Case Report

A case of pulmonary thromboembolism with synchronous and metachronous paradoxical embolism through the patent foramen ovale—A case report

Miloslav Pirkla,b,*, Andrej Myjavec, Tomáš Daněk, Miloš Černy

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A B S T R A C T

A rare case is presented in this article—namely consecutive and synchronous embolizations in the pulmonary artery and paradoxical embolizations in the systemic circulation. Although paradoxical embolizations represent a relatively rare cause of acute ischemic attack of any localization, this nosological unit should always be considered in cases where the source of thromboembolism is unclear, and particularly where pulmonary embolism in the premorbid history or limb phlebothrombosis verified by sonography is present in the history. In the acute phase of treatment it is essential to ensure surgical or endovascular reperfusion of the ischemic organ and then at the next time to prevent further such events especially by occlusion of patent foramen ovale.

1. Introduction

The incidence of paradoxical embolism is relatively low—approximately 2% of all arterial embolizations [1,2]. Any terminal part of the arterial bed may become the target of paradoxical embolization; however, the most commonly involved targets include the brain (up to 55% cases) and the limbs (up to 40% cases) [3,4]. It has been known that the source of the embolus is not identified in up to 40% of cerebrovascular thromboembolic events (denoted as cryptogenic strokes in Anglo-Saxon literature), and thus the question still remains what the percentage of paradoxical embolizations is among such cases [5,6]. In the text below, the authors present a case report of a man with pulmonary embolism concurrent with a massive attack of paradoxical embolization in the systemic circulation—synchronous and metachronous at the bifurcation of abdominal aorta and in the superior mesenteric artery. The mortality of aortic bifurcation embolism has been reported as much as up to 50% [7]; acute splanchnic ischemia due to sudden closure of the trunk of the superior mesenteric artery (SMA) is also associated with high mortality ranging between 50–75% [8,30].

2. Case report

A male patient, 66 years of age, was transported by EMS to a local hospital on 7 Sep 2010 due to sudden pain in both lower limbs. In addition, the patient reported at admission that he...
had felt pain in the chest and dyspnea day before. Personal medical history included arterial hypertension, dyslipidemia, permanent atrial fibrillation, status post pulmonary embolism (anticoagulant therapy with Warfarin was stopped in 2007). Critical acute ischemia of lower limbs was diagnosed at the primary examination, and the patient was transferred to the Division of Vascular Surgery of the Surgery Clinic at Regional Hospital in Pardubice. Triplex sonography of lower limb arteries was performed statim at the department, with the result raising suspicion of peripheral embolization with a closure more distally from common femoral arteries (CFA) bilaterally, therefore CT limb angiography was performed as the next step, which showed a saddle-shaped embolus of the abdominal aorta spreading into the periphery (iliaco-femoral bed bilaterally) (Fig. 1). Urgent surgical revision was indicated with indirect embolectomy of the aorto-iliac bifurcation, and thromboembolectomy from the femoral basins bilaterally, based on the established procedure of bilateral femoral arteriotomies (the surgery was done 4.5 hours after the aortic embolic event).

The patient was hospitalized at the ICU of Surgical clinic after the procedure. The patient was sedated, artificial pulmonary ventilation was applied, with the need of vasopressor circulatory support initially, and continually heparinized. On 8 Sep 2010, pulmonary spiral CT angiography and subsequently CT angiography of abdominal aorta and its branches were performed due to clinical suspicion of pulmonary embolism based on blood gas levels (and based on dyspnea attack in medical history before the event) and a rise in the intraabdominal pressure. Evidence of pulmonary embolism was found in all branches of pulmonary arteries bilaterally, and furthermore embolization in the superior mesenteric artery (SMA) about 6 cm at a distance from the aorta (Figs. 2, 3), gas in the walls of small intestinal (particularly in the ileum), massive presence of gas in mesenteric veins, gas in peripheral branches of the portal vein, particularly in the left hepatic lobe (Fig. 4). Urgent surgical revision of abdominal cavity was indicated (19 h after the first surgery), which found gangrene of the ileum and thromboembolism of the trunk of SMA. Embolectomy of SMA was performed, as well as partial resection

Fig. 1 – Saddle embolus of the aortic bifurcation propagating to the both iliac arteries, CT angiography of the abdominal aorta and lower extremities.

