Slovenian **Medical** Journal

Percutaneous closure of patent foramen ovale

Perkutano zapiranje odprtega ovalnega okna

Katja Prokšelj,[1,2] Janja Pretnar Oblak[3]

Abstract

Patent foramen ovale (PFO) is a remnant of an embryological atrial communication, which normally closes spontaneously after birth. However, it remains open in 25% of the general population. It is linked to several conditions due to a right-left shunt, including cryptogenic ischemic stroke, systemic embolism, migraine, and decompression illness. Percutaneous PFO closure is a relatively simple and safe procedure, which has been indicated in selected patients. Results from relevant studies show that closure is reasonable in younger patients with embolic ischemic stroke, where after thorough and comprehensive diagnostics and exclusion of alternative causes, the cause still remains undetermined. Even after percutaneous closure of PFO, lifelong secondary medical treatment is mandatory. To date, the results of the studies show that percutaneous closure is not indicated in the treatment of migraine, but is indicated in active and professional divers after decompression illness. Patients with an indication for percutaneous PFO closure should be referred to a multidisciplinary PFO council.

Izvleček

Odprto ovalno okno (OOO) je ostanek razvojne povezave med preddvoroma, ki se ob rojstvu običajno spontano zapre, pri približno 25 % populacije pa ostane odprto vse življenje. V redkih primerih je OOO zaradi desno-levega spoja lahko vpleteno v nastanek kriptogene ishemične možganske kapi, sistemske embolizacije, migrene in dekompresijske bolezni. Perkutano zapiranje OOO je preizkušen, razmeroma enostaven in varen poseg, ki pa prihaja v poštev le pri izbranih bolnikih. Študije namreč kažejo, da je smiseln predvsem pri mlajših bolnikih z embolično ishemično možgansko kapjo, ki tudi po natančnem stopenjskem diagnosticiranju in izključitvi ostalih alternativnih vzrokov ostaja nepojasnjena. Ne glede na opravljeno zapiranje OOO morajo bolniki s kriptogeno ishemično možgansko kapjo doživljenjsko prejemati tudi sekundarno medikamentno zaščito. Glede na doslej opravljene študije zaenkrat velja, da perkutano zapiranje OOO ni učinkovit način zdravljenja migrene, prihaja pa v poštev pri aktivnih potapljačih po preboleli dekompresijski bolezni in pri poklicnih potapljačih. Svetujemo, da se bolniki z indikacijo za zapiranje OOO napotijo na konzilij za OOO.

[1] Department of Cardiology, University Medical Centre Ljubljana, Ljubljana, Slovenia
[2] Department of Internal Medicine, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia
[3] Neurology clinic, University Medical Centre Ljubljana, Ljubljana, Slovenia

Correspondence / Korespondenca: Katja Prokšelj, e: katja.prokselj@gmail.com

Key words: cryptogenic ischemic stroke; embolic stroke of undetermined origin; patent foramen ovale; atrial fibrillation; hypercoagulable state

Ključne besede: kriptogena ishemična možganska kap; embolična možganska kap neopredeljenega izvora; odprto ovalno okno; atrijska fibrilacija; hiperkoagulabilno stanje

Received / Prispelo: 23. 8. 2020 | **Accepted / Sprejeto:** 30. 11. 2020

Cite as / Citirajte kot: Prokšelj K, Pretnar Oblak J. Percutaneous closure of patent foramen ovale. Zdrav Vestn. 2021;90(11–12):614–23.
DOI: https://doi.org/10.6016/ZdravVestn.3153

1 Introduction

Patent foramen ovale (PFO) is a remnant of an embryological atrial communication, which normally closes spontaneously in a newborn, after postpartal adaptation of blood circulation. The closure is firstly functional, as a result of the pressure difference between the atria, and then in the first year of life, the foramen ovale is closed anatomically by fibrous adhesions. Thus, the communication between the atria is eliminated. Despite the fact that the adaptation of blood circulation occurs in all healthy people, the foramen ovale does not close anatomically in all. In such instances, the foramen ovale remains patent and the condition is referred to as PFO (1-3). If in a person with PFO, right atrial pressure exceeds the left atrial pressure, blood bypasses the pulmonary circulation and flows through the PFO directly from the right into the left atrium, which is called a right-to-left shunt. This is a possible mechanism for paradoxical embolism. PFO is a common finding and studies show that it is present in approximately 25% of individuals in the general population (1,4). Usually, PFO is asymptomatic (1,5).

In rare cases, however, a right-to-left shunt due to the PFO may be involved in the development of cryptogenic ischemic stroke, systemic embolism, migraine, and decompression illness (2,3,6,7).

As PFO is considered a possible mechanism of paradoxical embolism, percutaneous PFO closure techniques were developed at the end of the last century in order to prevent recurrent paradoxical embolisms and related clinical events (8).

Primary surgical closure of PFO nowadays is no longer used and is indicated only in concomitant heart surgery for another indication. It has been replaced by a percutaneous technique, which is easy to implement and has few complications. During the procedure, the PFO is closed with a special closure device (occluder) consisting of two interconnected disks. The procedure is performed by femoral approach. The occluder is positioned in the atrial septum so that the discs embrace and close the PFO from both sides. Because the procedure is usually monitored with transoesophageal echocardiography, it is performed under general anaesthesia or deep sedation (9). Since the first description of a successful percutaneous PFO closure in 1983, it has become one of the most commonly performed percutaneous cardiac procedures to day (8).

This article discusses the indications for percutaneous PFO closure with emphasis on the most common condition, cryptogenic ischemic stroke.

2 Conditions associated with an increased incidence of patent foramen ovale

Since it is usually asymptomatic, patients are commonly not aware that they have PFO. It is often diagnosed incidentally during echocardiography, performed for another indication. PFO, diagnosed as an incidental finding, does not require additional investigations, follow-up or even percutaneous closure. Diagnostic procedures and closure are only indicated for selected subgroups of patients. PFO may be involved in the development of a cryptogenic ischemic stroke or other systemic embolism, migraine, and decompression illness (10,11).

2.1 Cryptogenic ischemic stroke

2.1.1 What is a cryptogenic ischemic stroke?

A cryptogenic ischemic stroke is difined as a stroke in which no direct cause can be found despite proper investigations (12).

Where there is a history of an ischemic stroke or transient ischemic attack (TIA), the aetiology should be defined and, if possible, the cause should be eliminated so that ischemic events do not recur. In most cases, the cause for an ischemic stroke is arterial occlusion. An occlusion of the major cerebral arteries is caused by either cardioembolism or artery-to-artery embolism from the large arteries. An occlusion of the smaller arteries is mostly caused by thrombosis; this is the lacunar infarct. According to the above, the TOAST classification (Trial of ORG 10172) with five basic groups is used to classify ischemic stroke according to aetiology: 1. large-artery atherosclerosis; 2. Cardioembolism; 3. small vessel occlusion; 4. stroke of other determined aetiology; 5. stroke of undetermined aetiology or cryptogenic ischemic stroke (Figure 1) (12).

Despite appropriate diagnostics as much as 20–30% of ischemic strokes remain unexplained, or cryptogenic, especially in younger patients (13). Sometimes the reason for this is inadequate diagnostic workup, several possible aetiologies may be present, or the aetiology remains unclear despite a comprehensive diagnostics.

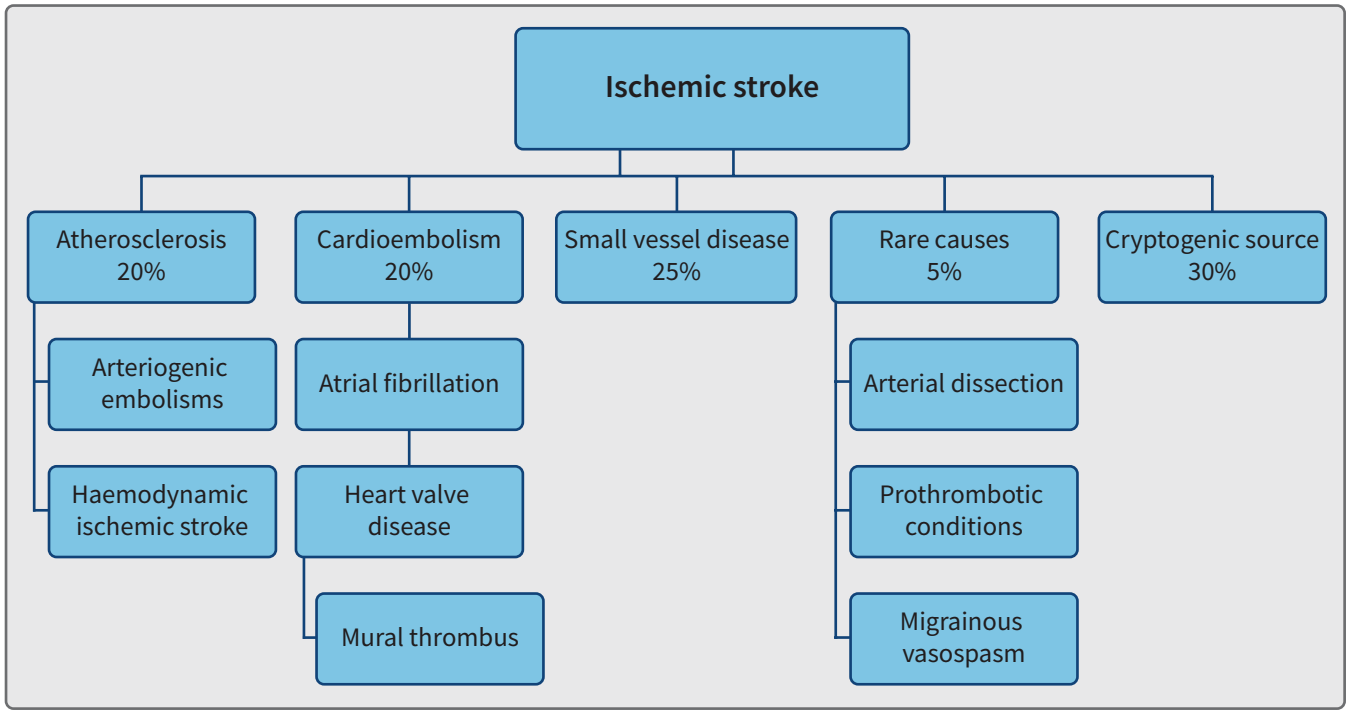

Figure 1: The TOAST classification - causes of ischemic stroke. Summarized after Adams HP, et al., 1993 (12).

Cryptogenic ischemic strokes of embolic origin are particularly problematic, as such ischemic strokes are more severe and they often recur.

2.1.2. What is ESUS?

In 2014, an international working group established the term Embolic Stroke of Undetermined Source (ESUS) (14). ESUS is referred to cryptogenic embolic (non-lacunar) cerebral infarction, which is not the result of extra- or intracranial atherosclerosis, and cardioembolic source as well as other causes of ischemic stroke are excluded by the classical examinations. The ESUS definition allows for a more comprehensive treatment of patients with cryptogenic ischemic stroke.

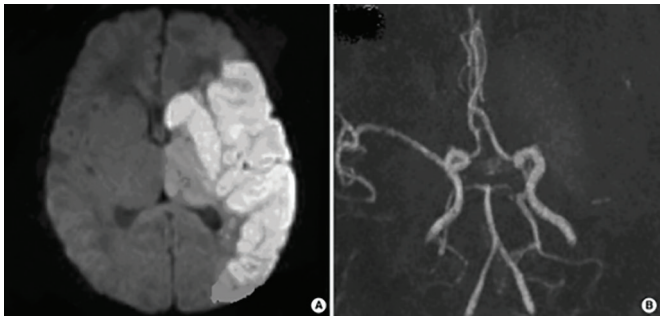

Figure 2: Typical appearance of embolic cerebral infarction: MRI of the head shows a wedge-shaped ischemic infarction (A), which occurred when the left middle cerebral artery was blocked (B).
Image is from authors' own archive.

In practice, the diagnosis of ESUS requires imaging – computed tomography (CT) or magnetic resonance imaging (MRI) of the head, which shows a wedge-shaped infarction characteristic of embolic origin (Figure 2). Ultrasound examination (US) is most commonly used to rule out pathology of the carotid arteries, and computed tomography (CT) or magnetic resonance (MRI) angiography (preferably in combination with ultrasound techniques) are used to show intracranial arteries. To rule out cardioembolic aetiology, transthoracic echocardiogram (TTE), a classic ECG, and, if this does not show pathology, at least a 24-hour Holter ECG monitoring should be performed (Figure 1). In some patients, especially younger ones, additional in-depth diagnostic workup is required, excluding various rarer conditions (prothrombotic conditions, autoimmune diseases, vasculitis, hereditary diseases, etc.) (15). Such examinations are a part of a subspecialist diagnostic workup, which is beyond the scope of this article.

2.1.3 The role of patent foramen ovale in the occurence of ESUS

The prevalence of PFO among patients with cryptogenic ischemic stroke is approximately 40% and it is even more common in young people (16). A meta-analysis of

23 studies evaluating cryptogenic ischemic stroke and PFO showed that the prevalence of PFO was 2.9-fold higher in patients with cryptogenic ischemic stroke than in healthy subjects (17).

