



# Patent Foramen Ovale and Diving

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## ABSTRACT

Although patent foramen ovale (PFO) was anatomically depicted in 1513 by Leonardo da Vinci and described as a thromboembolism route in 1877, it has been ignored for a long time as a potential way to produce pathological conditions. The unifying hypothesis associated with multiple clinical issues, such as cryptogenic stroke, migraine and decompression sickness is that a particle, inert gas bubbles or chemical substance in the venous circulation bypasses the lungs and enters to the systemic circulation via PFO. In this review, current data on the status of PFO in diving medicine are discussed.

**Keywords:** Patent foramen ovale, diving, decompression sickness

## Introduction

Foramen ovale is an interatrial connection that enables rapid transiting of umbilical blood to the brain and vital organs without any further oxygen loss during intrauterine period. After birth, the foramen ovale flap (septum primum) is closed on the septum secundum, physiologically when pulmonary vascular resistance and right atrium pressure drop. Fusion, which begins with contact, is completed irreversibly, in the first two years of life. Foramen ovale remains patent in 25% of the population (1,2). The patent foramen ovale (PFO) was drawn and depicted by Leonardo Da Vinci in the form of a “channel” centuries after the physiological closure was defined by Galen. Use of the term “channel” is unique in that century in terms of predicting the complex structure of PFO pathophysiology and pointing out that it is more than just a simple hole (3).

While individuals with PFO are generally identified incidentally in autopsies, antemortem diagnosis is often made during the etiological investigations of clinical pictures associated with PFO. In an autopsy study consisting of 965 people, PFO sizes were measured between 1-19 mm (4.9 mm on average) and the mean size was 3.4 mm in the first decade and was 5.8 mm in the tenth

decade. This is interpreted as the fact that small-size PFOs are closed over time and that large-sized ones remain open (4). The combining hypothesis for the association of PFO with numerous clinical conditions such as cryptogenic stroke, migraine, sleep apnea, pulmonary edema due to high altitude, platypnea-orthodeoxia, decompression sickness (DCS), is based on the passage of a particulate, gas bubble, or chemical substance in venous circulation to systemic circulation without being exposed to the lungs through a right-to-left shunt. The left atrium pressure is higher than the right atrium, which prevents passage by holding down the septum primum flap to septum secundum. Even if the flap is partially open, the blood flow will be from left to right. However, daily activities such as lifting, coughing, vomiting, and pushing which increase intrathoracic (ITP) and intraabdominal pressure may reverse the interatrial pressure gradient, creating a temporary right-to-left shunt. One of the most effective methods is an extended and forced Valsalva maneuver (VM) (1,2,5). The maneuver, originally described in 1704 by Mario Antonio Valsalva in detail in his work “De Aure Humana Tractatus” (Treatise on the Human Ear), is simply an effort of forced expiration against a closed airway. In order to prevent middle ear barotrauma, the VM is frequently used during diving and hyperbaric oxygen treatment.

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The response to the maneuver is related to the duration of the maneuver, the level of strain, the position of the body and the respiratory pattern (5). Astonishingly, while gentle VMs during diving do not increase the ITP at all, much larger increases are observed if maneuver is performed during challenging and crouching (6).

Another issue about PFO-mediated transition that has recently been discussed is the blood flow dynamics in the right atrium and its relationship with fossa ovalis. At the right atrium, the currents from the caval veins do not collide head to head, they turn forward and contribute to the rotation of the blood in the clockwise. This filling pattern associated with directing the atrial volume towards the tricuspid valve entry is extremely important in maintaining the continuous activity of the heart with minimal energy. This vortex formed at the right atrium entrance is thought to remove the blood out of PFO which carries the majority of thrombus material, bubble, vasoactive chemicals and which is coming with the inferior caval current directed at almost to the fossa ovalis at the beginning which (7,8).

