The Prevalence of Deep Venous Thrombosis in Patients with Suspected Paradoxical Embolism

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■ *Objective:* To determine the prevalence of venous thrombosis in patients with suspected paradoxical embolism.

■ *Design:* Observational study.

■ *Patients:* Two hundred sixty-four patients with clinically suspected embolic events underwent contrast transesophageal echocardiographic evaluation. Forty-nine patients (24 women, 25 men) had a patent foramen ovale. Forty-one patients had acute stroke, and 8 had acute limb ischemia.

■ *Setting:* Echocardiography laboratory of a community hospital.

■ *Measurements:* The presence of a patent foramen ovale was assessed by transesophageal contrast echocardiography. Forty-two patients had venographic evaluation of the lower-extremity venous system.

■ *Results:* Venous thrombosis was clinically suspected in 6 patients and documented in 24 of the 42 patients with patent foramen ovale who underwent venographic study (57%; 95% CI, 41% to 72%). Venous thrombosis was confined to calf or popliteal veins in 15 cases. Fifteen of 17 patients who had venographic evaluation within 7 days of the index event had thrombosis compared with 9 of 25 patients who had later evaluations ($P = 0.001$). More patients with venous thrombosis than without venous thrombosis had a history of previous thromboembolism (13 of 24 compared with 1 of 8, respectively; $P = 0.001$).

■ *Conclusion:* When a patent foramen ovale is detected in a patient with embolism, occult leg vein thrombosis is frequently present.

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According to a recent survey (1), paradoxical embolism is considered an infrequent event, accounting for fewer than 2% of all arterial emboli. Diagnosis of paradoxical embolism is based on three criteria: evidence of arterial embolism, a right-to-left shunt, and a thrombosis in the venous system or in the right atrium. Detection of small intracardiac shunts like those in patients with a patent foramen ovale has been facilitated by contrast echocardiography. Use of this technique has resulted in the identification of young patients with embolic stroke presumably caused by paradoxical embolism via a patent foramen ovale (1–3). In a recent study, patients with cryptogenic stroke had a higher prevalence of patent foramen ovale than patients with stroke of determined cause in all age groups, even after adjustment for the presence of recognized risk factors for stroke (4). However, investigators in previous studies did not do transesophageal echocardiographic evaluations for alternative cardiogenic causes or assess the frequency of venous thrombosis.

The objectives of our study were 1) to assess the frequency of venous thrombosis in patients with suspected paradoxical embolism in whom a patent foramen ovale detected by transesophageal echocardiography was the only possible cause of embolism; and 2) to assess the effect of a history of venous thromboembolism or arterial embolic events.

Methods

Patients

Between December 1988 and January 1991, 406 patients with clinically suspected embolic events underwent transesophageal echocardiographic evaluation to search for a cardiac cause. Contrast studies were done in the 264 patients in whom established sources of emboli (endocarditic vegetations, mitral valve stenosis, left ventricular thrombi or dyssynergy, spontaneous echocardiographic contrast, left atrial or appendage thrombi, or a myxoma) could not be found.

Forty-nine patients found to have a right-to-left shunt at the atrial level constituted the study sample. They were referred to the echocardiographic laboratory from various medical and surgical departments as well as from the neurology department. Physical examination, routine laboratory tests, electrocardiographic study, and chest radiography were done in all patients. No patient showed clinical evidence of an abnormal communication between the systemic and the pulmonary circulation.

Diagnosis of Embolism

All patients with limb ischemia underwent angiography. Brain computed tomographic scanning and duplex sonographic studies of the carotid arteries were done in all patients with stroke. Cerebral embolism was diagnosed in patients if a computed tomographic scan showed a territorial infarction corresponding to the neurologic deficit and if arteriosclerotic lesions of the ipsilateral carotid artery were excluded on the basis of the sonographic studies (5).

Anticoagulant Treatment

All patients with stroke received antithrombotic prophylaxis starting on the day of admission with either 5000 units of low-molecular-weight heparin (Fragmin, Kabi Pharmacia, Uppsala, Sweden) administered once daily or 5000 units of unfractionated heparin (Liquemin, Hoffmann-LaRoche AG, Basel, Switzerland) administered subcutaneously 2 or 3 times daily. In patients with embolic occlusion of a limb artery or documented venous thrombosis, heparin was infused continuously at a dosage that prolonged the activated partial thromboplastin time from 50 to 70 seconds. After 1 week of this treatment, these patients were usually given oral anticoagulant therapy.

