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The management of patent foramen ovale in divers: where do we stand?

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***Abstract*:** Diving is a fascinating activity, but it does not come without any cost; decompression illness (DCI) is one of the most frequent diseases occurring in divers. Rapid surfacing after diving causes alveolar rupture and bubbles release, which enter in the systemic circulation and could embolize numerous organs and tissues. The presence of patent foramen ovale (PFO) contributes to the passage of venous gas bubbles into the arterial circulation, increasing the risk of complications related to DCI. The diagnosis is established with a detailed medical history, a comprehensive clinical evaluation, and a multimodal imaging approach. Although the percutaneous closure of PFO is ambiguous for divers, as a primary prevention strategy, transcatheter management is considered as beneficial for DCI recurrence prevention. The aim of this study is to introduce the basic principles of DCI, to review the pathophysiological connection between DCI and PFO, to highlight the risk factors and the optimal treatment, and, last but not least, to shed light on the role of closure as primary and secondary prevention.

Keywords: decompression illness, decompression sickness, diving, patent foramen ovale, PFO

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Introduction

Patent foramen ovale (PFO) is the most frequent congenital cardiac lesion, persisting after birth. Its presence is crucial for the fetal blood circulation. After birth, this interatrial shunt is useless and closes normally in the majority of infants and children.[1,2] The prevalence of PFO is estimated to be about 20% in echocardiographic examinations and 25% in autopsy studies. Although the majority of patients with PFO remain asymptomatic through adulthood, a variety of pathological conditions have been linked with PFO, mainly cryptogenic strokes and secondarily migraines, decompression illness (DCI), and platypnea-orthodeoxia syndrome. DCI and air embolism through PFO mainly affect divers.[3]

The aim of this study is to introduce the basic principles of DCI, to review the pathophysiological connection between DCI and PFO, to highlight the risk factors and the optimal treatment, and, last but not least, to shed light on the role of closure as primary and secondary prevention.

Decompression sickness

Self-contained underwater breathing apparatus (SCUBA) diving is a mode of diving where the equipment is totally independent of surface supply to breathe underwater. Nowadays, more than 9 million SCUBA divers live in the United States and several hundred thousand divers are trained each year only in the United States. While diving is a fascinating, exciting, and generally safe activity, it does not come without a cost; official data report more than 1000 diving-related injuries and 100 deaths per year. Hypothermia, barotrauma, and DCI are some frequent complications of diving.[4–6]

DCI was first described in the 19th century when it was seen in the mineral and tunnel workers returning to the atmospheric pressure. It is defined

as the disease caused by intra- or extravascular bubbles that are created as a consequence of reduction in environmental pressure (decompression). The term includes both decompression sickness (DCS), in which dissolved inert gas creates *in situ* bubbles, and arterial gas embolism, in which alveolar gas or venous air emboli (through a right-to-left shunt) pass into arterial circulation.[7] Both clinical syndromes may appear in divers, mineral workers, and astronauts, while arterial gas embolism could be additionally caused by iatrogenic causes.[8]

Under hyperbaric conditions, expanding gas stretches, destroys alveolar capillaries, and causes pulmonary barotrauma. Consequently, alveolar gas passes into arterial circulation and eventually results in arterial gas embolism. This phenomenon typically occurs during quick surfacing at about 1.5 meters below sea level, especially with deep inhalation.[9]

DCS follows a different pathophysiological route. According to the Henry's law, the total amount of gases dissolved in tissues is proportional to their partial pressures. When the gas, mainly nitrogen, is inhaled in high pressures, tissue inert gas partial pressure increases, and it may cause a 'supersaturation' state when the rate of ambient pressure shrinkage overpasses the amount of inert gas washout from tissue. Under certain circumstances during diving (mainly too fast return to surface), the total tension exerted by the aqueous vapor and dissolved gases (carbon dioxide, oxygen, nitrogen, and helium) exceeds the local absolute pressure, resulting in the development and enlargement of both intravascular and extravascular bubbles. The amount of nitrogen depends on the diving depth and the duration of dive. The more the nitrogen load exists, the more the conservative regimen for ascent should be followed.[10]