Fig. 2 – Embolization in the mesenteric artery about 6 cm at a distance from the aorta, CT visceral angiography.
of 100 cm of the ischemic ileum with terminal jejunostomy. After the surgery, the patient was transferred to Anesthesiology department. The patient was ventilated for six days. The seventh day after last surgery he was transferred back to the ICU of surgical clinic. His condition further improved then. The nutrition was combined, oral intake was gradually reinitiated, jejunostomy was vital and fulfilled its elimination function. No further complications in terms of blood perfusion of lower limbs and the gastrointestinal tract (GIT). The wounds were healing primary. On 30 Sep 2010, echocardiography assessment was done, transthoracic and transesophageal (both with low examination feasibility), which showed slightly abnormal IVS movement, normal systolic function of LV with 70% EF, good kinetics of the right ventricle, mild pulmonary hypertension (sPAP 40 mmHg). No evidence of a thrombus in the left atrium (including the auricle); any defect of the atrial septum was
excluded; evidence of patent foramen ovale (PFO) was found with the left–right and right–left short circuit (R–L short-circuit was demonstrated by administration of an echocontrast medium and also without using the Valsalva maneuver). Femoropopliteo-crural flebothrombosis was found in the right lower limb based on triplex venous sonography of lower limbs. Warfarin therapy was titrated (up to the therapeutic INR range with the coverage using the full LMWH dose). Preliminary hematological screening of blood coagulability disorders was negative, and the Leiden mutation was excluded. Surgical wounds were healing primary, no GIT passage disorders, no signs of continued ischemization of the gastrointestinal tract; the limbs showed palpable pulsations in the periphery bilaterally; tendency to normalization of laboratory parameters.

Further procedure was agreed in cooperation with the Department of Cardiology. Early stomy negation was planned (with insertion of a caval filter before the procedure), with the decision regarding PFO to be taken subsequently. On 8 Oct 2010, the patient was discharged to home care (efficient INR 2.6 at dimission). Admission to the Surgery Clinic of Regional Hospital in Pardubice for jejunostomy negation was planned for 15 Nov 2010. However, the patient suddenly died at home on 16 Oct 2010. The autopsy found no fresh pulmonary embolism (small pulmonary embolization was described bilaterally); significant stenoses of coronary arteries were determined, as well as left ventricular hypertrophy and signs of chronic cardiac insufficiency. The autopsy also confirmed the PFO diagnosis. Cardiorespiratory failure was determined as the cause of death by the pathologist.

3. Discussion

The incidence of paradoxical embolisms is relatively low, forming less than 2% of system arterial embolizations [1]. The right–left short-circuit, temporary or permanent, is the path of paradoxical embolization. The analysis of right–left short-circuits showed that PFO was their cause in about 95%, pulmonary arteriovenous fistulae were the causes in 4%, and inter-atrial septum defects in 1% [9]. Other sources of paradoxical embolism may be defects of the ventricular septum, a case report of paradoxical embolization from partially thrombotized arteriovenous dialysis fistula [3] was described, and also from persistent left-sided upper vena cava leading into the superior left pulmonary vein [10].

PFO is not classified among atrial septum defects or among cardiac defects, but it is rather understood as a relatively common variant of the physiological condition [11]. It occurs upon unsuccessful fusion of the primary and secondary atrial septum. Anatomical patency of PFO persists in adult age in about 25–30% of regular population [11]. It is found in about 20.2–34.4% of persons undergoing autopsy, with age dependency [12]. On one hand, PFO prevalence decrease is clearly apparent in higher age groups (explained by possible spontaneous closure or premature death), [13,14] on the other, an autopsy study showed that PFO was increasing with age in older persons [15]. Mean size of PFO is 5 mm based on autopsies, while Popelová reported the PFO range of 3–24 mm [11].

