

## PARTICULAR SITUATIONS OF PARADOXICAL EMBOLISM - CASE PRESENTATIONS

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**Abstract:** Patent Foramen Ovale (PFO) is a congenital anomaly with a prevalence of 25% in the general population and approximately 55% in patients with cryptogenic stroke under the age of 55 years. We present two cases of patients with PFO discovered accidentally as a result of thromboembolic complications. The first patient, elderly with multiple risk factors for hypercoagulability was hospitalised with left upper limb ischemia secondary to thromboembolism through a previously silent PFO. The treatment included urgent thrombo-embolectomy and post-operative anticoagulation. In contrast, the second patient, a 33-year-old man with motor deficits of the left limbs, appeared without an apparent cause. Imaging examinations confirmed ischemic stroke without the presence of common aetiology. The transesophageal echocardiography (TEE) revealed a PFO. The patient was sent to percutaneous closure with good evolution.

**Key words:** patent foramen ovale, paradoxical embolism, limb ischemia, ischemic stroke.

### 1. Introduction

A patent foramen ovale (PFO) is a communication across the interatrial septum determined by a structural defect

of the septum primum and septum secundum with its base opening into the right atrium. The prevalence of PFO is 25% in the general population, but is significantly greater (more than 50%) in

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patients with cryptogenic stroke under the age of 55 years old. Young people are most affected by this structural defect, because of the fact that PFO, allowing paradoxical embolization of thrombotic material from the venous system to the arterial system, could play a key role in the pathogenesis of cryptogenic acute peripheral limb and cerebral ischemia without any obvious cause [8].

Thromboembolic strokes are the most frequent manifestations of paradoxical embolism while acute limb ischemia is less common. Using imaging methods, diagnosis of this condition became easier, but the therapeutic approach remains uncertain due to its rarity.

Treatment include heparin treatment or thrombolysis and surgical thrombectomy.

The aim of this paper is to present two cases of PFO discovered accidentally as a result of thromboembolic complications.

## **2. Case Presentations**

### **2.1. Case 1**

A 85-year-old woman with a past medical history of: stroke, hypertension, left ventricular hypertrophy, bigeminated ventricular extrasystoles, presented at the County Clinic Emergency Hospital of Brasov, Emergency Department in November 2020 for anterior chest wall pain and simultaneous pain in the left

upper limb, with an onset of approximately 3 hours, without having an associated personal and family medical history with these symptoms.

The initial diagnosis based on clinical and paraclinical data was acute coronary syndrome – ST elevation myocardial infarction (STEMI) and the patient was hospitalized in Coronary Intensive Care Unit. Subsequently, the mentioned pathology was denied. On physical examination, the patient appeared in moderate distress: tachycardia (93 beats per minute), hypertension - arterial blood pressure (ABP)=185/72mm Hg, oxygen saturation 95% on 3 liters/minute of oxygen per minute (3 l O<sub>2</sub>/min) through a nasal cannula. Examination of the cardiovascular system showed regular rhythm, with no obvious added sound, a left upper limb with pale skin, without arterial pulse at the left radial and brachial. Fine basal rales were heard throughout both lungs. The rest of the physical examination was normal.

Electrocardiogram (ECG) highlighted: sinus tachycardia with a ventricular rate of 93 beats/minute, QRS axis -30°, elements of left ventricular hypertrophy with secondary repolarization changes, monomorphic, isolated ventricular extrasystoles (Figure 1).

