Patent Foramen Ovale as a Risk Factor for Cryptogenic Stroke

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■ *Objective:* To determine and compare the prevalence of patent foramen ovale in patients with stroke of undetermined origin (cryptogenic) and in patients with stroke of determined origin to assess the possible role of patent foramen ovale as a risk factor for cryptogenic stroke.

■ *Design:* Cross-sectional study with nested case-control analysis.

■ *Patients:* A total of 146 patients (73 men, 73 women) with acute ischemic stroke referred to the echocardiography laboratory for evaluation.

■ *Setting:* Neurovascular Unit and Echocardiography Laboratory, Columbia-Presbyterian Medical Center, New York, New York.

■ *Measurements:* Patients were considered to have strokes of determined origin or cryptogenic strokes according to National Institute of Neurological Disorders and Stroke (NINDS) Stroke Data Bank criteria. The presence of patent foramen ovale was assessed by contrast echocardiography, performed blinded for type of stroke. The association between patent foramen ovale and type of stroke was tested after correcting for patients' demographic variables and stroke risk factors.

■ *Results:* The overall prevalence of patent foramen ovale was 26 of 146 patients (18%; 95% CI, 11.4% to 24.6%). Patients with cryptogenic stroke (31%) had a significantly higher prevalence of patent foramen ovale than did patients with an identifiable cause of stroke (69%) in both the younger (< 55 years; 48% compared with 4%; $P < 0.001$) and the older (≥ 55 years; 38% compared with 8%; $P < 0.001$) age groups. Multiple logistic regression analysis was used to identify the presence of a patent foramen ovale as strongly associated with the diagnosis of cryptogenic stroke (odds ratio, 7.2; CI, 2.4 to 21.7), irrespective of patient age and other stroke risk factors.

■ *Conclusions:* Patients with cryptogenic stroke have a higher prevalence of patent foramen ovale than patients with stroke of determined cause in all age groups, even after correcting for the presence of recognized stroke risk factors. This identifies patent foramen ovale as a risk factor for cryptogenic stroke. Regardless of patient age, contrast echocardiography should be considered when the cause of stroke is unknown.

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Approximately 40% of cerebral infarctions cannot be classified as strokes of determined cause despite a complete diagnostic work-up and are referred to as cryptogenic strokes (1). Patent foramen ovale has been suggested as a potential reason for paradoxical embolism in some patients (2-4). Among patients with stroke of undetermined origin aged under 40 (5), 50 (6), or 55 (7) years, contrast echocardiography has identified a high prevalence of patent foramen ovale. To our knowledge, however, the prevalence of patent foramen ovale in older patients with stroke, who represent most of the stroke population, has never been systematically evaluated. The aim of our study was to assess the prevalence of patent foramen ovale by contrast echocardiography in a group of patients with stroke unselected for age.

Methods

Patients and Criteria for the Diagnosis

From January 1990 to May 1991, 156 patients admitted for stroke to the Neurological Institute of the Columbia-Presbyterian Medical Center in New York City and consecutively referred to the echocardiography laboratory for cardiac evaluation were eligible for inclusion in the study. These 156 patients represented 66% of all patients admitted to the Neurovascular Unit during the recruitment period. The remaining 34% were excluded mainly because of refusals or logistic problems. In no case was the exclusion related to the patient stroke subtype. Echocardiography is done routinely for all patients admitted to the Neurovascular Unit. Only patients with completed ischemic strokes were included (neurologic deficit lasting over 24 hours and no sign of intraparenchymal hemorrhage seen on computed tomography); no age selection criteria were adopted. Ten patients (6.8%) had to be excluded because of technically inadequate echocardiographic images. The remaining 146 patients were entered in the prospective study.

As a part of their neurologic work-up, all patients had head computed tomography (CT) or magnetic resonance imaging (MRI), carotid and vertebral artery duplex Doppler ultrasonography, and transcranial Doppler examination of the middle and anterior cerebral arteries or basilar artery. A cerebral angiogram was done when clinically indicated.

