Prevalence of Patent Foramen Ovale in Young Patients With Cryptogenic Stroke

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Introduction and objective. Patent foramen ovale has been associated with stroke in young patients with «cryptogenic» stroke. The purpose of this study is to examine the prevalence of patent foramen ovale in this group of patients, as well as their anatomical and functional characteristics by contrast echocardiography, trying to determine ictus risk markers in young patients with acute ischemic stroke.

Patients and method. Prospective study of 90 patients under the age of 50 who were hospitalised consecutively due to a clinical presentation suggestive of stroke. No cause was found in 55 out of 90 (group I) and the rest, in which an stroke was finally disregarded, were used as the control group (group II). A transthoracic and transesophageal echocardiography examination with 2 types of contrast agents was performed in all patients to determine the presence of a patent foramen ovale and its anatomical and functional characteristics.

Results. Patent foramen ovale was observed more frequently in group I than in group II (43 versus 21%; $p < 0.05$). Among patients with a patent foramen ovale those with an ischemic stroke showed greater mobility of the oval membrane, more frequent «large» shunts of contrast in a single frame in the left heart, and more frequent shunts at rest. Transesophageal echocardiography without contrast showed a high sensitivity (90%) and specificity (93%) for detecting «anatomically permeable foramen ovale» whereas contrast transthoracic echocardiography showed a low sensitivity (13%). There were no differences between the two contrasts used.

Conclusions. Near half of young patients with ischemic stroke of an unknown origin have a patent foramen ovale. A bigger mobility of the membrane of the oval cavity and a «large» degree of shunt contrast as well as shunt at rest detected by contrast transesophageal echocardiography, seem to identify patent foramen ovale patients with ischemic stroke. In these patients, transthoracic echocardiography has low sensibility for detecting permeability of the foramen ovale.

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Prevalencia de foramen oval permeable en pacientes jóvenes con accidente isquémico cerebral de causa desconocida

Introducción y objetivos. El foramen oval permeable se ha asociado a infartos cerebrales en pacientes jóvenes con ictus criptogénico. El objetivo de este estudio es determinar la prevalencia en este grupo de pacientes de foramen oval permeable, así como las características anatómicas y funcionales del mismo, mediante ecocardiografía con contraste, tratando de determinar los marcadores de riesgo de ictus en pacientes jóvenes con un foramen oval permeable.

Pacientes y método. Estudio prospectivo en 90 pacientes menores de 50 años que ingresaron de forma consecutiva por sospecha clínica de accidente cerebrovascular. En 55 pacientes no se encontró ninguna causa (grupo I) y los restantes, en los que se descartó finalmente un ictus, fueron utilizados como grupo control (grupo II). A todos se les realizó un estudio ecocardiográfico transtorácico y transesofágico con 2 tipos de contrastes, para determinar la presencia de foramen oval y las características anatómicas y funcionales del mismo, comparando ambos grupos.

Resultados. En el grupo de estudio existió un mayor número de foramen oval permeable que en el grupo control (43 frente a 21%; $p < 0,05$). Comparando a los pacientes con foramen permeable de ambos grupos existieron diferencias significativas en la mayor movilidad de la membrana de la fosa oval, en el mayor número de pacientes con paso amplio de contraste, así como con paso del mismo en situación de respiración basal, en el grupo de pacientes que habían tenido ictus. La ecografía transesofágica sin contraste demostró una alta sensibilidad (90%) y especificidad (93%) para detectar «foramen permeable anatómico», mientras que la ecografía transtorácica con contraste demostró una baja sensibilidad para detectarlo (13%). No hubo diferencias entre los 2 contrastes utilizados.

Conclusiones. En casi la mitad de los pacientes jóvenes con ictus de origen desconocido se encuentra un foramen oval permeable. Una mayor movilidad de la membrana de la fosa oval y un paso amplio de contraste y en situación de

ABBREVIATIONS

PFO: patent foramen ovale.
TEE: transesophageal echocardiography.
TTE: transthoracic echocardiography.

respiración en reposo han resultado marcadores predictores de isquemia cerebral en estos pacientes. La ecografía transtorácica tiene una baja sensibilidad para detectar permeabilidad del foramen, y no existieron diferencias entre los dos contrastes utilizados.

