

Atherosclerotic Burden Findings in Young Cryptogenic Stroke Patients With and Without a Patent Foramen Ovale

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Background and Purpose—To further determine the mechanisms of cryptogenic stroke or transient ischemic attack in young patients, we evaluated indices of atherosclerosis in patients ≤ 55 years old diagnosed with cryptogenic cerebrovascular event comparing those with patent foramen ovale (PFO) with those without PFO.

Methods—This was a prospective study including 100 consecutive patients ≤ 55 years old (mean age, 45 ± 8 years; 56 males) diagnosed with cryptogenic stroke/transient ischemic attack. PFO was identified in 59 of these patients with the use of transesophageal echocardiography with contrast study. The following surrogate markers of atherosclerosis were evaluated in all patients: carotid intima media thickness as measured by carotid ultrasonography and endothelial function as determined by brachial flow-mediated vasodilation. The same measurements were obtained in a control group of 50 age- and sex-matched control subjects.

Results—Patients without PFO were more likely to be current smokers and obese and more frequently had a history of hypertension and dyslipidemia. Carotid intima media thickness measurements were higher ($P < 0.0001$) in patients without PFO (1.03 ± 0.31 mm) compared with those with PFO (0.75 ± 0.20 mm) and control subjects (0.79 ± 0.17 mm). The absence of PFO was also associated with lower brachial flow-mediated vasodilation (without PFO: $5.04 \pm 3.39\%$; with PFO: $7.16 \pm 4.09\%$; control subjects: $7.33 \pm 4.07\%$; $P = 0.02$). There were no differences in carotid intima media thickness and flow-mediated vasodilation between patients with stroke/transient ischemic attack with PFO and control subjects. The presence of PFO was independently associated with reduced carotid intima media thickness ($P < 0.0001$) and increased flow-mediated vasodilation ($P = 0.019$).

Conclusions—In patients ≤ 55 years old diagnosed with cryptogenic stroke/transient ischemic attack, the presence of PFO was associated with a lower atherosclerotic burden as measured by carotid intima media thickness and endothelial function with no differences compared with a control group without cerebrovascular event. These results suggest that an atherosclerotic-mediated mechanism may be involved in cryptogenic stroke/transient ischemic attack in patients without PFO, whereas a nonatherosclerotic mechanism may mediate the cerebrovascular event in the presence of PFO. (*Stroke*. 2009;40:419-425.)

Key Words: atherosclerosis ■ carotid arteries ■ patent foramen ovale ■ stroke

Approximately 40% of ischemic strokes are cryptogenic (ie, no clearly definable cause is found after extensive workup). Although atherothrombosis remains one potential cause of stroke in these patients, few data are available regarding the role of an atherosclerosis-mediated mechanism in cryptogenic stroke. Some studies have evaluated the presence of significant atheromatosis of the aortic arch in patients with cryptogenic stroke, but the association between aortic arch atheroma and cryptogenic stroke has been limited to patients

>60 years old.^{1,2} In fact, the role of atherosclerosis in young adults with cryptogenic stroke has been mostly limited to the evaluation of the prevalence of cardiovascular risk factors in these patients.³⁻⁵ Also, a role for patent foramen ovale (PFO) in the pathogenesis of cryptogenic stroke in patients ≤ 55 years old has been suggested on the basis of case-control studies that have shown a higher prevalence of PFO among these patients compared with stroke-free control subjects,⁶ but no studies have determined whether or not the atherosclerotic burden in young

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patients with cryptogenic stroke might vary depending on the presence of a PFO.

The B-mode ultrasound measurement of the intima media thickness of the carotid artery (CIMT) and the evaluation of endothelial function by the flow-mediated vasodilation (FMV) of the brachial artery have been shown to be reliable noninvasive imaging markers of global atherosclerotic burden.⁷⁻⁹ Also, several studies have associated CIMT and endothelial dysfunction with the occurrence of ischemic stroke of atherothrombotic origin.¹⁰⁻¹⁴

To further explore the mechanisms involved in cryptogenic stroke/transient ischemic attack (TIA) in young adult patients, we performed a prospective study evaluating the atherosclerotic burden as measured by CIMT and endothelial function test in patients ≤ 55 years old diagnosed with cryptogenic stroke/TIA comparing those with and those without PFO and with a control group of subjects matched for age and sex.