The existing literature supports that the bubbles can cause mechanical complications, embolic events, and biochemical disturbances. Extravascular bubbles could provoke painful tissue, mechanical distortion, and vascular obstruction with emboli-related local ischemia. Intravascular bubbles are usually associated with delayed onset of symptoms, up to 24 h, while the main underlying mechanism is endothelial damage. Disturbances in endothelial function could lead to capillary leak, plasma extravasation, hemoconcentration, and platelet dysfunction (Figure 1).[9,11]

Although venous gas emboli are frequent findings in divers, pulmonary circulation filters small quantities of emboli, reducing the clinical manifestations. When large loads of gas emboli exist in the venous circulation due to the infringement of ascent protocol, intense and severe symptoms, such as cough, dyspnea, and even pulmonary edema, may occur. Upon existence of a right-to-left shunt (R→L shunt), gas emboli can be delivered to the arterial circulation. PFOs are the most frequent R→L shunt and the main source of paradoxical embolism. Diving practices, such as prolonged Valsalva maneuver for equalizing pressure in the middle ear, rapidly increase the right atrial pressure. Therefore, bubbles pass from the right to the left atrium through PFO. The symptoms of obstruction of the arterial circulation are noisier and more critical, affecting mainly the central nervous system (CNS) and, as a result, they are adequately associated with neurological or decompression symptoms, even in patients that reverently followed the protocols.[12]

DCI is classified into Type I or Type II, depending on the clinical manifestations and the severity of disease.[9,13] Type I is considered as mild, with localized signs and symptoms. On the contrary, type II is systemic, more severe, and requires more specialized management (Figure 2).

Cutis marmorata is another manifestation of DCS. Although it is classified in Type I as a mild condition, it is frequently managed as Type II, because past experience has shown that cutis marmorata could be the forerunner of the development of neurological signs and symptoms. It usually appears as red-bluish, flat, itching, and painful spots and presents rapidly, during the first hours after diving.[14] The location of spots is gender-dependent; in men, they are found in shoulders and peri-umbilical area, while in women they are localized frequently in buttocks and the sides of trunk.[14] Cutis marmorata occurs mainly in infants and newborns with genetic syndromes, such as trisomy 13 or 18. In adult patients, it is a rare finding and it could be caused by either DCS or cardiogenic shock. Therefore, it has a pathognomonic role when it appears after diving.[15]

Several risk factors have been associated with the development of DCI. Males are considered more prone than females.[16] In addition, the previous experience of divers has been related to the risk for DCI.[17] Moreover, air travel after diving courses