Transthoracic echocardiography (US TTE) and transesophageal echocardiography (US TEE) (Fig. 5) are used in PFO diagnostics, including 3D and transcranial Doppler (TCD) – all these methods also with contrast medium administration (usually agitated physiological solution). US TEE is the gold standard of PFO diagnostics with almost 100% sensitivity and specificity when colored Doppler (Fig. 6) and a contrast medium are used [16].

In terms of PFO quantification, the distance of both leaves during the Valsalva maneuver is assessed where separation up to 2 mm means a mild defect, 2–4 mm moderate and over 4 mm means a severe defect. The right–left short-circuit is assessed predominantly using the agitated physiological solution (Fig. 7). It is examined during respiration at rest and after the Valsalva maneuver. The number of bubbles in a stopped echocardiography scan is assessed where 3–10 bubbles means a mild short-circuit, 10–20 moderate and over 20 a severe short-circuit (however, other quantification schemes also exist). Presence of bubbles in the left atrium to 3 cardiac excursions from appearance of the contrast medium in the right atrium gives evidence of a defect on the atrial level. AV short-circuit on the pulmonary circulation level should be considered upon later appearance of the bubbles [13].

Unlike the atrial septum defect, which signalizes fixed (anatomical) communication between the cardiac atriums
and allowing for bidirectional flow of the blood, a functional
defect is usually present in the event of PFO, which depends
on the pressure ratio in both atriums (both components of
the atrial septum usually overlap here), not causing a sig-
ificant short-circuit as a rule. The right–left short-circuit is
present if the pressure in the right atrium exceeds the
pressure in the left atrium.

The right-sided short-circuit may be temporary or perma-
nent. It is usually caused by elevated pressure in the right
atrium [16,17]. (Table 1)

The absolute majority of persons with PFO remain asym-
ptomatic for their whole lives. However, right–left short-circuit
may start to occur with increasing pressure in the right
atrium, which may open up the possibility of paradoxical
embolization in the further course [1,3].

The criteria that alert of possible paradoxical embolism are
as follows: (1) Thromboembolization in the system arterial bed
where no source of embolization is demonstrated in left-sided
heart compartments or in the arterial bed itself (partially
thrombosed aneurysms etc.); (2) Abnormal communication
between the arterial and venous system; (3) Presence of deep venous thrombosis in the limbs or pulmonary embolism; (4) Rising pressure in right-sided heart compartment that contributes to the right–left short-circuit [1,18].

Any terminal part of the arterial bed may be the target of paradoxical embolization; however, the brain (up to 55% cases) and limbs (up to 40% cases) are involved most often [3,4]. Other authors estimate the portion of extracerebral paradoxical embolization only as 5–10%. In the study of Rigatelli of 150 patients indicated for catetherization closure of PFO or an atrial septum defect, extracerebral paradoxical embolization was present in 9 patients (i.e. 6%), out of whom STE myocardial infarction was present in 5 patients and acute limb ischemia (a lower limb in all) was present in 4 cases [19].

As mentioned above, the cerebral vascular bed is the most common target of paradoxical embolization. It is known that the cause of 30–40% of cerebrovascular events (CVE) based on ischemia is not sufficiently clarified (these events are denoted as cryptogenic strokes in Anglo-Saxon literature) [5,6]. This percentage is even higher in younger patients, below 55 years of age, where the diagnosis of cryptogenic CVE is reported for 40–60% cases [20,21]. The question still remains what the percentage of paradoxical embolizations is among such cases. Cryptogenic CVE and a simple proof of PFO based on imaging methods certainly cannot be deemed equivalent. PFO was found more often, in 40–54%, in studies on patients with a CVE, for persons below 55 years of age and without risk factors of a cerebrovascular event [11]. Comparing PFO incidence in patients with cryptogenic CVE and in patients with an explained CVE, PFO incidence was reported in 46% and 11% [21].

Metaanalysis undertaken by Overell et al. compared cryptogenic CVE with CVE with a known cause. Association with cryptogenic CVEs was as follows: 22 studies reported the odds ratio (OR) of 3.16 for PFO; OR for ASA was equal to 3.65 based on 20 studies, and OR for PFO+ASA was 23.26. Association between cryptogenic CVE and PFO was the strongest for patients younger than 55 years of age [14]. However, not all studies confirmed the association between PFO and cryptogenic CVE. The study PICCS found no relationship between repeated CVEs and PFO presence or the magnitude of the short-circuit through PFO [14].

