High incidence of acute and subacute ischaemic foci on brain MRI in patients with a diagnosis of acute pulmonary embolism and confirmed patent foramen ovale

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Background. Pulmonary embolism (PE) is a common and potentially life-threatening diagnosis when a certain amount of thrombotic mass obstructs blood flow through the pulmonary circulation. The finding of acute and subacute ischaemic foci on magnetic resonance imaging (MRI) of the brain in a group of patients with this diagnosis in whom we demonstrate the presence of patent foramen ovale (PFO) by transoesophageal echocardiography (TEE) is surprisingly high.

Methods. A total of 129 patients with a diagnosis of pulmonary embolism (confirmed by computed tomography with contrast agent, CTA) who consented to further examination were examined by transthoracic echocardiography (TTE) and transoesophageal echocardiography (TEE) with contrast agent, underwent magnetic resonance imaging of the brain according to a specific protocol, and underwent a comprehensive baseline laboratory examination.

Results. In our group of 129 patients, we found the presence of PFO in 36.4% (n=47) of them. A total of 5.4% (n=7) patients had asymptomatic acute and subacute ischaemic changes on brain MRI; 6 of them had concomitant PFO. The statistically significant correlation between troponin levels and the presence of pathological findings on MRI and the trend of a similar correlation for NT-proBNP values is also very interesting finding.

Conclusions. The association between the presence of PFO and the occurrence of symptomatic or asymptomatic findings on brain MRI is a well-known fact (the issue of paradoxical embolism) but the high frequency of acute and subacute lesions on brain MRI in the group of patients with a diagnosis of acute PE is surprising.

Key words: paradoxical embolism, patent foramen ovale, pulmonary embolism, stroke

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INTRODUCTION

Thromboembolic disease (TED) is the third most common cardiovascular disease. It is a disease with a very serious prognosis. Acute pulmonary embolism (PE) is the most serious form, with an annual incidence estimated at 39 to 115 cases per 100,000 inhabitants. The incidence of deep vein thrombosis ranges from 53 to 162 per 100,000 inhabitants per year, with a prevalence estimated at 0.4% (ref.[1]). Thus, PE is diagnosed in between 6,000 and 20,000 patients per year in the Czech Republic. Clinical manifestations are highly variable, ranging from virtually clinically mute forms to life-threatening conditions or outright sudden death.

Nowadays, computed tomography (CT), or its modality CT angiography (CTA) is the gold standard in the diagnosis of PE. This method has been used for this purpose for 30 years, gradually almost replacing ventilation/perfusion scanning and catheter pulmonary angiography. According to various authors, sensitivity is reported to be > 83% and specificity > 96% (e.g., PIOPED study II) (ref.[2]).

Stroke is a disease of vascular origin with rapidly developing localized or even general symptoms of brain or central nervous system dysfunction. According to the very nature of the occurrence of stroke, stroke is divided to ischaemic stroke (IS) caused by insufficient blood supply to the CNS tissue, and haemorrhagic stroke (HS) caused by bleeding into the brain tissue. In HS, we can also distinguish subarachnoid haemorrhage (SAH) which is, in simple terms, bleeding into the external liquor system.

In terms of the thematic focus of this text, we will predominantly focus on ischaemic events, or a subset of cardioembolic ischaemic stroke, specifically the association between stroke, pulmonary embolism and the presence of patent foramen ovale (PFO). PFO is considered in the population as a benign abnormality of atrial septal development; the commonly reported incidence according to different authors is 15 to 25% (ref.[3,4]). From the haemodynamic point of view, in routine clinical practice we distinguish between PFO without functional shunt or with small left-to-right shunt and PFO with evidence of right-to-left shunt (spontaneous or provoked). In the case of PFOs with a persistent left-to-right shunt or a function-

ally closed tunnel, pulmonary embolism, by changing the direction of flow according to the pressure gradients to right-to-left (by increasing the pressure in the right-sided cardiac compartments), allows the emboli to pass into the left atrium or to be released from the PFO channel (in the case of in-situ thrombi) and thus to move further through the systemic circulation with the development of paradoxical embolism. If the embolus is carried into the brain, it underlies IS which either manifests or is clinically silent. There have already been studies that have shown a worse prognosis in patients with PE and the concomitant presence of a PFO, as well as up to a fivefold risk of developing stroke[5]. The occurrence of clinically silent ischaemic findings on MRI in patients with PE and PFO has also already been reported in some observational studies[6-8].