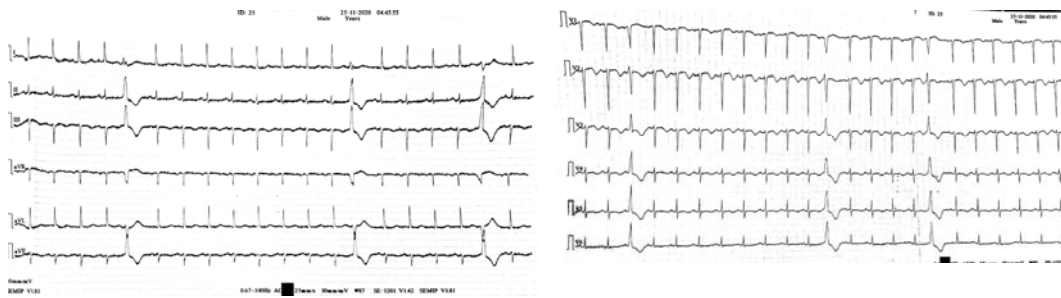


Fig. 1. ECG at hospital admission

The diagnosis of acute left upper limb ischemia was established and the patient was transferred urgently to the Vascular Surgery Department. Left axillary- brachial thrombo-embolectomy was performed with the Fogarty catheter, without obtaining a pulsating flow. It was decided to perform left carotid-axillary bypass with intervascular prosthesis 6. The postoperative evolution was good: left upper limb with distal pulse present, healing of surgical wounds without complications or fever.

Contrast transthoracic echocardiography (TTE) study was performed on postoperative day (POD) recommended by cardiological consultation and highlighted PFO with a right to left intracardiac shunt. TTE showed also nondilated left ventricle, normal left ventricular systolic function, moderate concentric hypertrophy, interatrial septal aneurysm, without any other significant issues (Figure 2).



Fig. 2(a): Transthoracic echocardiogram with intravenous agitated saline displaying a "slit-like" channel between the left and the right atria, revealing the presence of a persistent foramen ovale

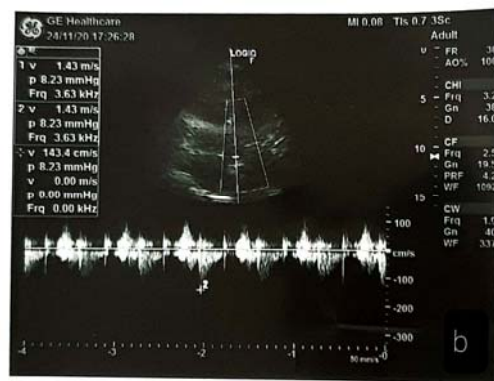


Fig. 2(b): Color flow Doppler was used to observe whether there was any right-left shunt at the foramen ovale of the interatrial septum.

Transesophageal Echocardiogram (TEE) was not performed because it had a low indication in this case. Suspicion of limb ischemia secondary to intracardiac thrombus was low in light of PFO identification at TTE. Identification of a PFO heightened suspicion for paradoxical embolism.

The second ECG highlighted a sinus rhythm, with a ventricular rate of 85 beats/minute, QRS axis 30°, elements of LV hypertrophy with secondary repolarization changes, monomorphic, bigeminated VE, no other evolving aspect compared with admission ECG (Figure 3).



Fig. 3. ECG during hospitalization

Laboratory: Basic and advanced blood investigations pointed out leukocytosis with neutrophilia, thrombocytosis, mild hypokalemia, cardiac enzymes within normal limits, normal renal function.

During hospitalization, as soon as the diagnosis of ischemia has been established the patient was anticoagulated with unfractionated heparin (UH), followed by vitamin K antagonists, analgesics, antibiotics, probiotics, antithrombotic agents, antihypertensive drugs (beta blocker after overcoming the acute ischemic episode, ACE inhibitors), magnesium.

Case particularity: Due to the patient's multiple comorbidities (e.g., hypertension,

stroke) and high surgical risk, anticoagulant treatment appears to be an acceptable therapeutic alternative to surgery for closure of patent foramen ovale.

## 2.2 Case 2

A 33-year-old male, former smoker, known with upper digestive bleeding, externalized by melena in the recent history, under investigation, presented in December 2020 at the County Clinic Emergency Hospital of Brasov for motor deficits of the left limbs and cutaneous paresthesia at this level, beginning in the morning. The patient wanted to get

dressed and suddenly appeared an episode of dizziness, remitted. The patient denied any chest pain, dyspnea or palpitations. From the family history, his father died of gastric cancer at the age of 42. His only medication was proton pump inhibitors.

