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Úloha foramen ovale patens v patofyziologii vzniku dekompresní choroby

The Role of Patent Foramen Ovale in the Pathophysiology of Decompression Sickness

Disertační práce

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Obsah

1 Introduction

The exposure to the hyperbaric environment during scuba (self-contained underwater breathing apparatus) diving is associated with unique effects on human physiology and with specific pathophysiologic consequences. In the last two decades, much attention has been paid to the risks related to patent foramen ovale (PFO) (Landzberg M.J., Khairy P., 2013). In divers, PFO is associated with the increased risk of decompression sickness (DCS) (Bove A.A., 2014).

Despite the high prevalence of PFO (25-30% in adults) (Hagen P.T. et al., 1984) and the existence of millions of divers worldwide (Vann R.D. et al., 2005), many questions regarding the role of PFO in the pathophysiololgy of DCS remain to be answered.

1.1 Historical Introduction

With the development of professional and recreational diving in the 20th century, the knowledge of DCS progressed. Its first recognition, however, dates to a much earlier period. Decompression sickness was first described in an animal model in 1670 by Robert Boyle (Boyle R., 1670). The first clinical cases of DCS were reported in 1845 (Triger M., 1845). More well-known is the description of 110 cases (of whom 14 died) during the construction of the Brooklyn Bridge in 1873 (Smith A.H., 1873). Only five years later, in his classical work La Pression Barometrique, French zoologist and physiologist Paul Bert postulated that DCS is caused by nitrogen gas bubbles and showed the advantages of breathing oxygen after developing DCS (Bert P., 1943). In 1908, following a series of animal decompression experiments, John Scott Haldane developed the first dive tables that advised staged decompression for

the British Admiralty (Acott C., 1999). This marked the development of further decompression models that are nowadays routinely used by recreational and professional divers to prevent DCS.

1.2 Decompression Sickness – Physiology and Pathophysiology

The diver is exposed to a hyperbaric environment during submersion. In scuba diving, air (or other breathing mixture of oxygen and inert gases) is breathed at ambient pressure. According to Henry's law, the amount of gases dissolved in tissues are equivalent to their partial pressures. Thus, at depth, the concentration of gases in tissues increases over time. The rate of gas saturation is dependent on the chemical composition and density of capillaries in a particular tissue (Doolette D.J., Mitchell S.J., 2001). As the diver ascends to the surface, a pressure gradient drives the dissolved gases back from peripheral tissues to venous blood and ultimately to the alveolar space from where it is expired out of the body. If the pressure drops too quickly, the tissues become supersaturated with gases not utilized by the body (nitrogen, inert gases) and a gas phase forms (Papadopoulou V. et al., 2013).

The process of bubble formation has attracted the interest of researchers for more than a century, but many aspects remain unclear. Although still being controversial, it is generally agreed that an *a priori* presence of some form of micronuclei is required for bubbles to form in divers. Nanobubbles spontaneously forming on hydrophobic surfaces are considered potential candidates for micronuclei, although their potential for growth is still debated, due to their high stability (Papadopoulou V. et al., 2013). The need of a hydrophobic surface might explain the results of some physiological studies, where adiposity was investigated as a risk factor of DCS (Papadopoulou V. et al., 2013).

It is of importance that the rate of saturation and desaturation differs among tissues. Mathematical models incorporating several tissue compartments are used to characterize whole body gas kinetics (Bove A.A., 2014). To prevent DCS, divers routinely use specialized dive computers or decompression tables that are based on these models. In Europe the most widespread is the 16-compartment model developed by Swiss physician Albert A. Bühlmann between 1959 and 1983 (several modified versions are used by contemporary diving computers) (Bühlmann A.A., 1983). Well established is also the United States Navy Air Decompression procedure based on the Thalmann algorithm designed in 1980 by Capt. Edward D. Thalmann, MD (United States Navy, 2008).

As noted earlier, decompression sickness is caused by the formation and growth of gas bubbles in supersaturated blood or tissues during the diver's ascent (Fig. 1). These bubbles cause either local tissue damage or embolize through venous blood (Vann R.D. et al., 2010). Small quantities of venous gas emboli (VGE) were confirmed by Doppler studies after most scuba diving (Dunford R.G. et al., 2002; Ljubkovic M. et al., 2011). In a study conducted by the Divers Alert Network (DAN, an international dive safety association providing expert medical advice), VGE were found in 91% of divers after multi-day repetitive diving (Dunford R.G. et al., 2002). In a study by Ljubkovic et al., VGE were found after 80% of single no-decompression air dives (Ljubkovic M. et al., 2011). Most divers with VGE, however, remain asymptomatic, as nitrogen bubbles are effectively filtered by pulmonary circulation. Symptoms may occur either with high bubble load (i.e. pulmonary gas embolism in case of severe violation of the decompression regimen) or due to paradoxical embolization (arterialization of bubbles) in a diver with a permanent or transient right-to-left shunt. In divers with a PFO, if paradoxical embolization occurs, arterialized

bubbles lodge in peripheral capillaries (Fig. 1). Furthermore, excess gas from supersaturated tissues promotes further growth of these bubbles. The resulting obstruction of capillaries causes local ischemia (Vann R.D. et al., 2010).

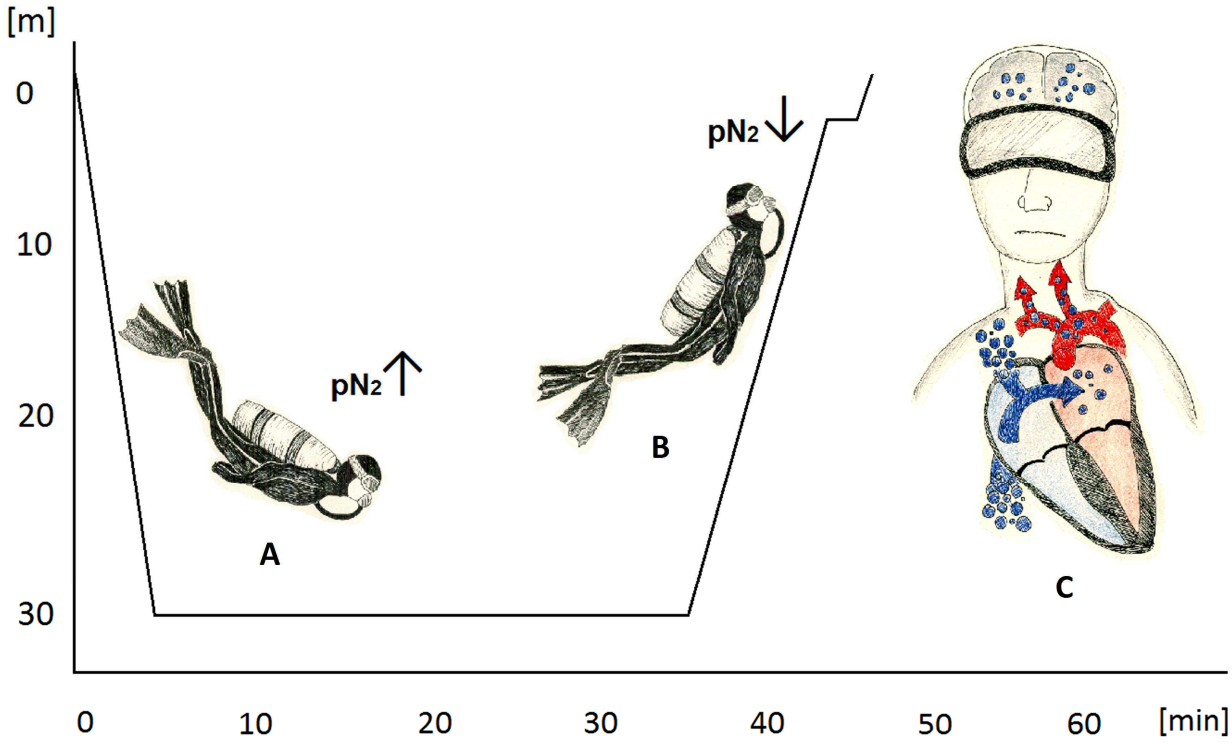

Fig. 1 – Pathophysiology of Bubble Formation and Embolization in Decompression Sickness

A dive profile of 30 m maximum depth and bottom time (time to ascent) of 35 min is depicted to demonstrate pathophysiology of bubble formation and embolization in divers. During descent, the diver breathes air at elevated ambient pressure, and excess nitrogen dissolves in tissues (A). During ascent, the ambient pressure drops and a pressure gradient drives nitrogen from tissues to venous blood (B). If the pressure drops too quickly, the tissues become supersaturated and nitrogen bubbles form and embolize through venous blood. In a diver with a PFO, a paradoxical right-to-left embolization of bubbles may occur and the bubbles lodge into peripheral capillaries (C). The resulting ischemia may manifest as decompression sickness.

The clinical picture of DCS is heterogeneous and reflects the amount of bubbles and the sites of their formation and embolization. Based on symptomatology, cutaneous, musculoskeletal, neurological and pulmonary forms of DCS are

recognized. The musculoskeletal form, manifesting as severe joint pain, is thought to be caused by local bubble formation in the avascular joint cartilage (Gempp E. et al., 2009). On the other side of the spectrum are diverse and potentially severe neurological manifestations in which it seems that bubble embolization through a PFO might play an important role.

1.3 Decompression Sickness – the Role of Patent Foramen Ovale

The connection between PFO and DCS was first described in the 1980s (Wilmhurst P.T. et al., 1986; Moon R.E. et al., 1989). Since then, a high prevalence of PFO has been repeatedly reported in divers with the neurological or cutaneous form of DCS (see Table 1). In an important study Torti et al. (Torti S.R. et al., 2004) reported an incidence of major DCS per 10,000 dives of 1.5 with no PFO, less than 1 with a grade 1 PFO, 3 with a grade 2 PFO and 9 with a grade 3 PFO. The associated odds would be 1 for a grade 1, 2 for a grade 2 and 6 for a grade 3 PFO compared to no PFO. However, this study had important limitations including its retrospective nature and possible selection bias (Germonpre P., Balestra C., 2004). In another study, the incidence of PFO was 77% among 61 divers who had suffered the cutaneous form of DCS, compared with 28% in controls (Wilmhurst P.T. et al., 2001). Additionally, besides the higher incidence of acute DCS, it has been suggested that repeated exposure to asymptomatic arterial embolisms could lead to chronic sequelae. Knauth and colleagues (Knauth M. et al., 1997) reported an association of PFO with multiple brain lesions in a follow-up study using magnetic resonance imaging. There is, however, an ongoing debate regarding whether this finding has a pathophysiological link to PFO or any clinical significance (Balestra C. et al., 2004).

Table 1 – Studies Evaluating the Presence of Patent Foramen Ovale in Divers with Decompression Sickness

Author	Year	Subjects, type of study	Main findings
Torti et al.	2004	Recreational divers (n = 230), cross-sectional study	Odds of suffering major DCS event were five times higher in divers with PFO, the risk paralleled PFO size, the overall risk was small (5 events per 10,000 dives)
Wilmhurst et al.	2001	Divers with cutaneous DCS (n = 61) vs. control divers (n = 123), case-control study	R-to-L shunt present in 77% of cases vs. 27.6% controls (p<0.01), large shunt present in 49.2% of cases vs. 4.9% controls (p<0.01)
Germonpré et al.	1998	Sports divers with neurological DCS (n = 37) vs. matched control divers (n = 37), case-control study	Prevalence of PFO was higher in subgroup of divers with cerebral DCS compared to matched controls (80% vs. 25%, p=0.01), but not with spinal DCS (35% vs. 50%, p=0.49)
Cantais et al.	2003	Consecutive divers with DCS referred for treatment in a hyperbaric chamber (n = 101) vs. control divers (n = 101), case-control study	Prevalence of PFO higher in a series of consecutive DCS cases vs. controls (59% vs. 25%, p<0.01), the proportion of major R-to-L shunt was higher in cochleovestibular and cerebral, but not in spinal and non-neurological DCS subgroups
Gempp et al.	2012	Consecutive divers with DCS referred for treatment in a hyperbaric chamber, recurrent cases (n = 24) vs. single episode (n = 50), case-control study	Diving experience, the presence of large R-to-L shunt and the lack of changes in the way of diving after prior DCS were independently associated with a repeated episode

DCS – decompression sickness, PFO – patent foramen ovale, R-to-L shunt – right-to-left shunt

Bearing in mind the high prevalence of PFO (Hagen P.T. et al., 1984), these reports raise concern among divers and involved medical professionals. Moreover, in divers with a PFO, a paradoxical embolization to the systemic circulation may cause various, mostly neurological or cutaneous DCS symptoms, even after a dive with an appropriate decompression regimen (Germonpré P., 1998). This unpredictable event has been coined “unprovoked DCS“.

Paradoxical embolization results from increased right atrial pressure due to hemodynamic changes that occur in divers. After submersion, blood redistributes from the periphery to the thorax, which results in an increased right atrial pressure (Marabotti C. et al., 2013). Moreover, divers may perform a Valsalva maneuver during or after the dive (to equalize pressure in the middle ear or while lifting heavy diving equipment), which further contributes to the increased right atrial pressure and might lead to transient right-to-left shunting through the PFO. On the other hand, it has been suggested that the transpulmonary passage might also play an important role in the occurrence of post-dive arterial gas emboli (Ljubkovic M. et al., 2012). However, the estimated prevalence of large pulmonary arteriovenous malformations is low (Cartin-Ceba R. et al., 2013) and the clinical significance of small functional shunts is doubtful (Lovering A.T. et al., 2010; Sastry S. et al., 2009). Moreover, it has been demonstrated that few post-dive bubbles reach cerebral vasculature even in divers with proven intrapulmonary arterial-venous anastomoses that open with exercise (Barak O.F. et al., 2015). Also, the numerous aforementioned clinical studies (see table 1) support the fact that PFO might be the major route of paradoxical embolization in divers. It is important to note, that a small shunt probably does not impart risk, while a large shunt should be considered to increase risk of decompression sickness. The prevalence of large PFOs is estimated to be 6-10% in

general population (Kerut E.K. et al., 2001) and the prevalence of PFO was reported to decrease with age in a large autopsy study of normal hearts (Hagen P.T. et al., 1984). On the other hand, there is some evidence for increasing patency of the foramen ovale in divers over years (Germonpre P. et al., 2005).