MATERIALS AND METHODS

Patients were enrolled in our observational registry between September 2016 and October 2019. They were 129 consecutive patients with a confirmed diagnosis of PE who consented to further examination and were examined after signing the informed consent (see Table 1). The diagnosis of PE was confirmed by CTA on admission. All patients underwent TTE and TEE, laboratory screening and brain MRI (specific embolization protocol) according to the protocol.

Magnetic resonance imaging

In our cohort, MRI of the brain was performed after confirmation of PE (influenced by the patient's clinical condition and consent to further examination). The examination was performed according to the embolization protocol (see Table 2). The assessment of acute ischaemic lesions was determined by DWI trace (b=1000). For the purpose of our study, asymptomatic ischaemic lesions were assessed as acute and subacute (summarized by age within 48 h of onset); other findings were described by the radiologist according to the usual standards (chronic ischaemic lesions, haemorrhagic lesions, etc.). This radiological classification of ischaemic lesions was used specifically to assess the temporal context, and is not interchangeable with the neurological classification of symptomatic ischaemic lesions (where temporal context is quite crucial in the choice of treatment, for example when thrombolytic treatment is indicated) (ref.[9]).

Echocardiographic examinations

Echocardiographic examinations were performed in patients early after confirmation of the diagnosis of PE on Vivid 7 devices with mandatory ECG registration by transthoracic and then transoesophageal probe (TTE, TEE). See Table 3 for specific examination methodology.

The parameters measured were morphology and function of the left atrium, left ventricle and right ventricle; haemodynamic parameters, and severity of valve abnormalities. Evaluation of the results of these examinations is not included in the content of this paper.

Table 1. Characteristics of the cohort.

Total patients	129	
Age	62.5	
Height (cm)	170.5	
Weight (kg)	87.2	
Body mass index	29.88	
Women	63	48.84%
Smoking	14	10.85%
PFO confirmed by TEE	47	36.43%
Arterial hypertension	79	61.24%
Atrial fibrillation	13	10.08%
History of stroke or transient ischaemic attack	10	7.75%
Dyslipidaemia	15	11.63%
Type 2 diabetes mellitus,		
insulin treatment	6	4.65%
treatment with oral medications	13	10.08%
treatment with diet	3	2.33%
Chronic coronary syndrome	17	13.18%
History of pulmonary embolism	12	9.30%
Malignancy	24	18.60%
Gastroduodenal ulcer disease	6	4.65%
Renal insufficiency	9	6.98%
Lung disease	10	7.75%
Ischaemic disease of the lower limbs	4	3.10%
Dyslipidaemia	36	27.91%
Hospital mortality	7	5.43%

Table 2. Embolization protocol – individual sequences.

Localizer
T2 weighted turbo spin echo (TSE)
Fluid attenuated inversion recovery (FLAIR)
Diffusion-weighted imaging (DWI)
3D time of flight magnetic resonance angiography (TOF MRA)

Examinations were performed on a Siemens Magnetom Avanto 1.5 T, Q engine (33mT/m), Tim 76x18 (Siemens AG, Erlangen, Germany) equipped with Syngo 2004A software.

Table 3. Optimization of the ultrasound device during the examination.

Nyquist limit setting in the range of 50 to 70 cm/s
Adjustment of depth, gain, mechanical index, compression or focus
B-mode 2D imaging – evaluation of 3-cycle sequences; 5 cycles in atrial fibrillation with a frame rate of 40–80/s
For CWD, PWD, TDI modalities – acquisition of 3-cycle sequences; 5 cycles in atrial fibrillation with a speed of 50–100 mm/s
Optimization of the sector width for the region of interest for Doppler examinations

During transoesophageal examination, the presence of shunt flow between the right and left atria was demonstrated by Doppler colour mapping (CFM) and by the use of contrast agent (administered via peripheral venous line; 6% hydroxyethyl starch solution) – both spontaneously and provoked by the Valsalva maneuver.

Laboratory examination

Cardiac troponin T was the main parameter monitored in our cohort using a highly sensitive electrochemiluminescence immunoassay (Elecsys Tropo T, Cobas 8000 e602, Roche Diagnostics, Mannheim, Germany). The lower detection limit of the method is 5 ng/L, the upper limit 14 ng/L, CV 13 ng/L 10%, intraassay CV < 5.2%. Aminoterminal fraction of natriuretic peptide (NT-proBNP) was another monitored parameter. The measurement was performed by electrochemiluminescence immunoassay (Elecsys proBNP gene 2, Cobas 8000 e602, Roche Diagnostics, Mannheim, Germany). The lower detection limit of the method is 5 ng/L, intraassay coefficient of variation (CV) <3.1%. Evaluation of other results of these tests is not included in the content of this paper.