The most important mechanism for the occurrence of ischemic stroke in PFO is supposed to be a paradoxical embolism. If this mechanism were to be unequivocally confirmed, the presence of a thrombosis in the venous system would have to be demonstrated in addition to the right-left shunt through the PFO. Most studies show that deep vein thrombosis is detected in only 8–10% of patients (18). Most patients with deep vein thrombosis have symptoms. Additional possible mechanisms are thrombus formation within the PFO channel due to blood stasis, and concomitant heart rhythm disorder (5).

2.1.4 The position of the profession regarding the patent foramen ovale closure in patients with ESUS

In 2012 and 2013, the results of three large randomized trials, CLOSURE I, PC Trial, and RESPECT were published, which did not confirm greater efficacy of percutaneous PFO closure compared to medical therapy alone to prevent recurrent ischemic stroke in patients younger than 60 years (19-21). They confirmed that the procedure itself is otherwise safe, although atrial fibrillation is more common after the closure. The trials have been criticized for having a too short follow-up time and a too low number of subjects, as complications were relatively rare.

The perspective on PFO closure in patients with cryptogenic ischemic stroke changed significantly in September 2017, when the New England Journal of Medicine published the results of three large randomized trials that confirmed a lower incidence of recurrent ischemic stroke in patients who had percutaneously closed PFO (22-24). However, atrial fibrillation still occurred more frequently after closure.

In the REDUCE trial, which included 664 patients younger than 60 years with moderate to large right-to-left shunts, after an average of 3.2 years of follow-up, ischemic stroke reoccurred in 1.4% of patients with percutaneously closed PFO, and in 5.4% of patients treated with antiplatelet medication alone (p=0.002) (22). Atrial fibrillation occurred more often in the PFO group after closure.

After prolonged follow-up of 980 patients in the RESPECT trial from mean of 2.1 years to 5.9 years, ischemic stroke reoccurred in 3.6% in the group with percutaneously closed PFO, and in 5.8% in subjects treated with medication alone. The difference was statistically significant (p=0.046) (23).

The CLOSE trial compared the effectiveness of different treatments in patients with a concomitant atrial septal aneurysm or a large right-to-left shunt. A total of 663 patients under the age of 60 were included, who were followed for an average of 5.3 years. They were randomized into three groups: a group with percutaneously closed PFO that received antiplatelet treatment, a group that received only anticoagulation therapy, and a group that received only antiplatelet treatment. In none of the 238 patients with closed PFO did the ischemic stroke reoccur, whereas it occurred in 6.0% of patients treated with antiplatelet medication alone (p<0.001) (24).

Based on the aforementioned studies from 2017 and a subsequent meta-analyses, the updated guidelines have stated that in patients with defined ESUS, it makes sense to determine whether they have a PFO, and, in the absence of clear contraindications to close it, especially in patients with large shunts and convincing radiologically proven ischemic infarctions. At the same time, the secondary prevention of ischemic stroke by means of medication remains the basis of treatment in all patients with ESUS after the closure of PFO (10,22-28).

2.2 Migraine

2.2.1 What is a migraine?

A migraine is a chronic neurological disease characterized by severe headaches with accompanying autonomic symptoms and aura. It affects 8–13% of the adult population (29,30). Despite numerous studies, the pathophysiology of a migraine has not been fully elucidated, so we do not currently have a medication that would completely cure patients. Migraine thus remains a chronic problem that greatly complicates the lives of many patients.

2.2.2 The role of patent foramen ovale in a migraine patient

Patients who have undergone PFO closure due to cryptogenic ischemic stroke or decompression illness prevention who have also had concomitant migraine, observed a reduction in the number of migraine headaches and less intense headaches after closure. This was first described by Wilmhurst et al. in 2000 (31). Subsequently, a number of studies have found that PFO is present in 47–48% of migraine patients, in contrast to the rest of the population, where PFO is present in 17–20% (32).

The proposed linking mechanism is thought to be the passage of microemboli or vasoactive substances (e.g. serotonin) via PFO into the left part of the heart and into the brain, which is thought to cause migraine symptoms. This mechanism has never been proven.

2.2.3 The position of the profession regarding the patent foramen ovale closure in migraine patients

A 2008 MIST study compared PFO closure with a sham procedure in migraine patients (33). Patients were followed for only 6 months and during this time there were no differences in the frequency of headaches between the two groups. In addition, a surprisingly high incidence of complications occurred in the group in which the closure device was inserted (6.8%). The MIST study therefore did not show any advantage of closing the PFO in migraine patients, but it was criticized mainly for the short duration of follow-up and the recruitment of patients with a very severe form of migraine. Subsequently, a PREMIUM study was published in 2017 with a longer duration of follow-up and a greater range of patients. Despite the changed patient selection and duration, this study also showed no efficacy of PFO closure in the treatment of migraine patients (34).

According to the studies performed so far, it is therefore considered that the closure of PFO is not an effective way to prevent or treat migraine.

2.3 Decompression illness

2.3.1 What is a decompression illness?

Decompression illness is caused by a drop in ambient air pressure and the formation of air bubbles in the blood. This phenomenon most often occurs when divers rise from the depths. The clinical picture covers the whole spectrum from asymptomatic neurological events to stroke and spinal myelitis (35).

2.3.2 The role of patent foramen ovale in decompression illness

Studies have shown that divers with decompression illness were more likely to have PFO compared to the control group of divers (60% vs. 36%) (36). Although the difference was not statistically significant, it was believed to be a clinically relevant finding. Subsequent studies have shown that the size of the PFO is also important. In a larger PFO, the likelihood of serious decompression illness lasting more than 24 hours is higher (37).

Table 1: Recommended standard diagnostic protocol for defining ESUS. Summarized after Hart RG, et al., 2014 (14).

Display of topographic characteristics of ischemic stroke:
• CT or MRI of the head
Display of arteries in the brain, neck and chest:
• Ultrasound of the carotid arteries • CT angiography and/or MRI angiography • Chest X-ray
Cardiac imaging:
• transthoracic echocardiography
Diagnosing cardiac arrhythmias and myocardial ischemia:
• ECG • 24-hour Holter monitoring (in case of normal ECG)
In addition, basic laboratory tests (biochemical blood tests, complete blood count, CRP, erythrocyte sedimentation rate, four-fraction lipidogram) are required to identify risk factors and to guide secondary prevention of ischemic stroke.

With the growing popularity of recreational sport diving, the question arose as to whether it would make sense to close the PFO in all diver candidates. A 2009 meta-analysis showed that the risk of decompression illness in divers with PFO was 4.23 (95% CI; 3.05–5.87) compared to those without it. Because the incidence of decompression illness is so low, the absolute risk even in patients with PFO is too low to justify routine testing for PFO or even its closure (38).

2.3.3. The position of the profession regarding patent foramen ovale closure in decompression illness

A prospective, non-randomized study published in 2011 followed 104 recreational divers for more than 5 years (39). Of these, 39 divers did not have PFO, 39 divers had PFO, and 26 divers had PFO closed. In the groups without PFO, with closed PFO and without PFO closure, there were 1.1±2.6; 0.8±1.4, and 3.3±6.9 ischemic brain changes during monitoring ($p = 0.039$). This is the only prospective study on this topic that confirmed the usefulness of the procedure in recreational divers, but was unfortunately too small for definite conclusion.

The opinion of most experts is that it is advisable to test divers after they have had decompression illness and still want to dive. Closing a PFO is probably reasonable for professional divers as well (10,15,28).

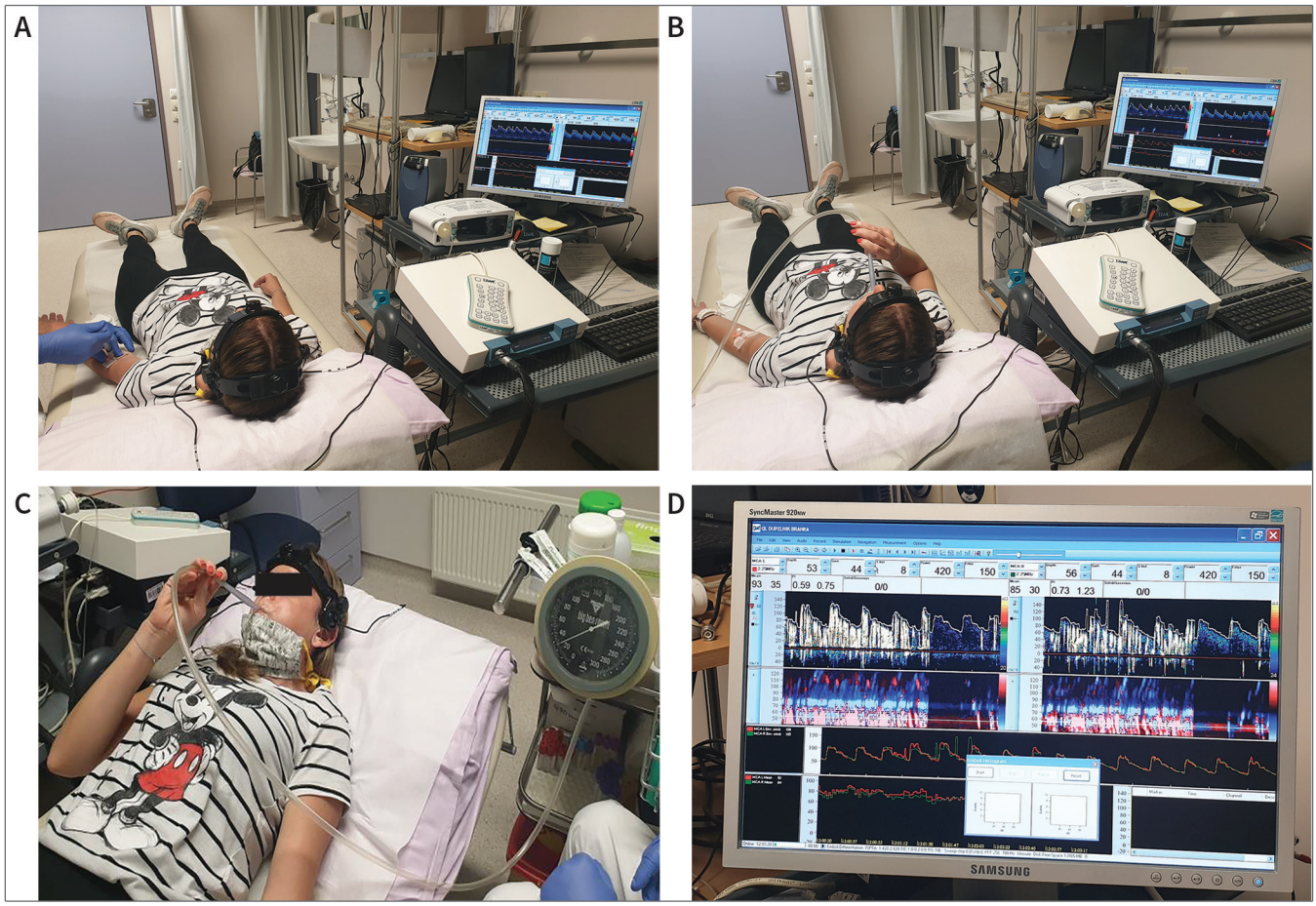

Figure 3: Transcranial Doppler Sonography with Valsalva manoeuvre.
(A) The subject has ultrasound (US) probes on her head over both middle cerebral arteries (MCA). The blood velocity curve through the right and left MCA is seen on the screen to the right. An ultrasound contrast agent is injected into the canal on the left elbow vein first at rest. (B) Contrast agent injection during the execution of the Valsalva manoeuvre. In the blood velocity curve through both MCAs, individual signals of the contrast - emboli - are detected. Contrast injected to the peripheral vein passed from the right atrium via PFO to the left atrium and subsequently to both MCAs. (C) Performing a Valsalva manoeuvre under the control of a manometer on the right. (D) Large amounts of emboli (or large amounts of contrast) in both MCAs during the Valsalva manoeuvre is evidence of a right-left shunt. Image is from authors' own archive.

3 Indications for percutaneous patent foramen ovale closure

According to the relevant studies, percutaneous PFO closure is currently recommended:

- in patients with ESUS, younger than 60 years, after complete diagnostic workup. Medical secondary prevention of ischemic stroke remains the cornerstone of treatment even after percutaneous closure of PFO.
- in professional divers (10,15,28).

Closure of the PFO is not indicated in patients with migraine and in recreational divers.

4 Stepwise diagnostic approach prior to patent foramen ovale closure

Diagnostic workup only applies in patients who are candidates for percutaneous closure, as is already an established clinical practice in Slovenia (40,41).