In spite of clear embolic etiology in CVE with evidence of PFO, venous thrombosis is found only in about 1/3 cases [13]. The study that compared the incidence of deep venous thrombosis (DVT) in patients with cryptogenic CVE compared to patients with CVE of known etiology using MRI venography determined more frequent incidence of DVT in patients with cryptogenic CVE (20% vs. 4%; \( p < 0.03 \)); similarly, the study determined also differences in PFO incidence (59% vs. 19%; \( p < 0.001 \)) [14].

A part of patients with PFO have also atrial septum aneurysm (ASA). The combination of PFO with ASA and/or Eustach valve means a higher risk of paradoxical embolism [20]. A study was published where the atrial septum excursions > 5 mm (not fulfilling current ASA diagnostic criteria) were found in patients with CVE in 55% compared to the control group where such excursions were found only in 17% [22]. PFO and ASA coincidence of 1% was reported; ASA was present in about 4% of patients in the PFO group. Prevalence of ASA alone was about 2%.

The width of PFO tunnel is another risk factor for paradoxical embolization. Schuchlenz reported in his original paper that PFO with the diameter of > 4 mm was associated with significant higher risk of TIA and ischemic CVE, particularly in patients after 2 and more events [23]. Younger age (< 55 years), presence of the right–left short-circuit already at rest, and the thrombophilic condition are also considered as risk factors for paradoxical embolization in PFO [24].

Currently, preventive treatment is not recommended for patients with PFO who have no other risk factors. Patients with a lower risk are usually indicated for administration of antiaggregation therapy (acetylsalicylic acid), while anticoagulation therapy is recommended for patients with a higher risk. The results of this therapy are comparable to those of catetherization therapy. However, serious adverse effects of anticoagulation therapy increase overall morbidity and mortality of the patients [13]. This must be taken into account particularly in younger patients with long life expectancy given that the risk of large bleeding associated with coumarin therapy is estimated as 1.5–11% events annually [24]. ACCP guidelines recommend antiplatelet therapy in patients with ischemic CVE and PFO, while anticoagulant therapy should be reserved for patients with evidence of deep venous thrombosis, and to patients with evidence of a procoagulation condition and those indicated for PFO closure where a high risk of CVE recurrence is present [24].

Currently, 4 therapeutic options are available in PFO treatment in indicated cases: Antiaggregation therapy, anticoagulation therapy, catetherization closure of PFO, and surgery closure of PFO. The only 2 studies of secondary CVE prevention in patients with PFO showed that the risk of recurrence is relatively low (about 1% per year) in patients on aspirin or short-term anticoagulation therapy [24].

Occluder therapy still remains controversial in PFO. Although various types of occluders have been used in Europe and Canada for PFO closure as part of CVE prevention, FDA has not approved their use for PFO closure [12] (they have been approved for the closure of atrial septum defects). The first randomized, controlled study of PFO closure due to ischemic CVE and/or TIA did not find any differences in the primary end-point, which was defined as CVE/TIA within 2 years, overall mortality after 31 day and within 2 years (CLOSURE I study) [25]. The occluder STARFlex closure device (NMT Medical) was used in this study. Currently, other studies are being conducted—CLOSE in France, PC in Switzerland (Amplatzer PFO occluder), RESPECT with Amplatzer PFO occluder and REDUCE with Helex septal occluder.

Indications for PFO closure have not been defined in any recommendations yet. In terms of cryptogenic CVE, some authors recommending closing all PFOs (where any unexplained system embolization occurred, another origin of embolization was excluded, PFO was demonstrated, and the right–left short-circuit was verified) [26]. French neurologists formulated other recommendations for PFO closure (Table 2) [26]. However, the age of the patient and the patient's general condition must be considered. Other discussed indications include relapsing migraines, PFO in divers, and others.

Surgical treatment is reserved for patients with PFO longer than 25 mm, insufficient rim of the tissue around PFO, or
Table 2 – Recommendations for PFO closure after CVE due to embolism or TIA.