The PFO-mediated shunt can be determined by different echocardiographic techniques, including transthoracic echocardiography (TTE), transesophageal echocardiography (TEE), and transcranial Doppler (TCD). Having superior image resolution, having ability to distinguish shunt localization, having ability to define morphology, presence of accompanying defects, number and size of these defects, completeness of septum apart from defect and the presence of anatomic structures that will affect the placement of the device and visualizing the three-dimensional appearance of PFO in mind make TEE the gold standard in the diagnosis of PFO (1,2,9,10). However, it comes after TTE or TCD in the evaluation hierarchy because it is a semi-invasive procedure with well defined staff training criteria, it has life-threatening complications such as esophagus hemorrhage, perforation and it is contraindicated in patients with severe bleeding risk. TTE is the most frequently used initial screening test because of its low cost, non-invasive nature and easy accessibility (9,10).

The most common contrast used in echocardiography routine is saline which is agitated by mixing with air. Air bubbles are cleared as they pass through the lungs, and those who can pass are dissolved in the blood. Because tissues are not supersaturated with nitrogen, DCS symptoms are not observed even if there is a high bubble passage (11). However, during echocardiographic studies with contrast agents, for safety reasons, oxygen should be available and the diver should not have dived within the last 24 hours (6). It has been shown that TCD has similar sensitivity to shunt detection, but it fails to differentiate cardiac and pulmonary localizations (2,9,10).

Provocative maneuvers that increase the ITP, also significantly increase the sensitivity of TTE and TEE. Because conscious sedation is applied during TEE, the effect to be achieved with a challenging VM is tried to be performed by abdominal compression. The timing of the bubbles in the left heart is very important in the separation of intracardiac and transpulmonary

shunts. In the presence of a shunt at the cardiac level, the bubbles are expected to be seen in the left heart in three cardiac cycles. In the presence of a large pulmonary shunt, it should be noted that contrast in the left heart can be seen in three cardiac cycles, and a more detailed imaging of the shunt to clarify localization should be performed with TEE. The systems used in grading are subjective and are usually based on semi-quantitative factors that focus on the number of bubbles seen in the left atrium. Therefore, there is no widely accepted schema (9,10). Another important point is the localization of contrast injection. Femoral injections have been shown to be more effective than conventional brachial injections. This effect is related to the blood flow dynamics in the right atrium and its relation with PFO, which is described above, and to the rapid bolus and shorter venous transit time provided by a larger diameter femoral catheter, and thus to the reduction of the dissolved bubbles (9,12).

### **Diving and Patent Foramen Ovale**

During diving, the environmental pressure increases by 1 atmosphere (760 mmHg) at every ten meters of depth. Increasing pressure does not affect the liquid and solid parts of the body, but forces gas-filled cavities and organs of the body to squeeze into smaller volumes. For this reason, divers inhale high pressure air (or mixture gas) to prevent the lungs from being collapsed with the aid of equipment (SCUBA) that allows the environmental pressure to be balanced with ambient pressure. During the dive, inert gas (nitrogen, helium) in the inhaled gas mixture is dissolved in the tissues, depending on the depth and duration. If the inert gas pressure in the lungs or gas mixture does not decrease, the dissolution may continue until equilibrium is reached between the breathing gas known as saturation and the tissues. The decrease in inert gas pressure in the lungs is possible with decrease in ambient pressure (decompression). When divers begin to rise to the surface, inert gas is transported from tissues to the blood and lungs and expelled from the alveoli. During decompression, the inert gas in the tissues can be effectively removed by slowing down the ambient pressure or waiting at certain depths (decompression stops). There are detailed decompression algorithms designed to control this process and ensure that the diver returns safely to the surface. In an inadequate decompression, supersaturation (over saturation) develops and a tendency to produce bubbles occurs (11,13-15).