The cardiac evaluation included electrocardiography, two-dimensional color-Doppler transthoracic echocardiography with contrast injection using Hewlett-Packard Sonos 500 equipment (Hewlett-Packard Imaging Systems Division, Andover, Massachusetts), and Holter monitoring using a Marquette 8000 Laser system (Marquette Electronics Inc., Jupiter, Florida) to detect possible arrhythmias. Routine laboratory tests included complete blood counts, coagulation studies, serum electrolytes, liver function tests, and cholesterol determinations. Most patients also had protein C, free protein S, antithrombin III, plasminogen, and lupus anticoagulant measurements. The presence of peripheral venous disease was searched for by Doppler sonography only if clinical suspicion existed. Pulmonary hypertension, which may affect the detection rate of patent foramen ovale, was systematically assessed by continuous Doppler interrogation of tricuspid regurgitant jet velocity (8). No patient

showed evidence of pulmonary embolism or infarction or signs of systemic embolization to other organs.

An infarct subtype diagnosis (9) was determined by a neurologist who was aware of the findings of echocardiography but blinded to the results of the contrast study. This classification to characterize each stroke by causal mechanism has been described in detail previously (1). The diagnosis was based on the neurologic and medical history, neurologic symptoms and signs, and findings from the diagnostic evaluation. Strokes classified as infarcts of determined cause were categorized as large vessel atherosclerotic or atheroembolic, small vessel lacunar, cardioembolic infarcts, or infarcts resulting from other determined causes (five cases of vertebral artery dissection and one case of vasculitis in our study patients). An atherosclerotic infarction was attributed to perfusion failure distal to the site of severe stenosis or occlusion of a major intracranial or extracranial vessel or represented cases where an extracranial lesion was insufficient in itself to account for stroke on hemodynamic grounds, but possibly served as an embolic source. Lacune was diagnosed in the case of a lacunar syndrome with a small, deep infarct or no lesion found on CT or MRI. A cardioembolism was diagnosed when a cardiac source was recognized: atrial fibrillation or flutter, bacterial endocarditis, significant valvular pathology including mitral valve prolapse, mitral annular calcification, myocardial infarction within the previous 6 weeks, intracardiac thrombus, atrial myxoma, or pulmonary venous thrombosis.

Patients who could not be classified into these traditional subtypes were diagnosed as having infarcts of undetermined cause, or cryptogenic infarcts. These patients had no bruit or transient ischemic attack ipsilateral to the hemisphere affected by the stroke, no definite cardiac source of embolism, and no hemodynamic extracranial or proximal intracranial disease. Patients with cryptogenic stroke usually presented with a nonlacunar clinical syndrome and had brain imaging evidence of more than just a small deep cerebral infarction.

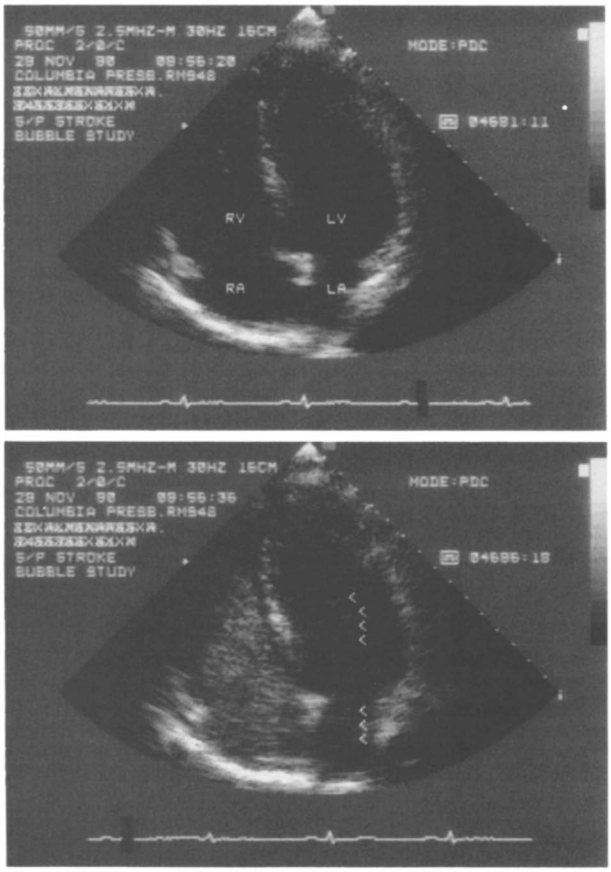

Figure 1. Example of right-to-left shunt by contrast echocardiography. Top. The apical four-chamber view is imaged before contrast injection. **Bottom.** After injection, contrast material fills the right side, and microcavitations (❮) are seen crossing to the left atrium and then to the left ventricle. LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

