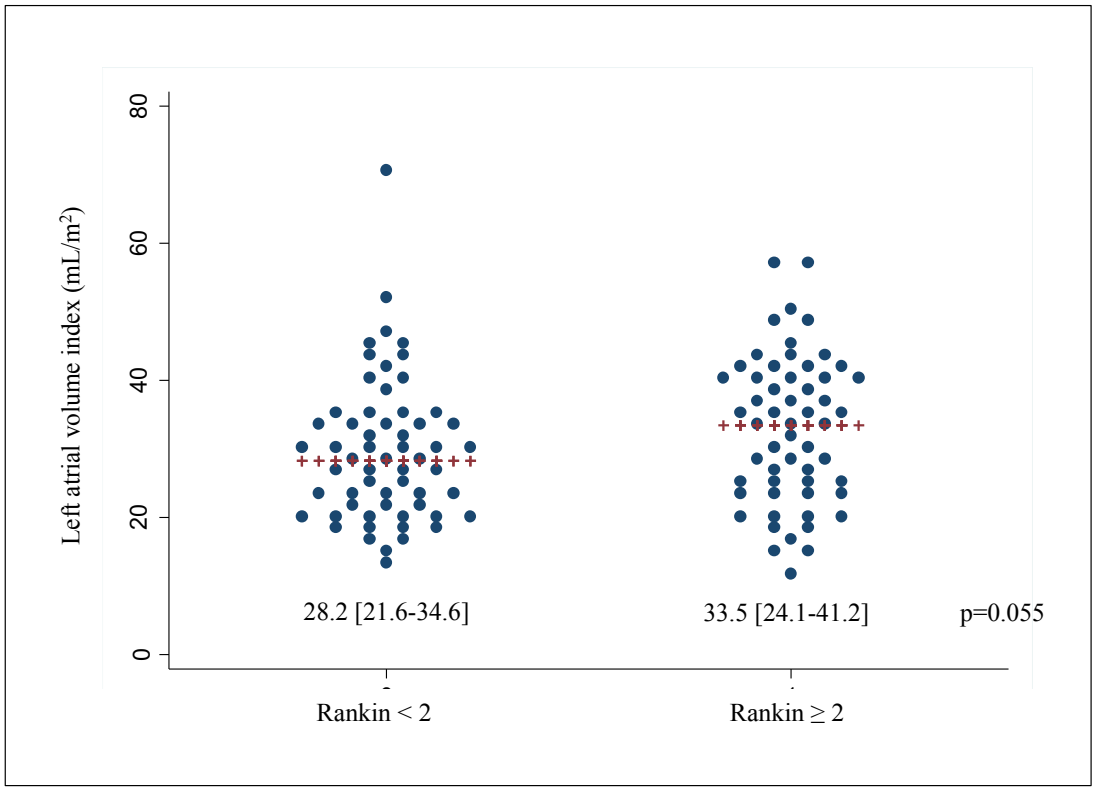

A
V1
0,1042 mV
80 msec
P-Wave Terminal Force =
Amplitude (µV) x Length (ms)
B
C

Figure 3.


Left atrial volume index (mL/m²)
0
20
40
60
80
28.2 [21.6-34.6]
33.5 [24.1-41.2]
p=0.055
Rankin < 2
Rankin ≥ 2

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APÊNDICE

Ficha de Coleta

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2.3. Peso:

2.4 Altura:

2.5 Cor: (1) Branca (2) Preta (3) Parda (4) Indígena

3. Comorbidades

3.1 HAS: (0) Não (1) Sim

3.2 DM: (0) Não (1) Sim

3.3 Cardiopatia isquêmica: (0) Não (1) Sim

3.4 Insuficiência Cardíaca: (0) Não (1) Sim

3.5 AVC prévio: (0) Não (1) Sim

3.6 Prótese valvar: (0) Não (1) Sim

3.7 Dislipidemia: (0) Não (1) Sim

3.8 Tabagismo: (0) Não (1) Tabagista ativo (2) Ex-tabagista

3.9 Etilismo: (0) Não (1) Sim

3.10 DPOC: (0) Não (1) Sim

3.11 DRC: (0) Não (1) Não-dialítico (2) Dialítico

3.12 Neoplasia: (0) Não (1) Sim

3.13 Obesidade: (0) Não (1) Sim

4. Medicações em uso

4.1 AAS: (0) Não (1) Sim

4.2 Varfarina: (0) Não (1) Sim

4.3 NOAC: (0) Não (1) Sim

4.4 Clopidogrel: (0) Não (1) Sim

4.5 Estatina: (0) Não (1) Sim

4.6 Beta-bloqueador: (0) Não (1) Sim

4.7 IECA/BRA: (0) Não (1) Sim

4.8 Amiodarona: (0) Não (1) Sim

4.9 Bloqueador Canal de Cálcio: (0) Não (1) Sim

4.10 Digoxina: (0) Não (1) Sim

4.11 Diurético: (0) Não (1) Sim

4.12 Nitrato: (0) Não (1) Sim

5. Características AVC

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5.2 Data alta:

5.3 Trombólise: : (0) Não (1) Sim

5.4 Rankin alta:

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6.6 Amplitude onda p:

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7.3 AE volume A4C:

7.4 AE volume A2C: