Heliyon 10 (2024) e35220

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

The discovery of in situ thrombus attached to the patent foramen ovale channel in myocardial infarction with normal coronary arteries

Xiao-qin Liu [†], Xing-ye Wang [†], Hang Xie, Xue-gang Xie, Yu-shun Zhang [*,1], Lu He [**,1]

Department of Structural Heart Disease, The First Affifiliated Hospital of Xi'an Jiaotong University, No. 277 Yanta West Road, Xi'an, 710068, China

ARTICLE INFO

Keywords:
Patent foramen ovale
Optical coherence tomography
Myocardial infarction

ABSTRACT

Objective: Paradoxical embolism caused by a patent foramen ovale (PFO) is a rare cause of myocardial infarction (MI) in individuals presenting with normal coronary arteries on angiography; however, the deduction is often made due to the inability to identify the exact thrombus that penetrates the atrial septum. Previous studies using optical coherence tomography (OCT) have reported in situ thrombi attached to PFO tunnel in patients with cryptogenic stroke. However, the presence of such thrombi in patients with cryptogenic MI (without a definite cause) remains uncertain. Method: We retrospectively analyzed OCT data collected from February to July 2023 on PFO tunnels in MI adults with normal coronary arteries on angiography. Results: Three patients diagnosed with cryptogenic MI and a PFO underwent OCT examination. These patients exhibited varying OCT findings. White thrombi and endocardial abnormalities in the channel were observed in two patients with MI. No thrombus or anomalous morphology on the endocardial surface was noted in the third patient. PFO closure was performed on all patients, and follow-up was completed by October 1, 2023. None of the patients reported recurrence of chest pain. Conclusion: In situ thrombus was identified within the PFO channel in patients with cryptogenic MI, potentially serving as a novel etiological factor for coronary thrombosis.

1. Introduction

Myocardial infarction (MI) remains the leading cause of death worldwide largely based on stenosis of the arterial cavity [1]. In approximately 6–8% of patients with acute MI, angiography reveals the presence of normal or near-normal coronary arteries. This condition, referred to MI with non-obstructive coronary arteries, encompasses a heterogenous disease entity [2]. Paradoxical embolism can lead to brain infarction, which is commonly observed in clinical settings; however, it can also act as a rare etiology for MI,

* Corresponding author. Department of Structural Heart Disease, The First Affifiliated Hospital of Xi'an Jiaotong University, No. 277 Yanta West Road, Xi'an, 710068, China.

** Corresponding author. Department of Structural Heart Disease, The First Affifiliated Hospital of Xi'an Jiaotong University, No. 277 Yanta West Road, Xi'an, 710068, China.

E-mail addresses: zys2889@sina.com (Y.-s. Zhang), 157732530@qq.com (L. He).

† These authors have contributed equally to this work and share first authorship.

1 These authors have contributed equally to this work and share Corresponding authorship.

https://doi.org/10.1016/j.heliyon.2024.e35220
Received 4 January 2024; Received in revised form 4 July 2024; Accepted 24 July 2024
Available online 28 July 2024

with a reported incidence of approximately 0.65 % [3]. As the most common cause of paradoxical embolism, a patent foramen ovale (PFO) can act as a conduit for the venous thrombus across the atrial septum to the arterial system. The most direct evidence for paradoxical embolism is the detection of a thrombus across the atrial septum. However, this is always challenging due to the transient nature of overriding thrombus, making it difficult to capture.

Another possible pathogenesis, known as in situ thrombus in the PFO tunnel, has also long been suspected. Optical coherence tomography (OCT) is currently the highest-resolution imaging technology widely used for the diagnosis, treatment, and follow-up of coronary heart disease [4]. OCT can provide clear measurements of the microstructure of atherosclerotic plaques and thrombotic lesions, guide the selection of stent size and optimization of stent treatment, and identify the causes of late interventional therapy failure. In contrast to its wide application in coronary artery disease, OCT has only recently begun to show its potential in evaluating PFO. Yan et al. preliminarily applied OCT imaging to explore the PFO tunnel and found an obvious thrombus load in the channel of the PFO in stroke patients compared with that in non-stroke patients [5]. Their study pioneered the in vivo visualization of microthrombi inside the tunnel, which was previously regarded as a hypothetical source of thrombi. However, whether thrombi can be detected in the PFO tunnels in patients with MI remains uncertain. Therefore, we retrospectively analyzed OCT data on PFO tunnels in young adult patients with MI with normal coronary arteries on angiography at our center.

2. Methods

2.1. Study participants

This study has been approved by the Institutional Review Board of the First Affiliated Hospital of Xi'an Jiaotong University, and written informed consent was obtained from all participants. From February to July 2023, MI patients at the First Affiliated Hospital of Xi'an Jiaotong University who met the following criteria were enrolled: age 18–55 years, normal coronary angiography results, no atrial fibrillation (AF) on prolonged Holter monitoring, no aortic disease or cardiac structural abnormalities other than PFO, large right-to-left shunt on contrast transthoracic echocardiography (cTTE), normal lower limb veins, and willingness to undergo OCT examination. Age $<$18 years, age $>$55 years, complications with other heart diseases, and pulmonary hypertension were the exclusion criteria.

2.2. Transthoracic echocardiography and cTTE evaluation

All participants underwent transthoracic echocardiography (TTE) and the cTTE bubble test. The parasternal, apical four-chamber, and subxiphoid views of TTE were used to evaluate the cardiac structures and detect valve vegetations. For cTTE, during the Valsalva maneuver, blood-activated saline was bolus-injected through the cubital vein, and the number of bubbles in the left heart was counted after the release of the Valsalva maneuver. The presence of more than 30 bubbles indicates a high degree of right-to-left shunt.

2.3. OCT procedure

An 8F MPA1 guiding catheter (Cordis, Miami, FL, USA) was introduced into the right atrial opening of the PFO channel over a J-guidewire. The OCT imaging catheter was successfully introduced into the left superior pulmonary vein via the guiding catheter along with a 0.014-inch guidewire (Runthrough NS, Terumo Medical Corp., Tokyo, Japan). The OCT catheter was pulled back to the left atrial aspect of the PFO, with OCT-lens marker positioned 1–2 cm from the left atrial opening of the PFO (Fig. 1A–B).With the injection of the contrast agent, the OCT catheter was automatically withdrawn from the left atrial to the right atrial side of the channel, and

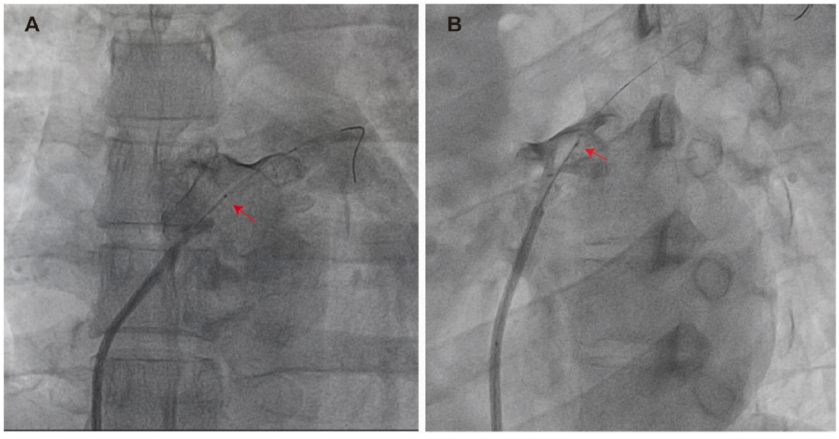

Fig. 1. Digital subtraction angiograph images of the optical coherence tomography examination, including the anteroposterior(A) and left anterior oblique views(B). Arrows represent the second OCT-lens marker.

images of the PFO channel were continuously stored. The OCT examination was terminated if the playback image was clear. Otherwise, a second check was launched until a clear picture was obtained by adjusting the position of the MPA1 and the OCT catheter.

Image analysis adhered to the following principles [6]. An in situ thrombus was defined as an irregular mass ≥100 μm on the endocardium. According to the number of thrombi, it was classified as one of four grades: small: 1–10; medium: 11–30; large: >30; and extremely large: >50. Thrombus area was calculated according to the maximum thrombus diameter. Thrombus volume was calculated as thrombus area × number of frames × 0.2. The total volume was calculated from the volume of each thrombus. The lateral area of the left atrium and right atrium was obtained using the endocardial contour function. Endocardial abnormalities of the PFO were classified as the following: (1) the endocardial surface was irregular: endocardial surface had microspiculation <100 μm; (2) endocardial surface discontinuity: a local endocardial surface defect. All OCT image analyses were performed by two independent analysts with no knowledge of patient information.

