

# Peripheral Ischemia Caused by Paradoxical Embolization:

## An Underestimated Problem?

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### Abstract

Although a patent foramen ovale (PFO) is often found in younger patients with transient ischemic attacks or stroke, paradoxical embolization through PFO is rarely considered as a cause of acute limb ischemia.

We report a single-center experience of 5 consecutive patients with limb-threatening ischemia due to paradoxical embolization within a one-year period. All patients were treated by catheter thrombectomy and long-term oral anticoagulation after surgery.

The fact that the 5 embolectomies made up 10% of all embolectomies performed in our center during this time interval may indicate that the role of paradoxical embolization is still underestimated in peripheral embolic disease.

**Key Words:** Paradoxical embolism, patent foramen ovale, peripheral ischemia.

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### Introduction

A PATENT FORAMEN OVALE (PFO) is often found in younger patients with stroke, (1–3). Although the embolic source in the venous system and the conditions for the development of a right-to-left pressure gradient enabling thrombus material to pass through the septal defect often remain unclear retrospectively, it is commonly accepted that paradoxical embolism is the pathophysiologic linkage between PFO and cerebral ischemia (3). In contrast to stroke, paradoxical embolization is still rarely considered as a possible cause of acute limb ischemia and might therefore be underestimated (4–7). We present a series of patients with PFO and acute limb ischemia encountered in a one-year period, presumed to be due to paradoxical embolization. We also review the literature on diagnostic procedures and therapeutic options to prevent recurrences.

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### Case Reports

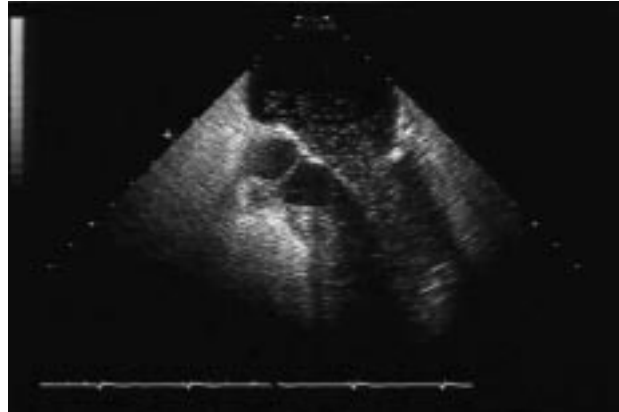
#### Case 1

A 78-year-old woman was admitted with acute ischemia of the right arm and treated with emergency catheter embolectomy of the distal brachial and cubital arteries. Electrocardiogram (ECG) recordings documented constant sinus rhythm. Transesophageal echocardiography did not reveal a cardiac source of embolization but showed tricuspid regurgitation in the presence of pulmonary hypertension (systolic PAP at least 45 mm Hg). The patient was finally discharged on oral anticoagulation therapy, but had to be readmitted three days later with acute ischemia of the right leg despite adequate anticoagulation (INR 3). Duplex sonography identified an embolic occlusion of the popliteal artery (Fig. 1). Aspiration embolectomy failed and surgical embolectomy had to be performed. The postoperative course was complicated by a retroperitoneal hematoma, requiring surgical treatment, and the onset of acute dyspnea. After recovery, a more extensive diagnostic evaluation at this point identified a 10 mm PFO with spontaneous right-to-left shunt (Fig. 2, Table 1). Furthermore, a clinically asymptomatic right popliteal vein thrombosis was



**Fig. 1.** Arteriogram demonstrating embolic material in the right popliteal artery.

diagnosed by compression ultrasound and multifocal pulmonary artery embolization by spiral CT scan. Because pulmonary embolism occurred de-



**Fig. 2.** Transesophageal echocardiography demonstrating a right-to-left shunt.

spite sufficient anticoagulation, a vena cava filter was implanted. Closure of the PFO was not performed, considering the advanced age of the patient and possible associated complications. Further follow-up was uneventful.

### Case 2

A 64-year-old man with sudden onset of severe leg pain three weeks prior was admitted with decompensated ischemia of the left leg. Duplex sonography and angiography revealed a thrombotic occlusion of the popliteal and distal femoral arteries, as well as a partial occlusion of the calf arteries in the absence of atherosclerotic wall lesions. Catheter embolectomy of the calf arteries was performed successfully, but the femoropopliteal artery rethrombosed. Therefore, a femoro-tibial vein bypass was implanted. Perioperative ECG recordings documented ventricular extrasystoles but constant sinus rhythm. Transesophageal echocardiography revealed a 6 mm PFO but no aneurysm (Table 1). Spontaneous right-to-left-shunt could not be documented, nor could a deep vein thrombosis. Oral anticoagulant therapy was started and had to be maintained to prevent bypass failure.