Palabras clave: *Foramen oval permeable. Isquemia cerebral. Ecocardiografía.*

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INTRODUCTION

Stroke is the third most common cause of death in developed countries,[1] behind ischemic heart disease and cancer. Disability often results from stroke, further adding to its importance. According to a study carried out in Spain,[2] the prevalence of stroke attacks is 264/100 000 people-years and the death rate is 88/100 000 people-years.

There are different possible causes of stroke, but approximately 20% are of cardioembolic origin.[3-5] If the cause of the ischemic event is not discovered, it is classed as cryptogenic. Stroke of unknown cause are particularly common in young adults, accounting for 10%-40% depending on the population.[6,7]

For some time, it has been debated whether paradoxical embolism through a patent foramen ovale (PFO) might explain many of these cases. Over the last decade, a high prevalence of PFO has been reported in patients with cryptogenic stroke compared to control groups.[7-9]

Transthoracic echocardiography (TTE) is the simplest and most sensitive technique for diagnosing structural heart diseases, many of which may be related to the production of stroke. Different authors have used this technique to show the increased prevalence of PFO in patients with cryptogenic stroke compared to the general population.[7,8] Transthoracic echocardiography does, however, have important limitations for visualizing the atrial septum, while transesophageal echocardiography (TEE) has proven to be very sensitive for detecting atrial septal defects.[10,11] The use of different contrasts has increased the sensitivity of echographic techniques for diagnosing shunts through the foramen oval.[12] Thus, contrast TEE appears to be the standard technique for diagnosis of PFO.[11,13]

Even so, cryptogenic stroke caused by paradoxical embolism remains a matter of debate. The physiopathological mechanisms, the factors causing stroke in patients with PFO, the risk markers for recurrence and the optimum treatment in these patients have yet to be satisfactorily determined. To help resolve these questions, we have started a prospective study in young patients with stroke of unknown origin.

OBJECTIVES

The objectives of this study are:

1. To study a consecutive population of young adult patients with cryptogenic stroke using TEE to determine the proportion with PFO.

2. To determine the sensitivity of TTE for diagnosing PFO.

3. To establish the utility of different echographic contrasts in the diagnosis of the patency of the foramen ovale, and to define which is most suitable.

4. To try to establish the risk markers for stroke in young patients with PFO compared to a control group.

PROTOCOL: PATIENTS AND METHODS

Between October 1999 and January 2002, all patients aged 50 years or less admitted to the Neurology Service with clinical suspicion of stroke with no apparent cause were included in this study. Stroke was defined as a focal neurological deficit with sudden onset that lasted for more than 24 hours in surviving patients, and transient ischemic attack was defined as a focal neurological deficit that completely resolved in the first 24 hours.[14]

Neurological examination

The Neurology Service performed a clinical history and full physical examination, chest x-ray, electrocardiogram and general blood analysis on all patients, and additionally a special hematological study to screen for thromboembolic disease. Cardiovascular risk factors were studied (high blood pressure, diabetes mellitus, obesity, hypercholesterolemia, hypertriglyceridemia and smoking) and the use of oral contraceptives was investigated. All patients were also submitted to carotid Doppler ultrasonography, computerized axial tomography and/or nuclear magnetic resonance imaging, as well as an arteriography and/or computerized cerebral tomographic angiography.

Patients with stroke were classified into different pathogenic groups in accordance with the modified criteria of Amarenco et al:[15] *a)* patients with stroke of definite or possible arterial or cardioembolic origin; *b)*