2.4. PFO closure and follow-up

After completing the OCT scan, all patients received interventional therapy with an occluder of the appropriate size. All patients were followed up at 1, 3, and 6 months after device implantation to evaluate the recurrence of ischemic symptoms. We utilized electrocardiography to identify arrhythmias, then TTE and cTTE to verify the stability of the occluder and residual shunt.

2.5. Statistical analyses

Statistical analyses were conducted using SPSS 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables are expressed as mean ± standard deviation or median (interquartile range), and categorical variables are expressed as numbers and proportions.

3. Results

Out of 64 consecutive candidates, 61 were excluded due to not meeting the criteria, and ultimately, 3 patients diagnosed with MI of unknown cause other than a PFO were included in the analysis(Fig. 2). We performed a retrospective analysis of these three patients. Table 1 presents the basic and intervention therapy information.

All patients experienced typical ischemic chest pain outside the hospital. The first patient had hypertension, which was well controlled for 2 years. A prolonged Holter monitoring of all patients revealed no occurrence of AF. No definite signs of thrombus were found by ultrasound in lower vein. Patient 1 and 3 were diagnosed with anterior MI, whereas patient 2 had anterolateral, anterior, and inferior MI based on the electrocardiograms and myocardial enzyme levels. TTE showed normal heart chamber sizes and valve status,

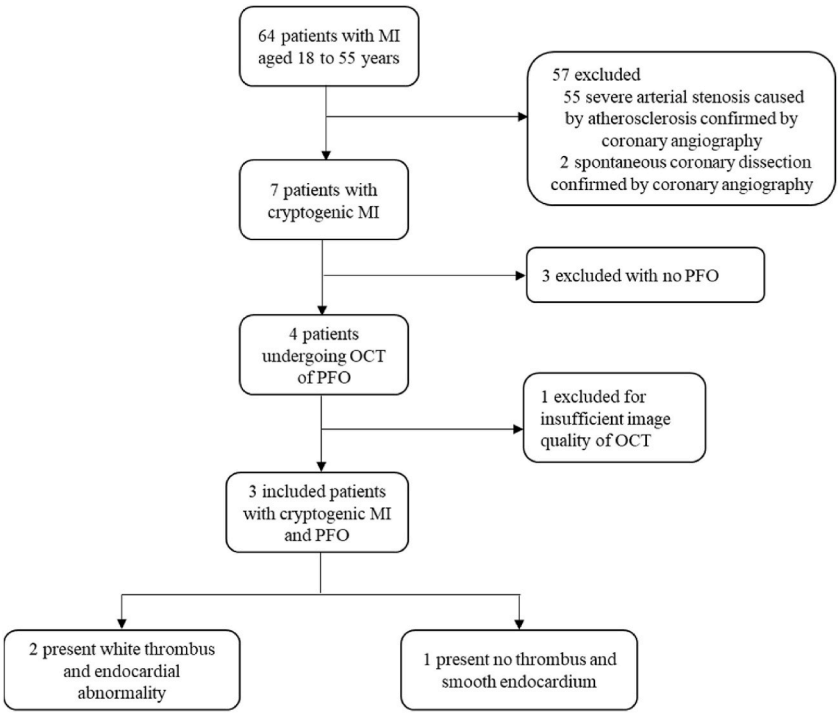

Fig. 2. Flow of participants for optical coherence tomography (OCT) examination of patent foramen ovale(PFO) in cryptogenic myocardial infarction(MI).

Table 1
Basic information and intervention therapy information.

variables	Results
Patients, n	3
Age, mean ± SD	41 ± 10
Man, n (%)	2(66.7 %)
Hypertension, n (%)	1(33.3 %)
Diabetes, n (%) smoking, n (%)	0
migraine, n (%)	0
	2(66.7 %)
Location of infarction, n (%)	
Anterior wall	2(66.7 %)
Anteriolateral, anterior and inferior wall	1(33.3 %)
Large RLS in cTTE, n (%)	3(100 %)
PFO size in fossa ovale angiography, mm, mean ± SD	2.6 ± 0.44
25 mm Occluder size, n (%)	3(100 %)

RLS, right to left shunt; cTTE, contrast transthoracic echocardiography; PFO, patent foramen ovale.

whereas cTTE revealed large right-to-left shunts in all patients. Selective coronary angiography showed no definite stenoses (Supplementary Figs. 1A–D), and fossa ovale angiography confirmed the diagnoses of PFO.