Gas bubbles that occur after supersaturation and do not cause any symptoms are called "silent bubbles" and can be detected by Doppler imaging in venous circulation (13,16,17). Bubbles, depending on their numbers and sizes, can cause clinical signs and symptoms of DCS by causing mild or severe damage in any part of the body. DCS is a systemic disease with complex pathogenesis including the development of mechanical distortion, ischemia, hypoxia, vascular occlusion, increased capillary permeability with endothelial damage, plasma extravasation, hemoconcentration, platelet activation and aggregation, leukocyte-endothelial adhesion, ischemia reperfusion damage due to mechanical, embolic and biochemical effects of bubbles (13,14,17). It is seen in pilots, astronauts, compressed-air (caisson) workers and known as "bends" colloquially. The traditional classification of

DCS based on the severity of clinical findings in the form of type 1/2 is based on the experience gained from caisson workers in the construction of the Dartford Tunnel in London (18).

Silent bubbles can also be seen after dives made according to the rules. In the presence of DCS, bubbles are usually found in high amounts (13,16,17). In a study conducted by the Divers Alert Network (DAN), venous gas bubbles were found with Doppler in 91% of divers after repeated dives at different depths, however DCS was not seen in any diver (19). The current data suggest that the risk of DCS development is 13%, even in the presence of a high amounts of bubbles (17). Under normal conditions, these gas bubbles go to the right heart, then to the lungs through venous circulation. The gas in the bubbles is eliminated by diffusion from pulmonary capillaries to alveoli. The size of the bubbles is 19-700  $\mu\text{m}$  and the diameter of the capillaries in the gas exchange area is 6-15  $\mu\text{m}$ , which explains the working mechanism of the pulmonary filter. A more rare and dangerous condition is that the transition of bubbles to arterial circulation through a right-to-left shunt at cardiac or pulmonary level (13,14,16,17,20).

Initial publications suggesting that venous gas bubbles may cause paradoxical embolism through a defect in the interatrial septum have begun to enter the literature from the late eighties (21). Although PFO has been known for a long time as a route of thromboembolism, it has begun to attract the attention of cardiology and neurology since the late eighties (22-25). The presence of a PFO to provide arterialization of silent bubbles has been considered to be a part of an incomplete “undeserved DCS” puzzle following a safe dive profile or arterial gas embolism without pulmonary barotrauma. However, it has paved the way for new discussions. The most important objection concerns the numbers. It is clear that only 0.005-0.08% of all recreational dives result in DCS; PFO is found in 25% of divers as in the normal population and we know that bubbles that can cause DCS are formed in 91% of divers. So, this ratio is much lower than expected. The second objection is that clinical observations made so far, correlate PFO with neurological damage, but this group constitutes only one third of all DCS cases. Although the majority of DCS cases occurring in recreational dives are presented with pain and sensory disturbances, the association with PFO has not been established (26). Recent publications suggest that the risk of developing DCS is associated with the diameter of the atrial defect rather than with the presence of PFO, and that stroke and DCS prevalence are higher than normal population in patients with migraine with aura and that migraine with aura may be regarded as an indicator of the presence of a large scale PFO (25,27,28).

Short-term increases in the ITP may be insufficient for passing of large amounts of bubbles. However, in professional and military diving, depending on the nature of the job, physical activities that form a significant increase in ITP are made in decompression period and in first 30-60 minutes after rising to the surface which are the periods with the highest level of bubble formation. In addition to professional activities such as lifting anchor, rope pulling, transferring people that are expelled from water to boat,

there are activities that increase the individual workload such as swimming to the boat from the exit point from the surface, climbing to the boat with heavy equipment such as diving cylinder. Unconscious VM is also frequently performed during this period. The activities during this period elicit the opening of intrapulmonary arteriovenous anastomoses, especially for those whose shunts open at a relatively low percentage of their maximal oxygen consumption ( $\text{VO}_{2\text{max}}$ ) (20,28). Undersea and Hyperbaric Medical Society (UHMS) Best Practice Guidelines recommend avoiding aerobic (running), anaerobic (lifting weight) exercises for four hours unless there is no operational requirement (29).