Diagnosis of Patent Foramen Ovale

All patients underwent transthoracic and transesophageal echocardiographic studies after informed consent had been obtained. Either a Diasonics CV (Diasonics Inc., Milpitas, California) or an Aloka SSD 870 (Aloka Co., Tokyo, Japan) with a 3.5-mHz transducer was used for transthoracic echocardiography, and either a Diasonics Varian 3400 with a monoplane 3.5-mHz probe or an Aloka SSD 870 with a biplane 5-mHz probe was used for the transesophageal echocardiography.

After visualizing both atria and the interatrial septum with the transesophageal probe, 10 mL of agitated normal saline solution was injected into an antecubital vein while the patient performed the Valsalva maneuver. When the first microbubbles appeared in the right atrium, the patient was asked to resume normal breathing. Contrast injections were repeated during normal respiration and, in cases of doubt, during a second Valsalva maneuver after a 3-minute interval to allow for disappearance of all microbubbles. A patent foramen ovale was diagnosed if two or more microbubbles crossed the interatrial septum immediately after the appearance of contrast material in the right atrium (6).

The transesophageal studies were recorded on videotapes and reviewed by a second observer from the same laboratory who was blinded to the initial assessment. Agreement on presence or absence of patent foramen ovale was reached in all cases.

Clinical Assessment

Immediately after the transesophageal echocardiographic study, patients with a patent foramen ovale were asked by the physician who did the examination about a history of previous venous thrombosis or pulmonary or systemic embolism and about a temporal relation of the actual embolic event with a Valsalva maneuver. Thereafter, the same physician inspected the legs for signs of venous thrombosis. All findings were recorded for later analysis. Screening for pulmonary embolism was not done routinely, but patients with clinical signs underwent ventilation-perfusion scanning.

Diagnosis of Venous Thrombosis

Bilateral ascending venography was proposed to all patients with a patent foramen ovale, and informed consent was obtained. The contrast agent used was iopamidol (Jopamiro, Gerot Pharmazeutika, Vienna, Austria [licensed by Bracco S.p.A., Milano, Italy]). Venous thrombosis was diagnosed in the presence of a constant intraluminal filling defect assessed by two independent observers.

The study design was approved by our institutional review board. For both ethical and methodologic reasons, we decided not to recruit a control group for venographic evaluation.

Because of the heterogeneity of the study sample, the sequence of individual examinations and intervals between examinations differed among patients.

Table 1. Localization of Venous Thrombosis in 24 Patients with Arterial Embolism and Patent Foramen Ovale

Localization	All Patients	Asymptomatic Patients
	n	
Calf veins	13	12
Extending to popliteal vein	2	2
Extending to femoral vein	8	4
Extending to iliac vein	1	0

Statistical Analysis

Data were analyzed using the Student *t*-test for numerical variables and the Fisher exact test for categorical variables (SAS Institute Inc., Cary, North Carolina). All *P* values are two-tailed. A *P* value less than 0.05 was considered to indicate significance (7). The 95% CIs for rates were calculated using the appropriate tables in *Documenta Geigy* (8).

Results

Characteristics of Patients with Patent Foramen Ovale

Transesophageal contrast study revealed a patent foramen ovale in 49 of 264 patients (19%; CI, 15% to 25%). Of these 49 patients, 24 were women and 25 were men (mean age, 58 years; age range, 31 to 85 years). The 49 patients had been admitted for stroke (36 cases), limb ischemia (7 cases), and venographically confirmed venous thrombosis (6 cases). The 6 patients with venous thrombosis (3 women and 3 men [mean age, 65 years; age range, 38 to 85 years]) developed arterial embolism during their clinical stay; 5 experienced stroke and 1 had brachial artery embolism. Contrast transesophageal studies were done 6 to 24 hours after the embolic event and 1 to 4 days after confirmation of venous thrombosis by venographic study. None of the remaining 43 patients showed clinical evidence of venous thrombosis of the legs. However, assessment was hampered in 3 of these 43 patients by acute ischemia caused by embolism in the femoral artery.

Pulmonary embolism was suspected in only 5 of the 49 patients. These 5 patients were admitted because of vein thrombosis, and ventilation-perfusion scan studies confirmed pulmonary embolism in all of them.

Seven patients without clinical signs of venous thrombosis (one woman and six men [mean age, 57 years; age range, 31 to 77 years]) did not undergo venographic study for various reasons: An alternative mechanism for the index event had been detected in four patients (one each with brain tumor, lacunar stroke, carotid artery stenosis, and subclavian artery stenosis). Venography was declined by the referring physician in two cases because the patients were known to have adverse reactions to the contrast agent, and in one case the patient refused to undergo venographic study.

