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High prevalence of patent foramen ovale in recreational to elite breath hold divers

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ABSTRACT

Objectives: During apnea diving, a patent foramen ovale may function as a pressure relief valve under conditions of high pulmonary pressure, preserving left-ventricular output. Patent foramen ovale prevalence in apneic divers has not been previously reported. We aimed to determine the prevalence of patent foramen ovale in apneic divers compared to non-divers.
Design: Cross sectional.
Methods: Apnea divers were recruited from a training camp in Cavtat, Croatia and the diving community of Split, Croatia. Controls were recruited from the population of Split, Croatia and Eugene, Oregon, USA. Participants were instrumented with an intravenous catheter and underwent patent foramen ovale screening utilizing transthoracic saline contrast echocardiography. Appearance of microbubbles in the left heart within 3 cardiac cycles indicated the presence of patent foramen ovale. Lung function was measured with spirometry. Comparison of patent foramen ovale prevalence was conducted using chi-square analysis, $p < .05$.
Results: Apnea divers had a significantly higher prevalence of patent foramen ovale (19 of 36, 53%) compared to controls (9 of 36, 25%) (X^2 (1, N = 72) = 5.844, p = .0156).
Conclusions: Why patent foramen ovale prevalence is greater in apnea divers remains unknown, though hyperbaria during an apnea dive results in a translocation of blood volume centrally with a concomitant reduction in lung volume and alveolar hypoxia during ascent results in hypoxic pulmonary vasoconstriction. These conditions increase pulmonary arterial pressure, increasing right-atrial pressure allowing for right-to-left blood flow through a patent foramen ovale which may be beneficial for preserving cardiac output and reducing capillary hydrostatic forces.

Practical implications

- PFO is associated with worse outcomes at altitude, and with developing unprovoked neurological decompression illness in SCUBA divers.
- Breath-hold divers have a greater likelihood of having a PFO compared to the general population.
- This may be either a result of high pulmonary vascular pressures associated with long breath holds and deep diving or it may confer and unknown benefit for these divers.

1. Introduction

The foramen ovale is a normal feature of the fetal heart, allowing blood to bypass the lungs during development. Upon delivery and the newborn's first breaths, the drop in right atrial pressure and rise in left

Abbreviations: PFO, patent foramen ovale; HAPE, high-altitude pulmonary edema; SCUBA, self-contained underwater breathing apparatus; DCS, decompression syndrome.

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atrial pressure closes the foramen ovale, which then seals over the subsequent months via an endothelial-to-mesenchymal transition leading to fibrosis.[1] However, for unknown reasons, the foramen ovale remains patent in 25–35% of adults – resulting in a patent foramen ovale (PFO).[2,3]

The PFO allows for blood to move left-to-right or right-to-left between the atria following whatever pressure gradient is present in that moment the pathway is open. At times, the PFO acts as a source of right-to-left shunt,[4] such as during end inspiration during diastole or following the release of a Valsalva maneuver,[5] when right atrial pressure exceeds left atrial pressure. The PFO may also act as a pressure relief pathway during conditions of high pulmonary arterial and/or right heart pressures whereby pressures may still be higher than normal, yet lower than they would be in the absence of a PFO.[6] Interestingly, there are known pathophysiological associations of PFO with conditions of high pulmonary arterial pressure such as high altitude pulmonary edema (HAPE)[2,7] and exaggerated pulmonary pressures with exercise in those with chronic mountain sickness.[8] The presence of a PFO is also associated with impaired ventilatory acclimatization to altitude,[2] impaired hypercapnic ventilatory responses,[2] impaired pulmonary gas exchange efficiency at rest,[2,4] and a higher core body temperature at rest and during exercise.[2,9] Thus, the presence of PFO is associated with numerous physiological and pathophysiological consequences.

