RESEARCH ARTICLE

Percutaneous closure of patent foramen ovale for the secondary prevention of decompression illness in sports divers: mind the gap

Martin Vanden Eede, MD [1]; An Van Berendoncks, MD [1]; Daniel De Wolf, MD [1], Catherine De Maeyer, MD [2], Hervé Vanden Eede, MD [3], Peter Germonpré, MD [4]

[1] Department of Cardiology, Antwerp University Hospital, Antwerp, Belgium
[2] Cardiocentrum Grens, Kalmthout, Belgium
[3] Department of Anesthesiology, Algemeen Ziekenhuis Heilige Familie, Reet, Belgium
[4] Centre for Hyperbaric Oxygen Therapy, Military Hospital, Brussels, Belgium

Corresponding Author: Martin Vanden Eede – *mvandeneede@gmail.com*

ABSTRACT

Objective: To evaluate the efficiency of percutaneous patent foramen ovale (PFO) closure on the recurrence of decompression illness (DCI).

Design: Retrospective, observational study with interview and questionnaire

Setting: Tertiary referral center.

Population: 59 scuba divers with a history of DCI who received a percutaneous PFO closure.

Main outcome measurements: Questionnaire about health status, dive habits and recurrence of DCI after PFO closure.

Results: A total of 59 divers with DCI were included. The most common manifestations of DCI were cutaneous or vestibular DCI. Procedural complications occurred in four patients but none with long-term consequences. Four patients had recurrence of DCI after closure during a 10-year follow-up. In three of these cases there was residual shunting, all of which were initially considered closed. The fourth patient had aggravating factors for his recurrent DCI. A quarter of the patients stated to have changed their diving habits. Four patients quit diving.

Conclusion: Percutaneous PFO closure for secondary prevention of DCI is associated with few, but not negligible, complications. As a large portion of our cohort changed their diving habit after closure it is difficult to ascertain the efficiency of PFO closure for secondary prevention of DCI. However, the study shows that PFO closure does not fully protect against DCI, emphasizing that the relationship between PFO and DCI is but an association. As such it is imperative that divers be counseled to ensure they understand the risks as well as the benefits of percutaneous PFO closure in their specific case.

INTRODUCTION

The presence of a patent foramen ovale (PFO) has been associated with several disease processes including cryptogenic stroke, migraine headache with aura, platypnea-orthodeoxia syndrome, shunt-induced cyanosis and peripheral embolism. Since 1986 a cardiac right-to-left shunt has also been associated with decompression illness (DCI) [1], and an increased risk for DCI in divers with a PFO has since then been reported repeatedly [2-4].

DCI is caused by the formation and growth of inert gas (usually nitrogen) bubbles in the body that result from too rapid a reduction of pressure. While submerged, the body is subjected to increased pressure. This increase in pressure results in saturation of tissues with inert gas, proportional to dive duration and depth. During and after ascent from the dive (decompression), the stored inert gas from the tissues diffuses into the venous system and often leads to bubble formation. These bubbles are small, usually relatively few in number, and do not give rise to any symptoms since they are trapped by the pulmonary capillaries and thus filtered out of the circulation.

However, in cases of a too-rapid reduction of pressure, these bubbles may become so abundant that they can overwhelm the pulmonary filter and make their way into the arterial circulation [5]. Furthermore, bubbles may bypass the lung filter through a right-to-left shunt such as

KEYWORDS: patent foramen ovale; PFO, decompression illness; DCI; percutaneous closure

a PFO and cause arterialization of bubbles or so-called paradoxical embolism [1,6,7]. In that case, even lower degrees of decompression bubbles could then result in DCI, with symptoms based on location and volume of bubbles, such as pain, vertigo, rash or, worst case, paralysis.