Theoretically, a PFO could contribute to the increased risk of DCS by other mechanisms than paradoxical embolization of nitrogen bubbles. Increased right atrial pressure in divers (Marabotti C. et al., 2013) might lead to significant shunting of nitrogen hypersaturated blood through the PFO. This blood would bypass lungs and increase nitrogen content of arterial blood and in the already hypersaturated peripheral tissues. This would lead to slower nitrogen desaturation and increased local bubble production in peripheral tissues. This mechanism was proposed by Bove (Bove A.A., 2015), but experimental data are still lacking. The possible pathophysiological involvement of PFO in DCS is summarized in Fig 2.

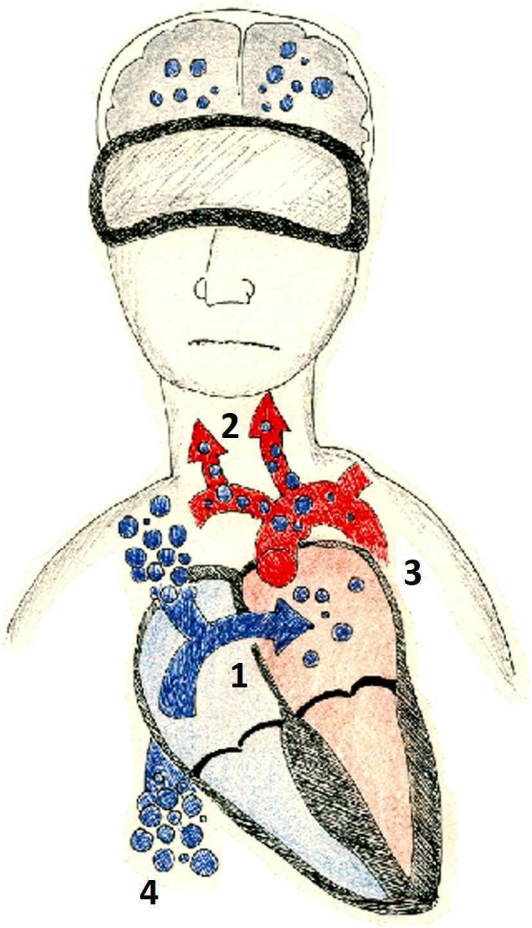

Fig. 2 – Possible Pathophysiological Role of Patent Foramen Ovale in Decompression Sickness

1 – hypersaturated venous blood containing nitrogen bubbles shunts from right to left atrium due to increased right atrial pressure, 2 – nitrogen bubbles are embolized into periphery and cause local ischemia, 3 – hypersaturated blood recirculates and increases peripheral nitrogen content, 4 – local nitrogen bubble production is increased in peripheral tissues and causes local damage, additional venous gas emboli are formed.

1.4 Patent Foramen Ovale – Diagnostic Imaging

Three ultrasonographic techniques are available for imaging of PFO or detection of right-to-left intracardiac shunts: transthoracic echocardiography (TTE), transesophageal echocardiography (TEE) and transcranial color-coded sonography

(TCCS). These methods may be used for screening, to plan and assist device closure and to monitor the presence of post-dive venous and arterial bubbles.

Transesophageal echocardiography has traditionally been considered the gold standard of PFO diagnostics (Pinto F.J., 2005). The proximity of the probe to atrial septum ensures optimal resolution and enables quality two-dimensional as well as three-dimensional imaging of PFO and surrounding structures (Fig. 3). In the diagnostic work-up of cryptogenic stroke, TEE importantly enables the visualization of other potential sources of embolism, e.g. a thrombus in the left atrial appendage or atherosclerotic lesions in the proximal aorta. On the other hand, in divers, there are several disadvantages to take into account. Especially in the context of PFO screening, both the semi-invasiveness and the cost of the procedure need to be considered. Furthermore, the patient positioning and sedation make it difficult to perform a sufficient Valsalva maneuver to visualize a shunt with the use of the contrast agent. On the other hand, if PFO closure is considered, TEE is an optimal tool to confirm the intracardiac localization of a right-to-left shunt and to reveal the anatomy. Transesophageal echocardiography is standardly used to assist trans-catheter PFO closure, although intracardiac echocardiography may be used as an alternative (Bartel T., Müller S., 2013).

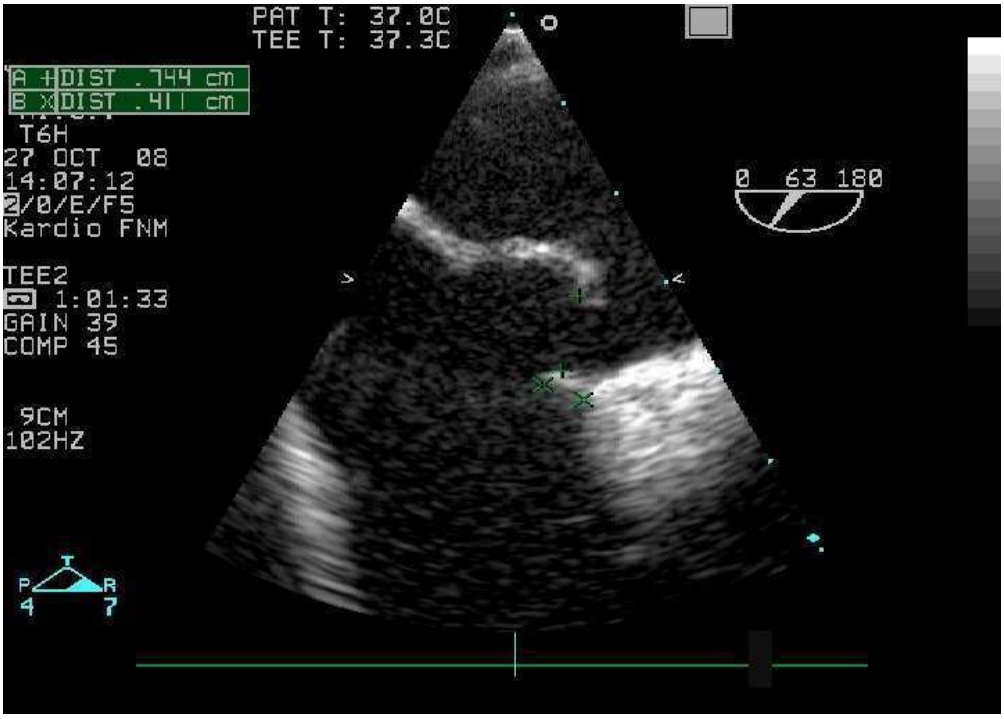

Fig. 3 – Transesophageal Echocardiography: Patent Foramen Ovale Visualization

A communication between the left and right atrium is clearly visible during Valsalva maneuvre. The diameter of the channel is measured – 0.744 cm, indicated by +.

In several studies, contrast-enhanced transthoracic echocardiography was shown to have similar sensitivity and specificity when compared to contrast-enhanced TEE (Van Camp G. et al., 2000; Thanigaraj S. et al., 2005; Clarke N.R. et al., 2004). On the other hand, in a study by Ha and colleagues (Ha et al., 2001, the sensitivity and specificity of TTE was found to be 63% and 100%, respectively, when compared to TEE as a gold standard. This would suggest that TTE could generate a significant proportion of false negative results. In addition, the spatial resolution is inferior to TEE. However, the negative results from TTE may be due to reduced sensitivity in detecting small shunts, which are not considered to be a risk. On the other hand, a potential advantage is that it is easier for the patient to perform a Valsalva maneuver. Thus, it remains to be determined whether TTE could be used as a screening tool. Besides PFO detection, TTE may be used to monitor post-dive

venous bubbles. In this setting, bubbles may be visualized in an apical four-chamber view (Fig. 4) and quantified either on still images or by using pulse-wave Doppler in the right ventricular outflow tract (Honěk J. et al., 2014; Blogg S.L. et al., 2014).

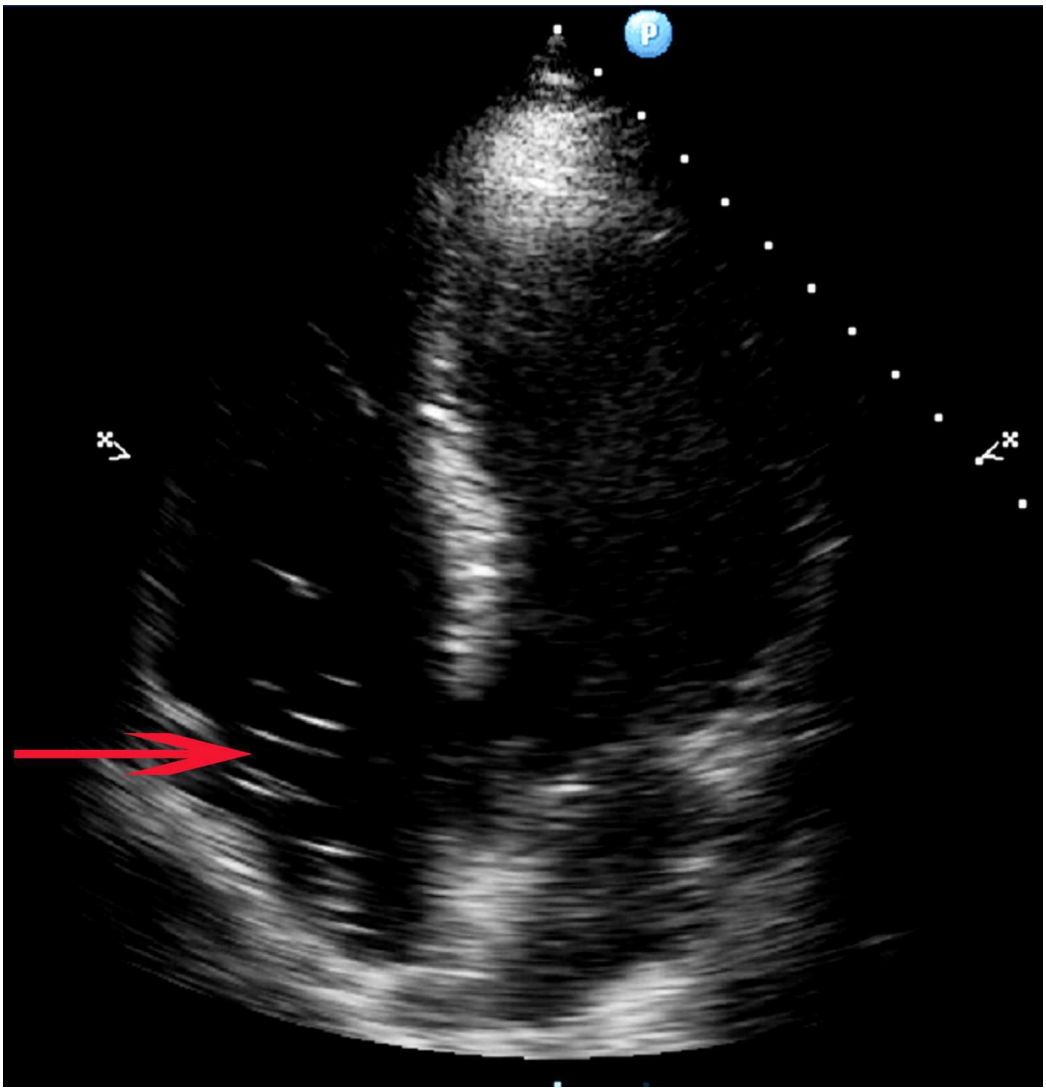

Fig. 4 – Echocardiographic appearance of post-dive venous bubbles

Transthoracic echocardiography apical four-chamber view: post-dive nitrogen bubbles (arrow) are apparent in right-sided, but not left-sided heart chambers in a diver with a patent foramen ovale and no right-to-left shunt during native breathing.

Transcranial color-coded sonography visualizes blood flow in the middle cerebral artery (MCA) through a temporal window in the skull. A pulse wave Doppler study is used to detect gas bubbles (either post-dive nitrogen bubbles or

microbubbles of ultrasonographic contrast) as high-intensity transient signals (HITS) (Fig. 5). The presence of HITS confirms right-to-left shunting. The localization of the shunt may be intracardiac or transpulmonary. The transpulmonary passage is longer and the bubbles usually appear after >15 cardiac cycles following the administration of ultrasonographic contrast (Sastry S. et al., 2009). When using standardized protocols, a sensitivity of 94-100% and specificity of 75-100% compared to TEE has been reported (Sastry S. et al., 2009; Droste D.W. et al., 2004). This makes TCCS a valuable screening tool. A possible concern is that the temporal window may be inadequate to visualize reliably the MCA in 10-12% of patients (Postert T. et al., 1997). However, this is dependent on the examiner, the sonographic equipment and the age of the patients (Spacek M. et al., 2014). Therefore, this might not be a limitation in young healthy subjects, such as most recreational and professional divers (Honěk J. et al., 2014). For screening, agitated saline or hydroxyethyl starch solutions or a dedicated contrast agent may be used (Droste D.W. et al., 2002). The monitoring for HITS should be performed according to a standardized protocol at rest and after a Valsalva maneuver (Jauss M., Zanette E., 2000). The shunt is graded as follows: 0 - no HITS, 1 - <10 HITS, 2 - >10 HITS but no curtain (uncountable number of bubbles), and 3 – curtain (Jauss M., Zanette E., 2000). Post-dive arterial gas bubbles may be assessed in the same manner. However, to date, there is no standardized protocol for this application. We suggest monitoring the MCA flow for 60 seconds during native breathing and subsequently three times for 40 seconds after a Valsalva maneuvre (Honěk J. et al., 2014).