4.1 Recommended investigations for diagnosing the presence and morphology of patent foramen ovale

In patients with ESUS (Table 1) (14) who are less than 60 years old (in the elderly PFO closure is not considered,

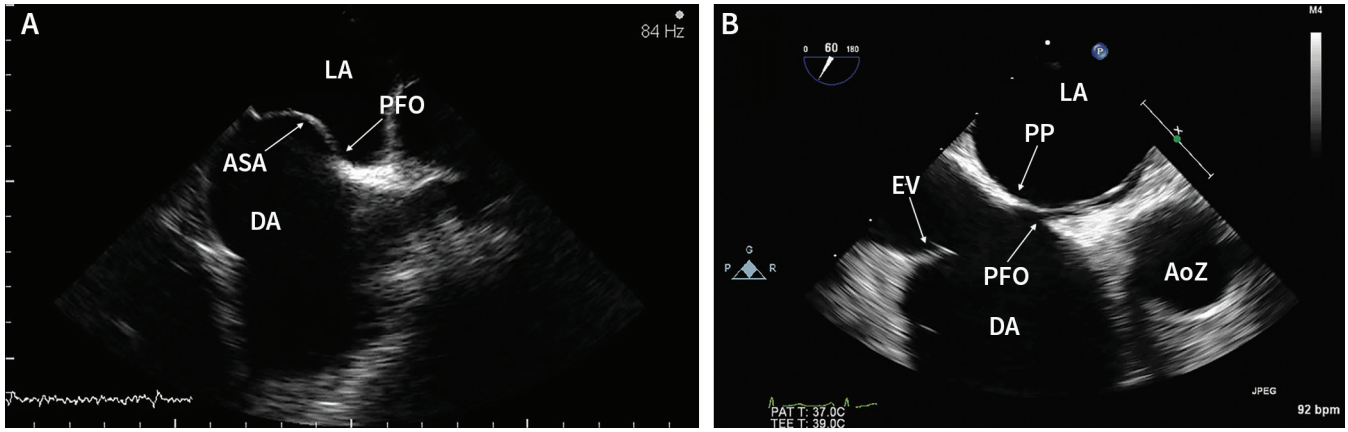

Figure 4: Transoesophageal echocardiography (TEE). TEE shows the patent foramen ovale (PFO), its size and associated structures such as (A) atrial septal aneurysm (ASA) and (B) Eustachian valve (EV).
Legend: AoZ – aortic valve, DA – right atrium, LA – left atrium, PP – atrial septum.
Image is from authors' own archive.

so diagnosing PFO is not indicated), the diagnostic algorithm should include the following investigations:

- transcranial Doppler sonography (TCD) with Valsalva manoeuvre,
- transthoracic echocardiography (TTE),
- transoesophageal echocardiography (TEE).

The first examination performed in patients with suspected PFO is transcranial Doppler sonography (TCD) (42). When using a probe through the transtemporal bone window, we monitor the rate of blood flow in the middle cerebral artery before and after injecting the contrast agent into the cubital vein. If a right-to-left shunt is present, microbubbles enter the cerebral circulation and a typical microembolic signal is detected. The examination is performed in basal conditions and when performing the Valsalva manoeuvre, which increases its sensitivity (Figure 3) (42).

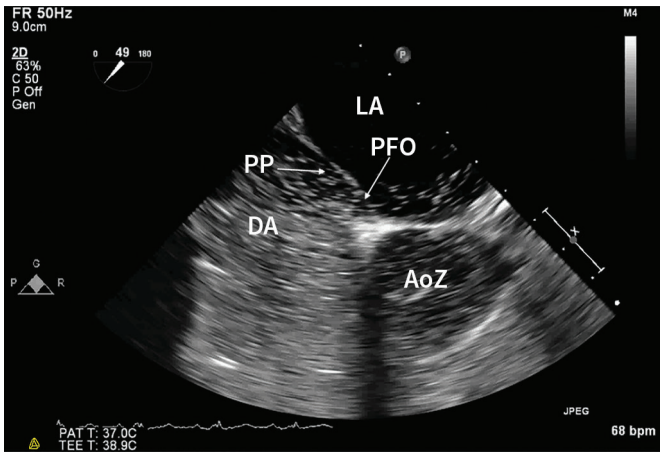

Figure 5: Contrast transoesophageal echocardiography (TEE). Contrast TEE shows the transition of contrast from right atrium (DA) to left atrium (LA) during Valsalva manoeuvre - right-to-left shunt.
Legend: AoZ – aortic valve, PFO – patent foramen ovale, PP – atrial septum.
Image is from authors' own archive.

Due to its high sensitivity (94%) and specificity (96%), TCD with contrast is an excellent screening method for suspected PFO. Because it is non-invasive, it has an advantage over TEE and its disadvantage is that it can only confirm the presence of a right-left shunt, but we cannot show the location of the contrast transition. Thus, we cannot reliably distinguish whether it is a shunt at the level of the heart or the pulmonary circulation. Echocardiography helps us here (42).

Echocardiography is the basic diagnostic method for detecting PFO. Transthoracic echocardiography (TTE) is important in patients with ischemic stroke mainly to exclude possible cardiac causes of ischemic stroke (e.g. mitral stenosis, myxoma, endocarditis,…), but does not allow accurate anatomical visualisation of PFO. With contrast TTE, using agitated saline, we can confirm the transition of contrast bubbles from the right to the left atrium, therefore right-to-left shunt, while a more precise evaluation of PFO with TTE is not possible. The investigation is less sensitive than TEE detecting PFO (around 55%), although very specific (up to 100%) (42,43).

Contrast transoesophageal echocardiography (TEE) is the most sensitive (94%) and specific (96%) method for diagnosing PFO (42,43). TEE not only confirms the presence of PFO, but also shows its anatomy, size and shape, and any additional structures such as atrial septal aneurysm (Figure 4 A), additional perforations, Eustachian valve (Figure 4 B), and Chiari network, which TTE and TCD do not enable. During TEE, left atrial appendage is screened to exlude thrombi. The examination