1. CVE or TIA→PFO (0.6% risk/year)→aspirin
2. repeated CVE or TIA→PFO closure
3. CVE or TIA→PFO+ASA (4% risk/year)→PFO closure
4. CVE or TIA→PFO+DVT→PFO closure
5. CVE or TIA→PFO+old ischemic cerebral changes on CT scan→PFO closure

catheterization treatment failure [27]. On the contrary, surgical treatment of PFO in cardiosurgical patients operated for other indications definitely seems not to be indicated. One retrospective study showed that PFO closure in such patients had no effect on long-term mortality, but more than doubled the risk of CVE in the post-operation period (still during hospitalization) compared to patients in whom PFO closure was not performed [19].

CT pulmonary angiography is most commonly used today for the diagnostics of pulmonary embolism, and particularly triplex sonography for that of the deep venous thrombosis.

The therapy of paradoxical embolism is local or systemic thrombolytic therapy, or therapy ensured by other radiointervention methods (aspiration thrombectomy) or surgical embolectomy, followed with full heparinization, with subsequent switching of the patient to chronic anticoagulation therapy with vitamin K antagonists or antiaggregation therapy [2]. Based on guidelines of the Czech Cardiological Society, paradoxical embolism with PFO with evidence of the right-left short-circuit, with concurrent acute pulmonary embolism, is an indication for thrombolytic therapy. If the target organ of paradoxical embolization is not exposed to urgent risk of ischemia (grade I or IIa for acute limb ischemia), the possibility of introducing a caval filter can be considered in the acute phase, with concurrent local fibrinolysis of the pulmonary artery, with or without intraarterial thrombolysis, which reduces the right-left short-circuit quite rapidly, besides others, and thus also the risk of early recurrence of paradoxical embolism [6].

Aortic bifurcation embolism is one of the most serious embolization events in the systemic circulation while untreated it leads to death within 24–48 h. In this event, the embolus becomes attached to the bifurcation point of the abdominal aorta and obstructs both common iliac arteries. Sometimes, the embolus may also spread to the periphery, which significantly worsens the prognosis of the involved individual even after revascularization [7].

This is a sudden event, critical and rapidly progressing to the shock condition. A typical symptom is sudden, severe pain of lower limbs and sometimes also with propagation to lower abdomen, while the clinical image of both lower limbs includes all “6P” symptoms typical for acute limb ischemia (pale, pulseless, painful, paralyzed, paraesthetic, perishing with cold) [28]. The diagnosis should be apparent already from the clinical image and/or from the sonographic finding. Other imaging examinations may uselessly prolong the period of limb ischemia and to further worsening of the patient’s prognosis; however, they may be needed sometimes to differentiate, for example, from aortic dissection.

Surgical therapy is the only proper therapy of this emergency condition, which means that thrombembolectomy of aortic bifurcation emboli and of apposition thrombi in the peripheral bed is done alternately and repeatedly using an embolectomic catheter, using arteriotomies in both groins, in the common femoral arteries.

In the post-operation period, the therapy focuses on vigorous anti-shock therapy and full heparinization, while particularly the reperfusion syndrome is specific for the post-operation period, both in the sense of threatening compartment syndrome of the revascularized lower limbs, and hyperkalemia from the reperfused, ischemically damaged soft tissues of the limbs, and acute renal insufficiency as a result of myoglobin precipitation in renal tubules with their necrosis. Mortality of this nosological unit ranges between 30–50% [7].

The incidence of acute mesenteric ischemia (AMI) in autoptic studies is 5.3–8.6/100000 autopsies [29].

Embolic etiology represents approximately 50% of all mesenteric ischemias (28–60%), and thrombotic approximately 25% (8.5–64%); mesenteric venous thrombosis is represented in 5–15% of all acute mesenteric ischemias (AMI) and nonocclusive mesenteric ischemia is described in 20–30% of all cases [30].