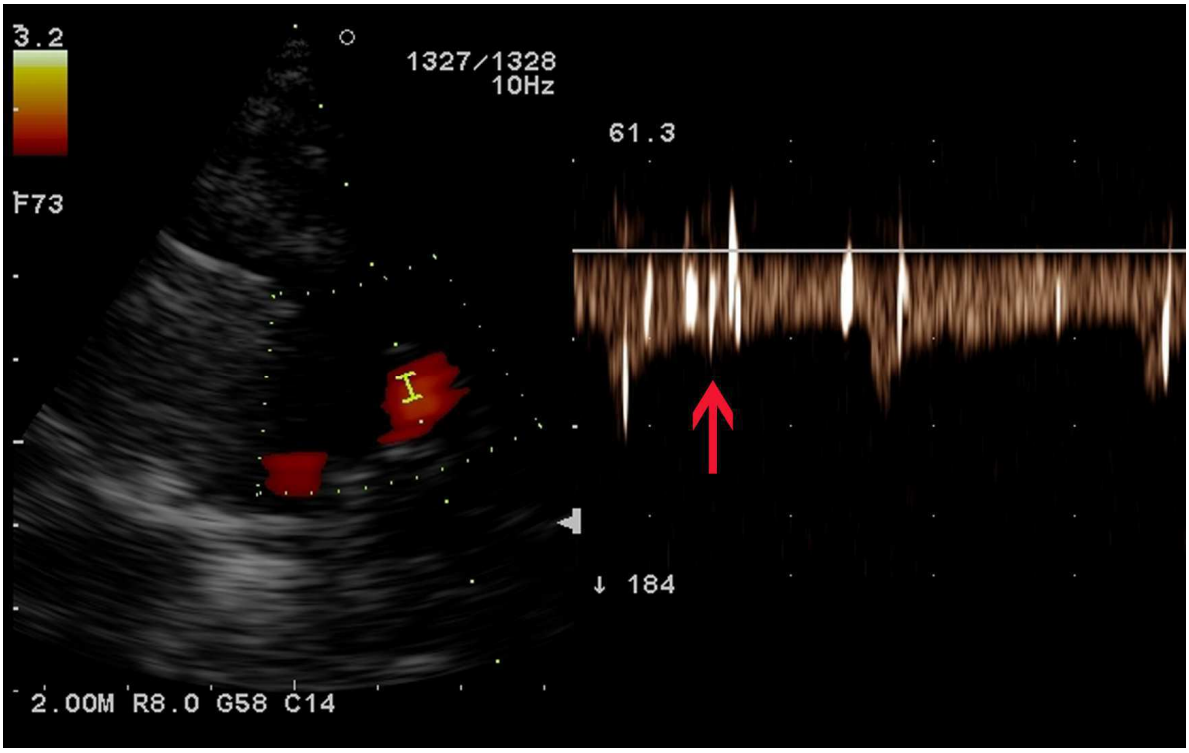

Fig. 5 – Arterial gas emboli visualized by transcranial Doppler ultrasonography

Transcranial Doppler ultrasonography: post-dive arterial gas emboli apparent as high-intensity transient signals (arrow) in the Doppler spectrum in the middle cerebral artery in a diver with a patent foramen ovale

1.5 Patent Foramen Ovale – Therapeutic Options

There is still a large knowledge gap with regards to the optimal risk stratification and management strategy in divers with a PFO. Routine screening for PFO in divers is currently not recommended in most countries (Undersea and Hyperbaric Medical Society, 2011; Torti S.R. et al., 2007). Suggested recommendations for divers with diagnosed PFO and a history of DCS include the cessation of diving, a conservative approach to diving, and PFO closure. However, to date there were no data that could guide our clinical decisions.

It has been suggested by several authors that a catheter-based PFO closure in divers might eliminate the arterialization of bubbles and prevent

unprovoked DCS (Billinger M. et al., 2011; Walsh K.P. et al., 1999; Lairez O. et al., 2009). However, so far there was no evidence to support the efficacy of catheter-based PFO closure on neither the reduction of arterial bubble counts nor the incidence of clinical overt DCS.

Similarly, although often advised, there were no data that would prove the efficacy of conservative dive profiles (CDP) for divers with a PFO. Conservative dive profiles are measures aiming to lower the probability of nitrogen bubble formation in order to decrease the risk of DCS. The probability of tissue supersaturation and subsequent bubble formation can theoretically be lowered by both minimizing tissue saturation (i.e. limiting nitrogen exposure) and allowing more time for the desaturation of tissues. To lower nitrogen exposure, various CDP recommendations limit maximum depth, dive time, number of dives per day or advise the use of mixtures with lower nitrogen content (enriched air nitrox) (Gempp E. et al., 2012; Klingmann C. et al., 2012). Similarly, to allow more time for desaturation, a slower ascent rate and performing longer safety stops is recommended (Klingmann C. et al., 2012). There is some evidence that pre-dive hydration and pre-dive exercise reduce the risk of DCS (Gempp E., Blatteau J.E., 2010).

2 Hypothesis

Arterialization of post-dive VGE through a PFO plays an important role in the pathophysiology of DCS and its prevention will decrease the incidence of unprovoked DCS.

3 Aims and Objectives

The aim of our research is to elucidate the pathophysiological role of PFO in decompression sickness.

In order to achieve the aims of the project we will:

1) Perform screening for the presence of PFO in a large population of Czech professional and recreational divers and assess their risk of unprovoked DCS.
2) Perform simulated dives in a hyperbaric chamber to compare the occurrence of venous and arterial gas emboli while using different decompression regimens in divers with a PFO.
3) Perform simulated dives in divers with a PFO and after catheter-based PFO closure in order to determine the effect of PFO closure on the occurrence of venous and arterial gas emboli.
4) Perform simulated dives with conservative profiles in divers with a PFO in order to determine the effect of these procedures on the occurrence of venous and arterial gas emboli.
5) Compare the efficacy of conservative dive profiles and catheter-based PFO closure on reduction of post-dive AGE.

4 Materials and Methods

4.1 Patients

A total of 489 consecutive divers were screened for PFO at our center between January 2006 and January 2014. TCCS was used for screening, the diagnosis of PFO was confirmed by TEE. The right-to-left shunt was graded by means of TCCS according to the International Consensus Criteria (Jauss M., Zanette E., 2000): (grade 1) 1-10 bubbles, (grade 2) >10 bubbles but no curtain (uncountable number of bubbles), (grade 3) curtain. Baseline data (demographic data, diving experience, DCS history) were collected from all divers in the time of the screening examination.

4.2 Simulated Dives

Simulated dives were performed in a hyperbaric chamber (HAUX Life Support, Karlsbad-Ittersbach, Germany) (Fig. 6) according to the Bühlman (Bühlman A.A., 1983) or US Navy decompression regimen (United States Navy, 2008), respectively.

In order to test the effect of catheter-based PFO closure on reduction of AGE, decompression dives according to the US Navy Air Decompression Procedure Revision 6 (United States Navy, 2008) were used. This decompression procedure was previously reported to generate significant amounts of venous and arterial gas emboli but no acute DCS symptoms (Ljubkovic M. et al., 2011; Valic Z. et al., 2005). (5,19). Two dive profiles were used. The divers chose one of the two simulated dives that best corresponded to their usual diving practice. Thirty-four divers performed a dive to 18 m with a bottom time of 80 min (dive A). The descent and ascent rate was equivalent to 9 m/min; the decompression stop was performed at 3 m for 7 min.

Thirteen divers performed a dive to 50 m with a bottom time of 20 min (dive B). The descent and ascent rate was 9 m/min; decompression stops were performed at 6 m for 4 min and at 3 m for 15 min.

In order to test the efficacy of CDP we chose three dives to the same maximum depth of 18 m with different decompression procedures. Divers were randomized into three groups: group A performed a standard Bühlmann regimen no-decompression dive (dive time 51 min, ascent rate 10 m/min), group B performed the same regimen with a slower ascent (51 min, 5 m/min), and a control group performed a staged-decompression dive according to the US Navy decompression regimen (80 min, 9 m/min, decompression stop 7 min at 3 m).

Fig. 6 – Hyperbaric Chamber

4.3 Post-Dive Bubble Detection and Symptom Assessment

Venous and arterial gas emboli were monitored within 60 min after surfacing (Carturan D. et al., 2002). In all divers the incidence of DCS symptoms was evaluated.

Venous gas emboli were assessed by experienced echocardiographers using TTE. An ultrasound system, Philips HD-10, with a 2–3.7 MHz multifrequency probe (Philips, Amsterdam, the Netherlands) was used. Bubbles were visualized by pulse wave Doppler in the right ventricular outflow tract from the parasternal short axis view and their detection was performed for 1 min. The test was considered positive if one or more bubbles were detected.

Arterial gas emboli were detected by means of TCCS in the middle cerebral artery, as previously described (Blersch W.K. et al., 2002). An experienced neurologist, who was blinded to whether the diver had a PFO or the PFO was previously occluded by a catheter-based device, performed the examination. The same ultrasound equipment as for the echocardiographic examination was used. Bubbles were detected for 1 min during native breathing and subsequently three times for 40 s after a Valsalva maneuver. The test was considered positive if one or more bubbles were detected.

The divers were observed and questioned for any DCS symptoms, with special attention to any neurological or cutaneous manifestations. If symptoms occurred, immediate treatment in a hyperbaric chamber was administered. Treatment table 5 of the United States Navy Diving Manual Revision 6 (United States Navy, 2008) was used as the treatment protocol.

4.4 Catheter-Based Patent Foramen Ovale Closure

The PFO closure procedures were performed in a single center (with the exception of two divers) between February 1, 2006 and April 30, 2013. The Amplatzer septal occluder (AGA Medical Corporation, Golden Valley, MN) was used in 5 (25%) divers. In the remaining 15 (75%) cases, the Occlutech Figulla PFO

Occluder N (Occlutech GmbH, Jena, Germany) was used. The procedure was performed as previously described (Meier B., 2005). In all divers, the indication for the procedure was a history of unprovoked DCS (i.e., without violation of decompression regimen) and the presence of a grade 3 PFO according to the International Consensus Criteria (Jauss M., Zanette E., 2000). There were no major complications, bleeding at the puncture site with no need of intervention occurred in one patient (5%).

4.5 Definitions

Arterial gas emboli were defined as HITS in the Doppler spectrum detected by TCCS in the middle cerebral artery (Blersch W.K. et al., 2002). Venous gas emboli were defined as HITS in the Doppler spectrum detected by TTE in the right ventricular outflow tract. Neurological symptoms of DCS were defined as headache, unusual fatigue, visual problems, limb weakness or paralysis, dizziness and paresthesia reported by the patient ≤24 h after the simulated dive. A history of unprovoked DCS was defined as any DCS symptoms that originated ≤24 h after a dive that complies to all rules advised to recreational divers (no decompression air dive performed within the limits of any commercially available recrerational diving table or computer, maximum depth 40 m, maximum ascent rate 10 m/min, safety stop performed as advised by computer/table).

4.6 Statistical Analysis

The distribution of data was evaluated by the Kolmogorov-Smirnov test. For categorical variables Fisher's test or $\chi 2$ test were used when appropriate. For

continuous variables the Kruskal-Wallis test and the Mann-Whitney U test were used when appropriate. Normally distributed data are presented as mean ± standard deviation (SD) and non-normally distributed data as median with interquartile range (IQR). A p-value of ≤ 0.05 was considered to indicate a statistically significant difference.

To assess for risk factors of unprovoked DCS the associations between variables and DCS endpoint were evaluated using survival analysis techniques. We used Cox proportional hazards models to compute a hazard ratio (HR) with 95% confidence interval (CI), both unadjusted and adjusted, for the potential confounding covariates. Total sum of dives value was used as a measure of time.

Due to the possibility of numerically unstable estimates and large standard error, we did not include all available covariates in the final Cox proportional hazards model. Therefore, a backward stepwise elimination algorithm with a likelihood ratio statistic to minimize the exclusion of predictors involved in suppressor effects was used. Variables with a p value ≤ 0.1 on univariate testing were included in the elimination algorithm. Goodness of fit of the model was tested with the Grønnesby and Borgan test for the Cox proportional hazards model, with the number of risk groups based on May and Hosmer.

Additionally, Kaplan-Meier survival curves were created and log-rank statistics were calculated. Schoenfeld residuals were calculated for all models to assess a significant departure from the model assumption.

All statistical analyses were done using GraphPad Prism 6 (GraphPad Software Inc., La Jolla, CA, USA) and IBM SPSS Statistics 23.0 (IBM, USA).

5 Results

5.1 Risk Factors of Unprovoked Decompression Sickness

A total of 489 divers were screened for the presence of a right-to-left shunt from January 2006 to January 2014 by means of TCCS. The screening program was offered to all registered Czech diving clubs, to professional police and firefighter divers and was regularly promoted through diving magazines, websites, instructor courses and diving and hyperbaric medicine meetings. Baseline data (demographic data, diving experience, DCS history) were collected from all divers in the time of the screening examination. The screening program is the main focus of the doctoral thesis of co-author Martin Šrámek, MD, who is also preparing the data for publication. Here we analyze the risk factors of unprovoked DCS. Survival analysis was used to identify the risk factors for unprovoked DCS.

Of the 489 divers (35.53 ± 8.95 years, 86.5% men) screened, 36 (7%) suffered from unprovoked DCS. The risk of unprovoked DCS was significantly higher in divers with a PFO according to the results of the log-rank test of the Kaplan-Meier analysis: $\chi 2$ (1) = 49.068, $p < 0.001$ (Fig. 7). Hazard ratio (HR) for unprovoked DCS in divers with a PFO was 52.371 (95% CI 7.173 - 382.382, $p < 0.001$). The prevalence of PFO was 97.2% in divers with a history of unprovoked DCS and 35.5% in controls ($p < 0.001$). There was no difference in sex, age, body mass index, and total number of dives between the respective groups. The results are summarized in table 2.

Table 2 – Results

Group	All divers (n = 489)	Controls (no unprovoked DCS) (n = 453)	Unprovoked DCS (n = 36)	Significance, p (DCS vs. controls)
Dives – total, mean (SD)	169 411, 346.44 (635.566)	156 693, 345.90 (647.689)	12 718, 353.28 (463.157)	0.17
Age (years) – mean (SD)	35.53 (8.950)	35.46 (9.051)	36.36 (7.628)	0.22
Male sex, total (%)	423 (86.5%)	393 (86.8%)	30 (83.3%)	0.61
BMI (kg/m2) – mean (SD)	26.09 (3.17)	26.09 (3.14)	26.18 (3.62)	0.99
PFO	196 (40.1%)	161 (35.5%)	35 (97.2%)	**< 0.001***
PFO 3	111 (22.7%)	80 (17.7%)	31 (86.1%)	**< 0.001***

DCS – decompression sickness, PFO – patent foramen ovale, BMI – body mass index, SD – standard deviation, * indicates a statistically significant difference.

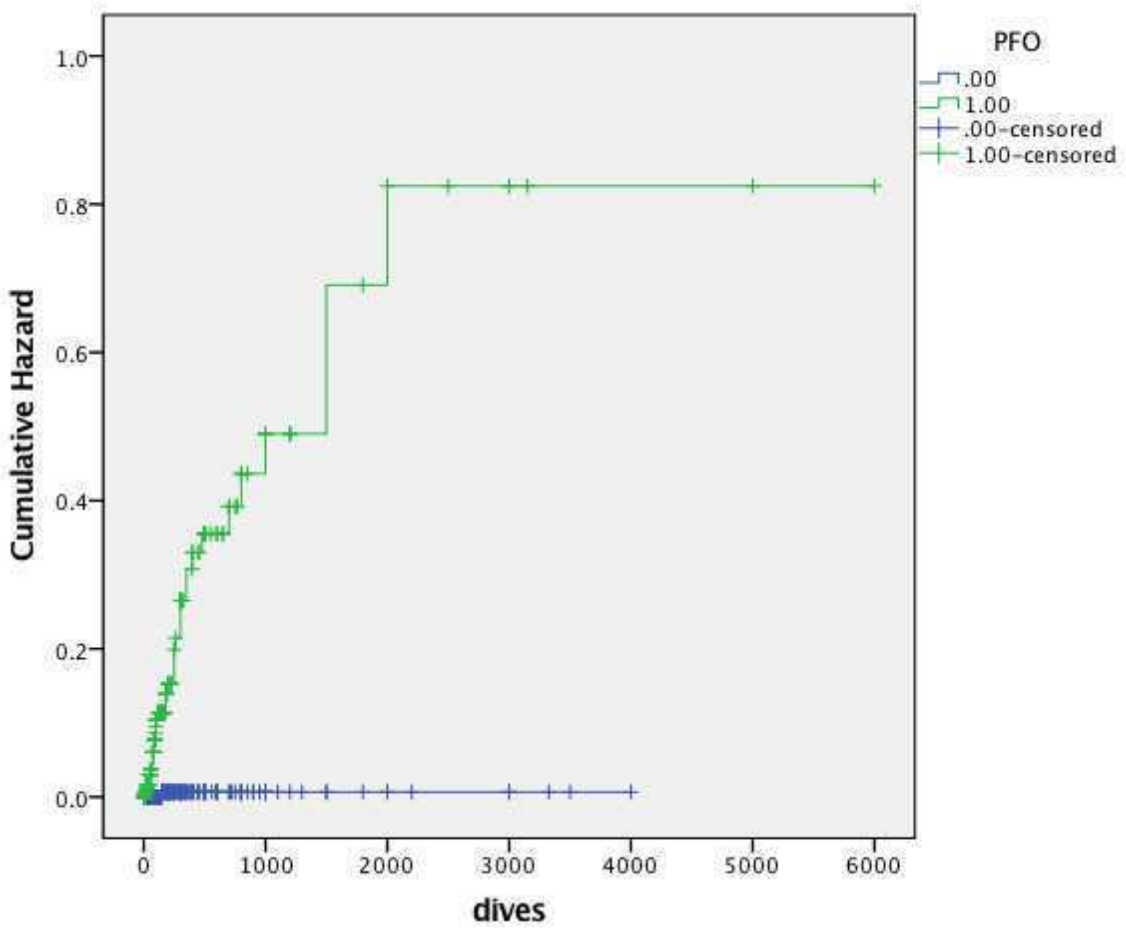

Fig. 7 – Kaplan Meier analysis - cumulative hazard of unprovoked decompression sickness in divers with and without a patent foramen ovale (PFO)

5.2 Study 1 – Comparison of Bühlmann and United States Navy Decompression Regimen

The aim of the study was to test the risk of paradoxical embolism of nitrogen bubbles after simulated dives in divers with a patent foramen ovale (PFO), and to compare the safety of commonly used decompression regimens. In 31 divers, previously diagnosed with a PFO, we detected VGE using TTE and AGE using TCCS after surfacing from simulated dives in recompression chamber. Three different

decompression procedures were compared – Bühlmann 18 m, US Navy 18 m and US Navy 50 m (Bühlman A.A., 1983; United States Navy, 2008).

In the Bühlmann 18m regimen, VGE were detected in 3 (21%) divers, no AGE (0%) were detected. In the US Navy 18 m regimen VGE were detected in 6 (67%) divers, AGE were found in 2 (22%) divers. In the US Navy 50 m regimen venous bubbles were detected in 7 (88%), AGE in 6 (75%) divers. Significantly lower number of VGE was detected after Bühlmann regimen dives (recommended for recreational diving in the Czech Republic) compared with the US Navy regimen dives (21% vs. 76%, p = 0.004).

5.3 Study 2 – Efficacy of Catheter-Based Patent Foramen Ovale Closure

In this study VGE and AGE were assessed by means of ultrasound in 47 divers (35±8.6 yrs, 81% males) after surfacing from a simulated dive in hyperbaric chamber. The divers chose between two dive profiles (Dive A or B). Thirty-four divers performed a dive to 18 m with a bottom time of 80 min (dive A). The descent and ascent rate was equivalent to 9 m/min; the decompression stop was performed at 3 m for 7 min. Thirteen divers performed a dive to 50 m with a bottom time of 20 min (dive B). The descent and ascent rate was 9 m/min; decompression stops were performed at 6 m for 4 min and at 3 m for 15 min. All divers had a large PFO (grade 3 according to the International Consensus Criteria) and previously suffered from DCS; in 20, the PFO was occluded with a catheter-based device (closure group), the other 27 divers did not undergo any closure procedure (PFO group).

There was no difference in VGE occurrence between the closure and PFO groups (80% vs. 74%, p = 1.0 for Dive A; 100% vs. 88%, p = 1.0 for Dive B, respectively). In the PFO group AGE were detected in 32% divers after dive A and

88% after dive B. Neurological symptoms of DCS were observed in 21% and 25% of divers in dive A and B, respectively. No divers in the closure group had post-dive AGE after both dives (Figs. 8 and 9). Also, none of these divers had DCS symptoms. However, the reduction in DCS incidence did not reach statistical significance. The occurrence of post-dive venous and arterial bubbles after dive A and B are summarized in Figs. 8 and 9, respectively.

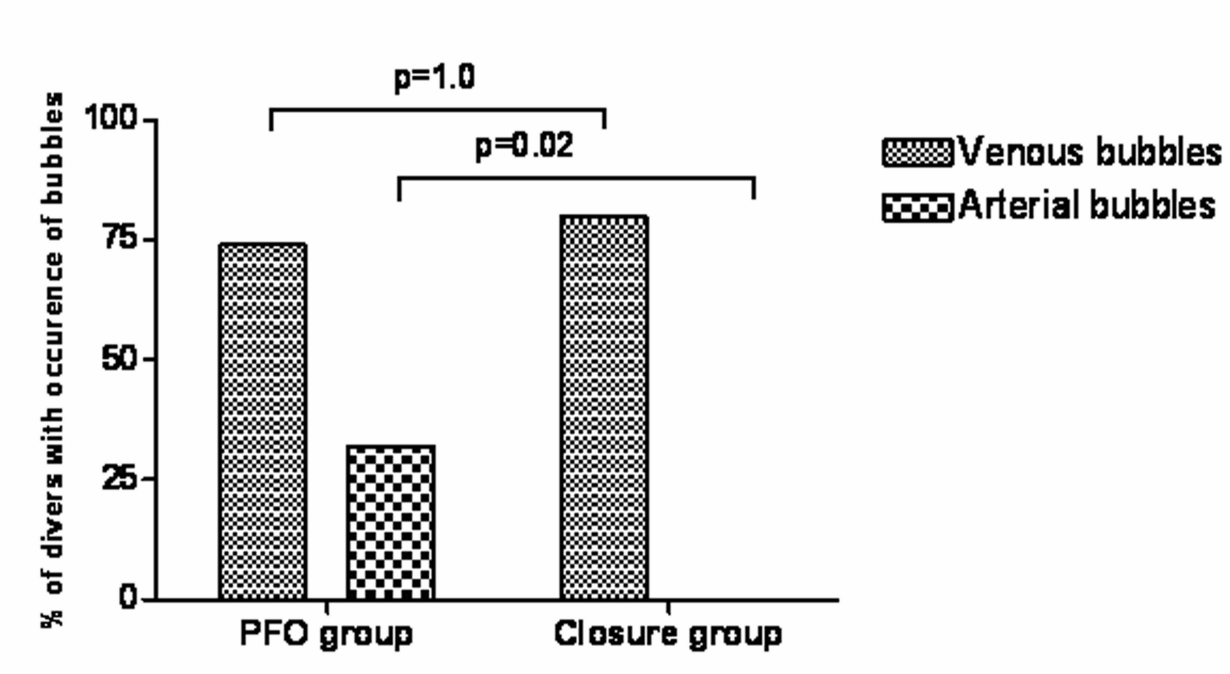

Fig. 8 – Occurrence of Arterial and Venous Gas Emboli after Dive A

The proportion of divers with the occurrence of venous and arterial gas emboli (bubbles) after dive A in divers with a patent foramen ovale (PFO group) and divers treated with a catheter-based patent foramen ovale closure (closure group). Dive A was a dive to 18 m, 80 min bottom time, 9 m/min ascent rate, decompression stop 7 min at 3 m.

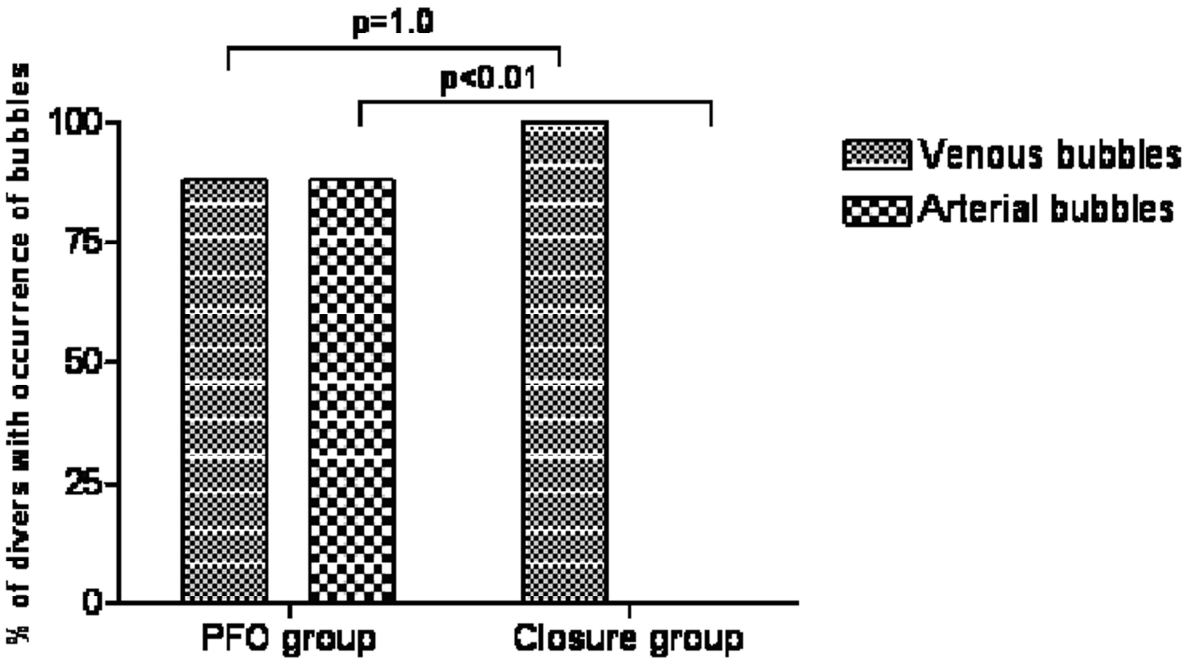

Fig. 9 – Occurrence of Arterial and Venous Gas Emboli after Dive B

The proportion of divers with the occurrence of venous and arterial gas emboli (bubbles) after dive B in divers with patent foramen ovale (PFO group) and divers treated with a catheter-based patent foramen ovale closure (closure group). Dive B was a dive to 50 m, 20 min bottom time, 9 m/min ascent rate, decompression stops 4 min at 6 m and 15 min at 3 m.