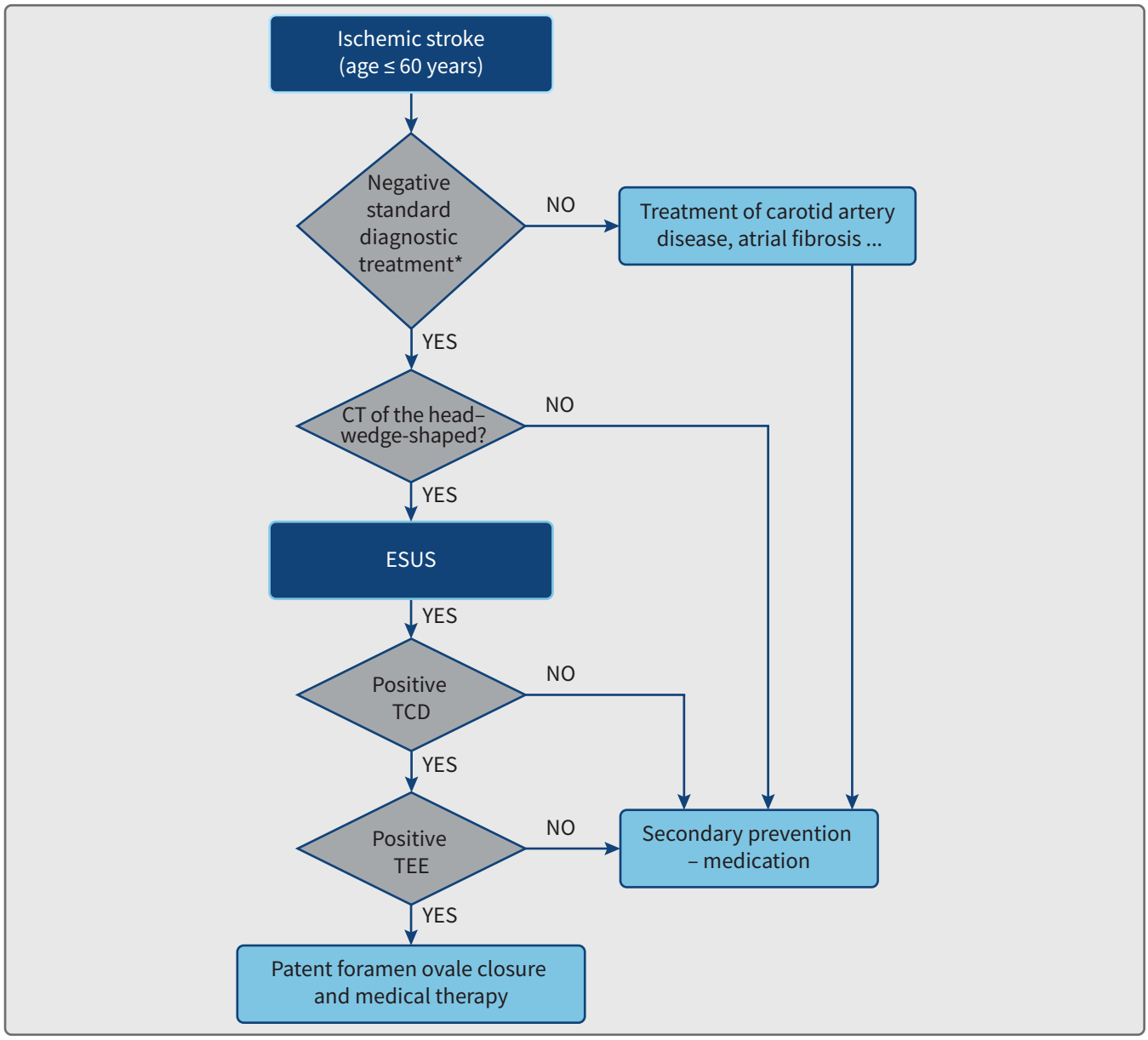

Figure 6: Proposed diagnostic algorithm for PFO closure in a patient with cryptogenic ischemic stroke **.
* Standard diagnostic treatment includes CT (MRI) of the head, CT (MRI) angiography, TTE, classic ECG (24-hour Holter monitoring), chest radiograph, and basic laboratory tests. Tests of haemostasis tests and rheumatologic tests are also required.
** Proposal submitted by the authors, based on the references given in the article.

is semi-invasive, therefore it is performed only when indicated.

In contrast TEE, agitated saline is used and injected in the cubital vein. The transition of microbubbles from the right to the left atrium in the first 3–5 cardiac cycles after injection confirms PFO. The transition of bubbles after 5 cardiac cycles is characteristic of the shunt at the level of pulmonary circulation in arteriovenous malformations and not of PFO. The test is performed first under basal conditions and then during the Valsalva manoeuvre, which temporarily increases the right-to-left shunt (Figure 5) and improves the sensitivity of the test. Inadequate manoeuvre may be the cause of a false negative result. TEE is the only test that can show the location of the PFO. Based on the number of contrast bubbles that pass from the right to the left atrium and that are shown in the image at the same time, we can estimate the size and significance of the PFO. In the transition of up to 5 bubbles, the shunt is defined as small, as moderate in 5–25 bubbles, and in more than 25 bubbles as a large shunt (43-46). The definition is arbitrary and is not generally accepted.

When diagnosing cryptogenic ischemic stroke, contrast TEE is indicated after contrast TCD and TTE examination in candidates for percutaneous closure of PFO; when the diagnosis of PFO is unclear or a possible other cause of ischemic stroke is sought; in high-risk PFO, especially in recurrent ischemic stroke, and in patients with atrial septal aneurysm or with a large shunt on TCD. When the TTE and/or TCD are negative, the TEE is not indicated (42,44).

4.2 Multidisciplinary council

PFO is a common finding in patients with various neurological symptoms. For uniform decision-making on the treatment of PFO, we therefore suggest that all patients with an indication for percutaneous PFO closure should be referred to a council consisting of a vascular neurologist and a cardiologist specializing in this field and, if necessary, an interventional cardiologist. Based on the diagnostic algorithm, the decision on the most appropriate treatment is made (Figure 6). A prerequisite for diagnostic treatment is that there is an indication for closure of PFO.

5 Conclusion

PFO is a common finding that occurs in about 25% of the general population. Due to an atrial right-to-left shunt, it may represent a mechanism for an embolic ischemic stroke. After accurate stepwise diagnosis of ischemic stroke and exclusion of other alternative causes of ischemic stroke, percutaneous closure of PFO can be indicated in patients with ESUS who are younger than 60 years. Patients with an indication for PFO closure should be discussed at the PFO council, thus ensuring uniform treatment according to expert recommendations. Prior to the procedure, the benefits and risks of the procedure must be discussed with the patient. Regardless of the PFO closure performed, lifelong secondary medical prevention must be continued.

Conflict of interest

None declared.