From retrospective and case-control studies, the risk of DCI in divers with PFO has been estimated to be two to five times higher than divers without a PFO. However, recreational diving within currently recommended safe diving practices has a low overall risk of approximately 1/4,000 dives [5,8,9]. Even with the increased risk, only a very small portion of divers with PFO will ever experience DCI. Therefore, baseline PFO screening in divers is not recommended by diving-related scientific societies [10]. Diagnostic evaluation for PFO after DCI is recommended in case of severe or repetitive DCI with cerebral, spinal, vestibulocochlear or cutaneous manifestations, especially in the absence of provocative features (such as a severe decompression or bubble-prone dive) [10-12].

Suggested recommendations for divers with diagnosed PFO after DCI include the cessation of diving, adopting a more conservative diving profile, or PFO closure. While percutaneous closure of PFO seems to gain acceptance for the secondary prevention of young cryptogenic stroke [13], controversy still exists regarding closure of PFO after DCI. There might be a role for percutaneous PFO closure, especially for large PFOs. However, current evidence on the efficacy of percutaneous closure of PFO for the secondary prevention of recurrent DCI in divers is inadequate in quality and quantity. Although percutaneous closure of PFO has been used for a number of years, rather indiscriminately, to reduce the risk of DCI, the rate of DCI recurrence after closure has not well been established. This is important because even though percutaneous PFO closure is perceived as a relatively safe procedure, it is associated with a low – but not negligible – risk of complications, including vascular injury, cardiac perforation, air embolization during implantation, device embolization, early and late thrombosis, and atrial arrhythmias [14]. Therefore, the aim of this report is to summarize data for evaluation of the efficiency and safety of percutaneous PFO closure on the secondary prevention of DCI, in a Belgian divers' cohort over a 10-year period.

METHODS

All patients with a diving-related DCI event who underwent percutaneous PFO closure between 2007 and 2016 in the University Hospital of Antwerp were included. Only patients who received the Occlutech® Figulla® Flex II PFO device (the most-used PFO occluding device in this center) were selected for further analysis. Based on medical file review the following data were collected: patient demographics, type of DCI, number of DCI events before PFO closure, diving habits, procedural complications, and recurrence of DCI after closure. In all patients the presence of PFO with right-to-left shunting was diagnosed with contrast transesophageal echocardiography (c-TOE) and performance of the Valsalva maneuver. The contrast solution, shaken gelofusine, was injected into the left median cubital vein. All c-TOE procedures were performed with the patient sedated, using 1mg of midazolam IV, and local anesthetics. In all patients, the percutaneous PFO closure procedure was performed with the patient under general anesthesia, via femoral venous access. Short-term follow-up consisted of a transthoracic echocardiography (TTE) the day after PFO closure.

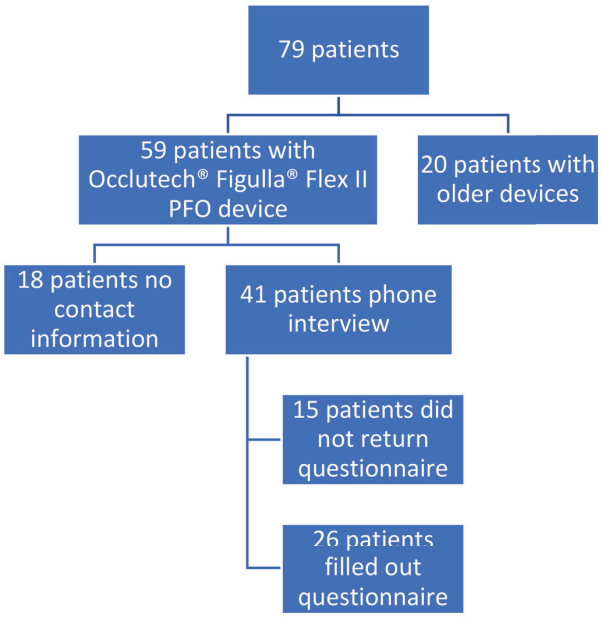
Evaluation of the PFO closure was performed with c-TOE at three months if the patient was a professional diver, and at six months for recreational divers. In case of residual shunting a control c-TOE was performed at three-month intervals until closure or up to 12 months after the percutaneous intervention. All patients were contacted in September 2017 by phone for an interview and asked to fill out a dedicated questionnaire to gather data about long-term follow-up.

