

Original article

Left Atrial Function Is Impaired in Some Patients With Stroke of Undetermined Etiology: Potential Implications for Evaluation and Therapy



Laura Sanchis,^{a,*} Silvia Montserrat,^a Víctor Obach,^b Álvaro Cervera,^b Ángel Chamorro,^b Bàrbara Vidal,^a Aleksandra Mas-Stachurska,^a Bart Bijmens,^c and Marta Sitges^a

^a Departamento de Cardiología, Hospital Clínic, IDIBAPS, Universidad de Barcelona, Spain

^b Departamento de Neurología, Hospital Clínic, Barcelona, Spain

^c ICREA-Universidad Pompeu Fabra, Barcelona, Spain

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ABSTRACT

Introduction and objectives: Stroke etiology remains undetermined in up to 30% of cases. Paroxysmal atrial fibrillation is found in 20% to 28% of patients with stroke initially classified as being of undetermined etiology. The aim of our study was to analyze left atrial function in ischemic stroke patients to identify patterns associated with cardioembolic etiology and to determine whether the patterns identified can be found in individuals initially classified as having a stroke of undetermined etiology.

Methods: We studied a cohort of in-hospital ischemic stroke patients referred for transthoracic echocardiography. Treating neurologists determined stroke etiology based on the TOAST classification. Left atrial contractile function was assessed using 2-dimensional echocardiography to determine their ejection fraction and speckle tracking to measure left atrial strain rate: a-wave. Left atrial function was compared between stroke etiology subgroups and healthy controls.

Results: Ninety-seven patients (aged 67 ± 15 years) with ischemic stroke (16.5% large-artery atherosclerosis, 15.5% small-vessel occlusion, 11.3% cardioembolic, 5.1% other determined etiology, 51.1% undetermined etiology) and 10 healthy volunteers (aged 63 ± 7 years) were included. Left atrial ejection fraction was significantly decreased only in patients with stroke of cardioembolic and undetermined etiology compared with the control group ($31.5 \pm 17.2\%$, $40.2 \pm 17.1\%$, and $59.1 \pm 8.4\%$, respectively; $P = .004$). The left atrial strain rate was significantly lower in patients with stroke caused by cardioembolic or undetermined etiology, or large-artery atherosclerosis compared with controls (-0.86 ± 0.49 , -1.31 ± 0.56 , -1.5 ± 0.47 , -2.37 ± 1.18 , respectively; $P < .001$).

Conclusions: Patients with stroke of undetermined etiology with left atrial function (ejection fraction and strain) similar to that of cardioembolic stroke patients may be misclassified and could potentially benefit from prolonged electrocardiography monitoring. Left atrial function analysis (ejection fraction and strain) might help to identify potential cardioembolic sources in patients with stroke of undetermined etiology.

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La función de la aurícula izquierda está alterada en algunos pacientes con ictus criptogénico: potenciales implicaciones en su evaluación y tratamiento

RESUMEN

Introducción y objetivos: El 30% de los casos de ictus sigue siendo de etiología desconocida (criptogénicos). En un 20-28% de los pacientes con ictus inicialmente clasificados como criptogénicos, se detecta posteriormente fibrilación auricular paroxística. El objetivo de este estudio es analizar la función auricular izquierda de pacientes con ictus isquémico para identificar patrones asociados a la etiología cardioembólica y determinar si se puede observar tales patrones en individuos clasificados inicialmente como ictus criptogénicos.

Métodos: Se incluyó una cohorte de pacientes hospitalizados por ictus isquémico remitidos a ecocardiografía transtorácica. Los neurólogos al cargo determinaron la etiología del ictus según la clasificación TOAST. Se evaluó la función contráctil de la aurícula izquierda utilizando ecocardiografía bidimensional para determinar su fracción de eyección, y mediante técnicas de deformación miocárdica (*speckle tracking* o rastreo de marcas) se determinó la onda a del *strain rate* (tasa de deformación). Se

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Ictus criptogénico

Ictus isquémico

Ictus cardioembólico

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* Corresponding author: Departamento de Cardiología, Hospital Clínic, Villarroel 170, 08036 Barcelona, Spain.
E-mail address: lsanchisruiz@gmail.com (L. Sanchis).

comparó la función de la aurícula izquierda entre los subgrupos etiológicos del ictus así como con un grupo de control de individuos sanos.

Resultados: Se incluyó a 97 pacientes (de 67 ± 15 años) con ictus isquémico (el 16,5% aterotrombóticos, el 15,5% lacunares, el 11,3% cardioembólicos, el 5,1% de otra etiología determinada y el 51,1% criptogénicos) y 10 voluntarios sanos (de 63 ± 7 años). Se observó una disminución significativa de la fracción de eyección de la aurícula izquierda solo en los pacientes con ictus cardioembólico y criptogénico respecto al grupo de control ($31,5 \pm 17,2\%$, $40,2 \pm 17,1\%$ y $59,1 \pm 8,4\%$ respectivamente; $p = 0,004$). El *strain-rate* de la aurícula izquierda fue significativamente inferior en los pacientes con ictus cardioembólicos, criptogénicos o aterotrombóticos en comparación con el grupo control ($-0,86 \pm 0,49$, $-1,31 \pm 0,56$, $-1,5 \pm 0,47$ y $-2,37 \pm 1,18$ respectivamente; $p < 0,001$).

