Prevalence of Patent Foramen Ovale Determined by Transesophageal Echocardiography in Patients With Cryptogenic Stroke Aged 55 Years or Older: Same as Younger Patients?

Dolores Mesa,a Martín Ruiz,a Mónica Delgado,a José Suárez de Lezo,a Manuel Pan,a Ignacio Tejero,a Daniel García,a Manuel Crespín,a Carmen León,a Francisco Toledano,a Francisco Mazuelos,a Juan J. Ochoa,b and Enrique Bescansa

aServicio de Cardiología, Hospital Universitario Reina Sofía, Córdoba, Spain
bServicio de Neurología, Hospital Universitario Reina Sofía, Córdoba, Spain

Introduction and objectives. To investigate the relationship between patent foramen ovale and cryptogenic stroke in patients aged ≥55 years.

Methods. This prospective study determined the presence of patent foramen ovale and atrial septal aneurysm using transesophageal echocardiography in 262 consecutive patients with a diagnosis of probable cryptogenic stroke. Data from 44 patients aged ≥55 years with cryptogenic stroke (Group A) were compared with those from 2 other groups: 194 patients aged <55 years with cryptogenic stroke (Group B) and 24 control patients aged ≥55 years with stroke of known origin, namely grade III–V aortic atheromatosis (Group C).

Results. The frequency of patent foramen ovale in Group A was similar to that in Group B (38% vs 36%; P = .85) but significantly higher than that in Group C (38% vs 8%; P = .029). The frequency of patent foramen ovale with concomitant atrial septal aneurysm was significantly higher in the study group (Group A) than in the control Group C (18% vs 0; P = .039) and non-significantly higher than in Group B (18% vs 11%; P = .11).

Conclusions. The frequency of patent foramen ovale alone or in association with atrial septal aneurysm in patients with cryptogenic stroke aged ≥55 years was similar to that in those aged <55 years, but higher than that in patients aged ≥55 years with stroke of atherosclerotic origin. These data suggest that paradoxical embolism could be a cause of stroke in both age groups.

Key words: Cryptogenic stroke. Transesophageal echocardiography. Patent foramen ovale. Aortic atheromatosis.

Prevalencia de foramen oval permeable diagnosticado mediante ecocardiografía transesofágica en pacientes de edad igual o mayor que 55 años con ictus criptogénico. ¿Es diferente en pacientes jóvenes?

Introducción y objetivos. El propósito de este estudio es analizar la relación entre foramen oval permeable e ictus criptogénico en pacientes de edad ≥55 años.

Métodos. Se estudió de forma prospectiva la presencia de foramen oval permeable y aneurisma del septo interauricular en 262 pacientes consecutivos con diagnóstico de probable ictus criptogénico mediante ecocardiografía transesofágica. Comparamos los datos de 44 pacientes de edad ≥ 55 años con ictus criptogénico (grupo A de estudio) con otros 2 grupos: 194 menores de 55 años con ictus criptogénico (grupo B) y 24 de un grupo control de 55 años o más con ictus de origen conocido (ateromatosis aórtica de grado II-III) (grupo C).

Resultados. La frecuencia de foramen oval permeable fue similar en el grupo A y B (el 38 frente al 36%; p = 0,85) y significativamente mayor que en el grupo C (el 38 frente al 8%; p = 0,029). La frecuencia de foramen oval permeable más aneurisma del septo interauricular concomitante fue más alta en el grupo de estudio (A) que en el grupo control (C) (el 18% frente a 0; p = 0,039) y más alta, pero sin significación, que en el grupo B (el 18 frente al 11%; p = 0,11).

Conclusiones. La frecuencia de foramen oval permeable fue similar en el grupo A y B (el 38 frente al 36%; p = 0,85) y significativamente mayor que en el grupo C (el 38 frente al 8%; p = 0,029). La frecuencia de foramen oval permeable más aneurisma del septo interauricular concomitante fue más alta en el grupo de estudio (A) que en el grupo control (C) (el 18% frente a 0; p = 0,039) y más alta, pero sin significación, que en el grupo B (el 18 frente al 11%; p = 0,11).

ABBREVIATIONS
ASA: atrial septal aneurysm
PFO: patent foramen ovale
TEE: transesophageal echocardiography
TTE: transthoracic echocardiography

INTRODUCTION

Numerous studies in young patients have shown a relationship between cryptogenic stroke and isolated patent foramen ovale (PFO) or PFO with concomitant atrial septal aneurysm (ASA). However, until recently, only few studies have addressed this association in older patients and the results were contradictory. Two recent studies have shown an association between atrial septal defects and cryptogenic stroke in older patients. In one of these studies, some of the patients may not have had cryptogenic stroke, since transesophageal echocardiography (TEE) was not used systematically to rule out other causes of stroke, such as atherosclerotic disease of the aortic arch. In the other study, isolated PFO was no more frequent in the group of older patients with cryptogenic stroke than in those with stroke of known cause, whereas PFO with concomitant ASA was more common in the group with cryptogenic stroke.