### Case 3

An 83-year-old woman presenting with limb-threatening ischemia of the right leg was admitted for catheter embolectomy of the iliacal, femoral and popliteal arteries. Because of the long-lasting ischemia (8 hours), subcutaneous medial and lateral fasciotomy of the lower leg also had to be performed. Serial ECG recordings documented a constant sinus rhythm. Transesophageal echocar-

**TABLE 1**  
*Results of Transesophageal Echocardiography in all 5 Cases (No Patient Had an Increased Membrane Mobility)*

Case	Size PFO	Aneurysm	Spontaneous	Pulmonary R-L Shunt	DVT Hypertension	PE
1	10 mm	N	Y	Y	Y	Y
2	6 mm	N	unknown	N	unknown	unknown
3	unknown	Y	Y	Y	unknown	Y
4	unknown	N	Y	Y	Y	Y
5	unknown	N	N	N	N	N

DVT = deep venous thrombosis; PE = pulmonary embolism; N = no; Y = yes; R-L = right to left; PFO = patent foramen ovale.

diography detected an aneurysm of the atrial septum and a PFO with spontaneous right-to-left shunt (Table 1). In the right pulmonary artery near the main truncus, a thrombus (25 × 10 mm) could be seen; it led to a luminal occlusion of 25%. However, the right ventricle was dilated and had normal function. Due to unfavorable conditions, pulmonary artery pressure could not be determined and deep vein thrombosis could not be identified by duplex sonography. Postoperatively, the patient received continuous unfractionated heparin followed by long-term warfarin therapy. Closure of the PFO was not performed, because of the pulmonary embolism and the advanced age of the patient.

#### Case 4

A 73-year-old man was admitted with ischemic paresthesia of the right lower limb of 3 days' duration and increasing dyspnea over the previous month. Clinically, the patient presented with a cold leg and no femoral or popliteal pulse. Two hours later, an acute artery occlusion of the left arm occurred, requiring urgent catheter embolectomy. Ischemia was caused by an extensive embolus of the subclavian and brachial arteries. Postoperative dyspnea and tachycardia with multiple extrasystoles occurred, and the right leg became paralyzed. Duplex sonography detected occlusion of the right superficial femoral artery and fresh emboli in the profunda femoral artery. Consequently, catheter embolectomy of the common, superficial and profunda femoral arteries was performed, successfully, followed by a patch angioplasty of the femoral artery. Transesophageal echocardiography identified a PFO with spontaneous right-to-left-shunt and hypertrophy of the left ventricle, but no aneurysm (Table 1). Multiple pulmonary emboli on both sides and a deep vein thrombosis (popliteal vein) were diagnosed by spiral CT. Oral anticoagulation was started to avoid further embolic events.

#### Case 5

A 62-year-old woman was admitted with acute ischemia of the left arm. The patient complained of sudden onset of arm pain followed by paresthesia. Duplex sonography revealed embolic occlusion of the distal axillary and brachial arteries. Transbrachial catheter embolectomy was performed successfully. Six months earlier, a PFO with a spontaneous left-to-right shunt had been diagnosed by transesophageal echocardiography, but there was no proof of intracardial thrombus or aneurysm (Table 1). At that time, treatment with digitalis and short-term warfarin therapy was started because of paroxysmal atrial fibrillation. Pre- and postoperative ECGs documented a constant sinus rhythm, and cranial CT detected a hypodense cortical area without neurological correlation. Warfarin therapy was reintroduced.

#### Discussion

Paradoxical embolization was first described by Cohnheim in 1877 (8). In most cases the passage for the thrombus from the venous into the arterial circulation was found to be a patent foramen ovale (9).

PFO has often been reported in patients with transient ischemic attacks (TIA) or stroke, and there is increasing evidence that a causative relationship exists between these two pathologies, especially in younger patients with sinus rhythm and normal cerebral arteries (1–3, 10). In contrast to cerebral embolization, PFO has rarely been reported in patients with peripheral ischemia.

Paradoxical embolization was found in 14 of 406 cases of arterial embolism in the series published by AbuRahma and Downham (6), which covered an 8-year period, and in 7 patients in the analysis of hospital records from 1970–1993 by Chaikof et al. (5). More recently, Travis et al. (7) published their data of a 10-year period from 1989–1999, in which paradoxical embolization

accounted for only 13 cases of acute arterial occlusion, including 3 cerebral and 2 bowel infarctions. All of these series were retrospective analyses that included a high percentage of cases with uncertain embolic sources and incomplete work-up.