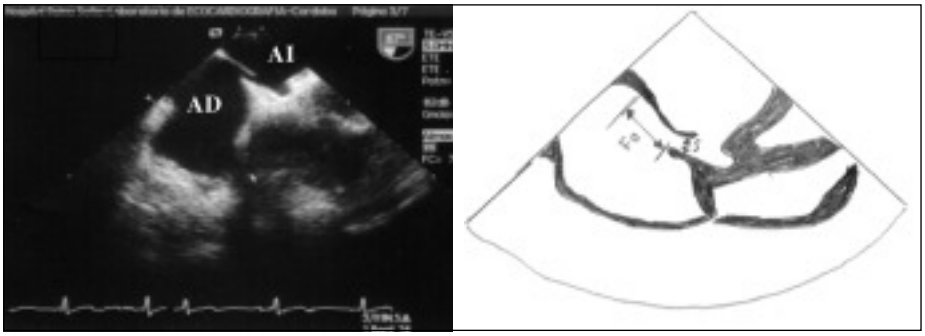

Fig. 1. Transesophageal image at 65º in the fossa ovalis. Left: opening between the septum primum and septum secundum. Right: schematic of the same image in which the measurement of the maximum opening between the septum primum and septum secundum is shown. RA indicates right atrium; LA, left atrium; FO, fossa ovalis; S, separation between the septum primum and the septum secundum.

patients with small vessel disease, and *c)* patients who do not belong to either of the previous two groups (stroke of unknown or undetermined origin).

Two groups were defined for the study: group I (study group) corresponding to group C according to the classification of Amarenco (patients with stroke of unknown or undetermined origin) and group II (control group), which included those patients for whom diagnosis of cerebral stroke was discarded (migraine, demyelinating disease, absence of pathology, etc.).

Heart examination

The patients underwent a heart examination at the same time, which included transthoracic and transesophageal Doppler echocardiography. The echocardiograms were recorded with an Acuson® Sequoia scanner equipped with a 2.5-5 MHz multi-frequency transthoracic harmonic probe or a 3.5-7 MHz muliplane, mulifrequency transesophageal probe.

Possible diseases that might cause stroke were investigated for each patient. Having ruled out other possible causes, we concentrated on the atrial septum, visualizing the patency of the foramen ovale, the separation between the septum primum and septum secundum (measuring the maximum opening between the two septa at rest in the vertical plane) and the mobility of the fossa ovalis at rest (maximum right and left excursion of the septum primum from a line perpendicular to the fossa ovalis plane) (Figure 1). We considered atrial septal aneurysm to be present if the total excursion of the atrial septum within the left and/or right atrium was 11 mm or larger[16] (Figure 2).

To study the patency of the foramen ovale, echographic contrast was injected into the femoral vein. This procedure has been shown to enhance the diagnostic potential of the echographic technique.[17] Two types of contrast were used for both TTE and TEE: agitated polygeline (Hemoce®) and D-galactose stabilized with palmitic acid (Levograf®, Levovist®). Hemoce® is a high osmolality volume expander. Pressure oscillations associated with sonication produce large bubbles that cannot cross the pulmonary barrier. Therefore the appearance of bubbles in the left heart chambers

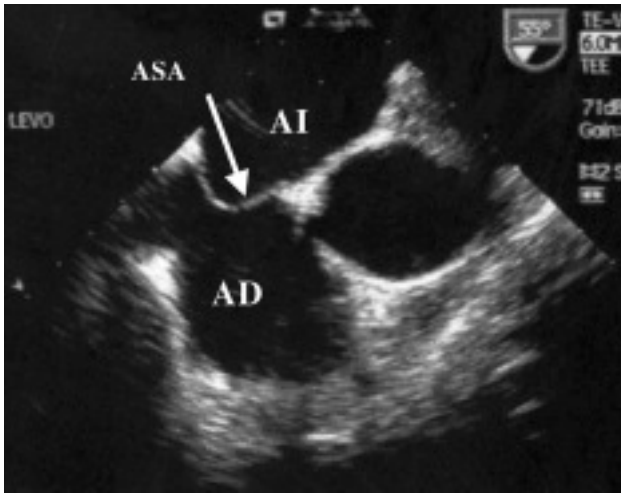

Fig. 2. Image of atrial septal aneurysm (arrow), in a patient with patent foramen ovale. RA indicates right atrium; LA, left atrium.

indicates right-to-left shunt at some point. Levograf® (D-galactose stabilized with palmitic acid), one of the latest generations of echo contrasts, is a suspension that can cross the pulmonary barrier so assessment must be performed within three seconds of its arrival in the right atrium.

Each patient received two consecutive injections of Hemoce®, the first at rest, the second with Valsalva maneuver, and a further two injections with Levograf® in the same conditions. All examinations were recorded with continuous video for later analysis.