References

1. Hagen PT, Scholz DG, Edwards WD. Incidence and size of patent foramen ovale during the first 10 decades of life: an autopsy study of 965 normal hearts. Mayo Clin Proc. 1984;59(1):17-20. DOI: 10.1016/S0025-6196(12)60336-X PMID: 6694427
2. Hara H, Virmani R, Ladich E, Mackey-Bojack S, Titus J, Reisman M, et al. Patent foramen ovale: current pathology, pathophysiology, and clinical status. J Am Coll Cardiol. 2005;46(9):1768-76. DOI: 10.1016/j.jacc.2005.08.038 PMID: 16256883
3. Calvert PA, Rana BS, Kydd AC, Shapiro LM. Patent foramen ovale: anatomy, outcomes, and closure. Nat Rev Cardiol. 2011;8(3):148-60. DOI: 10.1038/nrcardio.2010.224 PMID: 21283148
4. Horton SC, Bunch TJ. Patent foramen ovale and stroke. Mayo Clin Proc. 2004;79(1):79-88. DOI: 10.4065/79.1.79 PMID: 14708951
5. Mattle HP, Meier B, Nedeltchev K. Prevention of stroke in patients with patent foramen ovale. Int J Stroke. 2010;5(2):92-102. DOI: 10.1111/j.1747-4949.2010.00413.x PMID: 20446943
6. Meissner I, Whisnant JP, Kandheria BK, Spittell PC, O' Fallon WM, Pascoe RD, et al. Prevalence of potential risk factors for stroke assessed by transesophageal and carotid ultrasonography: the SPARC study. Stroke prevention: assessment of risk in a community. Mayo Clin Proc. 1999;74:862-9. DOI: 10.4065/74.9.862 PMID: 10488786
7. Chen GP, Goldberg SL, Gill EA. Patent foramen ovale and the platypnea-orthodeoxia syndrome. Cardiol Clin. 2005;23(1):85-9. DOI: 10.1016/j.ccl.2004.10.003 PMID: 15676271
8. Rashkind WJ. Transcatheter treatment of congenital heart disease. Circulation. 1983;67(4):711-6. DOI: 10.1161/01.CIR.67.4.711 PMID: 6825227
9. Meier B. Closure of patent foramen ovale: technique, pitfalls, complications, and follow up. Heart. 2005;91(4):444-8. DOI: 10.1136/hrt.2004.052258 PMID: 15772193
10. Messé SR, Gronseth GS, Kent DM, Kizer JR, Homma S, Rosterman L, et al. Practice advisory update summary: Patent foramen ovale and secondary stroke prevention: Report of the Guideline Subcommittee of the American Academy of Neurology. Neurology. 2020;94(20):876-85. DOI: 10.1212/WNL.0000000000009443 PMID: 32350058
11. Leong MC, Uebing A, Gatzoulis MA. Percutaneous patent foramen ovale occlusion: current evidence and evolving clinical practice. Int J Cardiol. 2013;169(4):238-43. DOI: 10.1016/j.ijcard.2013.08.095 PMID: 24071386
12. Adams HP, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke. 1993;24(1):35-41. DOI: 10.1161/01.STR.24.1.35 PMID: 7678184
13. Putaala J, Metso AJ, Metso TM, Konkola N, Kraemer Y, Haapaniemi E, et al. Analysis of 1008 consecutive patients aged 15 to 49 with first-ever ischemic stroke: the Helsinki young stroke registry. Stroke. 2009;40(4):1195-203. DOI: 10.1161/STROKEAHA.108.529883 PMID: 19246709
14. Hart RG, Diener HC, Coutts SB, Easton JD, Granger CB, O'Donnell MJ, et al.; Cryptogenic Stroke/ESUS International Working Group. Embolic strokes of undetermined source: the case for a new clinical construct. Lancet Neurol. 2014;13(4):429-38. DOI: 10.1016/S1474-4422(13)70310-7 PMID: 24646875
15. Pristipino C, Sievert H, D'Ascenzo F, Louis Mas J, Meier B, Scacciatella P, et al.; Evidence Synthesis Team; Eapci Scientific Documents and Initiatives Committee; International Experts. European position paper on the management of patients with patent foramen ovale. General approach and left circulation thromboembolism. Eur Heart J. 2019;40(38):3182-95. DOI: 10.1093/eurheartj/ehy649 PMID: 30358849