Our single-center experience of 5 consecutive patients presenting within less than 12 months with limb-threatening peripheral emboli of cryptogenic origin and a final diagnosis of PFO might indicate that the role of paradoxical embolization is still underestimated in peripheral embolic disease. This argument is strongly supported by the fact that the 5 embolectomies in our series made up about 10% of the embolectomies performed in our center within the time period between August 2001 and June 2002. On the other hand, the coincidence of a PFO and a peripheral embolic event in the same patient does not necessarily mean that there is a causal relationship (2). PFO was reported to be present in up to 25–35% of the general population at autopsy and in 10–18% in transthoracic contrast echocardiographic studies (9, 11), whereas Fisher et al. (12) reported an incidence of 9.2% in 1,000 consecutive patients who underwent transesophageal echocardiography for various indications.

Diagnosis of systemic embolization due to PFO therefore requires three conditions: (a) the presence of a thrombus through the PFO or the diagnosis of a thromboembolic source in the venous system; (b) the presence of a transient atrial pressure gradient allowing right-to-left transition of the embolic material; and (c) exclusion of a left-sided embolic source (10). In peripheral embolization, one might additionally require that the size of the PFO be large enough to allow passage of clots capable of blocking the lumen of the typically affected peripheral arteries, i.e., the popliteal and brachial arteries. Thomson and Evens (9) found PFO of 0.2–0.5 cm in 29% and PFO of 0.6–1.0 cm in 6% of their autopsies, whereas an average PFO size of 1.23 cm was reported by Bridges et al. in their series (13).

It is easy to detect a right-to-left shunt with contrast transcranial Doppler sonography of the middle cerebral artery, especially when Valsalva's maneuver is used for an increase in right atrial pressure (14, 15). Nevertheless, only transesophageal multiplane contrast echocardiography (transesophageal echocardiography) is capable of determining the exact morphological and functional characteristics of an atrial defect (16, 17). Transcranial Doppler sonography might therefore be used as a screening test; however, confirmation and specification by transesophageal echocardiography is still necessary (18).

As with stroke, morphologic and functional characteristics of the PFO can help to identify sub-

groups of patients at higher risk for paradoxical embolization and recurrences after a first event. These factors include PFO > 4 mm, detection of a spontaneous right-to-left shunt, large shunt volume, increased membrane mobility, and concomitant atrial septal aneurysm (17, 19–21).

A PFO > 4 mm was confirmed in only 2 cases of our series, but routine transesophageal echocardiography examinations in the series focused more on the detection of a PFO and on the identification of an interatrial shunt than on exact measurements of PFO size. Spontaneous right-to-left shunt was detected in 3 patients. In case 3, echocardiography also revealed a septal aneurysm. Pulmonary hypertension due to pulmonary embolism was detected in all three patients with a right-to-left shunt, and in all of these patients, deep venous thrombosis of the legs was confirmed by compression ultrasound. On the other hand, detection of deep venous thrombosis can be difficult, especially when diagnostic measures are performed late in the course of the illness (22). Even bilateral phlebographic examination immediately after stroke was reported to be successful only in about 10% of the patients (23). More extensive work-up, including bilateral duplex sonography, and magnetic resonance tomography of the pelvic veins, can increase the detection rate of venous thrombosis in the case of pulmonary embolism (24, 25); however, data on PFO are missing.

Obviously, the strict diagnostic criteria for paradoxical embolization formulated by Johnson (10) guarantee high specificity but lack sensitivity. As applied to our patients, the diagnosis of paradoxical embolization could be confirmed in only 3 of the 5 cases. From a more practical viewpoint, the diagnosis of paradoxical embolization might also be permitted in the case of confirmed PFO and the carefully elaborated exclusion of other thromboembolic causes (4, 26), which was the case in our remaining patients. On the other hand, the latter approach does not always allow distinction between a "causative" PFO and an "innocent" PFO (2), as might best be illustrated by case 5 of our series.

Valid data to determine the exact risk of recurrences in case of peripheral embolization due to paradoxical embolization are missing. In stroke, the Lausanne and the French study groups reported recurrences of 3.4–3.8% for stroke and 1.2–1.9% for transient ischemic attacks in patients treated with salicylic acid (26, 27). Low recurrence rates were also confirmed by a recent meta-analysis (28). Homma et al. were able to show that medical treatment can safely prevent recurrences even in cases with PFO and septal aneurysms (29). In contrast to this data, 9–11% high-risk patients were

formerly reported to suffer from recurrent cerebrovascular events annually (26, 30, 31).

Long-time results of surgical closure of the PFO are limited to small, uncontrolled series, for whom studies have reported recurrent cerebral events in 0–19.5% of those treated (30, 32, 33). In their retrospective analysis of 91 patients, Dearani et al. (33) found no cerebral infarctions during a 4-year follow-up, but identified TIAs in 16% of the surgically treated patients without evidence of a residual shunt, indicating incorrect diagnosis or additional embolic sources in many patients.