5.4 Study 3 – Efficacy of Conservative Dive Profiles

In this study VGE and AGE were assessed by means of ultrasound in 46 divers (36.4 ± 10 years; 72% men) with a grade 3 PFO. All divers performed a simulated dive to 18 m in a hyperbaric chamber. Divers were randomized into three groups: group A (n = 13; 36.5 ± 9 years; 77% men) performed a standard Bühlmann regimen no-decompression dive (dive time 51 min, ascent rate 10 m/min), group B (n = 14, 40.9 ± 12 years; 64% men) performed the same regimen with a slower ascent (51 min, 5 m/min), and a control group (n = 19; 33.0 ± 8 years; 74% men) performed a staged-decompression dive according to the US Navy decompression regimen (80

min, 9 m/min, decompression stop 7 min at 3 m). There was significantly lower occurrence of VGE in group A and B compared to controls (for group A, 31% vs. 74%, p = 0.03; for group B, 14% vs. 74%, p < 0.01). The reduction in AGE occurrence was not significant in group A compared to controls, but there was elimination of AGE in group B (for group A, 8% vs. 32%, p = 0.42; for group B, 0% vs. 32%, p = 0.03). There was no significant difference in the occurrence of venous or arterial gas emboli between groups A and B (venous, 31% vs. 14%, p = 0.38; arterial, 8% vs. 0%, p = 0.48). In the control group transient neurological symptoms (headache, unusual fatigue, transitory visual disturbances) were present in 21% of divers, no DCS symptoms were observed in groups A (p = 0.13) or B (p = 0.12). The occurrence of arterial and venous gas emboli is summarized in Fig. 10.

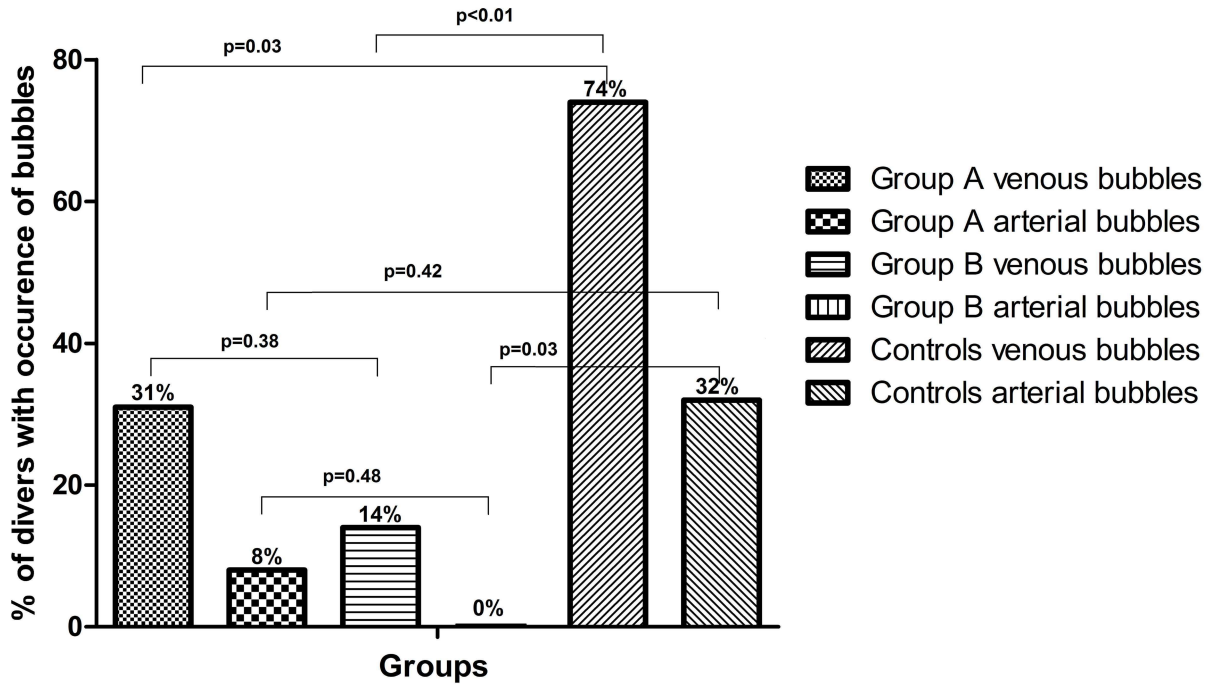

Fig. 10 – Summary of the Occurrence of Post-Dive Venous and Arterial Gas Emboli.
Group A - standard Bühlmann regimen no-decompression dive (maximum depth 18 m, dive time 51 min, ascent rate 10 m/min), Group B - (18 m, 51 min, 5 m/min), Controls - US Navy decompression regimen (18 m, 80 min, 9 m/min, decompression stop 7 min at 3 m)

5.5 Study 4 – Comparison of Conservative Diving and Catheter-Based Patent Foramen Ovale Closure

In this study we pooled and analyzed data form our previous studies (Honěk J. et al., 2014a; Honěk J. et al., 2014b) in order to compare the efficacy of conservative diving and catheter-based PFO closure. This yielded a total of 47 divers with a PFO. Nineteen divers with a PFO performed a decompression dive to 18 m for 80 min (control group), 15 divers after a catheter-based PFO closure performed the same dive (group 1) and 13 divers with a PFO performed a dive to the same depth for a non-decompression time of 51 min (group 2). Venous gas emboli were detected in 74% of divers in the control group, in 80% in group 1 (p = 1.0) and in 31% in group 2 (p = 0.03). Arterial gas emboli were found in 32% of divers in the control group, in 0% in group 1 (p = 0.02), in 15% in group 2 (p = 0.42). The results are summarized in Fig. 11.

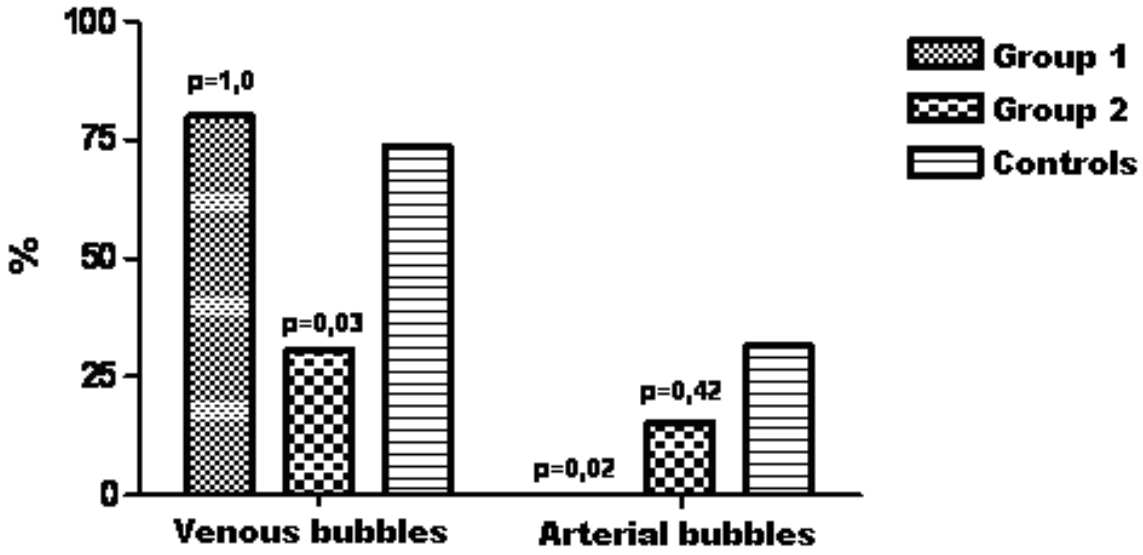

Fig. 11 – Summary of the Occurrence of Post-Dive Venous and Arterial Gas Emboli.
Group 1 – divers after catheter-based PFO closure, US Navy decompression regimen (18 m, 80 min, 9 m/min, decompression stop 7 min at 3 m), Group 2 – divers with a PFO, Bühlmann regimen no-decompression dive (maximum depth 18 m, dive time 51 min, ascent rate 10 m/min), Controls – divers with a PFO, US Navy decompression regimen (18 m, 80 min, 9 m/min, decompression stop 7 min at 3 m).

6 Discussion

Decompression sickness is known to be caused by nitrogen bubble formation during the diver's ascent (Vann R.D. et al., 2010). The diver is exposed to an elevated pressure of nitrogen when breathing compressed air during the submersion. This excess nitrogen dissolves in all tissues. The total nitrogen load is determined by the depth profile and the duration of the dive. During the ascent and hours after the dive, the excess gas is transported from the tissues back to the alveoli and exhaled. If the diver reaches the surface too early, the tissues get hypersaturated and intravascular and extravascular bubbles form and increase in size (Vann R.D. et al., 2010). To prevent DCS, divers perform the ascent according to decompression tables or a decompression algorithm implemented in a diving computer.

Despite these preventive measures, small numbers of intravascular bubbles can be ultrasonographically detected in venous blood even after a properly performed dive (Dunford R.G. et al., 2002). These bubbles are usually asymptomatic because most of the time, they are effectively filtered by the pulmonary circulation (Vann R.D. et al., 2010). However, some divers experience a DCS without any violation of the decompression regimen, an event that has been termed unprovoked DCS.

The concept, that a small number of bubbles embolizing to the systemic circulation through the PFO could cause DCS, was mentioned already in the 1980s (Wilmhurst P.T. et al., 1986; Moon R.E. et al., 1989). Several retrospective studies confirmed higher incidence of PFO in symptomatic divers (see table 1) in the two following decades. However, the role of PFO in the pathophysiology of DCS has since then been largely debated. To date there were no studies that would confirm

the hypothesis that the reduction of the number of AGE would decrease the risk of DCS. In addition, to date no studies focused specifically on unprovoked DCS.

We screened a relatively large population of Czech divers (N=489) and found that the prevalence of unprovoked DCS was 7%. The prevalence of PFO and, importantly, high-grade PFO was high in patients with a history of unprovoked DCS. There was no difference in sex, age, body mass index and total number of dives between the respective groups. Patent foramen ovale was found to be the only risk factor of unprovoked DCS using Cox proportional hazards model. To our knowledge, this is the first study to asses for risk factors of unprovoked DCS. However, some previous studies have focused on risk factors of DCS in general.

Traditionally, age, body mass index and repetitive diving were considered risk factors of DCS. Carturan and colleagues monitored 50 divers after two dive profiles and found ascent rate, age, aerobic fitness, and adiposity to be associated with higher post-dive VGE occurrence (Carturan D. et al., 2002). In a study performed by the Divers Alert Network (DAN) 67 recreational divers were monitored for two years for Doppler-detected VGE (Dunford R.G. et al., 2002). The incidence of high-bubble grade was approximately 20% higher for repetitive dives than for first dives, approximately 20% higher for males than females, also increased with age (by 25% in male and 55% in female divers, respectively). In a retrospective observational study male divers were also in higher risk of DCS, although this might have been influenced by their diving habits (St Leger Dowse M. et al., 2002). On the other hand, Gempp and colleagues found results similar to ours in a small case-controlled study of divers with recurrent DCS (Gempp E. et al. 2012). They found right-to-left shunt and lack of changes in the way of diving after prior DCS as the only predictors of neurological DCS recurrence. Age, gender and diving experience were not

associated with recurrent neurological DCS. Together with our results this suggests that PFO might play a more important role in at least a subset of DCS such as the neurological form or in unprovoked episodes.

In our experimental studies we focused on divers with a PFO in whom we assessed for post-dive VGE and AGE after various simulated dives in a hyperbaric chamber. In the first experimental study we assessed for post-dive VGE and AGE in divers with a PFO after Bühlmann and US Navy decompression regimen dives. Significantly lower number of VGE was detected after the Bühlmann regimen (recommended for recreational diving in the Czech Republic) compared with the US Navy regimen (21% vs. 76%, p=0.0038). The US Navy decompression regimen is characterized by a higher nitrogen exposure and a shorter decompression procedure. This led to a higher percentage of divers with venous and arterial emboli, as expected. Importantly however, even after the very conservative 18m Bühlmann dive, that would typically be performed by recreational divers, bubbles were found in 21% of the participants. Ljubkovic and colleagues found VGE in 75% of divers after an 18m dive with a slightly longer bottom time (60 min) and shorter decompression (no safety stop at 3 meters) performed according to the Norwegian Diving Tables (Ljubkovic M. et al., 2011). Similarly, Dunford and colleagues found VGE in 91% recreational divers (Dunford R.G. et al., 2002). However, in this study the divers participated in a multi-level multi-day repetitive recreational diving activity. The high incidence of VGE after repetitive dives and the relatively high incidence of VGE after a simulation of a single recreational dive, found in our study, might support the hypothesis that recreational scuba divers with a PFO might be susceptible to the occurrence of unprovoked DCS. On the other hand, we have not observed any arterial bubbles or DCS symptoms in this group. This could suggest that the amount

of the bubbles formed is generally low and other factors might play role in the sporadic occurrence of unprovoked DCS, such as differences in the level of pre-dive hydration or pre-dive exercise (Gempp E., Blatteau J.E., 2010).