The criterion for diagnosis of patent foramen ovale was passage of microbubbles (three or more) to the left atrium immediately after arrival in the right atrium. The number of microbubbles passing from left to right was counted visually by an experienced echocardiographer. The passage was classed as small when less then 20 microbubbles appeared in the left side of the heart and large when more than 20 microbubbles were counted during a cycle (Figure 3).

Transthoracic echocardiography was also employed in 85% of patients to compare the two techniques. Thus,

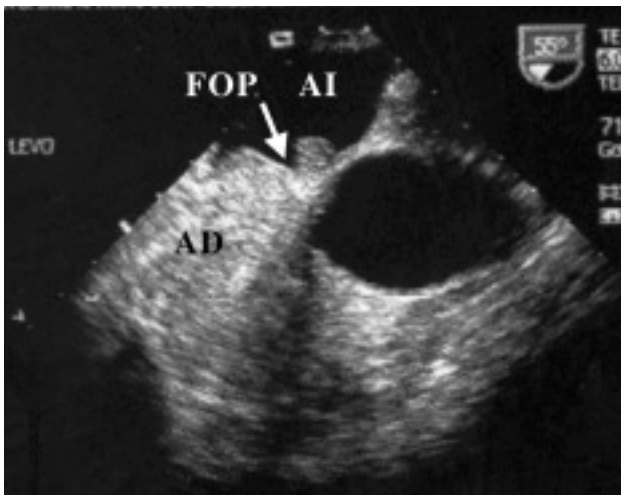

Fig. 3. Transesophageal image showing extensive passage of contrast (agitated Hemoce®) through patent foramen ovale from the right atrium to the left atrium. RA, right atrium; LA, left atrium.

TEE was used as the «gold standard».

Statistical analysis

Quantitative data are presented as mean±1standard deviation. Qualitative parameters are expressed as a percentage. Subgroups were compared using the χ^2 test for qualitative variables and the Student *t* test for quantitative ones. The level for statistical significance was set at $P<.05$. The diagnostic techniques were compared using the kappa test (percentage agreement above that expected by chance) taking a value above 80% as a very good agreement and one less than or equal to 40% as a bad agreement. We used the SPSS software to create the database and for statistical analysis of the data.

RESULTS

Between October 1999 and January 2002, 90 young patients were admitted to our hospital with clinical reasons for suspecting stroke of unknown origin. Diagnosis of stroke with no apparent cause was confirmed in 55 of these patients, and they were included in the study group or group I. Diagnosis of ischemic cerebral accident was discarded in the remaining 35 patients, who were assigned to the control group or group II.

The mean age of the study group was 40.1±10 years, compared to 37.7±11.3 years for the control group. Group I comprised 51% men compared to 37% in group II. The mean number of cardiovascular risk factors in group I was 1.2±1 in group I and 1.1±0.9 in group II. All patients in both groups had normal heart rhythm and no patient in either group presented organic heart disorder. The degree of aortic atheromatosis according to TEE was similar with all patients in group I and 93% of patients in group II presenting grade I (normal or minimal intimal thickening) according to the modified classification of Ribakov.[18] This low severity of atheromatosis is thought not to induce stroke.[19] No patient in either group showed clinical signs of deep vein thrombosis. The demographic and clinical data from the patients in each group is presented in Table 1. No significant differences were observed between the two groups for any variable.

All patients had normal TTE. No patent foramen ovale was visualized in patients of either group, but the passage of contrast was observed in four patients in the study group (11.4%). This difference was not statistically significant.

The TEE findings for both groups are presented in Table 2. A patent foramen ovale was visualized in 23 out of 55 (41.8%) patients in group I and in six out of 35 (18%) patients in group II. The difference was statistically significant ($P<.05$). The diameter of the patent foramen ovale was 1.36±1.5 mm for group I and 0.86±1.03 mm for group II, though the difference was not significant. The mobility of the fossa ovalis was, however, significantly greater for the study group (4.7±3.8 mm) than for the control group (2.83±1.6 mm) with $P<.05$. Three patients (5.6%) had atrial septal aneurysm in association with PFO in the study group,

TABLE 1. **Demographic and clinical data in both groups**

	Group Y	Group II	*P*
Patients, n	55	35	NS
Age, years	40±10	37±11	NS
Sex male, %	28 (51%)	13 (37%)	NS
No. risk factors	1.2±1.1	1.1±0.95	NS
ECG (SR)	100%	100%	NS
Pathologic TTE	0	0	NS
Aortic atheromatosis (grade Y)	100%	93%	NS

SR indicates sinus rhythm; TTE, transthoracic echocardiogram; NS, not significant.