On the other hand, although the bubbles are called “silent”, their acute, asymptomatic but repeated presence in circulation plays a role in the formation of cardiovascular, osteonecrotic and cerebral lesions in the long-term period (16). In particular, concerns about decreased neuropsychological performance, the question of whether “silent” bubbles cause “silent” cerebral damage, and the role of PFO in this damage, due to its contribution in arterial migration of bubbles, have been subject to numerous studies (30-33). With increased use of magnetic resonance imaging (MRI), white matter hyperintensities (WMHs) as an incidental finding in T2-weighted images were significantly much more seen in healthy divers with no DCS history than in non-diving controls, which has brought new questions that need to be answered. Cerebral WMHs are neuronal axon defects where the myelin is replaced by the central nervous system fluid. They are known as hyperintense lesions in T2-weighted, FLAIR and proton density images without showing significant hypointensity in T1-weighted images in MRI. Histologically, represent demyelination, axonal loss and astrocytic gliosis. Long-term results of WMHs associated with diving are not known for today. However, it is well known that WMHs increase dramatically over the age of 55 and increase the risk of stroke, dementia, and death (31,33,34). The relationship between increased WMHs and subclinical disturbances in neurocognitive functions has been shown in studies performed in U-2 pilots (35). This situation seems to be compatible with subtle cognitive disorders seen in healthy individuals with punctate WMHs (31,34,35). The acute and chronic consequences of gas bubbles passing through the venous circulation to the systemic circulation via PFO are still under investigation.

### **Closure of PFO: Results From Cardiology and Neurology Experience**

PFO, defined in the autopsy studies of Julius Cohnheim in 1877 as an unusual route for thromboembolism (22) was considered to be a rare condition until two observational studies in 1988 (23,24) in which the prevalence of PFO was found to be higher in patients with cryptogenic stroke at a young age (40-50% vs 10-15%,  $p < 0.001$ ). A retrospective analysis of the PICSS (PFO in Cryptogenic Stroke Study) which was a subgroup survey of the WARRS (Warfarin Aspirin Recurrent Stroke Study) that was a randomized trial, consisting of 2206 patients, showed that recurrent stroke risk in patients aged over 65 years with a history of cryptogenic stroke was 37.9% in patients with PFO and 14.5%

in patients without PFO at two years follow-up (36). In patients with atrial septal aneurysm (ASA) concomitantly, there is an increase in the risk of initial and recurrent stroke events (1,24). Although this relationship was originally thought to be related to the formation of thrombus caused by aneurysmal tissue, it was not confirmed. The current theory is that the presence of ASA increases the risk by causing more interatrial flow (1).

A meta-analysis of forty-eight observational studies including 10327 patients with cryptogenic stroke/transient ischemic attack (TIA) with PFO showed that the rate of recurrent events was 0.8 events/100 person-years in patients with PFO closure, whereas it was 5.0 in patients with medical treatment (37). However, large-scale, randomized controlled trials (RCTs) planned with the hypothesis that the closure of PFO in the prevention of cryptogenic stroke would be superior to medical treatment did not meet the proposed hypothesis. The first was CLOSURE I (Evaluation of the STARFlex Septal Closure System in Patients with a Stroke and/or Transient Ischemic Attack due to Presumed Paradoxical Embolism through a Patent Foramen Ovale). The study included 909 patients aged 18-60 years with a history of cryptogenic stroke or TIA, whose PFO was confirmed by TEE. Patients were randomized into two groups; antiplatelet therapy (clopidogrel for 6 months followed by aspirin) after percutaneous closure of PFO and only medical treatment (warfarin, aspirin or both, according to the researcher's decision). The PFO closure attempt failed in 14% of patients. At the end of the two-year follow-up, 5.5% in the group with PFO closure and 6.8% in the group receiving medical treatment had stroke or TIA (confidence interval: 0.45-1.35;  $p=0.37$ ). Although it was a well-designed study with the high number of participants, it had the power of only determining a 30% difference between the two groups (38).