In the second experimental study we demonstrated the effect of catheter-based PFO closure on the occurrence of AGE after simulated dives to 18 and 50 meters, respectively. No difference was found in the occurrence of VGE between divers with a high-grade PFO (PFO group) and divers after trans-catheter PFO closure (closure group). However, only in the closure group no AGE were detected. Moreover, in the deeper dive, where the nitrogen load was greater, AGE were observed in all divers with a PFO and detected VGE. Twenty-nine percent of these divers had cerebral DCS symptomatology. This is in agreement with a previous case-controlled study by Germonpré and colleagues (Germonpré P. et al., 1998), who found high prevalence of high-grade PFO in divers suffering from unprovoked cerebral DCS. In our study, no divers in the closure group had DCS symptoms after either the 18-m or the 50-m dive. It is plausible, therefore, that the presence of a PFO plays a key role in paradoxical embolization of venous bubbles after scuba dives and its catheter based-closure might have an effect in the prevention of unprovoked DCS recurrence in divers. This preventive strategy has previously been suggested by several authors (Billinger M. et al. 2011; Walsh K.P. et al., 1999; Lairez O. et al., 2009). However, to date there was a lack of any data in this field.

Other research groups have suggested that the transpulmonary passage might also play an important role in the occurrence of post-dive AGE. Ljubkovic and colleagues observed arterial bubbles in 9 of 34 divers who tested negative for PFO and argued that transpulmonary arterialization would occur if a large amount of bubbles were produced and an individual exhibited a higher susceptibility for the

transpulmonary passage (Ljubkovic M. et al., 2012). This was not observed in the closure group in our study, where no arterial emboli were detected, despite the fact that the occurrence of VGE was not different from the PFO group. Also, clinical studies support the fact that PFO might be the major route of paradoxical embolization in divers. Torti et al. reported that the odds of suffering a major DCS were 5x higher in divers with a PFO and that the risk paralleled PFO size (Torti S.R. et al., 2004). Wilmhurst et al. found that the incidence of PFO was 77% among 61 divers who had suffered the cutaneous form of DCS, compared with 28% in control subjects (Wilmhurst P. T. et al., 2001).

Theoretically, a PFO could contribute to the increased risk of DCS by other mechanisms than paradoxical embolization of nitrogen bubbles. Increased right atrial pressure in divers (Marabotti C. et al., 2013) might lead to significant shunting of hypersaturated blood through the PFO and thus slower nitrogen desaturation and increased local bubble production in peripheral tissues (Bove A.A., 2015). In our study there was no difference in VGE occurrence between the PFO and closure groups. However, our ultrasonographic methodology did not allow to asses venous bubble count as a continuous variable.

The absence of symptom-based clinical endpoints is the main limitation of this observational study. A randomized prospective follow-up trial would be necessary to assess the clinical relevance of catheter-based PFO closure in divers. Another potential limitation is the experimental setting of the study. There is some evidence that wet dives generate more venous bubbles than dry dives do (Møllerløkken A. et al., 2011). In our study, only the 18-m dive was a dry dive, in the 50-m dive, the divers were submersed in a water reservoir inside the hyperbaric chamber using their usual scuba equipment.

In the third experimental study we sought to determine the incidence of post-dive VGE and AGE after conservative dive profiles. We compared three different dives to a maximum depth of 18 m. Divers were randomized into three groups. The first dive represented usual recreational diving practice, the divers performed a standard Bühlmann regimen no-decompression dive (18 m, 51 min, ascent rate 10 m/min). The second group performed dive with the same depth and bottom time (18 m, 51 min) with a slower ascent rate (5 m/min). The control group performed a staged-decompression dive according to the US Navy decompression regimen (18 m, 80 min, 9 m/min, decompression stop 7 min at 3 m). This was a dive used in our previous experiments and generated significant amount of VGE. There was significantly lower occurrence of venous bubbles in the Bühlmann regimen dives compared to controls. However, AGE were eliminated only in the conservative dive with a slower ascent rate. Transient neurological symptoms (headache, unusual fatigue, transitory visual disturbances) were present only in the control group. This study is to our knowledge the first study to date to test the efficacy of conservative dive profiles on the reduction of arterial and venous gas emboli in divers with a PFO. It is plausible that slower ascent rate would decrease the incidence of unprovoked DCS in this group of divers as we have observed a significantly reduced occurrence of both VGE and AGE. However, we have to bear in mind that the incidence of unprovoked DCS is low and a larger-scale clinical study would be needed to confirm this hypothesis. In a small observational study by Klingmann and colleagues the incidence of DCS decreased after recommendation of conservative diving in divers with and without a right-to-left shunt (Klingmann C. et al., 2012). This study followed 27 divers with a history of previous DCS for a mean of 5.3 years.

The effectivity of conservative dive profiles and catheter-based PFO closure was compared in the fourth study. In this study we demonstrated that a conservative dive profile using the Bühlmann regimen does not lead to the complete AGE elimination, that can be achieved by PFO occlusion. This is in accordance with our clinical data showing an increased risk of unprovoked DCS in divers with a PFO and emphasizes the necessity of further studies that would confirm the safety of any conservative diving measures in divers with large PFOs. It is clear that modification of diving habits is the key to DCS prevention. However, the development of a clinically useful risk-stratification strategy and individualized diving tables require further experimental and clinical research. Similarly, catheter-based PFO closure seems to be a potentially highly effective measure but its precise role is to be determined.

7 Conclusions

In our research we aimed to describe the pathophysiological role of PFO in decompression sickness and to determine whether the prevention of arterialization of post-dive VGE would decrease the incidence of unprovoked DCS in divers. We have screened a large cohort of Czech divers for the presence of PFO and assessed for the incidence of unprovoked decompression sickness. Subsequently, we have studied the occurrence of venous and arterial gas emboli in divers with large PFOs or after catheter-based PFO closure using various simulated dives in a hyperbaric chamber. We have demonstrated that:

1) Patent foramen ovale was a risk factor for unprovoked DCS.
2) Bühlmann regimen dives were associated with lower occurrence of VGE compared to the US Navy air decompression procedure.

3) Catheter-based PFO closure led to complete elimination of post-dive AGE. The occurrence of VGE was not different between divers with a PFO and after catheter-based PFO closure.

4) Conservative dive profiles led to decreased occurrence of VGE, but not to complete elimination of AGE.

5) When compared with conservative dive profiles, catheter-based PFO closure was more effective in AGE reduction after a single simulated 18-meter dive.

Based on our results we suggest that PFO plays an important role in the patophysiology of DCS. The presence of a PFO is associated with increased post-dive occurrence of AGE and an increased risk of unprovoked DCS in divers. The most likely mechanism is paradoxical embolization of VGE, although decreased nitrogen desaturation due to right-to-left shunting might also play role. Catheter-based PFO closure and conservative dive profiles reduce post-dive AGE occurrence and might thus prevent DCS. The clinical efficacy of DCS prevention using these measures needs to be confirmed in further experimental and, importantly, also in long-term clinical follow-up studies.

8 Summary/Souhrn

Patent foramen ovale (PFO) has been associated with an increased risk of decompression sickness (DCS) in divers. Pathophysiologicaly this has been ascribed to paradoxical embolization of nitrogen bubbles from venous blood to systemic circulation, resulting in obstruction of peripheral capillaries and ischemic injury. However, the role of PFO has been largely debated and experimental and prospective clinical data has been missing. It is of note, that this hypothesis is not only of theoretical importance. The proof of PFO as a causative factor of DCS and, importantly, of unpredictable events (unprovoked DCS) could affect millions of divers worldwide through improved therapy and prevention.

In our research we aimed to describe the pathophysiological role of PFO in decompression sickness and to determine whether the prevention of arterialization of post-dive venous gas emboli (VGE) would decrease the incidence of unprovoked DCS in divers. We have screened 489 scuba divers for the presence of PFO by means of transcranial color-coded Doppler ultrasonography. In a retrospective analysis we found that the incidence of unprovoked decompression sickness was 7% among these divers and that PFO was the only risk factor.

Subsequently, we have studied the occurrence of VGE and arterial gas emboli (AGE) in divers with large PFOs or after catheter-based PFO closure in a series of experimental studies in hyperbaric chamber. We found that Bühlmann regimen dives (recommended for recreational divers in Europe) were associated with lower occurrence of VGE than US Navy decompression regimen dives. In another study we demonstrated that after two provocative dive profiles, that generated significant number of VGE, catheter-based PFO closure led to elimination of post-dive AGE and

DCS symptoms. In a following study conservative dive profiles (limited depth-time nitrogen exposure and prolonged decompression) led to decreased occurrence of VGE, but not to complete elimination of AGE. When compared with catheter-based PFO closure, conservative dive profiles were less effective in AGE reduction after a single simulated dive.

Based on our results, we suggest that the presence of a PFO is associated with increased post-dive occurrence of AGE and an increased risk of DCS in divers. Our original findings are that i) PFO was the only risk factor for unprovoked DCS, ii) catheter-based PFO closure and conservative dive profiles reduced post-dive AGE occurrence and might thus prevent DCS in divers with a PFO. However, the clinical efficacy of DCS prevention using these measures needs to be confirmed in further experimental and, importantly, in long-term clinical follow-up studies.

Foramen ovale patens (PFO) je spojováno se zvýšeným rizikem vzniku dekompresní choroby potápěčů (DCS). Patofyziologicky je tento jev vysvětlován paradoxní embolizací dusíkových bublin do systémového oběhu s následnou obturací kapilár vedoucí k ischemickému poškození tkání. Tato hypotéza, ač vyslovena již v 80. letech 20. století, je stále diskutována a doposud chyběla experimentální a prospektivní klinická data, která by ji podporovala. Její význam přitom není zdaleka jen teoretický. Průkaz PFO jako etiologického faktoru vzniku DCS a zejména nevyprovokované DCS (bez porušení dekompresních pravidel), by mělo zásadní význam i v terapii a prevenci této choroby, která představuje potenciální riziko pro miliony potápěčů na celém světě.

V našem výzkumu si klademe za cíl ozřejmit úlohu PFO v patofyziologii vzniku DCS a zjistit, zda prevence paradoxní embolizace dusíkových bublin, povede k

snížení incidence nevyprovokované DCS. Provedli jsme screening přítomnosti PFO pomocí transkraniální duplexní ultrasonografie u 489 potápěčů. V retrospektivní analýze jsme zjistili, že incidence nevyprovokované DCS byla 7% a že PFO bylo jediným rizikovým faktorem.

V dalším výzkumu jsme se zaměřili na detekci venózních a arteriálních dusíkových bublin po simulovaných ponorech v hyperbarické komoře. Zjistili jsme, že ponory provedené podle Bühlmannova dekompresního režimu (doporučeného pro rekreační potápěče v Evropě) byly spojeny s nižším výskytem jak venózních tak arteriálních bublin, než ponory provedené podle režimu US Navy. V jiné studii jsme zjistili, že katetrizační uzávěr PFO vedl k eliminaci arteriálních bublin po dvou profilech ponoru (do 18 m a do 50 m), po kterých byla v minulosti prokázána vysoká incidence žilních bublin. Konzervativní profily ponoru (omezení expozice zvýšenému parciálnímu tlaku dusíku, prodloužení dekompresního postupu), testované v dalším experimentu, vedly k významné redukci výskytu venózních bublin, ale ne k úplné eliminaci arteriálních embolů. Při přímém srovnání s katetrizačním uzávěrem PFO byly v eliminaci arteriálních bublin méně efektivní.

Na základě našich výsledků navrhujeme uzavřít, že PFO je spojeno se zvýšeným výskytem arteriálních dusíkových bublin po ponoru a se zvýšeným rizikem vzniku DCS u potápěčů. Našimi originálními výsledky pak je skutečnost, že i) PFO byl jediným rizikovým faktorem vzniku nevyprovokované dekompresní příhody, ii) katetrizační uzávěr PFO a konzervativní profily ponoru vedly k redukci výskytu arteriálních bublin po ponoru a mohou tak předcházet vzniku DCS u potápěčů s PFO. Klinická efektivita těchto postupů však musí být ověřena v dalších experimentálních a zejména longitudinálních klinických studiích.

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10 Attachments

1. Publication 1 – Nitrogen bubble detection after simulated dives in divers with patent foramen ovale. Is catheter closure indicated?
2. Publication 2 – Effect of Catheter-Based Patent Foramen Ovale Closure on the Occurrence of Arterial Bubbles in Scuba Divers.
3. Publication 3 – Effect of Conservative Dive Profiles on the Occurrence of Venous and Arterial Bubbles in Scuba Divers: a Pilot Study.
4. Publication 4 – Patent foramen ovale: transcatheter closure or conservative dive profile in decompression sickness prevention in divers?
5. Publication 5 – Patent Foramen Ovale in Recreational and Professional Divers: An Important and Largely Unrecognized Problem.

Attachment 1

Nitrogen bubble detection after simulated dives in divers with patent foramen ovale.

Is catheter closure indicated?

Detekce dusíkových bublin po simulovaném ponoru potápěčů s foramen ovale patens. Kdy doporučit katetrizační uzávěr?

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Cíl: Cílem práce bylo v simulovaném sestupu ověřit riziko paradoxní embolizace bublin u potápěčů s foramen ovale patens (PFO) a porovnat bezpečnost běžně užívaných dekompresních postupů.
Metodika: Tato studie navazuje na naši předchozí práci, kdy jsme provedli screening PFO celkem u 353 českých potápěčů pomocí transkraniální dopplerovské sonografie (TCD). U 31 potápěče s prokázaným PFO byl po simulovaných ponorech v barokomoře sledován výskyt venózních bublin pomocí transtorakální echokardiografie (TTE) a výskyt arteriálních bublin pomocí TTE i TCD. Počet bublin byl hodnocen jako malý (< 20) nebo velký (≥ 20). Byly porovnány tři rozdílné dekompresní postupy – Bühlmann 18 m, US Navy 18 m a US Navy 50 m.
Výsledky: Po ponoru Bühlmann 18 m byly detekovány venózní bubliny u 3 z 14 (21 %) potápěčů, arteriální bubliny nebyly prokázány (0 %). Po ponoru US Navy 18 m venózní bubliny detekovány u 6 z 9 (67 %), arteriální u 2 (22 %). Po ponoru US Navy 50 m detekovány venózní bubliny u 7 z 8 (88 %), arteriální u 6 (75 %). Při užití dekompresního postupu dle Bühlmanna vznikal signifikantně menší počet venózních bublin proti postupu dle US Navy (21 % vs. 76 %, P < 0,01).
Závěr: Na malém souboru potápěčů s PFO jsme ověřili známý fakt vzniku a paradoxní embolizace bublin po simulovaných ponorech. Signifikantně menší počet bublin vznikal při ponorech dle Bühlmanna, v ČR doporučovaných pro rekreační potápěče. Výsledky naznačují vyšší riziko paradoxní embolizace bublin při hlubších ponorech s relativně kratší dekompresí. Screening PFO lze doporučit všem potápěčům, volba dalšího postupu a indikace ke katetrizačnímu uzávěru je individuální, simulovaným ponorem lze ověřit individuální riziko.