In initial stages, clinical symptoms are very low in contrast to subjective complaints and reports of the patient. The symptoms include nausea, anorexia, fever, vomiting or diarrhoea, melena, enterorrhagia. The first attack with vomiting and severe abdominal pain, accompanied with low clinical finding, lasts approximately 6 h. A period of relative subjective calming of the patient follows for the next approximately 6 h as a rule; however, the critical condition continues and deepens, it is an image of paralytic ileus; the next phase is gangrene of the intestinal wall with peritoneal symptoms [31]. Embolic AMI should be considered always when severe abdominal pain occurs in a patient with the history of recent myocardial infarction, cardiac arrhythmia, cardiomyopathy or valvular defect or replacement. AMI diagnosis can be determined in most cases based on contrast CT with i.v. administration of contrast medium bolus. Alternatively, an even more specific image can be provided by visceral angiography or even selective mesenterial catheterization angiography. Another option is the laparoscopic revision after intravenous fluorescein application and exploration of the abdominal cavity in ultraviolet light [32].

Ischemic tolerance of the intestine has been reported as 120–180 min. Generally, every patient with this diagnosis should be revised through surgery, in particular considering the extensive collateral network that supplies the intestine and the possibility of embolization into more peripheral branches of the SMA, while depending precisely on these factors, intestinal viability may be prolonged up to several hours or days [7]. Generally accepted time limit that still allows for achieving full recovery after the revascularization procedure is the first 6 h from the onset of the symptoms [31]. Hospitalization mortality reaches 50–75% even today [8].

Surgical therapy of arterio-occlusive AMI (embolicogen or thrombotic) predominates, while for the therapy to be successful, it must be timely. In the event of embolicogenic closure, surgical embolectomy of the superior mesenteric artery should be done, and bypass surgery or thrombectomy with a patch angioplasty of the stenotized superior mesenteric artery if the...
condition is of thrombogenic origin. Both the angioplasty surgery and the bypass should be constructed from an autologous graft of vena saphena magna if possible—particularly in the event of gangrenous changes of the intestine with the need of its resection due to concerns about a possible infection of the prosthetic graft, which could be fatal for the patient. Bypass inflow is recommended from the supracleiacal aorta (atherosclerotic changes are seldom expressed here), but proximal anastomosis may be constructed also in the subrenal aorta or iliac artery. The outflow should be constructed into freely patent superior mesenteric artery, distally from the stenotic-occlusive process.

There is also a possibility of intervention therapy that includes particularly aspiration thrombectomy and stenting of the sclerotically stenotized AMS. However, this procedure is very demanding in terms of coordination of the teams, and it entails the essential disadvantage of missing direct revision and clarification of advancement of intestinal ischemia [30].

In his set, Edwards describes 76 patients with AMI during 10 years. 16 of these patients ended up with more exploration laparotomy for extensive intestinal gangrene incompatible with life. Only resection surgery in the intestine with no revascularization was performed in 18 patients, and revascularization was done in 43 patients (this set included 28 patients with concurrent resection of the ischemic part of the digestive tract). In further development, 44 patients underwent second-look laparotomy and one half also another intestinal resection due to continued ischemia. This set achieved hospitalization mortality of 62%, but moreover, 31% of the survivors ended up with the short bowel syndrome, on long-term parenteral nutrition at home [33].

The Edwards’s set included 32 patients with AMI embolization etiology, while another synchronous embolization occurred in 10 cases (31%), which was synchronous embolization in lower limbs in 9 of these cases [33].

4. Conclusion

A rare case (no similar found in literature) was presented in the previous case report summary, namely consecutive and synchronous embolizations in the pulmonary artery and paradoxical embolizations in the systemic circulation. Although paradoxical embolizations represent a relatively rare cause of acute ischemic attack of any localization, this nosological unit should always be considered in cases where the source of thrombembolism is unclear, and particularly where pulmonary embolism in the premorbid history or limb phlebothrombosis verified by sonography is present in the history.

Both the therapy and prognosis of any patient with paradoxical embolism is always given by the anatomical area involved, by the scope and duration of ischemia of the target organ whose arterial perfusion was thus affected. Therapy not only of the target and source of the embolism but also precisely of PFO is important for further fate of surviving patients.

REFERENCES