Methods

Study Population

This prospective study included a series of 100 consecutive patients ≤ 55 years old diagnosed with a cryptogenic stroke or TIA from June 2003 to March 2007 in 3 neurology departments of the province of Quebec, Canada. The diagnosis of stroke or TIA was made by a neurologist according to the National Institute of Neurological Disorders and Stroke Classification III.¹⁵ TIA was defined as a reversible episode of neurological deficit that resolved completely within 24 hours and was attributed to inadequate blood supply. Patients with transient focal neurological symptoms whose clinical features were not sufficiently clear to affirm the diagnosis of definite TIA were excluded. The diagnosis of cryptogenic stroke/TIA was established after a systematic etiologic workup, including brain CT and/or MRI, routine blood tests, detailed coagulation study (including protein C, protein S, antithrombin III, antiphospholipid antibodies, factor V Leiden, prothrombin variant G20210A), 12-lead electrocardiogram, echocardiography, 24-hour electrocardiogram Holter, extracranial Doppler ultrasonography with frequency analysis and B-mode imaging, and cerebral CT and/or MR angiography. Definite causes of stroke included significant large artery atherosclerosis ($\geq 50\%$ stenosis), small vessel occlusion, cardioembolic causes,¹⁶ complex atheroma of the aortic arch, nonatherosclerotic arteriopathies, and coagulopathies. Transesophageal echocardiography with a contrast study and Valsalva maneuver was performed in all patients to determine the presence or not of a PFO. All echocardiographic images were recorded and evaluated offline by a cardiologist unaware of clinical data in the core laboratory of the Quebec Heart Institute/Laval Hospital. The presence and diameter of PFO, the severity of the right-to-left shunt, and the presence of atrial septal aneurysm were determined. The presence of PFO was diagnosed on the basis of the observation of a right-to-left passage of contrast bubbles through a valve-like structure either spontaneously or after provocative maneuver (Valsalva) within 3 cardiac cycles after the complete opacification of the right atrium. The degree of right-to-left shunt was considered small if < 20 microbubbles appeared and large if ≥ 20 microbubbles appeared.^{17,18} Atrial septal aneurysm (ASA) was diagnosed when the atrial septum exhibited an excursion into the left or right atrium ≥ 11 mm or a total excursion ≥ 15 mm and the base of the aneurysmal septum was at least of 15 mm in diameter.¹⁹

Traditional cardiovascular risk factors were systematically recorded in all patients and included smoking status, history of hypertension defined as blood pressure $\geq 140/90$ mm Hg or treatment with antihypertensive medication, history of dyslipidemia defined as low-density cholesterol levels > 3.50 mmol/L or treatment with lipid-lowering medication, and history of diabetes defined as serum fasten blood sugar > 6.9 mmol/L or treatment with oral hypoglycemic agents or insulin. The body mass index and the waist

circumference were measured in all cases. Fasting blood samples were collected in all patients ≥ 3 months after the stroke/TIA to avoid any influence of the cerebrovascular event on laboratory tests. The following measurements were systematically performed: glucose, total cholesterol, low-density cholesterol, high-density cholesterol, ratio total cholesterol/high-density cholesterol, triglycerides, lipoprotein a, apolipoprotein B, homocysteine, high-sensitivity C-reactive protein, fibrinogen, and D-dimer. Care was taken to obtain blood samples in the absence of any infectious condition within the previous 10 days. In patients receiving warfarin therapy, this treatment was withdrawn and replaced by antiplatelet treatment with aspirin at least 4 days before blood sampling.

Carotid Ultrasound Examination and Measurements

Carotid B-mode ultrasound examination was performed in all patients by 2 experienced sonographers using a Hewlett-Packard ultrasound system equipped with high-resolution transducers and digital acquiring capability. Standardized carotid ultrasound scanning and reading protocols were used.²⁰ A transverse scan followed by a full circumferential longitudinal scan were performed to obtain appropriate images of the near and far wall of 3 predetermined carotid artery segments of both carotid arteries, including the proximal 10 mm of the internal carotid artery, the carotid bifurcation beginning at the tip of the flow divider and extending 10 mm below this point, and the arterial segment extending 10 mm below the bifurcation in the common carotid artery. The images of each study were digitally stored and measured offline by an experienced technician blinded to the clinical data. The maximum CIMT was identified and measured in each of the 6 artery segments of each carotid artery, and the mean of the maximum CIMT measurements of a total of 12 carotid segments was calculated for each patient.