TABLE 2. **Transesophageal echocardiographic findings in both groups**

	Group Y	Group II	*P*
Visualized PFO, %	42% (23)	18% (6)	<.05
Septal separation, mm	1.36±1.5	0.86±1.03	NS
Septal mobility, mm	4.7±3.8	2.8±1.6	<.05
ASA, no. of cases	3	0	NS
Contrast passage, %	43% (23)	21% (7)	<.05
«Extensive» contrast passage	83% (20)	28% (2)	<.01
PFO at rest, %	91.3%	57.1%	<.05

PFO indicates patent foramen ovale; ASA, atrial septal aneurysm; NS, not significant.

while no such aneurysm was observed in the control group (difference not significant) (Figure 3).

The echo contrast studies of patency of the foramen ovale showed right-to-left passage in 23 out of 55 patients (43%) in group I, minimal in three patients (5.6%) and extensive in 20 (37%). On the contrary, passage was observed in seven out of 35 patients (21%) in the control group, minimal in five patients (15%) and extensive in two patients (6%). The difference between groups of the number of patients with passage of contrast was statistically significant ($P<.05$), but when the size of passage of contrast was analyzed in patients with PFO, the differences between groups was even greater, with extensive passage of contrast in 20 out of 23 patients for group I (87%) and two out of seven patients for group II (28%) ($P<.01$).

In 91.3% of patients in group I, the passage of contrast occurred spontaneously at rest compared to 57.1% in group II, the difference being statistically significant ($P<.05$).

Patent foramen ovale was detected with contrast in 30 patients in both groups. The patency was visualized with TEE in 27 of these patients. In two patients, visualization of a PFO was not confirmed by passage of contrast, giving a sensitivity of 90% and a specificity of 93% for diagnosis of PFO using TEE (Table 3).

Strong agreement was observed on comparison of the two contrasts used for studying the patency of the foramen ovale, with a kappa value of 0.91. There were only two discrepancies; passage was observed in one patient with Hemoce® but not with D-galactose, while the other discrepancy was only quantitative, the passage appearing more extensive with Hemoce® and smaller with D-galactose

An analysis of the comparison between the two echographic techniques used to study PFO (TTE vs TEE) shows the lack of sensitivity of TTE for visualizing the foramen ovale. The ability of the two techniques to visualize passage of contrast through the patent foramen ovale showed low agreement between the two (kappa=0.18). Transthoracic echocardiography was only able to detect passage of contrast in four of the 30 patients in whom passage of contrast was seen using TTE. Conversely, no passage was seen with TTE that was not seen with TEE. The sensitivity of TTE for detecting PFO is therefore 13.3% and the specificity is 100% (Table 4).

TABLE 3. **Benefit of transesophageal echocardiogram in the diagnosis of patent foramen ovale versus contrast**

	PFO contrast	
Visualized PFO	**Yes**	**No**
Yes	27	2
No	3	60

PFO indicates patent foramen ovale; Se, sensitivity; Sp, specificity.

TABLE 4. **Benefit of transthoracic versus transesophageal echocardiography in the diagnosis of patent foramen ovale**

	PFO TEE	
PFO TTE	**Yes**	**No**
Yes	4	0
No	26	60

PFO indicates patent foramen ovale; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography; Se, sensitivity; Sp, specificity.