At admission, the patient was in moderate general condition, facial and conjunctival pallor, without edema in the lower limbs, normotonic, normo-kinetic muscular system in the right limbs, hypotonic, hypokinetic in the left limbs, chest wall symmetric, clear to auscultation bilaterally, no wheezes, no rales, with a

blood pressure of 140/80 mmHg, pulse rate of 103 beats/minute, regular rhythm, peripheral pulses present bilaterally, abdomen mobile with breathing, without distension, painless spontaneously or on palpation, intestinal transit present, normally, without melena, without detectable organomegaly, normal urogenital.

Emergency cardiological consultation was performed, ECG on admission reveals a sinus rhythm, ventricular rate 87 beats/min, QRS axis at  $60^\circ$ , normal PR interval, without repolarization changes (Figure 4).

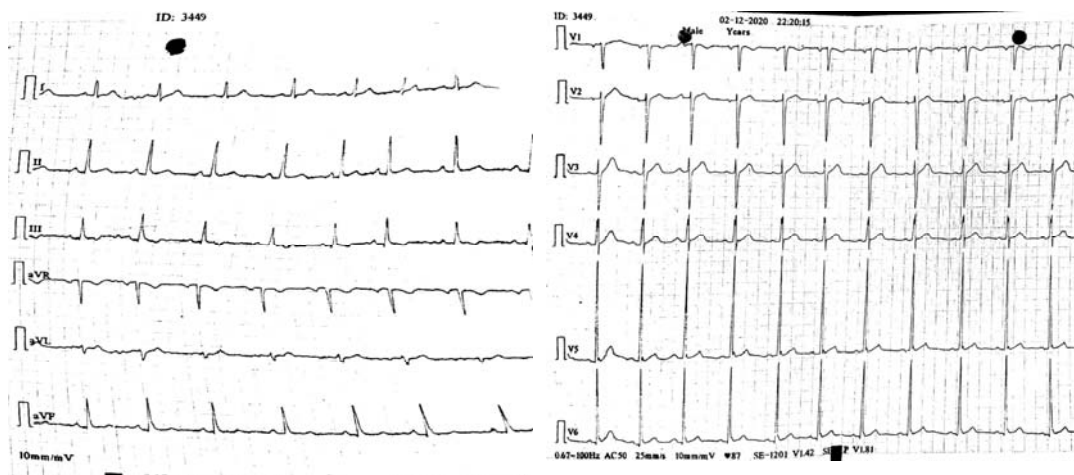


Fig. 4. ECG at admission

Emergency TTE showed an nondilated LV, normal LV systolic function, ejection fraction (EF)  $>50\%$ , without significant hemodynamically valvulopathies, the interatrial septum seems intact on TTE, normal diameter of ascending aorta, no dilated right cavities, right ventricle (RV)-

right atrium(RA) gradient RV-AV 20 mmHg, no dilated inferior vena cava with complete respiratory collapse.

The cranial computer tomography (CT) scan showed hypodense lesion area in the posterior arm of the right internal capsule of about 1.2 cm. (Figure 5)



Fig. 5. *Cranial computer tomography*

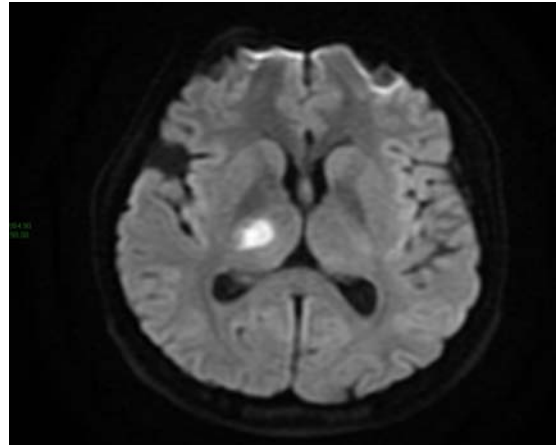


Fig. 6. *Magnetic resonance imaging T2*

Magnetic resonance imaging (MRI) of the brain shows acute temporal and right thalamic ischemic lesions, right frontotemporal arachnoid cyst (Figure 6).