Endothelial Function Testing

Endothelial function was evaluated by means of a brachial test as previously described.²¹ The tests were performed ≥ 3 months after the cerebrovascular episode in all patients after an overnight fast, between 7 and 8 AM, after a 15-minute rest in the supine position in a quiet dimly light room. Subjects had to have consumed no caffeine, alcohol, or chocolate and were not to have smoked in the last 12 hours. The patient had to be free of any clinically significant infectious condition within the 10 days before the test.

At each test, a 3-lead electrocardiogram was applied with continuous monitoring. The right brachial artery was imaged longitudinally just above the antibrachial fossa. Images were captured at the same time of the cardiac cycle (peak of R wave) with a high-resolution ultrasound apparatus (Hewlett-Packard 7-MHz linear-array vascular probe coupled to a Hewlett-Packard 5500 ultrasound machine). Still frames were recorded one per 5-second interval with the frames of the first and last 5 seconds of the subsequence discarded. A blood pressure cuff was then inflated on the upper arm to 220 mm Hg for 5 minutes. Immediately after release of the cuff, the brachial artery was continuously imaged, and 1 minute after release of the cuff, a set of 12 images was recorded during the next 90 seconds. Sublingual nitroglycerin of 0.3 mg was administered, and 9 more images were recorded 3 minutes later.

Recorded images were analyzed by an experienced technician blinded to clinical data using dedicated image analysis software (Dynamic Endothelial Assessment V2.0; Vasometrix). The mean calibrated diameter of the artery segment was calculated from an average of 120 computerized diameter measurements per digitalized frame. The average of all frames of each subsequence was then computed. The percent changes in arterial caliber after FMV and after nitroglycerin-mediated vasodilation from their respective basal states were determined. FMV was used as an index of endothelium-dependent dilation and nitroglycerin-mediated vasodilation as an index of endothelium-independent dilation.

Table 1. Clinical Characteristics of the Study Population Grouped According to the Presence or Absence of PFO and Compared With the Control Group

Variable	Stroke/TIA	Stroke/TIA	Control Group (N=50)	P Value	No PFO	No PFO	PFO
	No PFO (N=41)	PFO (N=59)			Versus PFO	Versus Control Group	Versus Control Group
Age, years	47±6	43±9	45±7	0.09	0.07	0.29	0.79
Female gender, n (%)	14 (34)	30 (51)	22 (44)	0.26	0.23	0.61	0.76
Current smoking, n (%)	18 (44)	11 (19)	11 (22)	0.02	0.03	0.09	0.87
Dyslipidemia, n (%)	27 (66)	17 (29)	11 (22)	0.0001	0.001	0.0003	0.73
Statin treatment, n (%)	27 (66)	14 (24)	3 (6)	<0.0001	0.0001	<0.0001	0.06
Hypertension, n (%)	16 (39)	9 (15)	6 (13)	0.006	0.02	0.01	0.91
Antihypertensive treatment, n (%)	15 (37)	8 (14)	2 (4)	0.001	0.02	0.004	0.26
Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker	14 (34)	8 (14)	1 (2)				
Calcium antagonists	1 (2)	0	0				
β-blockers	1 (2)	1 (2)	1 (2)				
Diuretics	3 (7)	1 (2)	0				
Blood pressure, mm Hg							
Systolic	127±14	118±13	119±12	0.007	0.01	0.02	1.0
Diastolic	79±8	75±9	75±7	0.06	0.14	0.08	0.94
Diabetes, n (%)	6 (15)	2 (3)	1 (2)	0.06	0.15	0.14	0.91
Body mass index, kg/m ²	30±7	27±4	26±4	<0.001	0.01	0.001	0.52
Body mass index ≥30 kg/m ² , n (%)	15 (37)	12 (20)	9 (18)	0.03	0.04	0.05	0.92
Waist circumference, cm	101±17	89±18	87±18	0.003	0.02	0.004	0.80
Oral contraceptives, n (%)	1 (7)	6 (20)	3 (14)	0.55	0.34	0.69	0.71
History of migraine, n (%)	4 (10)	14 (24)	4 (8)	0.08	0.18	0.99	0.17
Prior stroke, n (%)	7 (17)	9 (15)	...		0.81		
Cerebrovascular event type, n (%)					0.85		
Stroke	29 (71)	43 (73)	...				
TIA	12 (29)	16 (27)	...				
Antithrombotic treatment, n (%)							
Aspirin	33 (81)	23 (39)	0				
Clopidogrel	6 (15)	2 (3)	0	<0.0001	<0.001	<0.0001	<0.0001
Aspirin+clopidogrel	1 (2)	0	0				
Warfarin	1 (2)	34 (58)	0				

Control Group

A control group of 50 subjects matched with the study population for age and sex underwent the same examinations under the same conditions as patients with cryptogenic stroke/TIA, including blood sample measurements, CIMT, and endothelial function testing. The control group consisted of volunteers with no history of cardiac or cerebrovascular event.