Klíčová slova: foramen ovale patens, dekompresní nemoc, simulovaný ponor, transkraniální dopplerovská sonografie, paradoxní embolizace.

Nitrogen bubble detection after simulated dives in divers with patent foramen ovale. Is catheter closure indicated?

Purpose: The aim of the study was to test the risk of paradoxical embolism of nitrogen bubbles after simulated dives in divers with patent foramen ovale (PFO), and to compare the safety of commonly used decompression regimens.
Methods: This study adds on our previous studies, where we performed screening for PFO in 353 Czech scuba divers using transcranial doppler sonography (TCD). In 31 divers previously diagnosed with PFO we detected venous bubbles using transthoracic echocardiography (TTE) and arterial bubbles using TTE and TCD after surfacing from simulated dives in recompression chambers. The amount of bubbles was rated as small (<20) or large (≥ 20). Three different decompression procedures were compared – Bühlmann 18 m, US Navy 18 m and US Navy 50 m.
Results: In the Bühlmann 18m regimen venous bubbles were detected in 3/14 (21 %) divers, no arterial bubbles (0 %) detected. In US Navy 18 m regimen venous bubbles detected in 6/9 (67 %), arterial in 2 (22 %). In US Navy 50 m regimen venous bubbles detected in 7/8 (88 %), arterial in 6 (75 %). Significantly lower number of venous bubbles was detected after Bühlmann regimen dives compared with US Navy (21 % vs. 76 %, P < 0.01).
Conclusion: The well documented fact of bubble formation and paradoxical embolization in divers with PFO after simulated dives was tested on a small study group. Significantly lower number of venous bubbles was detected when using Bühlmann regimen (recommended for recreational diving in the Czech Republic). The results indicate higher risk of paradoxical embolization of bubbles in deeper dives with relatively shorter decompression procedure. PFO screening should be recommended to all divers, further approach and indication to catheter closure is individual, simulated dives can test individual risk.

Key words: Patent foramen ovale, decompression sickness, simulated dive, transcranial doppler sonography, paradoxical embolism.

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Úvod

Přístrojové potápění je celosvětově stále populárnější sport. V České republice je v současné době registrováno přes 250 potápěčských klubů a počet zájemců o potápění stále roste. Pobyt pod vodní hladinou je spojen se specifickými riziky, se kterými je veřejnost včetně zdravotníků doposud málo seznámena. Relativně častým následkem potápění je dekompresní nemoc (DCS) způsobená vznikem dusíkových bublin v těle potápěče. Bubliny vznikají při výstupu na hladinu, kdy může u potápěče s dýchacím přístrojem dojít k přesycení tkání dusíkem. Ke vzniku bublin dochází vzhledem k tlakovým poměrům především ve venózní krvi. Tyto bubliny následně embolizují do plic. Většina takových příhod probíhá subklinicky, pouze při masivní embolizaci dojde k projevům plicní formy DCS. U potápěčů s foramen ovale patens (PFO) dochází při provádění Valsalvova manévru (potápěč jej provádí během ponoru pravidelně k vyrovnání tlaku ve středouší) k pravo-levému zkratu přes mezisíňovou přepážku. Může tedy dojít k paradoxní embolizaci bublin do systémového oběhu. PFO jako rizikový faktor DCS u potápěčů s dýchacím přístrojem poprvé popsali Moon, et al. v roce 1989 (1). Dříve se spojovala paradoxní embolizace maléhо množství bublin přes PFO zejména s rozvojem neurologické formy DCS, novější práce však popisují i častější výskyt například kožních projevů (2). Dosud není spolehlivě vyřešena otázka screeningu a dalšího postupu u potápěčů s PFO. Výskyt PFO v populaci je přitom velmi vysoký, postihuje přibližně každého čtvrtého jedince (3). V naší předchozí práci jsme prokázali dobrou efektivitu screeningu PFO pomocí TCD (4, 5). V této práci se zaměřujeme na detekci dusíkových bublin po simulovaných ponorech potápěčů s prokázaným PFO. Naším cílem bylo v observační studii ověřit riziko paradoxní embolizace bublin a porovnat bezpečnost běžně užívaných dekompresních postupů pro potápěče s PFO.

Metodika

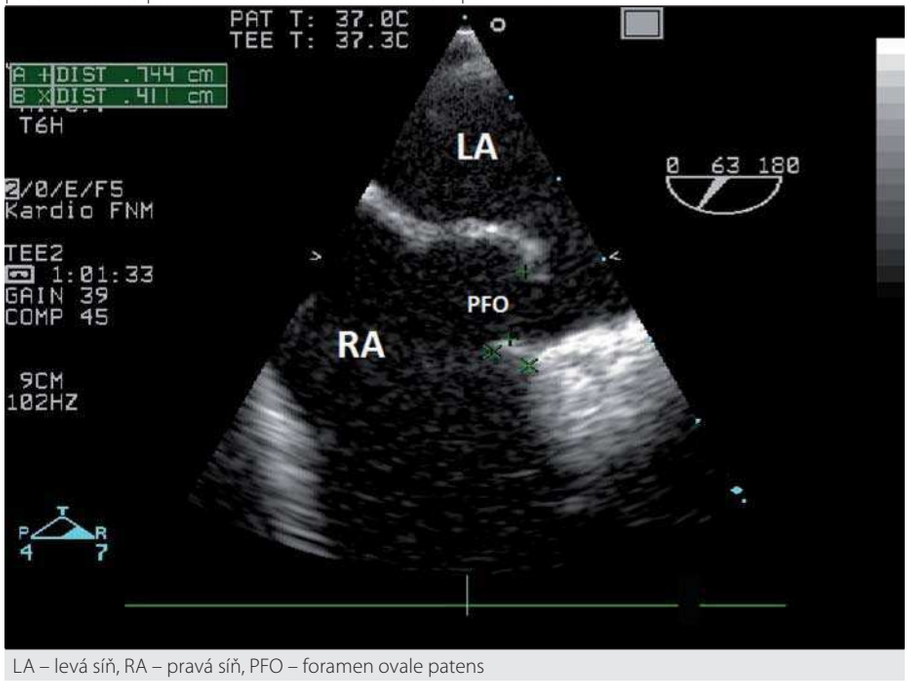
Tato studie navazuje na naší předchozí práci, kdy jsme provedli screening PFO celkem u 353 českých potápěčů pomocí transkraniální dopplerovské sonografie (TCD) (6). Sledování bylo umožněno zařazením vyšetření PFO do vstupní prohlídky potápěčů profesionálů v Ústavu speciálních služeb Ministerstva vnitra ČR. Tato pilotní studie prokázala dobrou senzitivitu TCD (100 %), prevalence PFO byla 25 % (4, 6). U 31 potápěčů s prokázaným PFO jsme sledovali žilní i arteriální bubliny po simulovaných ponorech v barokomoře. Všichni potápěči podepsali informovaný souhlas s účastí ve studii a u všech bylo provedeno tympanometrické vyšetření k ověření průchodnosti Eustachovy trubice. Ponory nebyly prováděny za účelem výzkumu a byly provozovány dle běžných dekompresních režimů. Studie spočívala v následné observaci potápěčů a vyšetření pomocí TCD a TTE. Byl ověřen vznik bublin po simulovaných ponorech za užití tří různých dekompresních postupů. Jednotlivé ponory byly prováděny nezávisle na sobě v různé dny, potápěči neprováděli žádný ponor 24 hodin před simulací. V první skupině byly použity v ČR běžně užívané Bühlmannovy tabulky (7). Byl zvolen ponor do 18 m na dobu 80 minut s dekompresní zastávkou ve třech metrech po dobu 24 minut, sestupová a výstupová rychlost 10 m/min. Ve druhé a třetí skupině byly použity dekompresní postupy podle US Navy air decompression procedure 1996 (8). Ve druhé skupině byl zvolen ponor do 18 m sestupovou rychlostí 10 m/min., čas na dně 80 min., výstup rychlostí 10 m/min. do třech m, kde byla dekompresní zastávka 7 min., stejnou výstupovou rychlostí dekomprese na atmosférický tlak. Ve třetí skupině byl zvolen ponor dle stejné tabulky (US Navy 1996) – sestup do 50 m, sestupová a výstupová rychlost stejná, čas na dně 20 min. a dekompresní zastávka v 6 m na 4 min. a ve třech m na 15 min.

Po vynoření byl u všech potápěčů hodnocen klinický stav (cílený dotaz na obtíže, orientační neurologické vyšetření). Do 30 min. po vynoření bylo u všech provedeno TTE a TCD. Použity byly ultrazvukové přístroje Philips HD10 a GE Vivid i s multipásmovou kardiologickou sondou o frekvenci 3 MHz s továrně nastaveným programem pro vyšetření srdce dospělého pacienta a pro TCD. Jednu minutu byl sledován výskyt bublin v pravostranných oddílech v 2D zobrazení z apikální čtyřdutinové projekce. Byl počítán absolutní počet bublin do 20, dále jen jako velký počet (≥ 20). Poté byl jednu minutu sledován výskyt bublin ve výtokovém traktu pravé komory (RVOT) pomocí pulzní dopplerovské ultrasonografie (PW), zobrazeno 2D v krátké ose. Počet bublin z obou měření byl sečten a uvádíme jej jako bubliny ve venózní krvi. Poté byl stejnou sondou sledován pulzní dopplerovskou ultrasonografií výskyt bublin v arteria cerebri media, přístroj nastaven v režimu TCD. Počet bublin kvantifikován v absolutním počtu do 20, dále jako velký počet (≥ 20). Charakteristiku jednotlivých skupin potápěčů uvádíme v tabulce 1 (tabulka 1).

Tabulka 1. Charakteristika jednotlivých skupin potápěčů. Počet jedinců ve skupině (N), zastoupení mužů a žen, průměrný věk, průměrný počet absolvovaných ponorů a průměrný body mass index (BMI)

skupina	ponor	N	muži	ženy	věk (roků)	počet absolvovaných ponorů	BMI (kg/m²)
1	Bühlmann 18 m	14	12	2	40,1 +/-7,6	356 +/- 181	26,5 +/- 3,3
2	US Navy 18 m	9	9	0	33,1 +/- 5,7	317 +/- 404	25,8 +/- 2,8
3	US Navy 50 m	8	8	0	33,5 +/- 5,9	404 +/- 548	25,4 +/- 2,6

Obrázek 1. Transezofageální echokardiografie. Pohled na mezisíňovou přepážku s foramen ovale patens v krátké příčné ose. Změřena šířka otevření po uvolnění Valsalvova manévru



LA – levá síň, RA – pravá síň, PFO – foramen ovale patens

Tabulka 2. Tabulka výsledků – srovnání ponorů Bühlmann 18 m, US Navy 18 m a US Navy 50 m. Počet jedinců ve skupině (N), počet potápěčů bez záchytu venózních bublin (venózní bubliny 0), se záchytem do 20 venózních bublin (venózní bubliny < 20), 20 a více venózních bublin (venózní bubliny ≥ 20), se záchytem jedné a více arteriálních bublin (bubliny na TCD ≥ 1)

simulovaný ponor	N	venózní bubliny			bubliny na TCD
		0	< 20	≥ 20	≥1
18m/80min., 3m/24min. - Bühlmann	14	11	3	0	0
18m/80min., 3m/7min. - US Navy	9	3	5	1	2
50m/20min., 6m/4min., 3m/15min. - US Navy	8	1	0	7	6

Tabulka 3. Srovnání dekompresních postupů Bühlmann 1983 a US Navy Air Decompression Procedure 1996. Počet jedinců ve skupině (N), počet potápěčů bez záchytu venózních bublin (venózní bubliny 0), se záchytem jedné a více venózních bublin (venózní bubliny ≥ 1), se záchytem jedné a více arteriálních bublin (bubliny na TCD ≥ 1)

dekompresní postup	N	venózní bubliny		bubliny na TCD
		0	≥ 1	≥ 1
Bühlmann	14	11 (79%)	3 (21%)	0 (0%)
US Navy	17	4 (24%)	13 (76%)	10 (59%)

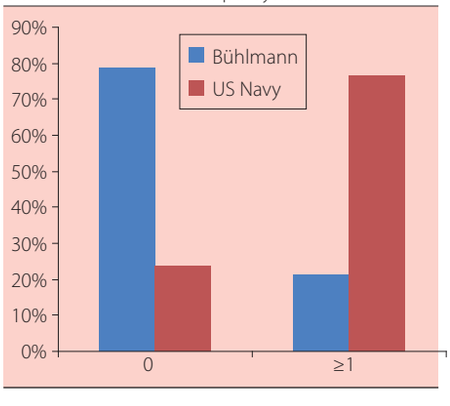
Výsledky

V první skupině byl použit dekompresní postup dle Bühlmanna, sestup do 18 m. Ve třech případech z 14 (21 %) byly detekovány bubliny v pravostranných oddílech (po 1 bublině v plicnici za 1 minutu). TCD neprokázala paradoxní embolizaci bublin u žádného potápěče (0 %).