Laboratory: hemoglobin 10.2 g/dL, hematocrit 30.8%, mild normochromic normocytic anemia, a consequence of prior history of gastrointestinal bleeding. Other evaluated laboratory parameters were within normal limits.

The patient was hospitalized in the Neurology Department, with the diagnosis of acute ischemic stroke in the territory of the right middle carotid artery. During hospitalization, the treatment was: antiplatelet agent (Aspenter 75 mg quaque die (qd)), low-molecular-weight heparin (LMWH) in therapeutic dose, statin (Sortis 80 mg qd), proton pump inhibitor (Controloc 40 mg qd), vitamins (Vit B<sub>1</sub>, B<sub>6</sub>), hydro-electrolytic rebalancing

therapy, neurotropic and neuro-roborant medication, with favorable evolution.

Cardiological reassessment included TTE to detect the cause of the stroke, Doppler ultrasound of the carotid arteries and the continuation of investigations for upper digestive bleeding. Bidimensional (2D) TTE may suggest FOP by extensive movement of the interatrial septum and by association of the interatrial septal aneurysm. Examination of color Doppler, recommended to be done with a low speed scale can highlight in some cases the presence of the shunt. The sensitivity of transthoracic ultrasound can be greatly increased by injecting bubbled saline and using challenge maneuvers to temporarily increase the pressure in the right atrium [9]. In 2D TEE with bubble study, PFO was confirmed (Figure 7).

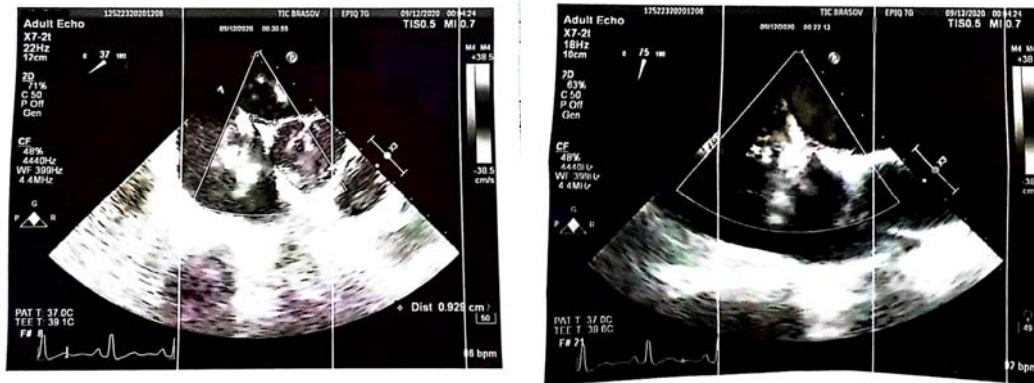


Fig. 7. TEE highlights PFO with left to right bidirectional shunt confirmed by examination with bubbled serum

The patient was discharged with the recommendations for further medical therapy with vitamin K antagonists (VKAs) or a new oral anticoagulant (NOAC) after investigating the causes of gastrointestinal bleeding with gastroscopy, proton pump inhibitor (Omez 20 mg qd), statin (Sortis 40 mg qd), neurotropic medication. The patient requires thrombophilia testing after 3-6 months of oral anticoagulant therapy.

The patient has indication of percutaneous transcatheter patent foramen ovale closure.