RESULTS

A total of 79 patients who had a percutaneous PFO closure after experiencing DCI were identified (Figure 1). In 20 of these 79 patients, devices that are no longer being manufactured were used; consequently, these patients were excluded for further analysis since these older devices are known to have higher rates of residual shunting and procedural complications. Thus 59 divers whose PFO was closed with an Occlutech Figulla Flex II PFO device were included. Forty-one divers received a telephonic interview and were asked to fill out a dedicated questionnaire to obtain specific dive-related information, which 26 out of 41 patients completed. Patient demographics can be found in Table 1. Eighteen patients could not be reached, and information was gathered by contacting their family physician. Median follow-up was 65 months (18-108 months, interquartile range /IQR 39 months).

Average patient age at time of closure was 41 years (17-65 years, SD 11.5 years). Our population has a male predominance of 72%. Mean body mass index (BMI) was 26.33 (19.95-35.80 kg, SD 3.4 kg). The majority of our patients included recreational divers. There were six

Figure 1: Inclusion flowchart



professional divers. The median diving experience for our population was 11 years (4-50 years, IQR 12 years) and the median number of dives was 466 dives (14-3,900 dives, IQR 544 dives). All patients experienced at least one DCI event before the procedure; 20 patients (33%) experienced more than one event. All DCI events were reported to have followed dives consistent with safe decompression policies, although this could not be verified (dive profiles not available and rarely the original medical report regarding the DCI). Post-hoc review of symptoms and dive profiles, whenever available, cast doubt on one reported DCI event; all other events were likely correctly diagnosed. Out of all reported events, 63% presented with cutaneous manifestations, 35% with vertigo and dizziness and 15% with cerebral events such as motor and sensory neurologic dysfunction. In 16% of the patients there was a combination of different DCI types. About half of the events (46%) occurred after consecutive dives. In all cases the PFO was considered significant (>30 bubbles). In 40 patients (68%) there was shunting in rest, while in 19 patients (32%) there was significant shunting only after Valsalva maneuver. There were no cases of atrial septal defect or cribriform septa.

Table 1: Overview of patient characteristics

CHARACTERISTIC	OUTCOME
gender	
female	27%
male	73%
biometrics	
mean BMI	26.33 (19.95-35.80)
mean height	1m77 (1m59 -1m92)
cardiac risk factors	
diabetes	0%
smoking	24%
hyperlipidaemia	30%
hypertension	17%
diving experience	
professional diver	10%
recreational diver	90%
median diving experience (years)	11 years (4-50 years)
median diving experience (number of dives)	466 (14-3900 dives)
type of DCI prior to closure	
cutaneous	63%
vestibular	35%
cerebral	15%
combination	16%
mean age at PFO closure	41 years (17-65 years)

Procedure and complications

A total of 57/59 procedures (96%) were considered successful. In two cases, there was malposition of the device, with one needing revision with a second occluder device. Complications occurred in four patients (7%). There were no life-threatening complications. Complications included one arteriovenous fistula in the right femoral artery needing surgical treatment; one case of a pseudoaneurysm (successfully treated with thrombin injection) in combination with an arteriovenous fistula in the right femoral artery, which was treated conservatively; and two cases of paroxysmal atrial fibrillation (AF) who received pharmacological reconversion with no recurrence of AF afterwards. All complications presented within six months of the procedure. There were no long-term consequences to these complications.