In this study, we used TEE to assess the prevalence of PFO in patients with cryptogenic stroke and compared the results obtained in patients aged at least 55 years with those in patients younger than 55 years.

METHODS

A prospective study was performed of all patients admitted to the neurology department with a presumptive diagnosis of cryptogenic stroke between January 2000 and May 2008. Patients were older than 14 years with no identifiable cause of stroke following a complete examination. Stroke was defined as cerebrovascular accident (rapid-onset focal neurologic deficit that persists fully or partially for more than 24 hours in surviving patients) or transient ischemic attack (rapid-onset focal neurologic deficit that is fully resolved in the first 24 hours). Stroke etiology was classified according to the criteria recommended by the Working Group on Cerebrovascular Disease of the Spanish Society of Neurology, which are similar to the TOAST classification and include 5 etiologic types based on clinical findings and the results of diagnostic tests. One of the types is stroke of unknown or undetermined cause.

The study protocol included the following elements:

- Systematic general examination. In all patients a detailed clinical history was taken along with a complete assessment of etiology comprising chest x-ray, electrocardiogram, Holter monitoring in the case of suspected supraventricular arrhythmia, cerebral imaging (computed tomography or magnetic resonance imaging), examination of the supra-aortic branches and cerebral arteries (Doppler study of the supra-aortic branches and/or computed tomography angiography and/or cerebral magnetic resonance angiography), and blood workup to rule out hypercoagulability.

- Cardiology examination. This included transthoracic echocardiography (TTE), which was performed whenever there was suspicion of cardioembolic stroke or in the absence of other causes identified in the prior etiologic study. When the result was normal or inconclusive, TEE was requested with assessment of PFO and aortic atheromatosis. Echocardiography was performed with an Acuson Sequoia ultrasound system with a multifrequency second harmonic transthoracic probe (2.5-5 MHz) and a multiplane, multifrequency transesophageal probe (3.5-7 MHz).

TEE was used in all cases to assess the etiology of stroke with special attention to the anatomy of the atrial septum, assessment of PFO, examination of the aorta and possible aortic atheroma, small tumors or excrescences on valves and septa, spontaneous echo contrast, and thrombi in the atrium or left atrial appendage.

The anatomy of the atrial septum was assessed and ASA was diagnosed when the total excursion of the septum into the left atrium, right atrium, or the sum of the excursion into both atria was at least 11 mm. For assessment of PFO the brachial vein was injected with 4% gelafundin in sterile saline. In all cases, injections were performed at rest and following Valsalva maneuver. PFO was diagnosed when 3 or more microbubbles were seen to pass to the left atrium within the first 3 beats of their arrival at the right atrium, both at rest and following Valsalva maneuver. An echocardiography specialist quantified the number of microbubbles passing from right to left atria; PFO was diagnosed as mild when the number of microbubbles in a cycle was <20 and extensive when 20 or more microbubbles were observed in a cycle (Figure 1). The size of the
The occurrence of PFO and atrial septal aneurysm was studied in the 3 groups and data from Group A (study group) were compared with those from Group B and Group C (control).

Statistical Analysis

The statistical analysis was carried out using the SPSS statistical package, version 12 for Windows. Continuous variables were expressed as means (SD). Categorical variables were expressed as percentages. The Kolmogorov-Smirnov test was used to assess whether variables obeyed a normal distribution. Quantitative variables were compared by t test for normally distributed variables and Mann-Whitney U test for variables with a non-normal distribution. Between-groups comparisons of qualitative variables were done with the Pearson $\chi^2$ test or the Fisher exact test. Values of $P<.05$ were considered to be statistically significant.

RESULTS

Of the 262 patients referred for TEE, 68 were aged at least 55 years. In 24 (35%) of those patients, stroke was not considered cryptogenic due to identification of complex atheroma plaques in the aortic arch by TEE (Group C), whereas in the remaining 44 (65%) patients it was considered to be cryptogenic stroke (Group B). General clinical characteristics are shown in Table 1, which compares the 2 groups of patients with cryptogenic stroke (Groups A and B), and in Table 2, which compares the 2 groups of older patients (Groups A and C).

In both groups of patients with cryptogenic stroke, there was a high frequency of PFO, with no significant differences between age groups (38% in Group A vs 36% in Group B; $P>0.05$) (Figure 2).
Among the clinical characteristics of stroke, there was a higher percentage of acute cerebrovascular accidents in the older patients in groups A and C (Table 2), whereas transient ischemic attack was more common in patients from Group B (Table 1). The frequency of cardiovascular risk factors was similar in both groups of older patients (Table 2). In contrast, diabetes and hypertension were less frequent in patients from Group B than in those from Group A, whereas smoking was more common in Group B (Table 1).