The study was approved by the ethics committee of the hospital, and all patients and control subjects gave written, informed consent.

Statistical Analysis

The χ^2 test or Fisher exact test was used to compare qualitative variables. Comparisons among numeric variables were performed using one-way analysis of variance and further 1:1 comparisons between groups were performed using the Tukey's post hoc test. Differences in total cholesterol and low-density lipoprotein cholesterol levels among groups were adjusted for lipid-lowering treatment status. Stepwise regression analysis was performed to determine the predictors of increased atherosclerotic burden (higher CIMT and lower brachial FMV values) in patients with cryptogenic stroke/TIA. Differences were considered statistically

significant at probability values <0.05. The data were analyzed using the statistical package program SAS v9.1.3 (SAS Institute Inc, Cary, NC).

Results

Patients and Clinical Atherosclerotic Risk Factors

From 217 consecutive patients ≤55 years old with ischemic stroke or TIA, a total of 100 patients (46%) were diagnosed with cryptogenic stroke or TIA and constituted the study population. The definite causes of stroke/TIA in the other 117 patients were distributed as follows: large artery atherosclerosis (17 patients [8%]), cardioembolic (18 patients [8%]), small vessel occlusion (26 patients [12%]), nonatherosclerotic arteriopathies (31 patients [14%]), and miscellaneous, including coagulopathies (25 patients [12%]). Mean age of the study population was 45±8 years and 44% were females. Seventy-two patients had a stroke and 28 patients were diagnosed of TIA with evidence of an ischemic lesion at MRI

Table 2. Biological Profile of the Study Population Grouped According to the Presence or Absence of PFO and Compared With the Control Group

Variable	Stroke/TIA No PFO	Stroke/TIA PFO	Control Group	<i>P</i> Value	No PFO versus PFO	No PFO versus Control Group	PFO versus Control Group
Glucose, mmol/L	5.4±2.2	4.9±0.6	4.8±0.7	0.04	0.30	0.03	0.45
Total cholesterol, mmol/L	4.2±0.7	4.6±0.9	4.6±1.0	0.07	0.08	0.13	0.99
LDL cholesterol, mmol/L	2.2±0.5	2.6±0.8	2.6±0.8	0.008	0.01	0.02	0.99
HDL cholesterol, mmol/L	1.4±0.4	1.5±0.3	1.5±0.4	0.71	0.76	0.73	0.99
Ratio total cholesterol/HDL	3.2±1.0	3.2±0.9	3.3±0.9	0.95	0.99	0.96	0.96
Triglycerides, mmol/L	1.6±1.2	1.2±0.5	1.1±0.6	0.02	0.10	0.02	0.67
Lipoprotein(a), mg/L	346±354	269±298	207±254	0.21	0.81	0.20	0.45
Apolipoprotein B, g/L	0.88±0.18	0.91±0.24	0.90±0.18	0.86	0.85	0.96	0.96
Homocysteine, μmol/L	10.2±5.6	8.5±2.5	8.4±2.6	0.05	0.10	0.06	0.95
Hs-CRP, mg/L	3.1±5.3	1.5±1.6	1.4±1.3	0.07	0.18	0.07	0.86
Fibrinogen, g/L	3.5±0.8	3.3±0.7	3.0±0.6	0.007	0.27	0.005	0.14
D-dimer, μg/L	0.11±0.04	0.15±0.11	0.12±0.05	0.53	0.51	0.72	0.96

LDL indicates low-density lipoprotein; HDL, high-density lipoprotein; Hs-CRP, high-sensitivity C-reactive protein.

in 10 of them. PFO was diagnosed in 59 patients. The clinical characteristics of the study population grouped according to the presence or absence of PFO and compared with the control group are shown in Table 1. Blood samples were obtained at a median of 4 months (range, 3 to 9 months) after the stroke/TIA episode in both patients with and without PFO. The results of the laboratory tests grouped according to the presence or absence of PFO and compared with the control group are shown in Table 2. Low-density lipoprotein cholesterol levels were higher in patients with PFO and control subjects compared with patients without PFO, but these differences were no longer significant after adjusting for lipid-lowering treatment status ($P=0.63$).