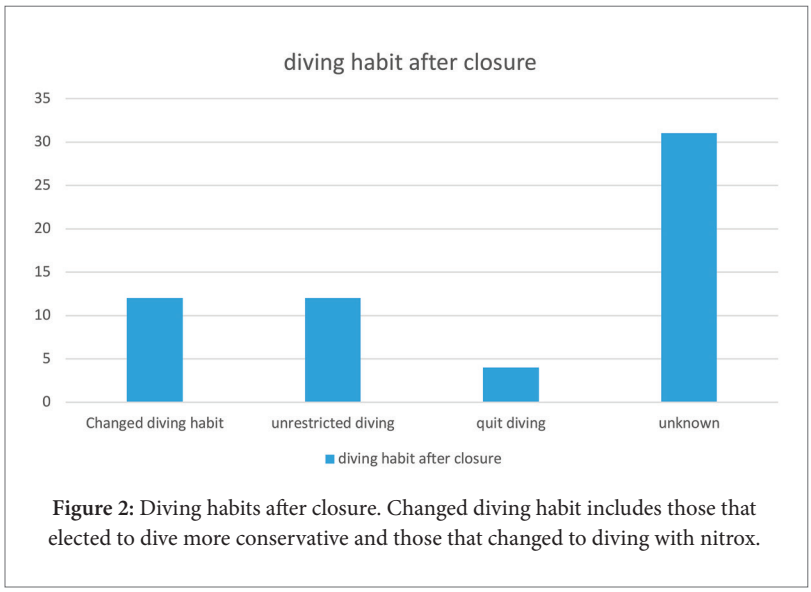


Figure 2: Diving habits after closure. Changed diving habit includes those that elected to dive more conservative and those that changed to diving with nitrox.

Residual shunting

In nine patients (15%) there was still residual right-to-left shunting at one year. However, in only two patients (3%) was this considered significant (>30 bubbles). The other seven patients (12%) had minimal residual shunting (<5 bubbles) and were therefore considered closed. In one case, opacification of the left atrium was seen after more than five heartbeats, but there was no visualization of shunting over the occluder device and thus, the PFO was considered closed. This was not present before and during his PFO closure, which makes lung shunting highly unlikely. No explanation was found for this finding. The diver in question has performed 120 uneventful dives since his closure, albeit adhering to more conservative diving profiles. The majority of the control c-TOEs were done by three cardiologists experienced in PFO imaging, with a minority (<5%) of the c-TOEs done by other cardiologists and cardiologists in training.

Return to diving

The mean time between the intervention and return to diving was six months (three months to 12 months, SD two months). A total of 6,865 post-closure dives were reported by 26 patients (Median 235 dives, IQR 312 dives). A quarter of the patients stated to have changed their diving habits: 10 patients chose to dive more conservatively (<30 meters in depth, no consecutive dives, no-decompression diving only); two patients switched to diving with nitrox (nitrogen/oxygen gas mixture with an oxygen concentration higher than the usual 21%) instead of air; and four patients quit diving altogether (Figure 2). None of these patients had recurrence of DCI on a total of 2,528 dives (Median 120 dives, IQR 450). Of the four who quit diving, two did so because of persistent residual shunting after PFO closure; one had developed a fear of diving, and the last one "took a break" from diving and did not (yet) restart.

Recurrence of DCI

In four patients, there was a new DCI event after PFO closure (Table 2). The first patient presented with recurrent DCI within three months after diving restriction was lifted (seven years prior to interview). This patient presented with identical symptoms (cutaneous DCI) compared to his pre-closure status after an air dive > 30 msw. It appeared subsequently that his PFO was never fully closed due to malposition of the occluder device. This patient has quit diving since then. The second patient also presented with identical DCI symptoms (cutaneous) within three months after diving restriction was lifted (three years prior to interview). Symptoms presented after an uneventful rebreather dive (70 msw, one hour) while adhering to decompression tables. He was considered closed at six months but control c-TOE after the event showed some residual shunting after Valsalva maneuver (10 bubbles). His current diving status is unknown. Of note, in both cases the c-TOE upon which PFO closure was confirmed was performed by a cardiologist in training. The third patient, a professional diver, presented with identical DCI lesions (cutaneous) four years after closure (four years