Detection

Patent foramen ovale was detected by means of the technique used in similar studies (7). Briefly, 10 mL of isotonic saline solution was mixed with 0.5 to 1.0 mL of air by means of two syringes mounted on a three-way stopcock. Visible air was extruded, and the suspension was then rapidly injected into a peripheral arm vein. An apical four-chamber view was used to evaluate for the presence of patent foramen ovale. If microbubbles were seen in the left-sided chambers within three cardiac cycles after they appeared in the right atrium, patent foramen ovale was considered to be present. It should be noted, however, that this was a functional rather than an anatomic definition of patent foramen ovale, as demonstrated by right-to-left shunt at the time of the test. A second injection during Valsalva maneuver was done to increase the sensitivity of the test (5), looking for right-to-left shunting during the release phase. An example of right-to-left shunting is provided in Figure 1. No side effects were observed during or after the test. Contrast studies were read by the consensus of two experienced echocardiographers who were blinded to the findings of patients' neurologic work-up. The interpretation was doubtful in only one case, in which the test was repeated and clearly documented the existence of a patent foramen ovale.

Statistical Analysis

The proportion of patients with arterial hypertension, diabetes mellitus, cigarette smoking, and previous stroke was compared in patients with cryptogenic and noncryptogenic stroke. The frequency of patent foramen ovale was compared in these two diagnostic subgroups and the two age subgroups (< 55 years or ≥ 55 years at the time of the stroke). Differences between proportions were tested by the chi-square test, which was replaced by the Fisher exact test in cases where the cell frequency was less than 5. Differences between mean values were tested by the *t*-test for unpaired data. Two-tailed *P* values were considered. Crude odds ratios for patent foramen ovale presence with 95% confidence intervals (CIs) were calculated for cryptogenic stroke diagnosis. In addition, crude odds ratios for the association of patent foramen ovale and individual stroke risk factors were calculated.

Logistic regression was used to test the association between patent foramen ovale (independent variable) and infarct subtype (dependent variable) after entering age and stroke risk factors as potential confounding variables in the model (10). Adjusted odds ratio and 95% confidence intervals were calculated from the beta coefficients and the standard errors.

Results

Patient Characteristics

Among the 146 patients studied (73 men, 73 women; mean age, 61.8 ± 15.3 years), 101 (69%) were diagnosed with strokes of determined cause and 45 (31%) with cryptogenic strokes (Figure 2). Forty-five patients were younger than 55 years at the time of the stroke; 21 (47%) of these patients had cryptogenic strokes. The remaining 101 patients were 55 years or older; 24 (24%) of these patients had cryptogenic strokes.

Twenty-one percent of the patients had a previous stroke; 64% had arterial hypertension; and 27% had diabetes mellitus. Twenty-one percent were smokers at the time of the stroke. Compared with the patients with

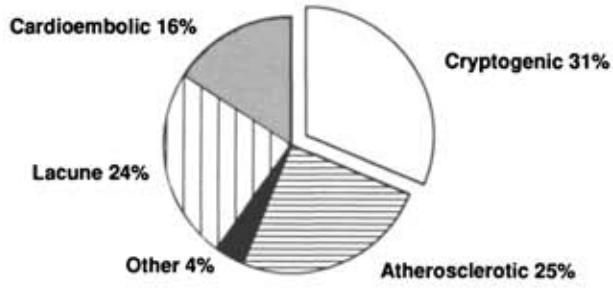

Figure 2. Stroke subtypes in the study group. The chart illustrates the stroke diagnostic subtypes in the patient group examined.

stroke of determined origin, patients with cryptogenic stroke were younger and had a lower prevalence of hypertension and diabetes mellitus (Table 1).

Prevalence by Age and Diagnostic Subtype

The overall prevalence of patent foramen ovale in the patients studied was 18% (26 of 146 patients). The prevalence of patent foramen ovale was not significantly different in those aged less than 55 years (11 of 45; 24%) or 55 years and older (15 of 101; 15%; $P = 0.16$).

A patent foramen ovale was detected in a higher proportion of patients with cryptogenic stroke compared with patients who had stroke of determined cause (42% compared with 7%; $P < 0.001$). An increased frequency of patent foramen ovale in patients with cryptogenic stroke was observed both in the younger (47% compared with 4%; $P < 0.001$) and in the older (38% compared with 8%; $P < 0.001$) age subgroups. Crude odds ratios for patent foramen ovale by diagnostic subtype and age group are shown in Table 2. Odds ratios for patent foramen ovale and cryptogenic stroke diagnosis were 9.8 for the entire study group, 20.9 for younger patients, and 7.1 for older ones.