Other Causes of Ischemic Events

Thirteen of the 42 patients who underwent venographic study had potential alternative causes of their embolic event: Artery-to-artery embolism was the possible cause of ischemia in 4 patients (carotid artery stenosis [2 patients], and subclavian artery stenosis [1 patient], popliteal artery stenosis [1 patient]). Lacunar lesion was the possible cause of stroke in 4 other patients. Embolism from the left atrium had to be considered in 5 patients with chronic or intermittent atrial fibrillation, but neither left atrial thrombi nor spontaneous echocardiographic contrast was detected in these patients.

Prevalence of Venous Thrombosis

Venographic study was done in 42 patients and showed abnormal findings in 24 patients (Table 1). The procedure was well tolerated by all patients, and no complications due to the contrast agent were observed. Venographic study was done within 1 week before or after the embolic event in 17 patients and showed venous thrombosis in 15 patients (Table 2). The other 25 patients underwent venographic study 8 to 90 days after the embolic event, and venous thrombosis was detected in 9 patients, yielding a significantly lower rate than that seen in patients who underwent evaluation within a week of the embolic event ($P = 0.001$). Of the 42 patients who underwent venographic study, 29 patients (16 women and 13 men [mean age, 59 years; range, 37 to 85 years]) had no detectable alternative cause of their ischemic event, and the only explanation for their event was paradoxical embolism via the patent foramen ovale. Nineteen of these 29 patients (66%; CI, 46% to 82%) had venous thrombosis of the lower limbs that was detected by venographic study; venous thrombosis had been clinically unsuspected in 13 of these 19 patients. The frequency of deep venous thrombosis in these patients was not statistically different from that seen in patients with alternative causes of ischemia ($P = 0.2$). However, among the 17 patients who had venographic evaluation within 1 week of the index event, the 15 patients with abnormal findings were those who did not have alternative causes of ischemia (*see* Table 2).

History of Venous Thromboembolism and Results of Venography

Thirteen of the 24 patients with an abnormal venogram had a history of venous thromboembolism

Table 2. Clinical and Historical Data in Patients with Abnormal and Normal Venograms

Data	Abnormal Venogram (n = 24)	Normal Venogram (n = 18)	P Value
Mean age ± SD, y	59 ± 15	57 ± 12	>0.2
Female/male, n/n	12/12	10/8	>0.2
Venographic evaluation within 1 week of index event, n	15	2	0.001
History of previous venous thrombosis, n	13	1	0.001
History of arterial embolic events, n	6	2	>0.2
Potential alternative cause of index event, n	5	8	0.2
Stroke as index event, n	19	16	>0.2
No clinical signs of thrombosis, n	18	18	0.03

(*see* Table 2). Of the 18 patients with normal venograms, only 1 had a history of venous thrombosis ($P = 0.001$).

Six of the 24 patients with an abnormal venogram had a history of previous arterial embolic events and none had a possible cause of embolism apart from a patent foramen ovale.

A close temporal relation between performance of the Valsalva maneuver and the actual embolic event was detected in 5 of 49 patients. In 2 of these patients, venograms were abnormal 2 and 4 days after the embolic event, respectively. In two other patients, venograms were normal 10 and 70 days after the embolic event, respectively. In 1 patient, venography was declined by the referring physician. In these 5 patients, no alternative mechanism for the embolic event could be detected.

Discussion

Recent reports have suggested that paradoxical embolism may be more common than previously thought (1–4). However, neither transesophageal contrast echocardiography nor any investigation of the veins was done in those studies. Transesophageal echocardiography has been shown to be superior to transthoracic echocardiography in recognizing patent foramen ovale by using either color-coded Doppler sonography or contrast injections (6, 9, 10). Autopsy studies have shown that the foramen ovale is patent in 27% of otherwise normal human hearts (11). The reported prevalence of patent foramen ovale as assessed by transesophageal contrast echocardiography varies considerably, ranging from 8% to 54% (6, 12, 13). The striking differences among rates may be attributable to several factors: the study population, the technique used, and the criteria applied for diagnosis of patent foramen ovale (14).

Selection bias was a factor in our study: Transesophageal contrast studies were done only in those patients in whom no other potential cardiac source of embolism could be detected by echocardiography. In our study, the detection rate for patent foramen ovale was only 19% (CI, 15% to 25%); this rate might be attributable to the underlying disease because stroke may hinder patients from performing an adequate Valsalva maneuver. An identical rate of 19% (CI, 15% to 25%) for patent foramen ovale was observed in our laboratory in a group of unselected patients: In an interlaboratory comparison, it was shown that our diagnostic criteria yielded a lower rate of patent foramen ovale than those applied by the other laboratory (14).