### 3. Discussions

#### 3.1. Case 1

Acute limb ischemia is the most common complication of intracardiac thrombo-embolism due to common conditions such as atrial fibrillation [7]. In the absence of heart disease or risk factors, other particular causes of thromboembolism should be discovered and appreciated. Due to the fact that PFO exists in 15-35% of the adult population,

paradoxical PFO mediated embolism would require a differential diagnosis for all types of unprovoked acute limb ischemia (i.e. idiopathic, without risk factors for hypercoagulability) [3], [5].

At presentation, the management of the patient's acute left upper limb ischemia had an immediate precedent and was achieved by prompt initiation of anticoagulation, emergent operative embolectomy.

In medical studies, rapidly initiated anticoagulant therapy has been applied in most cases (31/51 patients), and attempts to remove the embolus by fibrinolysis in 14 patients and embolectomy in 39 patients were achieved [6].

According to clinical guidelines, systemic anticoagulation should be continued for at least three months after initiation in cases of unprovoked thromboembolism or deep vein thrombosis (DVT) [4], [6].

In this case, the paradoxical embolism was initially suspected because the patient had no history of atrial fibrillation or previous arterial thromboembolism and had a normal ECG. Transthoracic

echocardiogram was performed with a bubble study and ultrasounds bilateral Doppler of the lower and upper limbs that revealed a PFO without intracardiac thrombus and DVT, respectively, ischemia in the right upper limb.

### 3.2. Case 2

PFO, because of its high prevalence in the general population and especially in patients with cryptogenic stroke, has long generated investigation and debate on its propensity for stroke by paradoxical embolism and its management for stroke prevention.

The RoPE score (risk of paradoxical embolism score), designed to estimate the probability that a stroke is due to the presence of PFO, uses 6 parameters: hypertension, history of diabetes, previous stroke /transient ischemic attack (TIA) history, smoking/non-smoking status, age, cortical infarction on imaging. Although the RoPE score is not validated to select patients who would benefit from PFO closure, it can be used as a guideline for PFO closure in those with very high scores or conservative treatment in patients with very low scores [12].

The treatment recommendations of current international medical practice guidelines differ greatly: American Academy of Neurology 2017, AHA/ASA 2018, NICE 2013, Netherlands Society of Cardiology 2016, closure of PFO in patients with cryptogenic stroke remain a controversial topic. Most do not routinely recommend closure of PFO in cryptogenic stroke, but instead recommend antiplatelet or antithrombotic treatment. Some of these guidelines were published

before the publication of randomized trials that showed a reduction in the risk of recurrent stroke with percutaneous closure of PFO versus medical treatment.

In patients younger than 60 years of age, options for the secondary prevention of recurrent cryptogenic stroke that is accompanied by the presence of PFO are: percutaneous closure (including antiplatelet therapy) or antithrombotic drug treatment alone: antiplatelet or anticoagulant [11].

Canadian medical practice guidelines recommend the closure of PFO plus antiplatelet therapy compared to antiplatelet therapy alone in patients aged 18-60 with cryptogenic stroke/ TIA [7].

In young patients (up to 60 years old) with PFO cryptogenic strokes or acute limb ischemia endovascular closure of a PFO is the best therapeutic option in the presence of a atrial septum aneurysm associated or not with right-to-left shunt. In all other situation the decision of treatment will be highly-individualized taking into account the risk of PFO induced thromboembolism recurrence, the high numbers needed to treat and the risks related to the procedure. Based on this evidence, the decision will be individualized to each patient [1], [11].

Analyzed all published data about this issue, the patient was transferred to other Primary Cardiac Center for percutaneous PFO closure.

### 4. Conclusions

In both cases, the imaging methods formed the diagnostic algorithm by using transthoracic ultrasound with bubbled saline followed by transesophageal



ultrasound to accurately assess the anatomy of the septum.

The RoPE score through the six evaluation parameters is used in patients with cryptogenic stroke who have demonstrated PFO and the absence of other causes of stroke. Its usefulness is due to its uniqueness in clinical prediction models and may highlight the likelihood that a patient with cryptogenic stroke will have a PFO.