Surrogate Markers of Atherosclerosis

CIMT and endothelial function measurements were obtained after a median of 4 months (range, 3 to 9 months) after the event. The mean values of CIMT and endothelial function measurements grouped according to the presence or absence of PFO and compared with the control group are shown in Table 3. The mean of the maximum CIMT measurements was significantly higher in patients without PFO compared with those with PFO (mean difference, 0.28 mm; 95% CI, 0.15 to 0.41) and control subjects (mean difference, 0.24 mm; 95% CI, 0.11 to 0.36). There were no differences in CIMT measurements between patients with PFO and control subjects. Patients without PFO exhibited an impaired endothelial function expressed as a lower brachial FMV compared with patients with PFO (mean difference, 2.12%; 95% CI,

0.05 to 4.18) and control subjects (mean difference, 2.29%; 95% CI, 0.03 to 4.78). There were no differences in FMV measurements between patients with PFO and control subjects, and there were no differences among groups in the values of endothelium-independent (nitroglycerin-mediated) vasodilation.

On univariate analysis, the variables associated with increased CIMT in patients with cryptogenic stroke were age ($r^2=0.31$, $P=0.002$), systolic blood pressure ($r^2=0.31$, $P=0.003$), homocysteine level ($r^2=0.24$, $P=0.02$), body mass index ($r^2=0.22$, $P=0.056$), and the absence of PFO (1.03 ± 0.31 mm versus 0.75 ± 0.20 mm, $P<0.0001$). On multivariate analysis, the independent variable associated with increased CIMT were systolic blood pressure ($P=0.049$) and the absence of PFO ($P<0.0001$). The 2 variables associated with reduced brachial FMV values on univariate analysis were current smoking ($4.95\pm 3.47\%$ versus $6.81\pm 4.04\%$, $P=0.046$) and the absence of PFO ($5.04\pm 3.39\%$ versus $7.16\pm 4.09\%$, $P=0.015$). On multivariate analysis, the only independent variable associated with low FMV values was the absence of PFO ($P=0.019$).

Echocardiographic Characteristics of Patent Foramen Ovale

Mean PFO diameter was 2.8 ± 1.5 mm and the degree of the right-to-left shunt was evaluated as large in 88% of the patients. A eustachian valve was associated with PFO in 16 patients (27%) and atrial septal aneurysm was diagnosed in 17 patients (29%). The clinical, laboratory, echocardiographic

Table 3. Atherosclerotic Burden of the Study Population as Evaluated by CIMT and Endothelial Function Test Grouped According to the Presence or Absence of PFO and Compared With the Control Group

Variable	Stroke/TIA No PFO	Stroke/TIA PFO	Control Group	<i>P</i> Value	No PFO versus PFO	No PFO versus Control Group	PFO versus Control Group
Mean maximum CIMT, mm	1.03±0.31	0.75±0.20	0.79±0.17	<0.0001	<0.0001	<0.0001	0.61
Single maximum CIMT, mm	1.84±1.41	1.18±0.34	1.23±0.37	<0.001	<0.001	0.002	0.96
FMV, %	5.04±3.39	7.16±4.09	7.33±4.07	0.02	0.03	0.04	0.98
Nitroglycerin-mediated vasodilation, %	17.5±6.9	19.6±7.5	20.1±5.0	0.23	0.40	0.34	0.97

Table 4. Clinical, Biological, and Echocardiographic Characteristics and Atherosclerotic Burden Profile of the Patients With Cryptogenic Stroke/TIA and PFO Grouped According to the Presence or Absence of Atrial Septal Aneurysm