Study patients were recruited from the echocardiographic laboratory. The patients were referred from several departments. Thus, the tests corroborating a cardiogenic mechanism for the presumed embolic event could not be done according to a fixed protocol. Twelve patients initially included in the study because of a patent foramen ovale were diagnosed on the basis of the results of transesophageal contrast echocardiography; however, subsequent diagnostic tests showed more probable noncardiogenic mechanisms for ischemic symptoms: artery-to artery-embolism in 6 patients, lacunar stroke in 5 patients, and brain tumor in 1 patient.

Five other patients with embolic stroke and atrial fibrillation may have had an embolic cause other than patent foramen ovale, although no left atrial thrombus or spontaneous echocardiographic contrast was detected.

Clinical signs of leg vein thrombosis are evident in fewer than 50% of patients who have pulmonary embolism. In contrast, a prospective study found a 71% rate of venous thrombosis in patients who underwent venographic study (15), and an autopsy study showed a rate of up to 83% (16). These findings clearly underscore the importance of performing appropriate tests of the leg veins when paradoxical embolism is suspected, even if clinical signs are inconspicuous.

Noninvasive testing of the lower limbs by plethysmography or ultrasound studies is impeded by the limited sensitivity of these studies in isolated calf vein thrombosis (17). Radionuclide scanning of the veins can overcome this problem (17), but, because of technical reasons, the availability of such scanning was limited at our hospital.

When all patients with arteriosclerotic lesions and a possible additional cardiac origin of embolus are excluded from the analysis, 19 of 29 patients (66%; CI, 46% to 82%) in our series had documented deep venous thrombosis, and in two thirds of patients thrombosis was clinically silent. These rates are consistent with those seen in patients with pulmonary embolism (15). Theoretically, thrombosis might have developed as a consequence of stroke or bed-rest rather than having been the cause of arterial embolism. The prevalence of deep venous thrombosis in patients with stroke varies between 20% and 80% but is reduced to 4% to 13% when low-dose heparin is administered prophylactically (18, 19). In an unpublished study done at our institution, deep venous thrombosis was not detected by duplex sonography in any of 56 bed-ridden patients who received heparin prophylactically. All patients with stroke in our series had received prophylactic heparin therapy, so secondary thrombosis was an unlikely factor in most cases, particularly because 63% (CI, 41% to 81%) of the abnormal venograms were obtained within 1 week of the ischemic event. Moreover, all 15 venograms obtained within the first week in patients without alternative causes of ischemia were abnormal. A trend toward a higher frequency of venous thrombosis in patients without alternative causes of ischemic events was observed when such patients were compared with patients who had alternative causes of ischemic events ($P = 0.2$).

Patients with an alternative cause of their ischemic event, however, do not constitute an appropriate control sample because some may well have experienced a paradoxical embolism in the setting of patent foramen ovale.

One third of our patients had a normal bilateral venogram, but such a finding does not rule out paradoxical embolism: Thrombosis may be localized in nonvisualized deep veins of the legs or the pelvis. In cases of delayed examination, the thrombosis may have undergone spontaneous lysis, complete embolization, or recanalization. These latter mechanisms may have operated in several of our cases because 16 of 18 normal venograms were obtained 8 to 90 days after the index event.

One of 18 patients with a normal venogram and 13 of 24 patients (54%; CI, 33% to 74%) with an abnormal venogram had a history of previous venous thromboembolism. This striking difference raises the possibility of an underlying coagulopathy. If a procoagulatory state were present, however, the issue would still remain whether venous thrombosis was attributable to insufficient prophylaxis by routine low-dose heparin therapy in this setting or was a primary event that enhanced the potential for paradoxical embolism.

Twenty-five percent (CI, 10% to 47%) of patients had previous arterial embolic events; in all 25%, patent foramen ovale was the only possible cause, raising the possibility of repeated paradoxical embolism in this sample.

In patients with embolic events, a history of previous venous thromboembolism and the onset of symptoms in association with a Valsalva maneuver should alert the clinician to the possibility of paradoxical embolism.

The demonstration of a right-to-left shunt—either by transesophageal contrast echocardiography or by transcranial Doppler sonography (20)—should prompt a diligent investigation of the venous system, regardless of whether clinical signs of venous thrombosis are observed. To confirm the diagnosis of paradoxical embolism, the interval between onset of symptoms and investigation of the venous system should be as short as possible.

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TO S.M

I am not willing you should go
Into the earth, where Helen went;
She is awake by now, I know.
Where Cleopatra's anklets rust
You will not lie with my consent;
And Sappho is a roving dust;
Cressid could love again; Dido
Rotted in state, is restless still:
You leave me much against my will.

Edna St. Vincent Millay
Collected Poems
Harper and Row, New York, 1956, p. 147

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