Patent Foramen Ovale and Stroke Risk Factors

Patent foramen ovale was found to be inversely associated with the presence of hypertension and diabetes mellitus (Table 3). No significant association was detected with smoking or with a previous stroke.

Logistic Regression Analysis

Logistic regression analysis showed that patent foramen ovale was independently associated with the diagnosis of cryptogenic stroke, even after controlling for age and hypertension or diabetes mellitus (Table 4). Hypertension was confirmed to be inversely associated with the diagnosis of cryptogenic stroke.

Discussion

Our study showed a high prevalence of patent foramen ovale in patients with stroke of undetermined origin, which raises the possibility of paradoxical embolism as a mechanism of stroke in some of these patients. This confirms previous observations (5-7), but expands the focus from younger patients with stroke to the larger group of patients with ischemic cerebral infarcts of unknown origin. In the largest published prospective study, Lechat and colleagues (6) found a prevalence of patent foramen ovale of 40% in 60 patients with stroke aged under 55 years and 10% in controls. The prevalence was 54% in patients with cryptogenic stroke compared with 21% in patients with stroke of determined origin. Likewise, Webster and colleagues (5) showed a prevalence of 50% in 40 patients with stroke who were under 40 years of age compared with 15% in the control group. In a smaller study, Jeanrenaud and colleagues found similar proportions (6). The patients in the study by Lechat and colleagues had a surprisingly low prevalence of traditional stroke risk factors, whereas this information was not provided in the study by Webster and coworkers. Although many of our patients did have these risk factors, we found that the difference in the frequency of patent foramen ovale in patients with cryptogenic stroke compared with those with noncryptogenic stroke remained even after controlling for differences in other risk factors such as age, hypertension, and diabetes mellitus. The prevalence of patent foramen ovale in patients with stroke of determined cause was similar to that reported in normal controls (5, 7). These observations support the role of patent foramen ovale as a risk factor for stroke of otherwise undetermined origin. We stress that these results should be extrapolated with caution to normal subjects, because we have shown here that a patent foramen ovale can be considered as a risk factor for cryptogenic stroke only in patients who have a stroke.

We found that the prevalence of detectable patent

Table 1. Patient Characteristics

Characteristic	Patients with Cryptogenic Stroke (n = 45)	Patients with Stroke of Determined Cause (n = 101)	P Value
Gender (M/F)	21/24	52/49	
Age*, y	55.8 ± 18.1	64.5 ± 13.2	0.005
Previous stroke, n(%)	7 (16)	24 (24)	> 0.2
Hypertension, n(%)	17 (38)	77 (76)	< 0.001
Diabetes, n(%)	5 (11)	35 (35)	0.003
Smoking, n(%)	10 (22)	20 (20)	> 0.2

* Mean value ± standard deviation.

Table 2. Prevalence of Patent Foramen Ovale According to Age and Stroke Subtype

Subgroup	Patent Foramen Ovale	Cryptogenic Stroke	Stroke of Determined Cause	Odds Ratio	95% CI
		n			
All ages (n = 146)	Yes	19	7	9.8	3.7 to 25.8
	No	26	94		
Age < 55 y (n = 45)	Yes	10	1	20.9	2.4 to 184.5
	No	11	23		
Age ≥ 55 y (n = 101)	Yes	9	6	7.1	2.2 to 22.9
	No	15	71		

foramen ovale did not change significantly with age at the time of stroke, being 15% and 24% in patients older or younger than 55, respectively. Stroke is predominantly a disease of the elderly, with only 3% of cerebral infarctions occurring in patients under 40 years of age (11). In our study, the older age group accounted for two thirds of the observed stroke cases; therefore, the absolute number of patients diagnosed with patent foramen ovale in the older group was larger than in the younger group. The implications of this finding in a larger, more representative stroke population than just young patients with unexplained strokes could have more public health consequences in terms of number of persons requiring diagnostic evaluation and therapy.

In the elderly, the higher prevalence of heart disease and large-vessel atherosclerosis makes the diagnosis of stroke of undetermined origin less frequent than in the young. Despite the completeness of the diagnostic work-up, undetermined or cryptogenic cerebral infarctions still accounted for 24% of patients over 55 years of age in our study, compared with 47% of younger patients. Strict criteria were adopted for defining infarct subtypes based on current diagnostic technology to prevent patient misclassification (12). To minimize the information bias, the subtype classification was done independently by a neurologist aware of findings from the diagnostic procedures, including echocardiography, but blinded to the contrast study. Two thirds of all patients in the neurovascular unit during the recruitment period actually had contrast echocardiography. Reasons for nonrecruitment were logistic problems and patient or physician refusal to participate; however, no selection occurred based on patient stroke subtype.