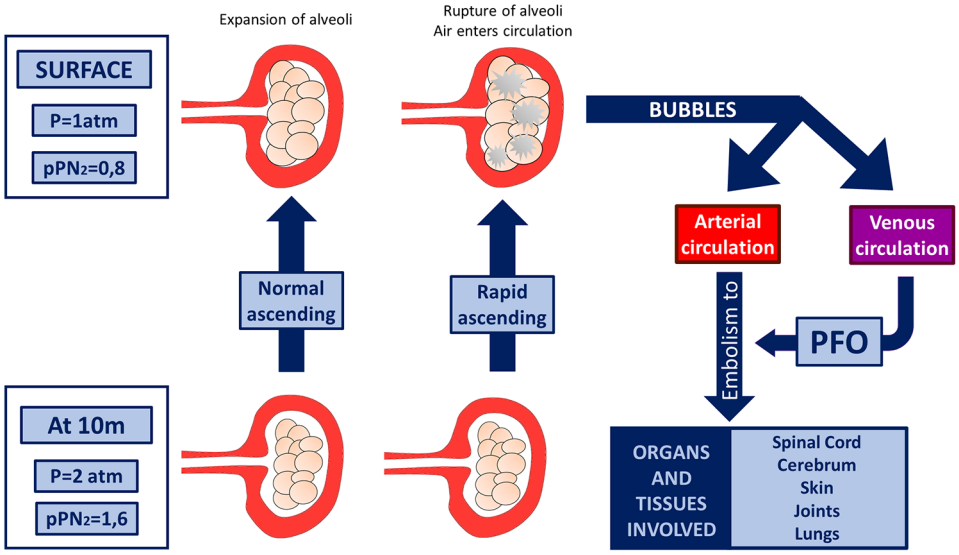

Figure 1. The main pathophysiological mechanism of decompression illness in patients with patent foramen ovale (PFO).

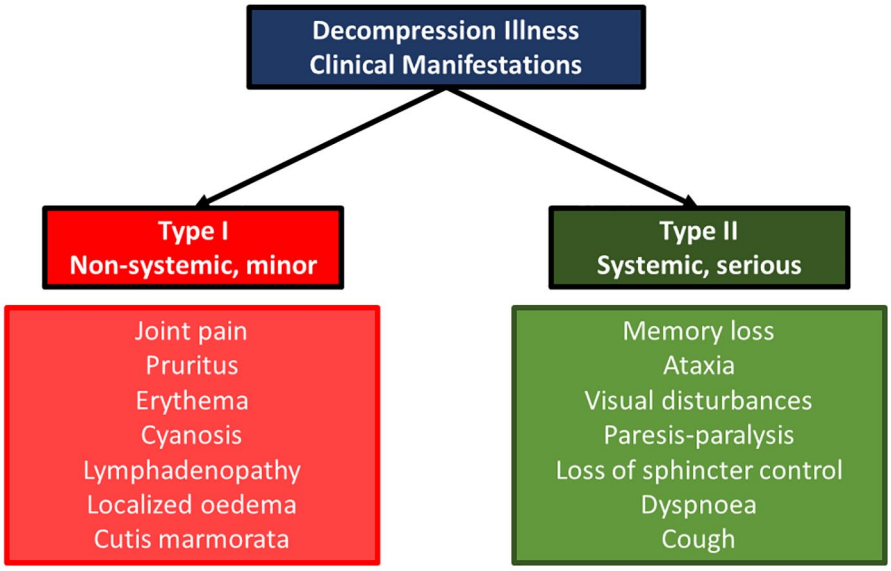

Figure 2. Decompression illness classification and clinical manifestations.

increases the risk for development of DCI, probably due to the high-pressure alterations.[18]

For preventing DCS, dive organizations have developed special protocols. These instructions urge divers to pause during the ascent for certain time frames. By applying this method, nitrogen partial pressure can be reduced adequately prior to the continuation of the ascent. Nowadays, complex, computing, personalized models have been developed for a more accurate and safe ascent.[19]

PFO presence and the risk for DCI

The prevalence of PFO in the general population is significantly higher than DCS in divers. Divers with PFO are at higher risk for developing DCI, compared with the general population. The association between risk of DCI and the presence of

PFO cannot be estimated accurately. Some studies report an odds ratio of about 2.5, while others support a higher risk.[20–22]

To the best of our knowledge, Moon *et al.* were the first to report a possible association between PFO and DCI in divers, by studying 30 divers with known disease. Surprisingly, they observed that a significant proportion of included subjects had PFO and established the PFO or any other R→L shunt as a major risk factor for developing DCI.[11] Germonpré *et al.* conducted a small, case–control study, including both divers with and without PFO. They concluded that clinical manifestations of DCS were significantly more frequent in patients with PFO, compared with those without.[23] Interestingly, the clinical manifestations were limited to the brain, but not to the spinal cord, confirming the animal model, in which nitrogen bubbles migrate preferably into the carotid and vertebral arteries.[24]