Table 2: Patients with recurrent DCI after PFO closure

Patient	1	2	3	4
c-TOE at 6 months after closure	significant shunting	minimal shunting	significant shunting	no shunting
c-TOE at 9 months after closure	no shunting	no shunting	no shunting	/
timing DCI after resuming diving	3 months	3 months	4 years	4 and 5 years
C-TOE after event	significant shunting	minimal shunting	significant shunting	no shunting

Note: Patient 4 had bubbles prone diving profiles that can explain his recurrent DCI events.

prior to interview). This event presented after a dive of 40 msw, 45 minutes with surface decompression, in accordance with the Netherlands Diving Center (NDC) decompression tables. He was considered closed at one year, but control c-TOE after the recurrence of DCI showed massive right-to-left shunting (>30 bubbles) after Valsalva. Most likely this patients PFO was never fully closed [15]. He refrained from a revision of the PFO closure and has quit diving. The fourth patient presented respectively two and three years after closure with new DCI events (one and two years prior to interview), but the symptoms were different from the DCI prior to his PFO closure. The first event presented after a consecutive dive to 30 msw for total duration of 30 minutes, with the first dive of the day performed at 54 msw for 40 minutes anda decompression stop at 12 msw. The second event presented after a comparable diving profile – i.e., a consecutive dive with depth and timing comparable to the first event. As these were bubble-prone dive profiles, there were factors considered aggravating for both DCI episodes after his PFO closure, and his new DCI events were considered not necessarily PFO-related. His control c-TOEs after both DCI episodes showed no residual shunting. This patient is currently an active diver (686 dives since PFO closure).

DISCUSSION

This study aimed to evaluate the efficiency of percutaneous PFO closure for secondary prevention of DCI. In our cohort, we found that four divers (6%) presented with recurrent DCI after percutaneous PFO closure. Of these four cases, three were found to have residual shunting after percutaneous closure of their PFO while being considered closed. Further, in two cases these examinations had been done by inexperienced cardiologists. This confirms the need for accurate assessment of any residual shunting after PFO closure as we have described before [15]. According to the joint position statement on PFO and diving [10], a repeat bubble contrast echocardiogram is required to confirm shunt closure before returning to diving. c-TOE in combination with Valsalva is traditionally viewed as the most reliable maneuver for assessment of PFO closure. However, the use of sedation makes the performance of the Valsalva maneuver more difficult [16-18], resulting in higher rates of false negative results, especially in case of smaller shunt [5,19]. This likely explains the three false negatives in our study. Other maneuvers have been proposed to address this problem such as abdominal compression, inferior vena cava compression, cough, sniff, and modified Müller (rapid forceful nasal inspiration) and have shown promise but require further investigation [20]. Alternatively, the Valsalva maneuver can be performed more easily during contrast transthoracic echocardiography (c-TTE) imaging, which has been shown to be comparable to c-TOE for specificity and sensitivity [21,22]. Therefore, c-TTE might be better suited for post-procedural evaluation of residual shunting. However, this remains to be determined in future studies.

Procedural complications were infrequent in our cohort, consistent with the literature [23]. Although there were no long-term consequences, these complications are not negligible and are a cause of distress in patients. This is important, especially when considering the current uncertainty around the efficiency of PFO closure for secondary prevention of DCI [12,24]. According to the previously mentioned joint statement, percutaneous PFO closure should be considered if the patient is unwilling to stop diving and/or if the dive profiles cannot be changed [10]. In addition, the UHMS Best Practice Guidelines state: "*Data*