The discrepancies between the results of observational studies and the CLOSURE I study were mainly attributed to the device used for the closure (2). The advantageous safety features of the Amplatzer PFO Occluder have enabled it to be preferred in other two RCTs: the RESPECT (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment) and the PC (Clinical Trial Comparing Percutaneous Closure of Patent Foramen Ovale (PFO) Using the Amplatzer PFO Occluder with Medical Treatment in Patients with Cryptogenic Embolism) (39,40). Although the studies resolved the problems related to the device, they did not eliminate the uncertainty about whether PFO is causative or incidental finding in cryptogenic stroke (2).

The relationship between PFO and migraine, as well as PFO-cryptogenic stroke relationship began to draw attention at the end of the nineties. The first studies which indicated that lungs act as a filter in removing the triggering agents acting in migraine pathogenesis from the venous circulation rather than releasing them, included divers who underwent transcatheter closure before return to diving after neurological DCS. In addition to the relief of migraine symptoms as a secondary gain after closure, it is also important to note that migraine with aura-PFO- DCS

relationship was revealed by this study (25). Observational studies and meta-analyses were followed by three consecutive RCTs, as in stroke cases. The first one was the MIST (Migraine Intervention With STARFlex Technology) study. It showed that the prevalence of shunt in patients with migraine with aura (60%) was much higher than in the general population, however there was no difference between closure and sham (imitation, skin incision in the groin) groups on primary and secondary endpoints. Hence, has created a disappointment (41). The much more remarkable feature of the MIST study was the sensational debate about the evaluation of device and residual shunts in the sixth month follow-up (42). PRIMA (Percutaneous Closure of PFO in Migraine with Aura) was a study with the use of the Amplatzer PFO Occluder that started in 2006 and ended prematurely due to slow participation in 2012. The primary endpoint was the number of days with migraine headache per month, and it was concluded that the closure of PFO in refractory migraine cases did not reduce the monthly migraine days (43). The PREMIUM (Prospective Randomized Investigation to Evaluate Incidence of Headache Reduction in Subjects with Migraine and PFO Using the Amplatzer PFO occluder Compared to Medical Management) study was initiated in the same year with the PRIMA study and used the same device. It was a sham-controlled study with larger number of participants, but it was not published yet (NCT00355056).

All of these data show that cardiology and neurology have shown much more progression than diving medicine in terms of PFO. PFO closure is a less risky procedure in patients with stroke and migraine than the disease itself, which is a factor in the progress. With the contribution of the studies, the number of procedures increased fifty times over the last decade which has brought important developments in technics and device (1). However, due to the fact that the results are not as spectacular as expected, it can be said that the current experiences do not add much to the relationship between diving and PFO. The risk-benefit ratio of closure also remains controversial for diseases other than diving.

### **PFO Screening in Medical Examinations to Fitness to Dive**

The purpose of medical examinations for professional divers, instructors, guides and divemasters is to determine whether there is a temporary or permanent impediment to diving or require further specialist assessment. It should also assess the functional capacity of the diver to undertake their work safely. Standards developed in the light of scientific evidence, expert opinions and experiences obtained from suitability examinations for diving determine the way to be followed in diving examinations. Standards are based on scientific evidence, expert opinions and experiences obtained from examinations of fitness to dive and help achieve these aims and promote a consistent approach to fitness assessments. In our country, medical examination and assessment of professional divers or diving instructors are carried out in accordance with the principles determined by the Professional Divers Regulation and the Turkish Underwater Sports Federation (TSSF) Equipped Diving Instruction. Legislation gives responsibility to the undersea and hyperbaric

medicine specialists in examination, assessment of suitability for diving and preparing health reports (44,45).