DISCUSSION

A causal relationship between PFO and cerebral embolism has not been clearly established,[4] but there is sufficient evidence to suggest that the mechanism in most cryptogenic stroke could be paradoxical embolism through a patent foramen ovale, particularly in young patients.[20-22] Venous thrombosis in lower limbs or elevated chamber pressure is not seen in most patients.[23] Thus many studies have concentrated on anatomical and functional findings to try to define the conditioning or risk factors for cerebral ischemia in patients with PFO associated with paradoxical embolism.[24-27]

The incidence in young patients of PFO detected by TEE is high in our population (43%) and similar to other populations though the exact figures depend on the groups selected.[7-9] The incidence of PFO is significantly greater in the study group compared to the control group. More importantly, for patients with PFO, there were other significant differences between the two groups. First, the mobility of the fossa ovalis was greater in patients who had suffered stroke, making it a risk marker in patients with patent foramen ovale. An explanation for this could be that preferential flow from the inferior vena cava towards the foramen ovale is favored.[28] Second, the number of patients with PFO with extensive passage of contrast was greater in the study group, thus constituting another risk marker for stroke in patients with PFO in agreement with other authors.[24-27] A single plane two-dimensional image could distort quantification of the contrast passing through the foramen ovale, but we used a multiplane TEE probe, counting the maximum number of microbubbles that passed to the left atrium in each case. No complication was attributed to puncture of the femoral vein, and we achieved a 100% success rate.

No patient showed physical signs of deep vein thrombosis in the study group, in agreement with other populations,[27] though we did not perform either venous Doppler or phlebographic examinations of lower limbs,

so we do not know the true incidence of this condition.

In our study the spontaneous passage of contrast through the PFO was clearly higher in the group of patients with stroke than in the control group. Likewise, some authors find that spontaneous passage or passage at rest through PFO is a risk marker of cerebral ischemia in patients.[22]

Three of the patients with stroke and PFO in our population also presented atrial septal aneurysm. This association has also been reported in other populations.[29-31] On the contrary, no such association was observed in the control group, though the difference is not significant given the low number of cases. Some studies suggest the association of PFO and atrial septal aneurysm would be a strong risk marker, both after the first episode of stroke and after recurrence of stroke.[30,31]

The first studies of PFO were performed with TTE,[7,8] but this technique has been superceded by TEE. Despite using state-of-the-art technology such as second harmonic imaging along with contrasts such as D-galactose, TTE had a low sensitivity for detecting passage of contrast through the foramen ovale in our population.

On the contrary, TEE without contrast was highly sensitive and specific for visualizing PFO. The foramen ovale was visualized as «open» in 90% of patients with passage of contrast through the foramen ovale. Other diagnostic techniques such as nuclear magnetic resonance are very sensitive for studying cardioembolic disease. However, this technique may give false positive results because the septum at the location of the fossa ovalis is very thin.[32] We therefore consider TEE better for diagnosis of this defect.

Most TEE studies of PFO use agitated saline solution,[6,24] and this combination is considered the technique of choice for diagnosis of this disease in living patients. However, the appearance of new echographic contrasts with microbubbles could provide more sensitive detection of patent foramen ovale. The performance of the two contrasts used in our study was similar, but the cost/benefit ratio for D-galactose would be worse given that it is more expensive.

Our work has defined the markers of risk of ischemic cerebral event in young patients with patent foramen ovale. We note, though, that further research is still required because our study has not investigated whether the recurrence of new ischemic episodes is subject to the same prognostic factors. If true, this would determine which patients require preventative treatment. The optimum treatment for such patients is also contentious, with several alternatives currently available and no study to indicate which would be the most appropriate.

CONCLUSIONS

A little less than half of the young patients with stroke of unknown origin have PFO diagnosed by contrast transesophageal echocardiography. Moreover, the high incidence in this group of patients is significantly higher than in a similar group of patients with no cerebral ischemic episode.

Patients with and without stroke who have patent foramen ovale have significantly different mobility of the fossa ovalis. This mobility is greater in patients with stroke. The passage of contrast is extensive in most patients with stroke and PFO. These two parameters are markers of risk of cerebral ischemia in young patients with PFO. Another risk marker of stroke in this group of patients is the passage of contrast at rest without resorting to the Valsalva maneuver.

Transthoracic echocardiography is a technique of limited use in the diagnosis of PFO because, even with state-of-the-art imaging and contrast techniques, its sensitivity is much lower than that of TEE.

Visualization of the foramen ovale with TEE is highly sensitive and specific for detecting PFO.

No significant differences were seen on comparison of the two contrasts used, thus contrasts of the latest generation (D-galactose) increase the costs of the study without improving the benefits.

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