Torti *et al.* examined 230 SCUBA divers with contrast transthoracic echocardiography (TTE), searching for PFO. A total of 63 subjects were diagnosed with PFO. The authors concluded that the presence of PFO is associated with an absolute risk of suffering about five DCI episodes per 10,000 dives, a risk five times higher compared with subjects without PFO.[21] Moreover, the risk of DCI depends on the size of PFO; the larger the diameter of PFO, the higher the risk.[21,25,26]

A most recent study conducted by Honěk *et al.* confirmed the previous findings. They studied 489 consecutive divers, detecting an interatrial shunt in 196 of them. The presence of PFO grade 3 was significantly associated with unprovoked DCS episode in professional SCUBA divers.[27]

A meta-analysis published in 2008, which included 654 divers, failed to prove a significant association between DCI and PFO existence, due to the small sample size.[28] On the contrary, the meta-analysis included in the recent European position paper estimated an odds ratio of 5.63 (95% confidence interval, CI: 3.14–10.09) for R→L shunt in patients with DCI, compared with the subjects without.[29]

In addition, subclinical cerebral damage due to the repeated embolization through PFO has been observed. Knauth *et al.*[30] studied prospectively 25 divers with R→L shunt, 13 of whom had PFO. Remarkably, multiple brain lesions were associated with the presence of a large PFO, highlighting the increased risk of divers for long-term cerebral damages. However, other studies report that no significant association was found between PFO presence and incidence or number of cerebral magnetic resonance imaging abnormal findings.[31] Up to date, no association between such lesions and impaired cognitive function has been confirmed.

Diagnostic approach

Current guidelines do not recommend routine screening for PFO in professional divers. More specifically, the joint position statement of South Pacific Underwater Medicine Society and the United Kingdom Sports Diving Medical Committee supports no routine screening, albeit with low-quality evidence (IV). Neither prospective observational nor randomized controlled trials evaluating the primary screening for PFO in divers exist.[32] However, investigation for interatrial shunt should be performed when other clinical entities associated with PFO, such as cryptogenic stroke, migraine with aura, or family predisposition, exist. In accordance with the previous recommendations, the European position paper is also against the routine screening, due to the mismatch between high prevalence of PFO and the low incidence of DCI. Primary investigation for PFO should be conducted only in specific cases of professional divers, with high-risk and frequent activities.[29]

For divers with a previous DCI event or for highly suspicious, asymptomatic divers, a specific diagnostic walkthrough should be followed. Unfortunately, clinical manifestations of DCS are numerous, non-specific, and non-pathognomonic. Furthermore, the existing laboratory tests and imaging examinations are inadequate for the diagnosis of DCI. The diagnostic workup of such patients should be conducted in referral centers where specialists can provide a holistic approach of divers. Therefore, false-negative cases for DCI will be decreased and an increased number of divers will receive optimal medical care.

The first step of diagnostic approach includes the assessment of the previous history, the symptoms, the signs, and findings from the clinical examination. A positive Valsalva-like maneuver is highly pathognomonic for DCS. Taking all the above into consideration, the physicians will conclude

whether the clinical event is likely or not to be DCI. The time onset of such symptoms contributes to the final diagnosis; DCI usually starts about 2 h after the ascent and rarely will be present for more than 2 days. The timing depends on the size of PFO; large or open shunts are associated with immediate symptoms, while symptoms appear after 30 min in smaller PFO.[29] Signs and symptoms related to DCI have been classified by Germonpré *et al.* into major and minor.[14] It should be noticed that numerous clinical manifestations could be very mild and self-limiting, thus they could evade diagnostic workup. Nevertheless, physical activities or Valsalva maneuvers which increase intrathoracic pressures could elicit the symptoms.

Three imaging techniques are mainly used for the diagnosis of any endocardiac shunt: TTE, transesophageal echocardiography (TOE), and transcranial Doppler (TCD) ultrasonography. All these techniques are useful tools for screening and assessing a possible shunt, along with detecting arterial or venous gas bubbles after a dive.