There is a general consensus that the PFO screening does not need to be routinely performed in all divers, but it is unclear when and who should be scanned. Despite the enrichment observed in the literature, deciding which diver should be referred to for closure is still a commonly asked clinical question and the answer is not clearly revealed. The ideal is to establish consistent and evidence based principles in the light of available data and to implement them in evaluations (28). A review of the current guidelines gives the following results: According to the DAN: "Although medical data suggest that there is a relationship between severe neurological DCS and the presence of PFO, the cause-effect relationship is not conclusively proven and associating a common finding (PFO) with a rare disease (DCS) is a commonly made mistake" (26). According to the United Kingdom Sports Diving Medical Committee (UKSDMC), for sport diving: "Testing is recommended to exclude the possibility of a shunt in case of neurological DCS in sport divers after a theoretically safe dive profile. Paradoxical embolism risk is greater in those with a large shunt. It therefore seems reasonable that sport divers known to have intra-cardiac shunts should be allowed to dive shallower than 15 m, provided no other cardiac contra indications exists" (28). Health and Safety Executive for professional divers: "Examination for the presence of an intracardiac shunt is not a requirement of either the initial or annual examinations. However, PFO screening should be performed in patients with neurological, cutaneous or cardio-respiratory DCS, especially in divers with history of migraine with aura, or in divers developing DCS after a dive profile which can be considered as safe; because PFO screening may contribute to the overall risk assessment when deciding to start diving and continue diving. The presence of a positive finding is not sufficient reason to decide whether the diver is unsuitable for diving. However, any diver who has suffered these should be assessed by a cardiologist with a special interest in diving medicine" (46). According to the National Institute of Clinical Excellence: "It is important to include a cardiologist with knowledge of diving medicine in the evaluation. If the assessment of PFO presence and size is inadequate, inappropriate advice may pose a risk in the future" (47). According to the UHMS Best Practise Guidelines: "PFO screening for divers with clinically severe or recurrent neurological DCS can help advise divers on changing dive profiles" (29). According to the Carl Edmonds's Diving Medicine for SCUBA Divers: "The risk from a PFO is not great enough for it to be appropriate to test all divers for it, and repair of the hole is probably more dangerous than diving with it" (48). The situation is similar in our regulations. There is no opinion on the obligation to scan for PFO in the Professional Divers Regulation and the TSSF Equipped Diving Instruction (44,45). According to "the TSSF Equipped Diving Instruction, Sixth Section, Health Conditions, Item 20b": "Unless evaluated as hemodynamically insignificant by a cardiologist; organic heart diseases such as cardiomyopathy, ischemic heart disease, valvular heart disease, cyanotic heart disease and right-to-left shunts are impediments to diving" (45).

The report produced from the consultation with UKSDMC members after the workshop held at the 43<sup>th</sup> Annual Scientific Meeting of the South Pacific Underwater Medicine Society is extremely important in terms of its content and setting out the need for this issue. According to this consensus statement: "Routine screening for PFO at the time of dive medical fitness assessment (either initial or periodic) is not indicated. An investigation for PFO should be considered in the history of cerebral, spinal, vestibulocochlear or cutaneous DCS, cryptogenic stroke, PFO or atrial septal defect in first degree relatives and current or past history of migraine with aura. If screening for PFO is performed, it should be done by centres well practiced in the technique. The screening must include bubble contrast, ideally combined with TTE because this best facilitates cooperation with provocation maneuvers. A spontaneous shunt without provocation or a large, provoked shunt is recognized as an unequivocal risk factor for cerebral, spinal, vestibulocochlear and cutaneous DCS. There is a lower but poorly defined risk in smaller shunts. Following diagnosis of a PFO, the diver may consider stop diving, adopting more conservative diving profiles or PFO closure options in consultation with a diving physician. Following closure of a PFO and before returning to diving, the diver requires a repeat bubble contrast echocardiogram demonstrating shunt closure, a minimum of three months after the closure. Diving should not be resumed until satisfactory closure of the PFO is confirmed, and the diver has ceased potent antiplatelet medication" (49).

The ultimate goal of practicing diving medicine is to protect the health of divers both during and after the dive. The diving-PFO relationship requires close cooperation with the cardiologist who will perform the procedure during screening, diagnosis, closure and follow-up. In addition, the use of experience of cardiology and neurology which have studies with high number of patients and resources should be considered in the design and methodology of future research. It should be emphasized that the most important factor in DCS development is the diving profile, that even the most successful closure procedure can not prevent DCS formation in the presence of an aggressive dive profile, and that the risk is only returning to normal and can never be reset.

## Ethics

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