to suggest PFO closure prevents DCS are incomplete and if it is suspected that a diver's repetitive DCS incidents are related to a PFO, reduction of decompression stress in future diving activities by more conservative diving practice is probably a better approach than PFO closure" [12]. As such it can be debated whether PFO closure was truly necessary in our cohort of mostly recreational divers. Indeed, Klingmann, et al. [25] reported a reduction from 34 to four events of DCI before and after adoption of more conservative dive profiles. Even more recently a study of 77 divers with PFO closure for DCI showed that a conservative dive profile was safe in those who refrained from PFO closure [26]. Thus, thorough counseling of divers with PFO or other right-to-left shunts as to the mechanisms of decompression bubble occurrence and shunting of bubbles through the PFO appears to be equally effective in reducing both the number of detectable bubbles and the incidence of DCI [25,27,28]. To date there is only one published trial evaluating prospectively the effect of PFO closure in recreational divers [29]. In this study, three groups of divers were followed up after DCI with subsequent investigation for the presence of a PFO: a group that did not have a PFO (39 divers); a group that chose not to have their PFO closed (39 divers); and a "closure" group (26 divers). After a follow-up period of a little more than five years and approximately 50 dives per year, a significant reduction in DCI recurrence was found in divers who had their PFO closed, compared to those who did not. It appears that the divers who had selected not to have their PFO closed did not make significant changes to their diving behavior. However, divers who did have their PFO closed still had a higher follow-up incidence of DCI compared to divers with no PFO. This may indicate a renewed "sense of security" resulting in a riskier diving behavior. Furthermore, even if the differences were statistically significant, there were only four DCI events in the "no-closure" group and one event in the PFO closure group, making statistical bias at least possible (if one more diver in the PFO closure group would have "admitted" to a new DCI event, all statistical significance would be lost).

In our population 25% of those who filled in the questionnaire stated to have changed their diving habits, even though their PFO was closed. It is possible that even a higher proportion of our population changed their way of diving, as only 44% of our patients returned the questionnaire describing their diving habits after PFO closure. Also, as it is impossible to quantify how many and how much participants' diving has been changed following the procedure, our findings must be interpreted with caution. Possibly half our population might have changed their diving habits, and even if not, this change in diving habits precludes any definite evaluation of the efficiency of PFO closure on the occurrence/recurrence of DCI. From a pathophysiological point of view, the most effective strategy to prevent DCI is by reducing "diving exposure." One must remember that DCI is caused by inert gas bubbles, and that closure of a PFO does not fully protect divers from DCI if significant numbers of gas bubbles are present after a dive. Moreover, DCI may still be caused by locally trapped gas bubbles [14], or bubbles that have arterialized through other pathways such as intrapulmonary arteriovenous anastomoses [30].

As such, one can argue that if there was a medical necessity for the recreational divers in our cohort to have had their PFOs closed, as they could easily have resorted to changing their dive profiles. Our observation is, however, that some divers find it very difficult to change their diving habits even after medical advice; to quit diving altogether is usually not an option. As the current evidence on the efficacy of percutaneous PFO closure for the secondary prevention of recurrent DCI in divers is uncertain [24] in combination with few but not negligible complications associated with the procedure, we advocate that patient selection for percutaneous PFO closure should be carried out only by experienced interventional cardiologists, in liaison with clinicians with specific expertise in diving medicine. It is imperative that divers be counseled by diving medicine experts to ascertain that they understand the risk-benefit of PFO closure for secondary prevention of DCI and that modifying their diving behavior is a realistic and feasible option.

LIMITATIONS

Our study has several limitations. First, the follow-up response rate was low, with only 44% of divers completing the questionnaire. As we can assume that in case of a new DCI event after closure the diver would have sought medical attention, it would not have influenced our findings on recurrence of DCI after closure. However, we did lose valuable insight into their diving habits after closure. Secondly, there is an uncertainty in the quality of c-TOE to assess residual shunting. Therefore, this study does not allow us to make definite assumptions about the efficiency of PFO closure in secondary prevention of DCI. However, this study shows the importance that the decision for PFO closure in prevention of secondary DCI should be an interdisciplinary process and that, when closure is decided upon, thorough evaluation is mandatory to ascertain closure success.