PFO has been shown to be highly common in recreational SCUBA divers experiencing decompression syndrome (DCS).[10] SCUBA diving can result in the formation of venous gas emboli, even when SCUBA divers adhere to recreational dive ascension rates and perform appropriate decompression stops on the ascent or perform no-decompression dives.[11] Due to the presence of a PFO, these venous gas emboli have the potential to bypass the pulmonary circuit and enter systemic and cerebral circulations resulting in neurological decompression symptoms.[11] Percutaneous closure of PFO has been shown to reduce the occurrence of SCUBA divers experiencing DCS, further supporting the link between the presence of PFO and DCS.[12] The prevalence of PFO has not been previously investigated in apnea divers – a pervasive profession/sport, characterized by transient bouts of hydrostatic- and arterial hypertension subsequent to peripheral vasoconstriction. This combination also increases central venous volume during deep dives, leading to an increase in central venous and right atrial pressures. Upon ascent, alveolar hypoxia would lead to hypoxic pulmonary vasoconstriction resulting in a continued increase in right heart pressures during the dive even as the hydrostatic forces are decreasing. This increase in right atrial pressure may allow for right-to-left blood flow through a PFO which would act to preserve cardiac output and reduce capillary pressures during the descent and ascent phases of an apnea dive. The repetitive nature of apnea diving and therefore increased right pressures may also stretch open an incompletely sealed foramen ovale, allowing it to be more readily detected. Thus, we hypothesized that PFO prevalence may be greater in apnea divers.

2. Methods

The study received approval from the University of Oregon Research Compliance Services and University of Split School of Medicine. Each participant provided written, informed consent before participation (University of Oregon IRB# 07302018.031; University of Split School of Medicine Ethics Committee #2181-198-03-04-19-0052). All studies were performed in accordance with the 2013 Declaration of Helsinki except for registration in a database. Apnea divers (n = 36, 9 female) were recruited from the apnea diver communities surrounding Split, Croatia and an international training camp in Cavtat, Croatia. Control participants (n = 36, 13 female) were recruited from the general population of Split, Croatia and Eugene, Oregon. Control participants had no significant apnea-diving history (e.g., no history of spearfishing or competitive apnea diving or similar history). Some Control participants (n = 19, 10 female) were prospectively enrolled from other studies which required them to be screened for PFO and undergo spirometry. The PFO status of these subjects was not known at the time of their enrollment in this study or other studies (University of Oregon IRB# STUDY00000174; STUDY00000019; 04302018.049).

Participants had spirometry assessed prior to participation. They performed forced vital capacity and slow vital capacity maneuvers utilizing a desktop spirometry system (CPFS/D USB Spirometer, Medgraphics Corporation, Saint Paul, MN, USA) or plethysmograph (Elite Series Plethysmograph, Medgraphics Corporation).

Participants were instrumented with an intravenous catheter and underwent PFO screening using transthoracic saline contrast echocardiography as described in detail elsewhere.[4,13] Briefly, transthoracic ultrasound was used to achieve an apical 4-chamber view of the participant's heart while saline contrast was injected into the antecubital vein. Saline contrast was created by vigorously agitating ~3 mL of saline with ~1 mL air between two syringes connected via three-way stopcocks. This procedure was completed while the participant was at rest and breathing normally and repeated with the participant performing a Valsalva maneuver. Participants were considered PFO-positive if contrast bubbles appeared in the left heart within 3 cardiac cycles of saline contrast appearing in the right ventricle either with or without Valsalva release. Ultrasound measures and bubble study evaluations in Croatia were conducted by three experienced ultrasonographers (T.D., R.N.L., A.D.) and reviewed by a Clinical Cardiac Physiologist accredited by the British Society of Echocardiography (A.D.). In Eugene, these measures were conducted and reviewed by Registered Diagnostic Cardiac Ultrasonographers, and we have shown excellent agreement in assigning bubble scores in blinded physicians and ultrasonographers.[14]

All statistical analyses were conducted via GraphPad Prism version 8.4 (GraphPad Software, San Diego, CA, USA). Spirometry was compared between Divers and Controls utilizing Student's unpaired *t*-test. PFO prevalence was compared using a Chi-square analysis with significance set at a priori as $p < .05$.

3. Results

Apnea divers had a significantly higher PFO prevalence (19 of 36, 53%) than controls [9 of 26, 25%; $X^2(1, N = 72) = 5.844$, $p = .0156$]. Divers were significantly taller and had larger FVC and FEV1, but similar FVC/FEV1 ratio compared to controls (Table 1).

4. Discussion

The elevated prevalence of PFO in breath-hold divers, compared to non-diver controls, provides insight into a potentially new role of PFO in the unique physiology of apnea divers. The prevalence of PFO in the general population has previously been reported to be approximately ~35%.[15] The prevalence of PFO has been shown to be greater, compared to the general population, in a variety of pathologies including those diagnosed with obstructive sleep apnea.[16] It is unclear why the rate of detection of PFO is greater in apnea divers than the general population, or whether the apparent increase reflects a benefit or detriment to apnea

Table 1
Anthropometric and spirometric evaluation of Divers and Control.