Undoubtedly, TOE remains the gold standard for detecting and evaluating any interatrial shunt. The proximity of the probe to the atrial septum, the right, and the left atria provides an optimal depiction of cardiac structures.[33] In addition, two- and 3-dimensional imaging, in combination with encoloured Doppler function, contribute to the precise evaluation of the characteristics of the shunt. Undoubtedly, bubble test or contrast agent administration is crucial for performing an optimal TOE. However, TOE cannot be considered as panacea, since it is an uncomfortable procedure which premises the decent cooperation and preparation of the patient and a mild sedation is usually required for the examination.

TTE is an alternative to TOE and usually precedes any other cardiac examination. TTE is inexpensive, easy-to-perform, well-tolerated, and suitable for the vast majority of the patients. For the detection of PFO, contrast agent should be administered or bubble test should be performed.[34] Although numerous studies support that contrast-enhanced TTE is equally accurate to TOE for PFO diagnosis, TOE is considered as the gold standard in both guidelines and clinical practice. Nevertheless, TTE is more useful than TOE in the detection and quantification of the bubbles occurring after dive.

TCD depicts the blood flow through the middle cerebral artery. Using Doppler function, nitrogen bubbles occurring from dive or microbubbles from contrast material can be spotted and counted. The presence of such bubbles is pathognomonic for R→L shunt, either endocardiac or transpulmonary shunt. The location of the shunt cannot be predicted accurately using transcranial ultrasonography. However, there are some empirical patterns; the bubbles' passage through the transpulmonary passage is usually delayed and bubbles appear in middle cerebral artery, after at least 15 cardiac cycles. Moreover, TCD ultrasonography cannot add useful information about the location of the shunt in interatrial septum, its diameter, its morphology, and its hemodynamic status.

Generally, the combination of different techniques is mandatory, for achieving the highest accuracy on PFO diagnosis. According to the last consensus statement by Pristipino *et al.*,[35] the first step should include TTE or TCD. If they are negative, the workup for PFO should be stopped. If a R→L shunt is identified, then a TOE should be performed, in order to provide more comprehensive details, regarding the location, the size, and the anatomy of PFO. Of note, all the examinations should be performed, after contrast agent administration. Early contrast appearance in the left chambers, namely within three beats of the contrast appearance in the right heart, is indicative for intracardiac shunt, while later appearance of bubbles is associated with pulmonary shunt. The number of bubbles that pass through PFO is indicative of the hemodynamic response and the size of the shunt. The minimum number of bubbles required for a positive saline test remains ambiguous; Mariott *et al.*[36,37] supported that even one bubble is sufficient. In addition, there is no universal agreement on the number of bubbles and the shunt grading. Rana *et al.*[38] defined grade 1 to be under 5 bubbles, grade 2 between 5 and 25 bubbles, grade 3 more than 25 bubbles, and grade 4 was linked with the chamber opacification.

Management

SCUBA divers with PFO are at higher risk of developing DCI. However, existing literature is controversial and of low evidence regarding the optimal management of such patients. Either conservative or interventional approach could be followed. According to the recent recommendations,