Statistical methods

The statistician used the following methods: Fischer's exact factorial test, Kruskal Wallis's test.

Total of 204 consecutive patients with confirmed diagnosis of pulmonary embolism.

Total of 129 patients consent to further examination and sign the informed consent.

RESULTS

The presence of PFO was the main parameter observed in our group. It was found in 37.9% of men (n=25) and 34.9% of women (n=22). Our observed prevalence of PFO in the patient population after PE diagnosis is higher compared to the commonly reported prevalence of PFO in the unselected population (15–25%) (ref.[3,4]).

Table 4. Association between acute and subacute ischaemic findings on MRI and the presence of PFO.

PFO	Acute/subacute lesions on MRI	
	YES	NO
YES	6	41
NO	1	81

P = 0.01, Fischer's exact factorial test used.

A total of 7 patients showed asymptomatic acute or subacute ischaemic lesions on brain MRI during the embolization protocol. There was a statistically significant correlation (using Fisher's exact factorial index) between the presence of these lesions and the presence of PFO (*P*=0.01, see Table 4). The association between the presence of PFO and brain MRI findings is generally known (see above) but in our group, this is a unique demonstration of new changes in direct temporal association with the diagnosis of pulmonary embolism.

As to the laboratory results, there is a significant association between the level of troponin in the baseline samples, correlating statistically significantly with the presence of PFO (*P*=0.062, using Kruskal Wallis's test, see Fig. 1). Another parameter of major importance from the cardiologist's point of view, NT-proBNP, showed a trend to this effect without demonstrating a statistically significant correlation (*P*=0.62, using Kruskal Wallis's test, see Fig. 2).

A statistically significant correlation of troponin levels (*P*=0.02, Kruskal Wallis's test, see Fig. 3) with the type of findings on brain MRI is another demonstrable association found in our cohort is. NT-pro BNP (*P*=0.3, Kruskal Wallis's test, see Fig. 4) again showed a trend to this effect.

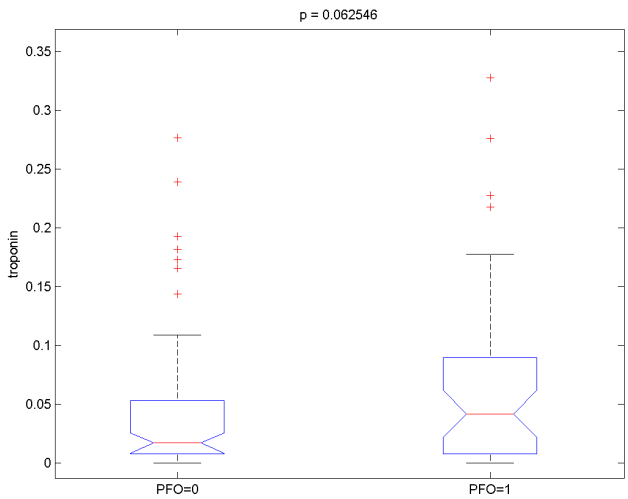

Fig. 1. Relationship between troponin levels and the presence of PFO (Kruskal Wallis's test).

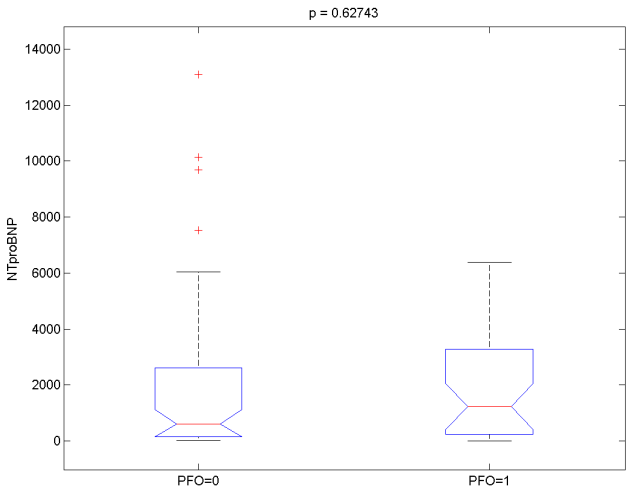

Fig. 2. Relationship between NT-proBNP and the presence of PFO (Kruskal Wallis's test).