Clinical signs or symptoms of deep vein thrombosis were only present in 3 patients from Group B, whereas PFO was more common in Group A than in Group C (38% vs 8%; *P*=.029) (Figure 2). There were also no differences in the size of PFO between groups A and B (2.1 [2.5] mm vs 4 [1.7] mm; *P*>.05) or in the transit of contrast agent, which was extensive in most cases (87% in Group A vs 77% in Group B; *P*>.05). There were no cases of significant passage of contrast agent through a PFO in Group C (*P*<.01 compared with Group A).

Similar results were obtained for PFO with concomitant ASA. There was no significant difference in frequency between the groups of patients with cryptogenic stroke (18% in Group A vs 11% in Group B; *P*>.05) (Figure 3) but there was a higher frequency in Group A than Group C (18% vs 0%; *P*=.039) (Figure 3). However, the presence of aneurysms not associated with PFO was more common in Group A than Group B (4.8% vs 0.5%; *P*<.05) and slightly lower than in Group C (4.8% vs 8%), although the difference did not reach statistical significance.

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Clinical signs or symptoms of deep vein thrombosis were only present in 3 patients from Group B.
Group A (associated in 1 case with pulmonary thromboembolism) and 2 patients from Group B, all of whom had PFO. There were no cases in Group C.

DISCUSSION

Cryptogenic stroke is less common in older patients than in their younger counterparts. In our experience, covering almost 8 years of exhaustive study, we have only encountered 44 cases of cryptogenic stroke in older patients, compared with 194 cases in younger patients. However, cryptogenic stroke in older patients represents a major healthcare challenge, since minimally invasive diagnostic techniques such as TEE are underutilized and yet could reveal new etiologies for this disease.

When studied systematically with TEE in all patients with stroke of unidentified cause, older patients with cryptogenic stroke have a higher prevalence of PFO than in those with stroke of known cause. The prevalence of PFO in older patients with cryptogenic stroke was lower than in younger patients (28% vs 44%), probably because many cases were not authentic cryptogenic stroke, as a result of not having failed to study the intracranial vessels in half of the cases. Unlike in our study and others, these authors did not use TEE systematically, and as a result, not all of the patients would have authentic cryptogenic stroke. In our study, this was the case in 35% of older patients, who proved to have complex atheromatous plaques in the aortic arch according to the result of TEE.

A recent study involving systematic use of TEE for younger patients, the data have been less clear for older patients. Only a small number of case–control studies have been undertaken in older patients and the results were contradictory, largely due to the use of different techniques for the diagnosis of PFO. As a result, meta-analyses such as that reported by Overell et al could not provide conclusive data.

The study by Handke et al also found a higher prevalence of PFO in older patients with cryptogenic stroke than in those with stroke of known cause. However, the prevalence of PFO in older patients with cryptogenic stroke was lower than in younger patients (28% vs 44%), probably because many cases were not authentic cryptogenic stroke, as a result of having failed to study the intracranial vessels in half of the cases. Unlike in our study and others, these authors did not use TEE systematically, and as a result, not all of the patients would have authenticate cryptogenic stroke. In our study, this was the case in 35% of older patients, who proved to have complex atheromatous plaques in the aortic arch according to the result of TEE.

A recent study involving systematic use of TEE
for the classification of stroke only observed a trend
towards statistical significance for the increased
frequency of PFO in older patients with cryptogenic
stroke. However, that study was limited by having
a retrospective design.

Similar results to those seen for isolated PFO
were obtained for PFO with concomitant ASA, with
a higher prevalence in both groups of patients with
cryptogenic stroke than in older patients with stroke
of known cause. These results are consistent with
the results obtained in more recent studies involving
older patients with cryptogenic stroke.\(^1\)\(^2\)\(^3\)\(^4\)\(^5\)\(^6\)\(^7\) Mas et al\(^8\)\(^9\)\(^10\)\(^11\) reported that the occurrence of PFO and ASA was
associated with an increased risk of stroke due to
paradoxical embolism, a finding that contrasts with
the low prevalence (1.7%) of this association in the
general population.\(^12\) Thus, our results may indicate
that the presence of PFO and ASA might also be
associated with an increased risk of stroke in older
patients. Nevertheless, the frequency of isolated
ASA without PFO in the 2 groups of older patients
with stroke was notably lower than the association
of PFO and ASA, with no differences between the
groups, a finding that is consistent with previous
reports.\(^13\)\(^14\)

TEE offers the advantage of providing anatomical
and functional data relating to PFO, such as the
extent of right-to-left shunt. This was extensive
in most cases of cryptogenic stroke in both age
groups, a finding that is consistent with previous
reports describing the relationship between the
extent of passage through the PFO and the risk of
stroke.\(^16\)\(^17\) Something similar occurs with the size of
the PFO,\(^16\)\(^17\) which was also greater in both groups
of patients with cryptogenic stroke, although this
difference did not reach statistical significance,
probably as a result of the low frequency of PFO in
older patients with atheroembolic stroke.