	Divers n = 36 PFO prevalence: 53%	Control n = 36 PFO prevalence: 25%
Height (cm)	181.2 ± 7.6***	175.1 ± 7.2
Weight (kg)	77.8 ± 15.3	72.5 ± 12.6
Age (years)	35.5 ± 10.0	28.1 ± 8.6
BMI (kg/m^2)	23.5 ± 3.5	23.6 ± 3.3
FVC (L)	6.1 ± 1.4**	5.2 ± 1.0
FEV1 (L)	4.8 ± 1.0†	4.1 ± 0.8
FEV1/FVC	0.79 ± 0.07	0.80 ± 0.10

*** p = .0008, two-tailed unpaired Student's *t*-test.
** p = .0025, two-tailed unpaired Student's *t*-test.
† p = .0016, two-tailed unpaired Student's *t*-test.

divers. Explanations for this finding remain speculative at this time. The prevalence of PFO was also found to be greater in HAPE-susceptible individuals at low altitude.[7] The rate of PFO detection increased further (from 56% to 69%) with ascent to altitude and concomitant increases in pulmonary pressure associated with an exaggerated hypoxic pulmonary vasoconstriction[7]. This suggests that a PFO may act as a pressure relief pathway and yet pulmonary pressure would still be elevated, though not as much as it would be in the absence of a PFO.

While an in-depth review of the physiology of apnea diving is beyond the scope of this work, it is important to note some of the physiological responses to an apneic dive. The combination of peripheral vasoconstriction from the mammalian dive reflex and increased hydrostatic pressure results in significant translocation of blood into the thorax, increasing central venous volume and central venous pressure as well as stroke volume and pulmonary capillary hydrostatic pressure.[17] The combination of chemoreceptor stimulation from acidotic hypercapnic hypoxia elicits a significant sympathetic response, likely dramatically increasing mean arterial pressure, though data to confirm this is lacking.[18] Simulated dives in a pressure chamber showed a substantial increase in mean arterial pressure.[19] As depth increases, lungs compress in response to increased hydrostatic pressure, and can result in reduction of lung volume below residual volume at relatively modest depths (40–50 m), further increasing pulmonary pressure.[18] At the nadir of the dive, the diver is hyperoxic due to increased barometric pressure increasing PO_2 in accordance with Boyle's law. However, the diver is still consuming oxygen while submerged, gradually decreasing alveolar PO_2. As the diver ascends from the nadir of their dive, compression of the lung decreases as does barometric pressure. During the ascent phase, the combination of oxygen consumption and decreasing barometric pressure leads to a rapid decrease in alveolar and arterial PO_2. At the cessation of the dive, arterial PO_2 has been measured as low as 27 mm Hg,[20] and as low as ~20 mm Hg after "dry" apneas.[21] This severe level of hypoxemia may result in a significant hypoxic pulmonary vasoconstriction resulting in prolongation of elevated right heart pressures during the ascent portion of the dive.

While SCUBA-diving in general is not associated with a greater prevalence of PFO, SCUBA-associated DCS is linked with a highly increased prevalence of PFO.[10] Compared to ascending to high altitude or apneic diving to significant depths, SCUBA-diving has relatively modest increases in pulmonary vascular pressure due to the absence of a hypoxic stimulus and associated hypoxic pulmonary vasoconstriction. In contrast, both apneic diving and ascending to altitude cause an increase in pulmonary vascular pressure caused at least in part by hypoxic pulmonary vasoconstriction. This would be particularly true in apnea divers who train in swimming pools and become gradually more and more hypoxic as their lungs are depleted of oxygen. In addition to hypoxic pulmonary vasoconstriction, apneic divers who are diving to great depths have the added impact of lung compression, which can result in reduction of lung volume to below residual volume beyond the relatively routine depths of 40–50 m,[18] providing a further cause for elevated pulmonary pressure. Additionally, breath hold diving has been shown to induce endothelial dysfunction and increased levels of plasma microparticles.[22] Endothelial microparticle levels have been correlated to the hemodynamic severity of pulmonary hypertension.[23]

While the record depths for apneic dives are in excess of 200 m, divers regularly achieve depths sufficient enough to induce hyperbaric stress on the cardiopulmonary circuit. For example, a routinely performed dive to 50 m, would cause a reduction in lung volume to <20% of lung volume at the surface. The combination of lung compression and centralization of blood volume from the periphery into the thorax elicits a substantial increase in pulmonary vascular pressures. Increases in pulmonary arterial pressure result in a buildup of 'backpressure' (increased right ventricular afterload), as structures must generate higher pressures to continue circulating blood, as mean arterial pressures during a simulated dive to 50 m can exceed 200 mm Hg.[19] This increase in right ventricular afterload may lead to increased pressure in the right atrium,[24] resulting in dramatically increased right atrial pressures relative to left atrial pressures.