The three patients presented different OCT images (Fig. 3A–C). The first patient presented a low reflective mass of four different-sized parts, indicating a small number of thrombi in the channel. The thrombus area and total volume were calculated as 0.28 mm^2 and 0.088 mm^3, respectively. In addition, endocardial irregularities were observed in the channel. The second patient had one thrombus in the channel and endocardial surface discontinuity. The thrombus area and total volume were calculated as 0.67 mm^2 and 0.134 mm^3, respectively. However, in the third patient, OCT revealed no thrombus and no anomalous endocardial surface morphology. Moreover, we measured the left and right atrial lateral areas of the three PFO tunnels (Table 2). None of the patients reported discomfort during the OCT examination.

The PFOs were closed with a 25-mm Amplatzer PFO closure device after OCT examination. The patients were discharged from the hospital 1 day after closure and were prescribed oral aspirin and clopidogrel. None of the patients had experienced a recurrence of chest pain at follow-up. electrocardiography and TTE findings were normal at follow-up, and no residual shunt was found.

4. Discussion

In this study, we identified the presence of in situ thrombus within the PFO channel in MI patients with normal coronary arteries. These patients had no other cause for their condition other than the presence of a PFO. This finding suggests that in situ thrombus in PFO is a potential thromboembolic source for coronary thrombosis.

PFO is an intracardiac conduit for an embolized thrombus that travels from the venous system to the arterial system, causing stroke [7–9], renal infarction [10], splenic infarction [11], and MI [3]. A few cases of paradoxical embolism-related MI have been reported [12–14]. Jungbluth summarized 27 cases of MI caused by paradoxical embolism that were reported globally and found that the vast majority were identified on autopsy [15]. Furthermore, the PFO itself can act as an initial site of thrombosis [16]. Before the application of OCT in congenital heart disease, the presence of in situ thrombus in the PFO was considered hypothetical. In Yan et al.'s preliminary research, it was observed that all patients with cerebral infarction exhibited varying degrees of thrombotic load in the PFO tunnel [5]. When the sample size was increased, 84 % of stroke patients had an in situ thrombus in the PFO tunnel, and 63 % had endocardial abnormalities, while no thrombus or endocardial abnormalities were noted in asymptomatic PFO patients. In situ thrombi are independently associated with stroke events [6]. This is an interesting finding, suggesting that in situ thrombus serves as a common mechanism underlying PFO and stroke and is a valuable predictor of stroke. However, in situ thrombi in patients with MI have not been

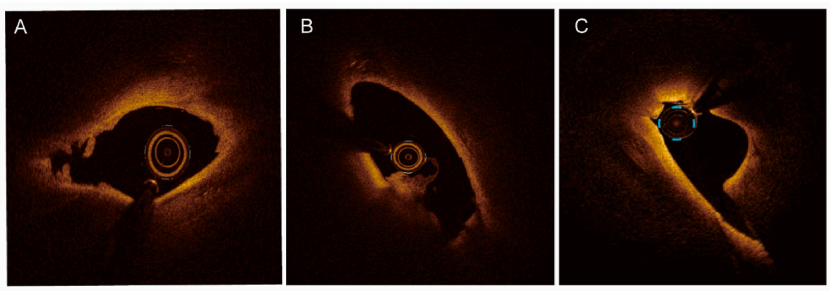

Fig. 3. Optical coherence tomography imaging of patent foramen ovale channel of three patients with myocardial infarction, A and B present white thrombus and endocardial abnormality while C shows no thrombus and smooth endocardium.

Table 2
OCT data of PFO tunnel in patients with MI.

	Number of thrombi,n	Thrombus area, mm^2	Total volume, mm^3	Left atrial lateral area, mm^2	Right atrial lateral area, mm^2	Endocardial abnormalities
No.1	4	0.28	0.088	5.22	5.51	Irregularity
No.2	1	0.67	0.134	3.18	8.14	Discontinuity
No.3	ND	ND	ND	3.79	8.02	ND

OCT, optical coherence tomography; PFO, patent foramen ovale; MI, myocardial infarction; ND, not detected.

studied.