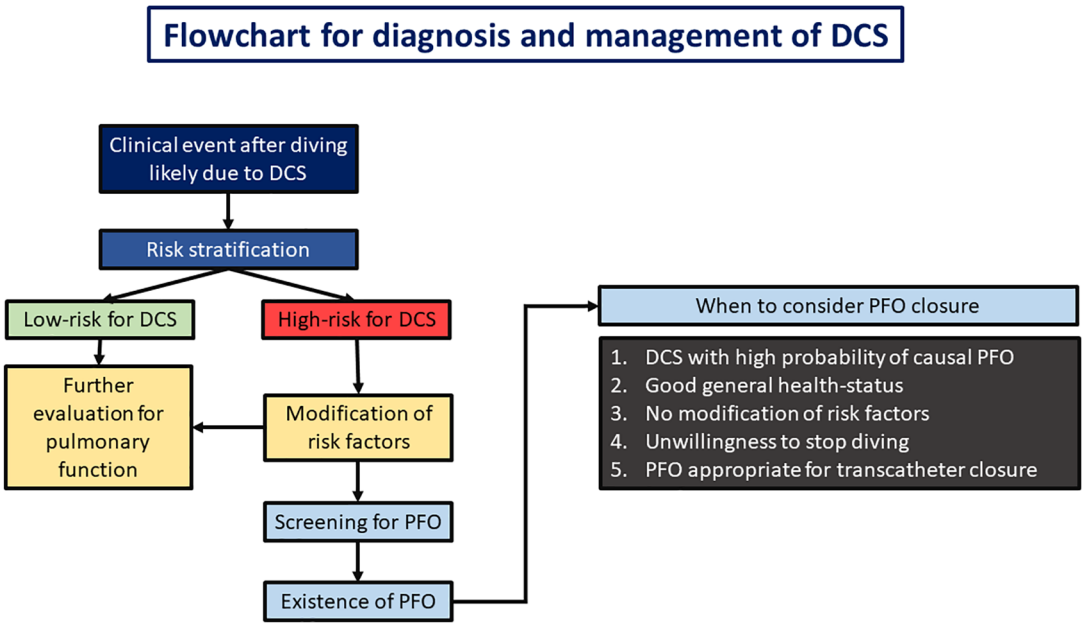

Figure 3. Flowchart proposing diagnosis and management of DCS.

a flowchart for diagnosis and management of DCS has been depicted in Figure 3.

Conservative management

For divers with a history of DCS, the non-invasive approach includes the conservative dive profiles. Various conservative dive profiles have been proposed, but no regimen has been established as gold standard.

Honěk *et al.* tried to answer this dilemma by conducting a study with divers following different dive patterns and assessing the presence and the quantity of bubbles in both arterial and venous circulation. Although they failed to discover the optimal dive method, they recommend that a stricter diving regimen should be applied in order to eliminate the risk of paradoxical embolization and prevent unprovoked DCI in SCUBA divers with PFO.[39]

Taking Honěk's finding into account, Klingmann *et al.* proposed the following recommendations: no repetitive or deeper than 25 m sea water or decompression dives, eliminating Valsalva's maneuvers during diving, a 5-min stop at 3 m sea water diving, and controlled-restricted nitrox inhalation. They supported that the application of the previous instructions into diving practice was associated with a highly significant reduction of DCI recurrence, especially for patients with R→L shunt. Nonetheless, the study design and the small sample remain a major limitation of the specific project.[40]

Moreover, lifestyle modifications and health maintenance should be included in the first step of the conservative management of DCS. Smoking, alcohol, obesity, and dehydration have been related to increased incidence of DCS. Consequently, cessation or modification of the previous factors will have a positive impact on divers' clinical manifestations.[29]

While large, reliable studies about conservative treatment have not been conducted yet, the compliance to the 2015 joint position statement's guidelines is beneficial for the prevention of recurrent DCS.[41]

Interventional management

Primary PFO occlusion without previous DCI event lacks evidence. It has been performed only in patients with high-risk PFO within a study assignment. Honěk *et al.* tried to evaluate the effect of percutaneous PFO closure on the occurrence of arterial and venous bubbles after simulated dives. While no difference occurred between occlusion and control group regarding venous

bubbles, the PFO closure eliminated entirely the presence of bubbles in the arterial circulation system. Therefore, this study established PFO occlusion as a feasible approach for preventing DCI.[12]

Pristipino *et al.* do not recommend PFO occlusion as a primary prevention strategy. It should be considered only in divers who want to continue unrestricted diving and always in conjunction with expert physicians in diving medicine.[29] On the contrary, the previous consensus paper was more flexible regarding the PFO closure in asymptomatic divers.[32] Smart *et al.* propose three solutions: stop diving, conservative diving, or PFO occlusion, leaving the decision to diver and his or her physician.