The patent foramen ovale diameter may increase with age (13). This might make the elderly more susceptible to paradoxical embolism, especially after maneuvers that increase the pressures in the right-sided heart cavities, such as cough or defecation (14, 15). The prevalence of venous thrombosis, which might represent one of the main sources for such embolism, is also increased in the elderly (7, 16). In our study, the events preceding stroke occurrence, as well as the prevalence of venous thrombosis, were not specifically investigated. It has been shown, however, that venous thrombosis may escape clinical detection in over 50% of cases (16). Future studies should include systematic assessment for venous thromboses and hypercoagulable states, which could help establish a cause-effect relation between patent foramen ovale and stroke.

We observed an inverse relationship between patent foramen ovale and presence of hypertension and diabetes mellitus. Neither of these risk factors was part of the definition of infarction subtypes, even though they may play a precursor role in the pathogenesis of infarctions of determined cause. The inverse relationship may reflect the large proportion of hypertension and diabetes in the patients with stroke of determined origin.

We used contrast echocardiography to detect patent foramen ovale. This technique is highly sensitive and specific for this diagnosis, particularly when done in association with Valsalva maneuver or cough (17-19). It is also a safe procedure (7, 20, 21).

Recent studies (22, 23) indicated than transesophageal echocardiography can detect intracardiac lesions not detected by conventional transthoracic studies in patients with stroke of undetermined origin. In the same studies, the addition of contrast injection to the transesophageal examination appeared to improve the sensitivity for the detection of patent foramen ovale. Therefore, a transesophageal study with contrast injection may be indicated in patients with cryptogenic stroke who have a normal transthoracic echocardiogram and contrast

Table 3. Association of Traditional Stroke Risk Factors with Patent Foramen Ovale in the Study Population

Risk Factor	Patent Foramen Ovale		Odds Ratio	95% CI
	Present	Absent		
	n			
Normotensive	16	36	3.7	1.5 to 8.9
Hypertensive	10	84		
Nondiabetic	24	82	5.6	1.3 to 24.9
Diabetic	2	38		
Smoker	7	23	1.6	0.6 to 4.3
Nonsmoker	19	97		
No previous stroke	23	92	2.3	0.6 to 8.2
Previous stroke	3	28		

Table 4. Association of Patent Foramen Ovale and Other Selected Variables with the Diagnosis of Cryptogenic Stroke Using Logistic Regression Analysis

Variable	Odds Ratio	95% CI
Patent foramen ovale	7.2	2.4 to 21.7
Age < 55 y	1.8	0.7 to 4.4
No hypertension	3.3	1.4 to 7.9
No diabetes	1.9	0.6 to 5.9

study, especially when a possible source of embolism at the atrial level is suspected (22).

The therapy for patients with ischemic stroke and a patent foramen ovale remains unestablished. Patients with venous thrombosis documented by venogram or Doppler-sonography are usually treated with prophylactic anticoagulation (7). It remains unclear whether anticoagulation would provide benefit to patients with ischemic stroke and patent foramen ovale even in the absence of clearly documented thrombosis (24). Further prospective studies are required to assess the risk for recurrence of stroke in patients with stroke and patent foramen ovale, and randomized treatment protocols may be needed to test the efficacy of oral anticoagulation in these patients.

The amount of blood shunting through the patent foramen might be a criterion on which to base decisions about interventions. In the case of large shunts, percutaneous closure of the foramen may be indicated (25, 26). Recent studies (27-29) have shown that target organ involvement (the delivery of microbubbles to the brain) can be detected by transcranial Doppler done during contrast echocardiography. This approach might be of value in assessing the clinical relevance of the shunt and in monitoring the results of the foramen closure.

Our data show a high prevalence of patent foramen ovale in patients with stroke of undetermined origin, including those over 55 years of age. Because the incidence of cerebral infarcts and venous thrombosis increases with age, the detection of patent foramen ovale in older patients might be of greater relevance than its detection in younger patients. Therefore, we believe that when a diagnostic work-up fails to reveal a cause for the stroke, patients, regardless of age, should have contrast echocardiography.

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