Variable	PFO Alone (N=42)	PFO+ASA (N=17)	P Value
Age, years	44±8	43±11	0.68
Female sex, n (%)	19 (45)	11 (65)	0.17
Current smoking, n (%)	7 (17)	4 (24)	0.69
Dyslipidemia, n (%)	13 (31)	4 (24)	0.75
Hypertension, n (%)	7 (17)	2 (12)	0.63
Diabetes, n (%)	1 (2)	1 (6)	0.22
Body mass index, kg/m ²	27±4	27±4	0.92
Waist circumference, cm	93±13	83±27	0.09
Oral contraceptives, n (%)	3 (16)	3 (27)	0.41
History of migraine, n (%)	9 (21)	5 (29)	0.67
Prior stroke, n (%)	8 (19)	1 (6)	0.26
Cerebrovascular event, n (%)			0.56
Stroke	32 (76)	11 (64)	
TIA	10 (24)	6 (35)	
Laboratory tests			
Total cholesterol, mmol/L	4.6±0.9	4.8±0.8	0.37
LDL cholesterol, mmol/L	2.6±0.8	2.7±0.6	0.61
HDL cholesterol, mmol/L	1.5±0.3	1.5±0.2	0.44
Triglycerides, mmol/L	1.1±0.5	1.2±0.7	0.45
Homocysteine, μmol/L	8.6±2.4	8.4±2.7	0.75
Hs-CRP, g/L	1.6±1.8	1.4±1.3	0.67
Fibrinogen, g/L	3.3±0.7	3.2±0.6	0.76
D-dimer, μg/L	0.16±0.12	0.11±0.05	0.10
Echocardiographic parameters			
PFO diameter	3.2±2.0	2.7±1.3	0.37
Degree of shunt			0.09
Small, <20 microbubbles	7 (17)	0	
Large, ≥20 microbubbles	35 (83)	17 (100)	
Eustachian valve, n (%)	12 (29)	4 (24)	0.61
Atherosclerotic burden			
Mean maximum CIMT, mm	0.76±0.21	0.72±0.17	0.46
Single maximum CIMT, mm	1.22±0.37	1.11±0.21	0.20
FMV, %	7.0±3.6	7.6±5.1	0.63
NMV, %	19.5±7.8	19.9±6.9	0.89

LDL indicates low-density lipoprotein; HDL, high-density lipoprotein; Hs-CRP, high-sensitivity C-reactive protein; NMV, nitroglycerin-mediated vasodilation.

graphic, and atherosclerotic burden characteristics of the patients with PFO associated with atrial septal aneurysm compared with those with PFO alone are shown in Table 4. There were no significant differences in cardiovascular risk factors or surrogate markers of atherosclerosis between patients with and without atrial septal aneurysm.

Discussion

The results of the present study showed that young adult patients with cryptogenic stroke or TIA exhibited significant differences in atherothrombotic burden profile depending on

the presence or absence of PFO, suggesting that different pathogenic mechanisms are involved in the occurrence of a cerebrovascular event in patients with and without PFO. Patients without PFO had a higher prevalence of traditional cardiovascular risk factors compared with patients with PFO and compared with a control group of subjects with a cardiovascular risk factor prevalence representative of the general population of the same age and sex. Patients with cryptogenic stroke/TIA and no PFO had a higher atherosclerotic burden as determined by higher CIMT and impaired endothelial function compared with patients with PFO and control subjects. Furthermore, PFO was independently associated with a lower atherosclerotic burden. Finally, no differences were observed in patients with stroke/TIA and PFO according to the presence or absence of ASA.

Lamy et al⁴ have shown that young patients with cryptogenic stroke exhibited significant differences in stroke risk factors depending on the presence or absence of PFO. In accordance with the results of the present study, patients with PFO were younger and less likely to have traditional cardiovascular risk factors as hypertension, hypercholesterolemia, or current smoking. In addition, the present study also demonstrated a higher prevalence of obesity and higher waist circumference values among patients without PFO compared with those with PFO. These 2 risk factors for atherosclerosis have recently been associated with carotid atherosclerosis and with a higher risk of ischemic stroke.^{22–24} Importantly, the prevalence of cardiovascular risk factors among patients with cryptogenic stroke/TIA without PFO was also significantly higher than that observed in a control group with a prevalence of cardiovascular risk factors similar to that reported by the Heart and Stroke Foundation of Canada for the general population of the Quebec province in the same range of age and sex.²⁵ However, it is well known that traditional cardiovascular risk factors may only partially explain the atherosclerotic burden and cardiovascular risk for a specific patient, and noninvasive tools for obtaining a more precise evaluation of the presence and severity of atherosclerosis, the so-called surrogate markers of atherosclerosis, have been extensively developed in recent years.^{7–14} Data on atherosclerotic burden in patients with cryptogenic stroke have been mostly limited to the evaluation of the presence of atherosclerotic aortic arch plaques by transesophageal echocardiography.^{26–30} These studies reported an incidence of 10% to 39% of relevant aortic plaques in patients with cryptogenic stroke, but the patients included in these studies were significantly older than our study population and the presence of aortic atherosclerotic plaques was mainly limited to patients >60 years with an incidence as low as 4% in patients <60 years. Interestingly, Handke et al³⁰ have recently shown that the absence of PFO was associated with a higher thickness of atherosclerotic aortic plaque in patients ≥55 years old diagnosed with cryptogenic stroke. The present study assessed, for the first time, the atherosclerotic burden in young adult patients with cryptogenic stroke/TIA by using 2 noninvasive surrogate markers of atherosclerosis and also evaluated the potential influence of the presence of PFO on these atherosclerotic markers. The absence of PFO was independently