An alternate explanation is that rather than the act of deep apnea dives exacerbating otherwise minor intracardiac shunts, the preexistence of such a shunt facilitates the ability of these individuals to better compensate while performing deeper dives. During the late stages of a dive and particularly during the ascent,[25] the PO_2 within the alveoli decreases, resulting in hypoxic pulmonary vasoconstriction and increasing pulmonary vascular pressures. A PFO may function as a 'pressure relief valve', reducing the fraction of cardiac output sent to the lungs, thereby limiting the increase in right ventricular afterload, the rise in pulmonary vascular pressure, and aiding in the preservation of left-ventricular cardiac output while protecting fragile pulmonary capillaries from being subjected to extreme hydrostatic pressures. The blood being shunted right-to-left would have a minimal impact on overall arterial oxygenation as the impact of a shunt on pulmonary gas exchange efficiency decreases as the PO_2 of the right atrial venous blood approaches the PO_2 of the arterial blood. Additionally, the PFO functioning as a pressure relief pathway for pulmonary pressure may even be protective against pulmonary barotrauma, as exaggerated pulmonary pressure has been proposed as a contributing factor to pulmonary hemorrhage/edema following diving. PFO functioning as a pressure relief pathway may allow for increased frequency or depth of apneic dives without complications and therefore may explain the higher prevalence among individuals who frequently experience extreme hyperbaria associated with apneic diving.[26]

While PFO has been associated with increased risk of DCS in SCUBA diving, the relationship between DCS and PFO in breath-hold diving is less clear. Similar to SCUBA divers, PFO represents a potential pathway for arterialization of venous gas emboli in breath-hold divers. However, even with very deep breath hold dives we (unpublished observation) and others have found very low venous gas bubble load in breath hold divers (grade 1 on a scale to 5). However, even in SCUBA divers, DCS is not solely dependent on gas bubble load, but also additional factors including endothelial dysfunction[27] and microparticle formation.[28] DCS in breath-hold divers has been linked to these factors.[22] There are also numerous reports of white matter lesions consistent with neurological DCS in Ama divers (traditional Japanese and Korean pearl and seafood divers) as well as DCS in freedivers and spearfishers.[29] Thus, the higher frequency of PFO in breath hold divers may present a risk factor for developing DCS via arterialization of venous gas emboli, but DCS is not solely dependent on this mechanism.

This study has significant limitations. Transcranial doppler can be more sensitive for the detection of PFO compared to transthoracic echocardiography. As such, the rate of detection of PFO reported in this study may be lower than actual prevalence. Similarly, using 1 mL of blood in the agitated saline mixture can also increase sensitivity of the detection method. However, since both Divers and controls were evaluated using the same ultrasound method and both groups were evaluated without the addition of 1 mL blood to the saline mixture, it is unlikely that this altered the reported findings. Additionally, in our hands transthoracic saline contrast echocardiography data are strongly associated with TCD data when detecting right-to-left shunt through a PFO, particularly when using TCD to measure both middle cerebral artery and posterior communicating artery microembolic signals.[30] Apnea divers experience significant elevations in pulmonary pressure due to the combined effects of hypoxia and lung compression while diving which may ultimately result in substantial increases in right atrial pressure for an unknown period after the dive. A PFO may be more readily detectable during that period. As the time interval between the last dive and visiting the lab was not standardized, the rate of detection of PFO reported in Divers may underestimate the true PFO prevalence.

5. Conclusion

We found a significantly greater prevalence of PFO in recreational-to-elite apneic divers. This greater prevalence may be either the result of right ventricular afterload caused by lung compression and hypoxic pulmonary vasoconstriction or possibly serves to mitigate barotrauma associated with frequent or extremely deep apneic dives. In either case, PFO presence may lead to a "self-selection" for being an apnea diver and consequently may influence the prevalence of PFO in this population. Whether or not the presence of PFO is beneficial remains unknown. Future studies investigating cardiopulmonary interactions in apnea divers with and without PFO during apneas and/or bouts of hypoxia may provide additional information on the responses of these individuals to arterial hypoxemia and the effect PFO has on exacerbating or mitigating these effects.

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Declaration of interest statement

Authors have no competing interests or conflicts of interest.

Confirmation of ethical compliance

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