Despite uncertain long-term results, percutaneous PFO closure as a minimally invasive procedure is now acceptable (13, 34–42). Bridges et al. (13) reported four TIAs in 34 patients, and 6 residual shunts were identified within 4–8 months after the intervention. In an uncontrolled study by Wahl et al. (36) dealing exclusively with PFO, the technical success rate was 98% and the complication rate 10%. During the follow-up, residual shunting was detected in 27% of the patients. Freedom from recurrence of the combined endpoint of TIA, ischemic stroke, and peripheral embolization in the study of Sievert et al. (38), dealing with 281 septal defects, was 95.7% at one year and 94.1% at 3 years. These mid-term-results were confirmed by others concentrating on PFO only (35, 37, 40, 42). Braun et al. (41) even published a 0% recurrence rate of stroke and peripheral emboli in 246 patients with percutaneous PFO closure over an average of 15.1 months and a TIA rate of only 1.7% within the same time period (Table 2).

Nevertheless, neither surgical nor percutaneous closure can treat or prevent pulmonary embolism in cases of deep venous thrombosis. Therefore, antithrombotic therapy is still considered to be the

first-line therapy in cases with venous thromboembolism (28) (Table 3). All of our patients received unfractionated heparin followed by acenocoumarol with a target INR of 2–3. In one of our cases, a vena cava filter was additionally implanted because pulmonary embolism occurred despite satisfying anticoagulation therapy. Patients in whom venous thromboembolism cannot be confirmed can be treated with aspirin alone. A recent subanalysis of the Warfarin-Aspirin Recurrent Stroke Study stated that with either medical therapy, the presence of PFO in stroke patients did not increase the chance of adverse events, regardless of PFO size or the presence of atrial septum aneurysm (29).

**Summary**

According to our experience, it must be assumed that paradoxical embolization through PFO

**TABLE 3**

*PFO: Recommended Therapeutic Approach—Consider as First-Line Therapy*

<b>oral anticoagulation</b>	in all cases with proven DVT or PE or concomitant disease requiring oral anticoagulation
<b>ASA</b>	in all other cases with first event
<b>percutaneous PFO closure</b>	in all patients with contraindications for medical therapy in all patients with recurrences under medical therapy in all high-risk-patients*

\*one of the following: large PFO, spontaneous R-L-shunt, increased membrane mobility, atrial septal aneurysm. DVT = deep venous thrombosis; PE = pulmonary embolism; ASA = acetylsalicylic acid.

**TABLE 2**

*Technical Success, Early Complication Rates and Embolic Recurrences in Trials with >100 Patients Dealing with Percutaneous Closure of PFO.*

author	n	Technical Success	Device Migration	Pericardial Tamponade	Follow-up	TIA	Stroke	Peripheral Embolization
Onorato et al. (42) (2003)	256	100%	0%	0.4%	1.6 y	0.4%	0%	0%
Martin et al. (40) (2002)	110	100%	0.9%	0.9%	2.3 y	0.9%	0.9%	0%
Braun et al. (41) (2002)	276	100%	0.7%	0%	1.3 y	1.7%	0%	0%
Wahl et al. (36) (2001)	132	98%	3%	0.8%	1.8 y	4.5%	0%	1.5%
Sievert et al. (38) (2001)	281	100%	0.7%	0%	1 y	2.5%	0.7%	0%

n = patient number; y = year(s); TIA = transient ischemic attacks.

is still underestimated in peripheral embolic disease. Therefore, all cryptogenic embolizations should undergo multiplane contrast transesophageal echocardiography or at least contrast transcranial Doppler sonography of the middle cerebral artery as a screening test. Once a PFO has been confirmed, bilateral compression ultrasound or bilateral phlebography of the legs should be performed. Pulmonary embolism as a cause of right atrial pressure increment is best detected by lung scintigraphy or CT angiography. Anticoagulant therapy with a target INR of 2–3 should be started in all cases with proven venous thromboembolism. Aspirin alone might be equally effective in preventing recurrences in cases without detection of a thromboembolic source. Percutaneous closure of the PFO can be considered as first line therapy in high-risk patients as well as in patients at risk for anticoagulant therapy. Percutaneous closure of the PFO should also be performed in cases of recurrences most likely related to paradoxical embolization despite adequate antithrombotic or antiplatelet therapy, or in patients who have contraindications for these drugs.

To optimize the therapeutic approach in symptomatic PFO, randomized controlled studies directly comparing medical versus interventional therapy are urgently needed (43).

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