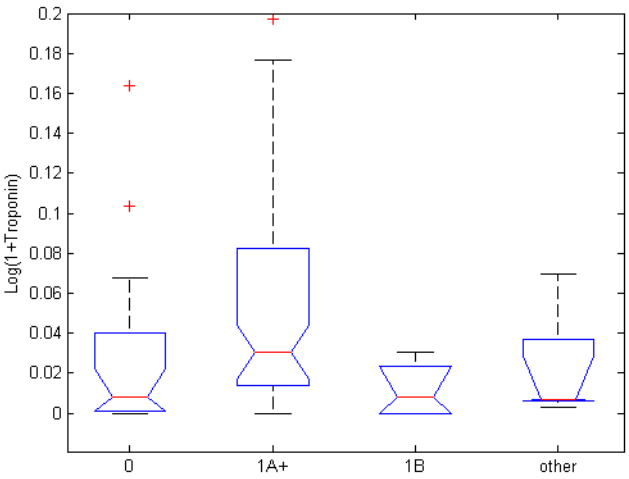

Fig. 3. Correlation between troponin levels and brain MRI findings (Kruskal Wallis's test).
0 – no lesion, 1A+ – acute and subacute ischaemic foci, 1B – chronic ischaemic foci, other – other findings.

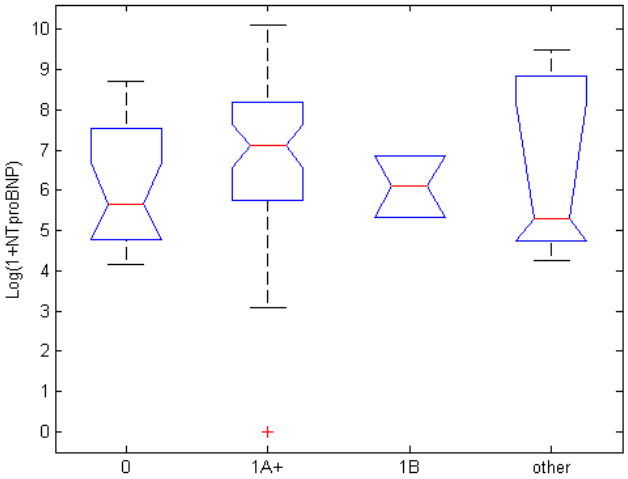

Fig. 4. Correlation between NT-proBNP levels and brain MRI findings (Kruskal Wallis's test).
0 – no lesion, 1A+ – acute and subacute ischaemic foci, 1B – chronic ischaemic foci, other – other findings.

DISCUSSION

The unusually high presence of PFO in our cohort (36.5% versus 15–25% reported in observational studies) may be explained by the high-risk profile of our study population. Therefore, we cannot discuss that the risk factors for PE are directly related to the presence of PFO. The introduction of TEE into the usual examination management of patients with confirmed PE could yield very interesting results: the confirmation of a higher frequency of PFO in patients with PE in a large cohort could trigger a debate on the inclusion of PFO as a risk factor for TED.

The statistically significant correlation between the incidence of acute and subacute ischaemic lesions on brain MRI and the presence of PFO leads us to the idea of routine follow-up of patients with PE in this direction. Knowing the clear association between the presence of PFO and the risk of IS, and considering the possibility of therapeutic intervention in the secondary prevention of paradoxical embolism with a very good resume, certain authors are already discussing the so-called primary prevention – of course in a very well-treated population. If our data were confirmed in a larger population, this would certainly be a group of patients who could benefit from primary (in terms of clinical manifestations) preventive interventions. At the same time, from the interventional cardiologist's perspective, a number of other questions arise – would primary prevention apply only to PFO with spontaneous right-to-left shunt or to all patients with proven PFO (spontaneous and provoked)? Could we expect the same good technical results of interventional PFO closure in this group of patients as in secondary prevention of paradoxical embolism? Would the incidence of potential downstream risks, such as the incidence of atrial fibrillation, be different?

Troponin, NT-proBNP (and of course other laboratory parameters) are often positive in acute conditions (not only in cardiology); we evaluate not only absolute values but also the dynamics. Even in the context of stroke, the demonstration of troponin positivity has long been known – often to surprisingly high values[10,11]. The clearly established association between troponin levels and the presence of PFO is, however, unique. The association between the extent of the finding and the troponin level is also a frequently debated topic in clinical practice. In our group, the findings were clinically mute; in routine clinical practice, this is debated (absolute value and possibly the dynamics of these markers) in a population with proven clinical stroke where differential diagnosis from positivity of these markers of primary cardiogenic aetiology is very poor.