Transcatheter PFO closure has been studied extensively for secondary prevention of DCI in divers. Nevertheless, no randomized trial comparing invasive *versus* conservative management has been conducted yet and the existing evidence is established on lower quality studies (Table 1).

Walsh *et al.* were the first to evaluate the use of closure devices for preventing DCI. Indeed, they included seven divers with previous episodes of DCI and PFO. During the 1-year follow-up after the PFO closure with Amplatzer® device, all the divers returned to their exercise without complaining for any decompression event.[42] Billinger *et al.* conducted a prospective, non-randomized study, in order to evaluate the efficacy of PFO closure on preventing neurological manifestations in divers with history of DCI. The authors grouped the sample population into three arms: the first with the patients without PFO, the second with those with PFO who were treated conservatively, and the third with those with PFO who were managed with transcatheter closure. It was the first study proving that PFO closure was associated with less incidence of events associated with DCI and fewer ischemic brain lesions during the long-term follow-up. Remarkably, the third group was not only superior to the second but also to the first. It could be hypothesized that patients of the first group may have transpulmonary R→L shunt.[43]

Koopsen *et al.* studied retrospectively a total of 62 patients with DCI, 35 of whom were diagnosed with PFO or atrial septal defect (ASD) by TOE. A proportion of those patients ($n = 21$) underwent percutaneous occlusion of the interatrial shunt and most of them returned to unrestricted diving. During a long-term follow-up, none of them suffered from recurrent DCI. Despite the small sample and the single-arm design of this project, it was confirmed again that PFO closure remains safe and effective for divers who want to dive professionally again.[44] These results were in accordance with another retrospective, single-arm trial. A total of 105 divers with previous DCI or high-risk PFO were managed percutaneously and the vast majority of them returned to unrestricted diving.[45] Henzel *et al.* studied 11 divers with more than one event of DCI, treated with PFO occlusion in a long-term follow-up. All of them returned to diving following safe diving practices and none suffered from decompression episode again.[46]

Recently, Honěk published their long-term findings from DIVE-PFO registry. During a mean duration of 7.1 years, 153 divers with high-grade PFO were followed. Fifty-five were treated invasively and the rest followed a conservative protocol. None of the subjects from the closure group suffered from DCI, while 11 individuals from the non-invasive group had at least one episode. Despite the selection bias of DIVE-PFO registry, catheter-based therapy seems to be more effective than conventional approach.[47]

Nevertheless, after percutaneous closure, the risk of recurrence of DCI cannot be eliminated. Vanden Eede *et al.* report that 4 out of 59 divers with history of DCI, who underwent PFO closure, suffered again from the same disease. Interestingly, three of them had residual shunt, which is probably linked with the recurrence.[48] Pristipino *et al.*[29] highlighted the necessity for the entire closure of shunt; otherwise, unrestricted diving should be avoided. Smart *et al.* advise divers not to return back in their exercise until the confirmation of satisfactory PFO closure. Therefore, a bubble-test/contrast echocardiogram should be performed 3 months after the procedure.[32]

In the recent European position paper, Pristipino *et al.*[29] do not recommend PFO closure as a first-line solution, due to the lack of large-scale randomized controlled trials. Transcatheter PFO occlusion should be considered only in patients with previous DCI with high probability of causal PFO, who are not willing to stop diving and to modify the risk factors for DCI. Reduction of risk for decompression event could be achieved by lifestyle modifications, no decompression dives,

Table 1. The role of transcatheter PFO closure in primary and secondary prevention of DCS.