Conclusiones: Los pacientes con ictus criptogénico que presentan una función auricular izquierda (fracción de eyección y *strain*) similar a la de los pacientes con ictus cardioembólico podrían estar clasificados de forma incorrecta, por lo que en ellos sería útil una monitorización electrocardiográfica prolongada. El análisis de la función auricular izquierda (fracción de eyección y *strain*) podría ser útil para identificar a los pacientes con ictus cardioembólico inicialmente mal clasificados como criptogénicos.

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Abbreviations

AF: atrial fibrillation
LA: left atrium
LAEF: left atrial ejection fraction
LASR: left atrial strain rate

INTRODUCTION

Stroke is a major cause of mortality and disability in adults, especially cardioembolic stroke, but the etiology can remain undetermined even after comprehensive study.^{1–3} Other causes of stroke⁴ include large-artery atherosclerosis, small-vessel occlusion, or other determined etiology. When echocardiography shows significant left ventricle dysfunction masses, cardioembolic stroke is relatively easy to diagnose. Nevertheless, most cardioembolic strokes are secondary to atrial fibrillation (AF),⁵ which is a well-established independent risk factor for this etiology.⁶

Approximately 10% of patients with acute ischemic stroke or transient ischemic attack will have newly diagnosed AF during their hospital admission for stroke⁷; an additional 12% of patients may be found to have AF when screened by continuous long-term electrocardiographic monitoring,^{8,9} which has been recently introduced in the recommendations for the management of patients with an acute ischemic stroke or transient ischemic attack without other apparent cause.¹⁰ Given the major burden of AF, it is possible that some cardioembolic strokes could be misclassified as being of undetermined etiology; if a cardioembolic source could be confirmed, this group of patients would benefit from anticoagulation therapy. Previous studies have suggested that unknown AF could be present in 20% to 28% of patients with stroke of undetermined etiology.^{11–15}

It is well known that left atrial (LA) size predicts AF and stroke^{16,17} and is also related to stroke in patients without previous AF.^{18,19} Left atrial function, assessed by volumetric changes (left atrial ejection fraction [LAEF]) or by deformation imaging (LA strain [LAS] and LAS rate [LASR])^{20–23} has also been linked to paroxysmal AF.^{15,24–26} In patients with stroke of undetermined etiology, LAS (s-wave) has been related to paroxysmal AF.²⁷ Additionally, in patients with persistent AF, LAS was a predictor of stroke²⁸ even in patients with a low risk score for stroke.²⁹ More recently, diagnosis of paroxysmal AF with continuous Holter monitoring has been related to LA function changes in patients with stroke of undetermined etiology¹⁵; patients with AF showed a more reduced LA function than those without AF.

The CHA₂DS₂-VASc (congestive heart failure, hypertension, age ≥ 75 [doubled], diabetes, previous stroke [doubled], vascular disease, age 65–74, and sex [female]) score³⁰ includes clinical parameters to establish stroke risk in patients with AF. It is also a strong predictor of ischemic stroke in patients with coronary artery disease without AF.^{31,32}

Considering the potential burden of AF in stroke patients and the large number of patients with stroke of undetermined etiology, we hypothesized that some strokes classified as being of undetermined etiology might have a cardioembolic source, with silent, undiagnosed, underlying AF; in this sense, the evaluation of surrogates of atrial disease such as LA size and function could depict a subgroup of patients at risk of having AF and a potential reclassification to cardioembolic stroke. Therefore, the aim of our study was to characterize LA function in patients admitted to hospital with ischemic stroke in order to identify LA function patterns that could identify potentially misclassified stroke of undetermined etiology that actually has cardioembolic source. Long-term monitoring could be useful in these patients, and the introduction of anticoagulation therapy, as appropriate, could potentially reduce their risk of stroke recurrence.

METHODS

We included a retrospective cohort of in-hospital patients with ischemic stroke referred for transthoracic echocardiography after hospital admission between 2010 and 2013. The final diagnosis, based on the TOAST classification,⁴ was established by the treating neurologist.

Patients

The retrospective cohort included patients admitted to the stroke unit of our center due to ischemic stroke who had undergone transthoracic echocardiography to assess the etiology. For etiological work-up, echocardiography is mainly performed in patients with large-vessel infarction and no significant ($< 50\%$) extracranial or intracranial stenosis. The exclusion criteria were hemorrhagic stroke, severe reduction of left ventricular ejection fraction ($< 35\%$), severe valvular heart disease, the presence of prosthetic heart valves, or active endocarditis. Stroke risk was assessed using the CHA₂DS₂-VASc score.³⁰ Healthy volunteers without previous known cardiovascular disease were recruited and age-matched with patients in order to have reference values of normal LA function. All participants signed an informed written consent form and the study was approved by our ethics committee.

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