associated with a higher atherosclerotic burden as determined by higher CIMT and impaired endothelial function. Previous studies have demonstrated an association between CIMT measurements and endothelial dysfunction with cerebrovascular events due to large vessel atherosclerotic disease,^{10–14} similar to that observed in the present study in patients with cryptogenic stroke/TIA without PFO. These data strongly suggest atherothrombosis as the most plausible pathophysiological mechanism involved in the cryptogenic stroke of young adult patients without PFO.

PFO was diagnosed in 59% of the patients included in the study, and this high rate of PFO was consistent with previous studies showing that approximately half of the patients ≤ 55 years old diagnosed with cryptogenic stroke had a PFO.⁶ Patients with PFO exhibited a prevalence of cardiovascular risk factors similar to that observed in a control group of subjects of the same age and sex without cerebrovascular event and was significantly lower than that observed in patients without PFO for all traditional cardiovascular risk factors except diabetes. Also, patients with PFO had similar CIMT and endothelial function values compared with the control group and much lower values than those obtained in patients without PFO. The lack of differences in atherosclerotic burden between patients with cryptogenic stroke/TIA with PFO and the control group and the pronounced differences of both groups compared with patients without PFO suggest that the pathogenic mechanism responsible for cerebrovascular events in the presence of PFO is not an atherosclerotic-mediated one. A cardioembolic link between PFO and stroke due to a paradoxical embolism from a thrombotic process in the venous system has been suggested.^{6,31,32} Other proposed alternative mechanisms of cardioembolism linking PFO and stroke have been embolism from a mural thrombus formed locally at the atrial septum within the PFO conduit¹⁹ or a greater potential for atrial arrhythmias and thrombus formation in the presence of atrial septal abnormalities.³³ Much of the controversy regarding the role of PFO in the pathogenesis of stroke has been generated by 2 large prospective studies, the PFO-ASA study¹⁹ and the PFO In Cryptogenic Stroke Study (PICCS),³⁴ which compared patients with cryptogenic stroke with and without PFO, and showed no differences in cerebrovascular event recurrence between the 2 groups at midterm follow-up. The results of the present study would support the notion of cryptogenic stroke in young adult patients with PFO as a distinct entity for which specific therapeutic research programs must be carried out to improve clinical outcomes. The presence of ASA associated with PFO has been associated with a higher risk of recurrent cerebrovascular events¹⁹ and a higher rate of multiple cerebral ischemic lesions as determined by diffusion-weighted imaging.^{35,36} We failed to demonstrate any significant differences in atherosclerotic burden according to the presence or absence of ASA, and this suggests that the mechanisms of stroke might be similar in patients with PFO with and without ASA.

Limitations

The study protocol did not include a systematic screening for silent vein thrombosis in the study population. This was left

to the discretion of the physician responsible for the patient and was only performed in a minority of patients, precluding knowledge of the exact incidence of venous thrombosis in these patients. However, previous studies have shown a very low incidence of venous thrombosis of lower extremities in such patients,³⁷ and larger studies including patients with cryptogenic stroke have already obviated the need for systematic screening for venous thrombosis in these cases.¹⁹ The number of patients with PFO and ASA was limited and further larger studies will be required to better understand the role of ASA in patients with cryptogenic stroke and PFO. Finally, echocardiographic studies were not performed in subjects without stroke/TIA (control group) precluding knowledge of the prevalence of PFO in this group.

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Disclosures

None.

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