16. Lamy C, Giannesini C, Zuber M, Arquizan C, Meder JF, Trystram D, et al. Clinical and imaging findings in cryptogenic stroke patients with and without patent foramen ovale: the PFO-ASA Study. Atrial Septal Aneurysm. Stroke. 2002;33(3):706-11. DOI: 10.1161/hs0302.104543 PMID: 11872892
17. Alsheikh-Ali AA, Thaler DE, Kent DM. Patent foramen ovale in cryptogenic stroke: incidental or pathogenic? Stroke. 2009;40(7):2349-55. DOI: 10.1161/STROKEAHA.109.547828 PMID: 19443800
18. Lethen H, Flachskampf FA, Schneider R, Sliwka U, Köhn G, Noth J, et al. Frequency of deep vein thrombosis in patients with patent foramen ovale and ischemic stroke or transient ischemic attack. Am J Cardiol. 1997;80(8):1066-9. DOI: 10.1016/S0002-9149(97)00604-8 PMID: 9352979
19. Furlan AJ, Reisman M, Massaro J, Mauri L, Adams H, Albers GW, et al.; CLOSURE I Investigators. Closure or medical therapy for cryptogenic stroke with patent foramen ovale. N Engl J Med. 2012;366(11):991-9. DOI: 10.1056/NEJMoa1009639 PMID: 22417252
20. Meier B, Kalesan B, Mattle HP, Khattab AA, Hildick-Smith D, Dudek D, et al.; PC Trial Investigators. Percutaneous closure of patent foramen ovale in cryptogenic embolism. N Engl J Med. 2013;368(12):1083-91. DOI: 10.1056/NEJMoa1211716 PMID: 23514285
21. Carroll JD, Saver JL, Thaler DE, Smalling RW, Berry S, MacDonald LA, et al.; RESPECT Investigators. Closure of patent foramen ovale versus medical therapy after cryptogenic stroke. N Engl J Med. 2013;368(12):1092-100. DOI: 10.1056/NEJMoa1301440 PMID: 23514286
22. Søndergaard L, Kasner SE, Rhodes JF, Andersen G, Iversen HK, Nielsen-Kudsk JE, et al.; Gore REDUCE Clinical Study Investigators. Patent foramen ovale closure or antiplatelet therapy for cryptogenic stroke. N Engl J Med. 2017;377(11):1033-42. DOI: 10.1056/NEJMoa1707404 PMID: 28902580
23. Saver JL, Carroll JD, Thaler DE, Smalling RW, MacDonald LA, Marks DS, et al.; RESPECT Investigators. Long-term outcomes of patent foramen ovale closure or medical therapy after stroke. N Engl J Med. 2017;377(11):1022-32. DOI: 10.1056/NEJMoa1610057 PMID: 28902590
24. Mas JL, Derumeaux G, Guillon B, Massardier E, Hosseini H, Mechtouff L, et al.; CLOSE Investigators. Patent foramen ovale closure or anticoagulation vs. antiplatelets after stroke. N Engl J Med. 2017;377(11):1011-21. DOI: 10.1056/NEJMoa1705915 PMID: 28902593
25. Mir H, Siemieniuk RA, Ge L, Foroutan F, Fralick M, Syed T, et al. Patent foramen ovale closure, antiplatelet therapy or anticoagulation in patients with patent foramen ovale and cryptogenic stroke: a systematic review and network meta-analysis incorporating complementary external evidence. BMJ Open. 2018;8(7):e023761. DOI: 10.1136/bmjopen-2018-023761 PMID: 30049703
26. De Rosa S, Sievert H, Sabatino J, Polimeni A, Sorrentino S, Indolfi C. Percutaneous closure versus medical treatment in stroke patients with patent foramen ovale: A systematic review and meta-analysis. Ann Intern Med. 2018;168(5):343-50. DOI: 10.7326/M17-3033 PMID: 29310133
27. Ahmad Y, Howard JP, Arnold A, Shin MS, Cook C, Petraco R, et al. Patent foramen ovale closure vs. medical therapy for cryptogenic stroke: a meta-analysis of randomized controlled trials. Eur Heart J. 2018;39(18):1638-49. DOI: 10.1093/eurheartj/ehy121 PMID: 29590333
28. Kuijpers T, Spencer FA, Siemieniuk RA, Vandvik PO, Otto CM, Lytvyn L, et al. Patent foramen ovale closure, antiplatelet therapy or anticoagulation therapy alone for management of cryptogenic stroke? A clinical practice guideline. BMJ. 2018;362:k2515. DOI: 10.1136/bmj.k2515 PMID: 30045912
29. Lipton RB, Stewart WF, Diamond S, Diamond ML, Reed M. Prevalence and burden of migraine in the United States: data from the American Migraine Study II. Headache. 2001;41(7):646-57. DOI: 10.1046/j.1526-4610.2001.041007646.x PMID: 11554952
30. Henry P, Auray JP, Gaudin AF, Dartigues JF, Duru G, Lantéri-Minet M, et al. Prevalence and clinical characteristics of migraine in France. Neurology. 2002;59(2):232-7. DOI: 10.1212/WNL.59.2.232 PMID: 12136063
31. Wilmshurst PT, Nightingale S, Walsh KP, Morrison WL. Effect on migraine of closure of cardiac right-to-left shunts to prevent recurrence of decompression illness or stroke or for haemodynamic reasons. Lancet. 2000;356(9242):1648-51. DOI: 10.1016/S0140-6736(00)03160-3 PMID: 11089825
32. Schwedt TJ, Demaerschalk BM, Dodick DW. Patent foramen ovale and migraine: a quantitative systematic review. Cephalalgia. 2008;28(5):531-40. DOI: 10.1111/j.1468-2982.2008.01554.x PMID: 18355348
33. Dowson A, Mullen MJ, Peatfield R, Muir K, Khan AA, Wells C, et al. Migraine Intervention With STARFlex Technology (MIST) trial: a prospective, multicenter, double-blind, sham-controlled trial to evaluate the effectiveness of patent foramen ovale closure with STARFlex septal repair implant to resolve refractory migraine headache. Circulation. 2008;117(11):1397-404. DOI: 10.1161/CIRCULATIONAHA.107.727271 PMID: 18316488
34. Tobis JM, Charles A, Silberstein SD, Sorensen S, Maini B, Horwitz PA, et al. Percutaneous closure of patent foramen ovale in patients with migraine: the PREMIUM trial. J Am Coll Cardiol. 2017;70(22):2766-74. DOI: 10.1016/j.jacc.2017.09.1105 PMID: 29191325
35. Germonpré P. Patent foramen ovale and diving. Cardiol Clin. 2005;23(1):97-104. DOI: 10.1016/j.ccl.2004.10.005 PMID: 15676273
36. Germonpré P, Dendale P, Unger P, Balestra C. Patent foramen ovale and decompression sickness in sports divers. J Appl Physiol. 1998;84(5):1622-6. DOI: 10.1152/jappl.1998.84.5.1622 PMID: 9572808
37. Torti SR, Billinger M, Schwerzmann M, Vogel R, Zbinden R, Windecker S, et al. Risk of decompression illness among 230 divers in relation to the presence and size of patent foramen ovale. Eur Heart J. 2004;25(12):1014-20. DOI: 10.1016/j.ehj.2004.04.028 PMID: 15191771
38. Lairez O, Cournot M, Minville V, Roncalli J, Austruy J, Elbaz M, et al. Risk of neurological decompression sickness in the diver with a right-to-left shunt: literature review and meta-analysis. Clin J Sport Med. 2009;19(3):231-5. DOI: 10.1097/JSM.0b013e31819b0fa2 PMID: 19423977
39. Billinger M, Zbinden R, Mordasini R, Windecker S, Schwerzmann M, Meier B, et al. Patent foramen ovale closure in recreational divers: effect on decompression illness and ischaemic brain lesions during long-term follow-up. Heart. 2011;97(23):1932-7. DOI: 10.1136/heartjnl-2011-300436 PMID: 21917666
40. Zaletel M, Koželj M, Podnar T, Peternel P. Odprto ovalno okno. Zdrav Vestn. 2006;75(2):93-100.
41. Rojko M, Černič Šuligoj N, Zorc M, Kar S, Noč M. Perkutano zapiranje odprtega ovalnega okna in okvare medpreddvornega pretina. Zdrav Vestn. 2019;88(11-12):576-81.
42. Zito C, Dattilo G, Oreto G, Di Bella G, Lamari A, Iudicello R, et al. Patent foramen ovale: comparison among diagnostic strategies in cryptogenic stroke and migraine. Echocardiography. 2009;26(5):495-503. DOI: 10.1111/j.1540-8175.2008.00852.x PMID: 19452605
43. Silvestry FE, Cohen MS, Armsby LB, Burkule NJ, Fleishman CE, Hijazi ZM, et al.; American Society of Echocardiography; Society for Cardiac Angiography and Interventions. Guidelines for the Echocardiographic Assessment of Atrial Septal Defect and Patent Foramen Ovale: From the American Society of Echocardiography and Society for Cardiac Angiography and Interventions. J Am Soc Echocardiogr. 2015;28(8):910-58. DOI: 10.1016/j.echo.2015.05.015 PMID: 26239900
44. Pizzino F, Khandheria B, Carerj S, Oreto G, Cusmà-Piccione M, Todaro MC, et al. PFO: button me up, but wait … Comprehensive evaluation of the patient. J Cardiol. 2016;67(6):485-92. DOI: 10.1016/j.jjcc.2016.01.013 PMID: 26917197
45. Rana BS, Thomas MR, Calvert PA, Monaghan MJ, Hildick-Smith D. Echocardiographic evaluation of patent foramen ovale prior to device closure. JACC Cardiovasc Imaging. 2010;3(7):749-60. DOI: 10.1016/j.jcmg.2010.01.007 PMID: 20633854
46. Kerut EK, Norfleet WT, Plotnick GD, Giles TD. Patent foramen ovale: a review of associated conditions and the impact of physiological size. J Am Coll Cardiol. 2001;38(3):613-23. DOI: 10.1016/S0735-1097(01)01427-9 PMID: 11527606