As mentioned, the advantage of our study over
others carried out in patients with cryptogenic stroke
is that TEE was used systematically. Although
TEE has increased the diagnostic potential during
assessment of cryptogenic stroke, its indications
for cerebral ischemia are not well established,\(^18\)\(^19\)\(^20\)\(^21\) and its use is restricted in older patients. However, our
results suggest that TEE should be systematically
included in the assessment of the cause of cryptogenic
stroke in this age group, since it allows other
potentially treatable causes to be detected. In our
study, this was the case in 35% of older patients with
complex atheromatous plaques in the aortic arch,
a frequency that is very similar to that reported in
other studies.\(^9\)

TEE offers advantages over other diagnostic
techniques for the study of PFO, such as TTE,
which has a lower sensitivity\(^22\) and poorer definition
of the anatomy of the atrial septum. In contrast,
transcranial Doppler has a high sensitivity for
the detection of right-to-left shunt, but does not
discriminate between intracardiac and extracardiac
shunt and provides no information on the anatomy
of PFO.\(^23\)

In terms of the clinical characteristics of the patients
in this study, the distribution of cardiovascular risk
factors between the 3 groups was similar to that
described in the literature,\(^24\)\(^25\) with no differences
between the 2 groups of older patients and a lower
prevalence in younger patients with cryptogenic
stroke, except for smoking.

Few cases had evidence of deep vein thrombosis,
consistent with other studies addressing PFO and
cryptogenic stroke.\(^26\)\(^27\) Furthermore, systematic
assessment of deep vein thrombosis was of limited
diagnostic value in those studies. Nevertheless,
pathophysiologic findings that are common to
this age group, such as the increased likelihood
of paradoxical embolism\(^28\) and venous thromboembolic
disease,\(^29\) alongside the increased frequency of PFO
in older patients with cryptogenic stroke, as in
our study, appear to support a causal relationship
between PFO and stroke in patients 55 years of age
or older.

The presence of PFO in older patients with
cryptogenic stroke is associated with an increased
risk of adverse events, despite antiplatelet or
anticoagulant therapy, whereas this is not the case in
younger patients.\(^30\) This suggests that older patients
with cryptogenic stroke should be studied in greater
depth and treated more aggressively. Currently,
there is no evidence supporting the superiority of
percutaneous closure over medical treatment in
patients with cryptogenic stroke and PFO,\(^31\) and
although ongoing randomized trials (RESPECT,
CLOSURE) may provide some clarification, they
have enrolled almost no patients aged over 60 years,
and these are the patients who could most benefit
from this treatment strategy.

Limitations

No systematic TEE study was performed in
patients aged at least 55 years in whom a cause of
stroke was identified in the general tests, since the
test was carried out at the request of the neurologist,
and as a result it was not possible to assess the
prevalence of PFO in this group.

Since the study was undertaken in patients as part
of daily clinical practice, there was not control group
of older patients without cerebrovascular disease.

Despite an enrolment period of almost 8 years, the
main study group (patients ≥55 years) was not very
large, and this may have limited the statistical power
of some of the results. However, we believe that
this reflects the very low prevalence of cryptogenic
stroke in older patients when an extensive study is undertaken to identify the cause of stroke. The control group of older patients with severe atheromatosis observed by TEE was also quite small, since the cause of stroke was identified in most patients as part of the routine study, a finding that is also consistent with the percentages reported in the literature.

Finally, patients in whom other causes of stroke were observed in TEE were excluded, with the exception of those older patients with complex atheromatous plaques in the aortic arch, who formed the control group. As a result, other uses of TEE in this context cannot be assessed as a result of having focused on PFO.

CONCLUSIONS

Patients of all ages (older or younger than 55 years) with cryptogenic stroke have a higher frequency of PFO, with or without ASA, compared with patients with similar characteristics but with cardioembolic stroke, as indicated by the presence of complex aortic atherosclerotic plaques. This indicates that paradoxical embolism could be the underlying pathophysiologic cause of this type of stroke.

In older patients with stroke of unknown cause, TEE offers a high diagnostic yield for the detection of complex atheromatous plaques in the aortic arch as a cause of atheroembolic stroke. Although this group represents a minority of older patients with ischemic stroke, systematic study with TEE in these patients could have important therapeutic implications.

REFERENCES