If the RoPE score is high, patients are most likely prone to a pathogenic PFO rather than an incidental defect but with a lower risk of recurrence of stroke.

The decision to close PFO or drug therapy is given by the RoPE score through the probable biological mechanism along with the inclusion of other factors and the involvement of neurologists as well as cardiologists.

Patent foramen ovale, even was considered a variant of the normal, is incriminated in various thromboembolic pathology like cryptogenic stroke and acute limb ischemia. Current pharmacologic and nonpharmacologic treatment options included endovascular and surgery closure of a PFO up to 60 years old and anticoagulants, individualized to each patient are still being evaluated in international clinical trials.

## References

1. André, C.: *Endovascular closure of patent foramen ovale: a critical appraisal of published trials*. In: Arquivos de Neuro-Psiquiatria (Oct 2019), Vol. 77(10), p. 731-740. doi: 10.1590/0004-282X20190120
2. Devuyt, G., Bogousslavsky, J.: *Patent foramen ovale: The never-ending story*. In: *Curr Treat Options Cardio Med* 7,227239 (2005). <https://doi.org/10.1007/s11936-005-0051-x>
3. Hagen, P.T., Scholz, D.G., Edwards, W.D.: *Incidence and size of patent foramen ovale during the first 10 decades of life: an autopsy study of 965 normal hearts*. In: *Mayo Clin Proc.* (1984) Vol. 59, p. 17e20. doi: 10.1016/s0025-6196(12)60336-x.
4. Herman, G.M.D., Gornik, H.L., Barrett, C., et al.: *2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice guidelines*. In: *J Am Coll Cardiol.* (2017) Vol. 69, p. e71e126. doi:10.1177/1358863X17701592
5. Joshi, S.D., Chawre, H.K., Joshi, S.S.: *Morphological study of fossa ovalis and its clinical relevance*. In: *Indian Heart J.* (2016) Vol. 68, p. 147e52.-4. doi: 10.1016 /j.ihj.2015.08.001
6. Kearon, C., Akl, E.A., Ornelas, J., et al.: *Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report*. In: *Chest* (2016), Vol. 149, p. 315e52. doi: 10.1016/j.chest.2015.11.026.
7. Kirchhof, P., Benussi, S., Kotecha, D., et al.: *2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS* In: *Europace* (2016) Vol. 18, p. 1609e78. <https://doi.org/10.1093/eurheartj/ehw210>

8. Kuijpers, T., Spencer, A.F., Siemieniuk, A.C.R., et al.: *Patent foramen ovale closure, antiplatelet therapy or anticoagulation therapy alone for management of cryptogenic stroke? A clinical practice*. In: *BMJ* (2018) Vol. 362 p. k2515. doi:10.1136/bmj.k2515.
9. McNally, M.M., Univers, J.: *Acute limb ischemia*. In: *Surg Clin North Am.* (2018) Vol. 98, p. 1081e96. doi:10.1016/j.suc.2018.05.002.
10. Mojadidi, M., Zaman, M.O., Elgendy I.Y., et al.: *Cryptogenic Stroke and Patent Foramen Ovale*. In: *J Am Coll Cardiol.* (2018) Vol. 71, p. 1035–43. doi: 10.1016/j.jacc.2017.12.059
11. Morais, L.A., Sousa, L., Fiarresga, A., et al.: *RoPE Score as a Predictor of Recurrent Ischemic Events after Percutaneous Patent Foramen Ovale Closure*. In: *Int Heart J.* (2018) Vol. 59(6), p. 1327-1332. doi:10.1536/ihj.17-489.
12. Sondergaard, L., Kasner, S.E., Rhodes, J.F. et al.: *Patent foramen ovale closure or antiplatelet therapy for cryptogenic stroke*. In: *N Engl J Med.* (2017) Vol. 377, p. 1033–1042. doi: 10.1056/NEJMoa1707404.