CONCLUSION

The association between the presence of PFO and stroke has long been known, although the real contribution of paradoxical embolism as a causal cause of IS has long been questioned by various authors[12]. We demonstrated a statistically significant correlation of acute and subacute ischaemic lesions on brain MRI in a cohort of patients with pulmonary embolism with proven PFO. Similarly, there was a statistically significant correlation between troponin level and the presence of PFO, as well as troponin level (and trend for NT-proBNP) and the type of brain MRI findings. All of these observed parameters have considerable potential in determining the prognosis or possibility of later onset of clinically manifest strokes. Unfortunately, the size of the cohort (patient recruitment was negatively affected mainly by the change in the structure of our department to a CoViD unit) does not allow us to draw any major conclusions; however, if these associations are demonstrated in a larger cohort, then a certain well-selected and well-researched group of patients

with pulmonary embolism and PFO may be the subject of discussion regarding primary preventive measures in the management of paradoxical embolization.

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REFERENCES

1. Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing GJ, Harjola VP, Huisman MV, Humbert M, Jennings CS, Jiménez D, Kucher N, Lang IM, Lankeit M, Lorusso R, Mazzolai L, Meneveau N, Ní Áinle F, Prandoni P, Pruszczyk P, Righini M, Torbicki A, Van Belle E, Zamorano JL; ESC Scientific Document Group. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J 2020;41(4):543-603.
2. Stein PD, Hull RD, Pineo G. Strategy that includes serial noninvasive leg tests for diagnosis of thromboembolic disease in patients with suspected acute pulmonary embolism based on data from PIOPED. Prospective Investigation of Pulmonary Embolism Diagnosis. Arch Intern Med 1995;155(19):2101-4.
3. Homma S, Messe SR, Rundek T, Sun YP, Franke J, Davidson K, Sievert H, Sacco RL, Di Tullio MR. Patent foramen ovale, Nat Rev Dis Primers 2016;2:15086.
4. Wessler BS, Thaler DE, Ruthazer R, Weimar C, Di Tullio MR, Elkind MS, Homma S, Lutz JS, Mas JL, Mattle HP, Meier B, Nedeltchev K, Papetti F, Di Angelantonio E, Reisman M, Serena J, Kent DM. Transesophageal echocardiography in cryptogenic stroke and patent foramen ovale: analysis of putative high-risk features from the risk of paradoxical embolism database. Circ Cardiovasc Imaging 2014;7(1):125-31.
5. Konstantinides S, Geibel A, Kasper W, Olschewski M, Blümel L, Just H. Patent foramen ovale is an important predictor of adverse outcome in patients with major pulmonary embolism. Circulation 1998;97(19):1946-51.
6. Clergeau MR, Hamon M, Morello R, Saloux E, Viader F. Silent cerebral infarcts in patients with pulmonary embolism and a patent foramen ovale: a prospective diffusion-weighted MRI study. Stroke 2009;40(12):3758-62.
7. Goliszek S, Wiśniewska M, Kurnicka K, Lichodziejewska B, Ciurzyński M, Kostrubiec M, Gołębiowski M, Babiuch M, Paczynska M, Koć M, Palczewski P, Wyzgał A, Pruszczyk P. Patent foramen ovale increases the risk of acute ischemic stroke in patients with acute pulmonary embolism leading to right ventricular dysfunction. Thromb Res 2014;134(5):1052-6. doi: 10.1016/j.thromres.2014.09.013
8. Doyen D, Castellani M, Moceri P, Chiche O, Lazdunski R, Bertora D, Cerboni P, Chaussade C, Ferrari E. Patent foramen ovale and stroke in intermediate-risk pulmonary embolism. Chest 2014;146(4):967-73. doi: 10.1378/chest.14-0100
9. Bücke P, Cohen JE, Horvath T, Cimpoca A, Bhogal P, Bäzner H, Henkes H. What You Always Wanted to Know about Endovascular Therapy in Acute Ischemic Stroke but Never Dared to Ask: A Comprehensive Review. Rev Cardiovasc Med 2022;23(10):340.
10. Kral M, Sanak D, Veverka T, Hutyra M, Vidnis D, Kuncarova A, Bartkova A, Dornak T, Svabova M, Kubickova V, Zapletalova J, Herzig R, Skoloudik D. Troponin T in acute ischemic stroke. Am J Cardiol 2013;112(1):117-21.
11. Kral M, Sanak D, Veverka T, Hutyra M, Vindis D, Bartkova A, Kuncarova A, Dornak T, Cechakova E, Herzig R, Langova K, Kanovsky P, Skoloudik D. Troponin T: correlation with location and volume of acute brain infarction. Int J Cardiol 2015;181:127-32.
12. Sanak D, Hutyra M, Kral M, Spacek M, Bartkova A. Soumrak kryptogenni ischemicke CMP – kardioembolizace je nejcastejsi příčina. Cesk Slov Neurol N 2018;81/114(3):290-7. (In Czech)