Authors	Year of publication	Number of patients (% treated invasively)	Prevention	Design	Conclusion
Walsh *et al.*[42]	1999	7 (100%)	Secondary	Case-series	No further decompression illness in any of the divers during the 12-month follow-up.
Billinger *et al.*[43]	2011	65 (40%)	Secondary	Nonrandomized, control study	PFO closure seems to prevent DCS recurrence during the 5-year follow-up.
Honěk *et al.*[12]	2014	47 (100%)	Primary	Case-controlled	PFO closure led to the total elimination of arterial bubbles after simulated dives.
Pearman *et al.*[45]	2015	105 (100%)	Secondary	Retrospective	The majority of divers being able to successfully return to unrestricted diving.
Koopsen *et al.*[44]	2018	62 (33.9%)	Secondary	Retrospective	PFO closure is effective and safe for divers to return to unrestricted diving.
Henzel *et al.*[46]	2018	11 (100%)	Secondary	Retrospective	No recurrent DCS episode after PFO occlusion.
Vanden Eede *et al.*[48]	2019	59 (100%)	Secondary	Retrospective	PFO closure does not fully protect against DCI, as four patients had recurrent DCI during 10-year follow-up.
Honěk *et al.*[47]	2020	153 (36%)	Secondary	Nonrandomized control study	PFO closure was more effective in DCS prevention than the conservative approach in patients with a high-grade PFO.

DCI, decompression illness; DCS, decompression sickness; PFO, patent foramen ovale.

less frequent dives, and inhaling higher concentrations of oxygen before diving.[29,32,39,40]

As a collateral benefit, PFO occlusion is an effective therapy with great success rates and few complications. It has been considered as the safest procedure of interventional cardiology. Generally, it acts as a 'mechanical vaccination', by lifelong protection against paradoxical embolism, which could cause myocardial infarction, stroke, or peripheral embolization.[49,50] However, it should not be offered as panacea; every intervention involves a number of risks. First of all, cardiac arrhythmias, especially atrial fibrillation, may occur after the occluder placement. A recent meta-analysis estimates the incidence of atrial fibrillation about to 3%, a percentage that cannot be overlooked in young adults.[50,51] Device erosion and migration are other rare complications.[50,52] In addition, nickel hypersensitivity developed by nitinol-based device has been documented as a possible adverse effect of PFO closure. While the cases requiring surgical explantation are few, nickel hypersensitivity could be associated with numerous mild symptoms occurring after the occlusion.[53–56]

Future perspectives

The technological advancements and the flourishing of SCUBA diving lead to the more focused research on the safety of the diving. Using deep learning and artificial intelligence, scientists attempt to develop improved ascending protocols, individualized for the special characteristics of every diver. Transcriptome analysis of divers with DCS could also help to the better comprehension of this disease.[57] Regarding the role of

PFO closure for secondary prevention of DCI, no randomized controlled study has compared the invasive *versus* conventional management. In addition, more studies about the risk stratification of divers with PFO should be conducted.[58] The right assessment of clinical, imaging, and laboratory findings, as well as the diving characteristics, could assist to provide individualized approach to each patient.

Conclusion

DCI is considered as one of the most frequent diseases of divers. Recently, the role of PFO in its pathophysiology has been better explained. Nevertheless, the management of divers with PFO, whether conservative or interventional treatment should be followed, should be based on a shared decision making. Larger randomized studies should be conducted in order to shed light on the optimal prevention and treatment of DCI.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Anastasios Apostolos: Conceptualization; Data curation; Investigation; Resources; Validation; Writing – original draft; Writing – review & editing.

Maria Drakopoulou: Investigation; Methodology; Resources; Validation; Writing – original draft; Writing – review & editing.

George Trantalis: Data curation; Investigation; Writing – original draft; Writing – review & editing.

Andreas Synetos: Conceptualization; Investigation; Methodology; Writing – review & editing.

George Oikonomou: Investigation; Resources; Writing – review & editing.

Theodoros Karapanayiotides: Supervision; Validation; Writing – review & editing.

Costas Tsioufis: Project administration; Supervision; Writing – review & editing.

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