In this study, we analyzed the microstructure of PFO tunnel using OCT in young adult patients with MI whose coronary arteries were normal and found in situ thrombi in the PFO tunnels. Similarly to the displacement of venous thrombosis in the lower extremity, there is also a possibility that in situ thrombus will translocate into the left atrium and eventually cause MI. Interestingly, the two patients with in situ thrombi had migraine attacks in their daily lives, whereas the other patient without migraines had no in situ thrombi. This suggests that, in addition to enrolling more MI participants in the future to determine the incidence of thrombus, further research is needed to explore the possible association of in situ PFO thrombi with migraines.

Diagnosing MI due to PFO is often challenging because PFO, which occurs in 25 % or higher of the general population [17,18], may be a co-manifestation rather than a causative factor. Clinically, it is necessary to carefully consider PFO as the cause of coronary embolism in the absence of obstructive stenosis on coronary angiography and intra-cardiac factors such as AF. Furthermore, once PFO is considered, the treatment strategy may not be completely consistent with that of atherosclerotic coronary artery disease, as stent implantation and statin therapy may not be necessary [19]. Despite the lack of randomized controlled trial data, PFO occlusion for secondary prevention is feasible in appropriately selected MI patients [19]. Case-control research with large samples has analyzed closure therapy in non-cerebrovascular peripheral embolism and found that the prognosis is comparable to that of cerebrovascular events [20]. PFO closure in our three patients with MI yielded a positive effect, and the long-term prognosis requires further follow-up.

5. Limitations

First, because the MIs were initially diagnosed at an outside facility, there was a time lag between the diagnosis of acute MI and the OCT examination. Antiplatelet and anticoagulant therapies administered outside our hospital may have affected the results. However, these therapies in patients with stroke in previous studies did not appear to affect the observation of thrombus [6]; instead, antiplatelet and anticoagulant therapy provided evidence that the in situ thrombus was not caused by the catheter entering the PFO. Second, we only reported three patients with MI due to PFO because of its rare incidence, and further studies with larger sample sizes are warranted to confirm the association between cryptogenic MI and in situ thrombus formation.

6. Conclusion

In situ thrombus attached to the PFO channel was identified in MI patients with normal coronary arteries. This may be a new source of coronary thrombosis and provide a new perspective on future research about the pathogenic relationship between PFO and MI.

Funding

None.

Ethics statement

This study has been approved by the Institutional Review Board of the First Affiliated Hospital of Xi'an Jiaotong University with number XJTU1AF2023LSK-009.

Consent for publication: The authors confirm that written consent for submission and publication of images and associated text has been obtained from the participants in accordance with COPE guidance.

CRediT authorship contribution statement

Xiao-qin Liu: Writing – original draft, Methodology, Investigation, Conceptualization. **Xing-ye Wang:** Writing – original draft, Formal analysis, Conceptualization. **Hang Xie:** Investigation, Formal analysis. **Xue-gang Xie:** Formal analysis, Data curation. **Yu-shun Zhang:** Writing – review & editing, Conceptualization. **Lu He:** Writing – review & editing, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to

influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e35220.

References

[1] H. Hu, Y. Lin, X. Xu, S. Lin, X. Chen, S. Wang, The alterations of mitochondrial DNA in coronary heart disease, Exp. Mol. Pathol. 114 (2020), https://doi.org/10.1016/j.yexmp.2020.104412.

[2] H.R. Reynolds, N.R. Smilowitz, Myocardial infarction with nonobstructive coronary arteries, Annu. Rev. Med. 74 (Jan 27 2023) 171–188, https://doi.org/10.1146/annurev-med-042921-111727.

[3] F.X. Kleber, T. Hauschild, A. Schulz, A. Winkelmann, L. Bruch, Epidemiology of myocardial infarction caused by presumed paradoxical embolism via a patent foramen ovale, Circ. J. 81 (10) (2017) 1484–1489, https://doi.org/10.1253/circj.CJ-16-0995.

[4] A. Gupta, A. Shrivastava, R. Vijayvergiya, et al., Optical coherence tomography: an eye into the coronary artery, Frontiers in Cardiovascular Medicine 9doi (2022), https://doi.org/10.3389/fcvm.2022.854554.

[5] C. Yan, H. Li, Preliminary Investigation of in situ thrombus within patent foramen ovale in patients with and without stroke, JAMA 325 (20) (May 25 2021) 2116–2118, https://doi.org/10.1001/jama.2021.4359.