CONCLUSIONS

Although closure success and complication rate seem in line with previously reported data, uncertainties in the evaluation of complete closure and continuing to dive "bubble-prone" dive profiles are likely responsible for a non-negligible number of recurrent DCI (four out of 55 divers who continued diving after PFO closure). Even though the post-closure DCI incidence rate cannot be estimated in this study, as we have no precise data on the number and type of dives performed after closure, it does illustrate that the relationship between PFO and DCS is an association: Not all DCS is due to the presence of a PFO, and closure does not uniformly prevent it. Therefore, we should ensure that divers understand the uncertainties about the efficacy of transcatheter closure of a PFO and the possibility of complications [27]. This implies a multidisciplinary approach with evaluation and counseling, not only by a cardiologist but also by an experienced diving medicine specialist. The divers should understand that modifying diving behavior is a realistic and feasible option. They should have the statistics of DCI risk in diving versus the risk of complications of PFO closure explained, and to be cautioned that there is no formal medical indication to close the PFO solely for diving. If PFO closure is discussed, this should be assessed and decided only on a case-by-case basis followed by adequate assessment of the PFO closure to confirm there is no or little residual shunting.

Funding details

No funding was received.

Disclosure statement

The authors report no conflicts of interest.

Ethics

This study has been approved by the Ethics Committee of the University Hospital of Antwerp under registration number B300201835468

Acknowledgments

The authors wish to thank Myrion de Baar, Eline Vermeiren and Stephanie De Deckere of the University of Antwerp for their contribution in setting up the population database and Prof. Dr. B. Paelinck for his help in assessing the echocardiographic data.

REFERENCES

1. Wilmshurst PT, Ellis BG, Jenkins BS. Paradoxical gas embolism in a scuba diver with an atrial septal defect. Br Med J (Clin Res Ed). 1986;293(6557):1277.

2. Germonpre P, Dendale P, Unger P, Balestra C. Patent foramen ovale and decompression sickness in sports divers. J Appl Physiol (1985). 1998;84(5):1622-1626.

3. Moon RE, Camporesi EM, Kisslo JA. Patent foramen ovale and decompression sickness in divers. Lancet. 1989;1(8637):513-514.

4. Honěk J, Šefc L, Honěk T, Šrámek M, Horváth M, Veselka J. Patent foramen ovale in recreational and professional divers: an important and largely Unrecognized problem. Can J Cardiol. 2015;31(8):1061-1066.

5. Vann RD, Butler FK, Mitchell SJ, Moon RE. Decompression illness. Lancet. 2011;377(9760):153-164.

6. Germonpre P. Persistent (patent) foramen ovale (PFO): implications for safe diving. Diving Hyperb Med. 2015;45(2):73-74.

7. Wilmshurst PT. The role of persistent foramen ovale and other shunts in decompression illness. Diving Hyperb Med. 2015;45(2):98-104.

8. Bove AA. Risk of decompression sickness with patent foramen ovale. Undersea Hyperb Med. 1998;25(3):175-178.

9. 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):1014-1020.

10. Smart D, Mitchell S, Wilmshurst P, Turner M, Banham N. Joint position statement on persistent foramen ovale (PFO) and diving. South Paci fic Underwater Medicine Society (SPUMS) and the United Kingdom Sports Diving Medical Committee (UKSDMC). Diving Hyperb Med. 2015;45(2):129-31.

11. Sykes O, Clark JE. Patent foramen ovale and scuba diving: a practical guide for physicians on when to refer for screening. Extrem Physiol Med. 2013;2(1):10.

12. UHMS. UHMS Best Practice Guidelines: Prevention and treatment of decompression Ssickness and arterial gas embolism, https://www.uhms.org/2016-medical-examiner-of-divers-presentations/meetings-and-courses/medical-examiner-of-divers-2018/useful-resources/uhms-best-practice-guidelines-prevention-and-treatment-of-decompression-sickness-and-arterial-gas-embolism-2011.html. 2010.

13. Sondergaard L, Kasner SE, Rhodes JF, Andersen G, Iversen HK, Nielsen-Kudsk JE, et al. Patent foramen ovale closure or antiplatelet therapy for cryptogenic stroke. N Engl J Med. 2017; 377(11):1033-1042.