[6] C. Yan, H. Li, C. Wang, et al., Frequency and size of in situ thrombus within patent foramen ovale, Stroke 54 (5) (May 2023) 1205–1213, https://doi.org/10.1161/strokeaha.122.041524.

[7] L. Søndergaard, S.E. Kasner, J.F. Rhodes, et al., Patent foramen ovale closure or antiplatelet therapy for cryptogenic stroke, N. Engl. J. Med. 377 (11) (Sep 14 2017) 1033–1042, https://doi.org/10.1056/NEJMoa1707404.

[8] J.L. Mas, G. Derumeaux, B. Guillon, et al., Patent foramen ovale closure or anticoagulation vs. Antiplatelets after stroke, N. Engl. J. Med. 377 (11) (Sep 14 2017) 1011–1021, https://doi.org/10.1056/NEJMoa1705915.

[9] P.H. Lee, J.K. Song, J.S. Kim, et al., Cryptogenic stroke and high-risk patent foramen ovale: the DEFENSE-PFO trial, J. Am. Coll. Cardiol. 71 (20) (May 22 2018) 2335–2342, https://doi.org/10.1016/j.jacc.2018.02.046.

[10] G. Stefan, A.M. Badea, D. Spataru, S. Stancu, Paradoxical renal embolization via patent foramen ovale: a case of complicated pulmonary embolism and renal infarction mitigated by accessory renal arteries (Nephrology images), J. Nephrol. (Jul 25 2023), https://doi.org/10.1007/s40620-023-01722-9.

[11] O.M.P. Jolobe, Paradoxical embolism as a cause of renal and/or splenic infarction, QJM 113 (6) (Jun 1 2020) 442–443, https://doi.org/10.1093/qjmed/hcz284.

[12] J.H. Chong, A. Baumbach, M.Y. Khanji, A middle-aged woman with recurrent chest pain with troponin elevation and unobstructed coronary arteries, JAMA Cardiology 6 (5) (2021), https://doi.org/10.1001/jamacardio.2021.0116.

[13] M. Namasivayam, R. Spina, L. Bobillo, M.P. Feneley, D.W. Baron, Acute myocardial infarction due to paradoxical embolism, Int. J. Cardiol. 209 (2016) 190–191, https://doi.org/10.1016/j.ijcard.2016.01.105.

[14] J.H. Chong, A. Baumbach, M.Y. Khanji, A middle-aged woman with recurrent chest pain with troponin elevation and unobstructed coronary arteries, JAMA Cardiol 6 (5) (May 1 2021) 600–601, https://doi.org/10.1001/jamacardio.2021.0116.

[15] A. Jungbluth, R. Erbel, H. Darius, H.J. Rumpelt, J. Meyer, Paradoxical coronary embolism: case report and review of the literature, Am. Heart J. 116 (3) (Sep 1988) 879–885, https://doi.org/10.1016/0002-8703(88)90356-0.

[16] A.Y. Elgendy, J.L. Saver, Z. Amin, et al., Proposal for updated nomenclature and classification of potential causative mechanism in patent foramen ovale-associated stroke, JAMA Neurol. 77 (7) (Jul 1 2020) 878–886, https://doi.org/10.1001/jamaneurol.2020.0458.

[17] R. Huber, U. Grittner, F. Weidemann, et al., Patent foramen ovale and cryptogenic strokes in the stroke in young fabry patients study, Stroke 48 (1) (2017) 30–35, https://doi.org/10.1161/strokeaha.116.013620.

[18] I. Koutroulou, G. Tsivgoulis, D. Karacostas, et al., Prevalence of patent foramen ovale in the Greek population is high and impacts on the interpretation of the risk of paradoxical embolism (RoPE) score, Ther Adv Neurol Disord 13 (2020 Oct 10) 1756286420964673, https://doi.org/10.1177/1756286420964673.

[19] A. Islam, A. Muath, R.A. Abdullah, Acute myocardial infarction secondary to paradoxical embolism, European Journal of Case Reports in Internal Medicine (2020), https://doi.org/10.12890/2020_001951.

[20] J.I. Farjat-Pasos, P. Guedeney, C. Houde, et al., Transcatheter closure of patent foramen ovale in patients with peripheral (noncerebrovascular) embolism, J. Invasive Cardiol. 34 (10) (Oct 2022) E720–e725.