14. Wahl A, Praz F, Stinimann J, Windecker S, Seiler C, Nedeltchev K, et al. Safety and feasibility of percutaneous closure of patent foramen ovale without intra-procedural echocardiography in 825 patients. Swiss Med Wkly. 2008;138(39-40):567-572.

15. Vanden Eede M. Recurrent cutaneous decompression illness after PFO device implantation: a case report. Undersea Hyperb Med. 2016;43(7):841-845.

16. Kuhl HP, Hoffmann R, Merx MW, Franke A, Klotzsch C, Lepper W, et al. Transthoracic echocardiography using second harmonic imaging: diagnostic alternative to transesophageal echocardiography for the detection of atrial right to left shunt in patients with cerebral embolic events. J Am Coll Cardiol. 1999;34(6):1823-30.

17. Van Camp G, Franken P, Melis P, Cosyns B, Schoors D, Vanoverschelde JL. Comparison of transthoracic echocardiography with second harmonic imaging with transesophageal echocardiography in the detection of right to left shunts. Am J Cardiol. 2000;86(11):1284-1287, A9.

18. Pinto FJ. When and how to diagnose patent foramen ovale. Heart. 2005;91(4):438-440.

19. Johansson MC, Eriksson P, Guron CW, Dellborg M. Pitfalls in diagnosing PFO: characteristics of false-negative contrast injections during transesophageal echocardiography in patients with patent foramen ovales. J Am Soc Echocardiogr. 2010; 23(11):1136-1142.

20. Thiagaraj AK, Hughes-Doichev R, Biederman RWW. Provocative maneuvers to improve patent foramen ovale detection: A brief review of the literature. Echocardiography. 2019.

21. Marriott K, Manins V, Forshaw A, Wright J, Pascoe R. Detection of right-to-left atrial communication using agitated saline contrast imaging: experience with 1162 patients and recommendations for echocardiography. J Am Soc Echocardiogr. 2013;26(1):96-102.

22. Trevelyan J, Steeds RP. Comparison of transthoracic echocardiography with harmonic imaging with transoesophageal echocardiography for the diagnosis of patent foramen ovale. Postgrad Med J. 2006;82(971):613-4.

23. Merkler A, Gialdini G, Yaghi S, Okin P, Iadecola C, Navi B, et al. Long-term risk of complications after percutaneous transcatheter Closure of patent foramen ovale (S51.003). Neurology. 2017;88(16 Supplement):S51.003.

24. NHS. Percutaneous closure of patent foramen ovale for the secondary prevention of recurrent paradoxical embolism in divers: guidance, https://www.nice.org.uk/guidance/ipg371/chapter/1-Guidance 2010.

25. Klingmann C, Rathmann N, Hausmann D, Bruckner T, Kern R. Lower risk of decompression sickness after recommendation of conservative decompression practices in divers with and without vascular right-to-left shunt. Diving Hyperb Med. 2012;42(3): 146-150.

26. Koopsen R, Stella PR, Thijs KM, Rienks R. Persistent foramen ovale closure in divers with a history of decompression sickness. Neth Heart J. 2018;26(11):535-539.

27. Martinez-Quintana E, Gopar-Gopar S, Rodriguez-Gonzalez F. Diving and percutaneous closure of persistent (patent) foramen ovale. Diving Hyperb Med. 2015;45(2):126-128.

28. Honek J, Sramek M, Sefc L, Januska J, Fiedler J, Horvath M, et al. Effect of conservative dive profiles on the occurrence of venous and arterial bubbles in divers with a patent foramen ovale: a pilot study. Int J Cardiol. 2014;176(3):1001-1002.

29. 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):1932-1937.

30. Madden D, Lozo M, Dujic Z, Ljubkovic M. Exercise after SCUBA diving increases the incidence of arterial gas embolism. J Appl Physiol (1985). 2013;115(5):716-722.