V druhé skupině v simulaci US NAVY 18 m byl prokázán vznik bublin u 6 z 9 (67 %) potápěčů. U jednotlivých potápěčů bylo naměřeno 1, 2, 3, 4, 8 a více jak 20 venózních bublin. U dvou (22 %) potápěčů byla prokázána paradoxní embolizace do mozkových tepen pomocí TCD (5 a 8 bublin). Oba potápěči měli po sestupu DCS – první celkovou únavu a bolest ramene, druhý silnou bolest hlavy.

Ve třetí skupině po simulovaném ponoru dle US NAVY do 50 m bylo u 7 z 8 (88 %) potápěčů naměřeno velké množství venózních bublin. U šesti (75 %) potápěčů byla pomocí TCD prokázána paradoxní embolizace (3, 5, 8, 9, 14 a > 20 bublin). Jeden potápěč s velkým PFO a zkratem při nativním dýchání bez Valsalvova manévru měl DCS – silnou bolest hlavy.

Graf 1. Srovnání dekompresních postupů Bühlmann 1983 (modře) a US Navy Air Decompression Procedure 1996 (červeně). Vlevo procentuální počet potápěčů bez záchytu venózních bublin po vynoření. Vpravo procentuální počet potápěčů se záchytem jedné a více venózních bublin po vynoření



Ponory s dekompresním postupem dle Bühlmanna s relativně delší dekompresí vykazovaly signifikantně menší riziko vzniku dusíkových bublin v žilním systému ve srovnání s ponory v režimu US NAVY (21 % vs. 76 %, P-Value 0,0038). Vyšší výskyt bublin v levostranných oddílech korespondoval s výskytem bublin v pravostranných oddílech a současně s vyšším výskytem DCS u potápěčů. Vzhledem k malému počtu výskytu DCS a bublin v levostranných oddílech jsme však tyto jevy nemohli statisticky zpracovat (tabulka 2, 3).

Diskuze

PFO může u potápěče při dekompresi způsobit paradoxní embolizaci dusíkových bublin a vznik DCS – nejčastěji s neurologickou symptomatologií (9). Možnost katetrizačního uzávěru PFO otevřela otázku, zda provádět screening u anomálie tak časté – podle literatury 20–30 % (10). Na rozdíl od kryptogenní mozkové příhody je kauzalita neurologické DCS vždy zřejmá – v naší předchozí práci bylo prokázáno PFO u všech potápěčů s neurologickou formou DCS, katetrizační uzávěr vedl k eliminaci obtíží (11). Naše úsilí bylo směřováno k nalezení jednoduché screeningové metody na průkaz PFO a určení velikosti zkratu (5). V této práci jsme se zaměřili na ověření bezpečnosti běžně užívaných dekompresních postupů u potápěčů s diagnostikovaným PFO. Práce ukazuje na rizikovost dekompresního potápění (sestup do velkých hloubek s následnou stupňovitou dekompresí podle tabulek) u potápěčů s PFO a naopak naznačuje relativní bezpečnost při dodržování bezdekompresních limitů doporučených pro rekreační potápěče (sestup do menší hloubky na maximální povolenou dobu bez nutnosti následného provádění stupňovité dekomprese) (graf 1). Tento fakt otvírá otázku dalšího postupu u potápěčů s nově diagnostikovaným PFO. Nabízí se tři možnosti: katetrizační uzávěr PFO, zákaz potápění, potápění s dodržováním speciálních bezpečnostních doporučení. Existují navrhovaná bezpečnostní doporučení mezinárodní organizace Divers Alert Network (DAN), která omezují maximální hloubku ponoru na 18 m, počet ponorů na jeden za 24 hodin a zakazují překračovat bezdekompresní limity (např. pro hloubku 18 m je maximální povolená délka pobytu pod hladinou 50 min.). V této studii jsme ukázali, že tvorba bublin a výskyt DCS se liší podle zvoleného dekompresního režimu (hloubka, čas na dně, rychlost výstupu, čas a hloubka dekompresních zastávek). Při dodržení postupu Bühlmann 18 m nedocházelo k incidenci DCS, na rozdíl od méně konzervativních režimů dle US Navy (12).

Individuálně může tvorba bublin záviset na dalších faktorech, avšak podle našich zkušeností byl rozdíl jen u mělkého ponoru, u hlubšího již bylo u 7 z 8 potápěčů detekováno velké množství bublin (13, 14, 15). Ponor dle US NAVY do 18 m vedl u většiny potápěčů ke tvorbě bublin, tak jak uvádí literatura (12). Při ponoru do 50 m mělo bezprostředně po vynoření v žilní krvi 7 z 8 (88 %) potápěčů takové množství bublin, že to u 6 z 8 (75 %) potápěčů umožnilo paradoxní embolizaci a v jednom případě vyvolalo DCS.

Ověřili jsme tedy, že při tzv. dekompresním potápění dochází u potápěčů s PFO ke vzniku velkého množství venózních bublin a následně k jejich paradoxní embolizaci a rozvoji DCS. Ke vzniku menšího počtu venózních bublin však dochází i při sestupech podle tabulek Bühlmann 1983 určených pro rekreační potápěče. Některé studie naznačují možnou souvislost těchto subklinických událostí s akumulací ischemických ložisek v mozku (16).

Z výše uvedeného vyplývá, že screeningové vyšetření PFO pomocí TCD a TTE lze doporučit jak u profesionálních, tak aktivních sportovních potápěčů (17). Domníváme se, že katetrizační uzávěr PFO je vhodný zejména u symptomatických profesionálních potápěčů, kdy ve většině případů nelze navrhovaným bezpečnostním doporučením vyhovět. U rekreačních potápěčů lze doporučit konzervativnější přístup k potápění (navrhovaná bezpečnostní doporučení DAN). V našem souboru jsme uzávěr indikovali v případě, že se jednalo o větší defekt u profesionálů (ASD), nebo u opakovaných DCS a nálezu embolizačních ložisek na MRI mozku. Symptomatologii lze ověřit

simulovaným sestupem. Vyloučíme-li zkratovou vadu charakteru malého defektu septa síní a zjistíme-li, že se jednalo o hrubou dekompresní chybu – potápěče jen poučíme a katetrizační uzávěr neindikujeme. Tato observační studie si neklade za cíl srovnávat individuální rozdíly v tvorbě bublin, tak jak jsou známy z literatury, (13, 14, 15) nebo stanovit indikační kritéria k uzávěru PFO.

Závěr

Na malém souboru potápěčů s PFO jsme ověřili známý fakt vzniku a paradoxní embolizace bublin po simulovaných ponorech. Signifikantně menší počet bublin vznikal při ponorech dle Bühlmannových tabulek v České Republice doporučovaných pro rekreační potápěče. Výsledky naznačují vyšší riziko paradoxní embolizace dusíkových bublin při hlubších ponorech s relativně kratší dekompresí. Screening PFO lze doporučit všem aktivním potápěčům, volba dalšího postupu a indikace ke katetrizačnímu uzávěru je individuální, simulovaným ponorem lze ověřit individuální riziko.

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Attachment 2

Effect of Catheter-Based Patent Foramen Ovale Closure on the Occurrence of Arterial Bubbles in Scuba Divers.

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Effect of Catheter-Based Patent Foramen Ovale Closure on the Occurrence of Arterial Bubbles in Scuba Divers

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Objectives This study sought to evaluate the effect of catheter-based patent foramen ovale (PFO) closure on the occurrence of arterial bubbles after simulated dives.

Background PFO is a risk factor of decompression sickness in divers due to paradoxical embolization of bubbles. To date, the effectiveness of catheter-based PFO closure in the reduction of arterial bubbles has not been demonstrated.

Methods A total of 47 divers (age 35.4 ± 8.6 years, 81% men) with a PFO (PFO group) or treated with a catheter-based PFO closure (closure group) were enrolled in this case-controlled observational trial. All divers were examined after a simulated dive in a hyperbaric chamber: 34 divers (19 in the PFO group, 15 in the closure group) performed a dive to 18 m for 80 min, and 13 divers (8 in the PFO group, 5 in the closure group) performed a dive to 50 m for 20 min. Within 60 min after surfacing, the presence of venous and arterial bubbles was assessed by transthoracic echocardiography and transcranial color-coded sonography, respectively.

Results After the 18-m dive, venous bubbles were detected in 74% of divers in the PFO group versus 80% in the closure group ($p = 1.0$), and arterial bubbles were detected in 32% versus 0%, respectively ($p = 0.02$). After the 50-m dive, venous bubbles were detected in 88% versus 100%, respectively ($p = 1.0$), and arterial bubbles were detected in 88% versus 0%, respectively ($p < 0.01$).

Conclusions No difference was observed in the occurrence of venous bubbles between the PFO and closure groups, but the catheter-based PFO closure led to complete elimination of arterial bubbles after simulated dives. (Nitrogen Bubble Detection After Simulated Dives in Divers With PFO and After PFO Closure; NCT01854281) (J Am Coll Cardiol Intv 2014;7:403–8) © 2014 by the American College of Cardiology Foundation

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Scuba (self-contained underwater breathing apparatus) diving is a popular sport that attracts millions of participants worldwide (1). The general risk of death or major injury during scuba diving is small (<0.001% per dive) (2). However, some risk associated with decompression sickness (DCS) still exists.

DCS is caused by nitrogen bubble formation in hypersaturated tissues during the diver's ascent (3). These bubbles either cause local tissue damage or embolize through venous blood (3). Small quantities of venous gas bubbles are believed to be common after most scuba diving (4,5).

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Although most divers remain asymptomatic, symptoms may occur with high bubble load (pulmonary gas embolism) or may be due to paradoxical embolism (arterialization of bubbles) in a diver with a transient right-to-left shunt. The connection between a patent foramen ovale (PFO) and DCS was first described in the 1980s (6,7). Since then, a high prevalence of PFO has been repeatedly reported in divers with the neurological or cutaneous form of DCS (8,9). Multiple brain lesions have also been suggested as possible chronic sequelae of repeated exposure to asymptomatic arterial embolisms (10). The high prevalence of PFO in the general population (11) raises concern among divers and involved medical professionals.

Abbreviations and Acronyms

DCS = decompression sickness

PFO = patent foramen ovale

TCCS = transcranial color-coded sonography

TTE = transthoracic echocardiography

It has been suggested that catheter-based PFO closure might prevent the arterialization of bubbles and reduce the risk of DCS (12–14). The effect of PFO closure to prevent paradoxical embolization of injected bubbles has previously been demonstrated (15). However, there are currently limited clinical data supporting the effectiveness of PFO closure in divers (12,13) and no data confirming its effect on post-dive reduction of arterial gas emboli. The aim of this study was to test the effect of catheter-based PFO closure on the occurrence of arterial bubbles after simulated dives.

Methods

Patients. A total of 183 consecutive divers were screened for PFO at our center. Transcranial color-coded sonography (TCCS) was used for screening, and the diagnosis of PFO was confirmed by transesophageal echocardiography. The right-to-left shunt was graded by means of TCCS according to the International Consensus Criteria (16): grade 1, 1 to 10 bubbles; grade 2, >10 bubbles but no curtain (uncountable number of bubbles); grade 3, curtain. Significant PFO (grade 3) was found in 47 divers. Twenty divers (age 38.8 ± 9.5 years, 80% men) with a history of unprovoked DCS underwent catheter-based PFO closure (closure group). The other 27 divers (age 33.0 ± 6.6 years, 81% men) were either asymptomatic or did not agree with PFO closure, or their PFO closure had not been performed prior to study onset (PFO group). A total of 136 divers (age 33.6 ± 8.3 years, 85% men) that did not have a grade 3 PFO were not included in the study. In this group, 118 tested negative for PFO, 13 had a grade 1 PFO, 5 had grade 2 PFO, mean body mass index was 25.9 ± 3.1 kg/m^2, mean number of logged dives was 225 ± 479, and mean number of logged decompression dives was 47 ± 136. A history of DCS was reported in 11 (8%) of the 136 divers.

Inclusion criteria for the closure group were as follows: age ≥19 years; a PFO that had been occluded by a catheter-based procedure; and a signed informed consent form. Inclusion criteria for the PFO group were: age ≥19 years; a previously diagnosed grade 3 PFO according to the International Consensus Criteria (16); and a signed informed consent form. Exclusion criteria for both groups were: another dive performed in the preceding 24 h and disagreement to being included in the study. The study was approved by the local ethics committee and all study subjects gave written informed consent to participate in the study.

Procedures. The PFO closure procedures were performed in a single center (with the exception of 2 divers) between February 1, 2006, and April 30, 2013. The Amplatzer septal occluder (AGA Medical Corporation, Golden Valley, Minnesota) was used in 5 (25%) divers. In the remaining 15 (75%) cases, the Occlutech Figulla PFO Occluder N (Occlutech GmbH, Jena, Germany) was used. The procedure was performed as previously described (17). In all divers, the indication for the procedure was a history of unprovoked DCS (i.e., without violation of decompression regimen) and the presence of a grade 3 PFO according to the International Consensus Criteria (16). There were no major complications, and bleeding at the puncture site with no need of intervention occurred in 1 (5%) patient.

Simulated dives. To test the effect of catheter-based PFO closure on the reduction of arterial bubbles, decompression dives according to the U.S. Navy Air Decompression Procedure 1996 (18) were used. This decompression procedure was previously reported to generate significant amounts of venous and arterial bubbles but no acute DCS symptoms (5,19). Two dive profiles were used. The divers chose 1 of the 2 simulated dives that best corresponded to their usual diving practice. Thirty-four divers performed a dive to 18 m with a bottom time of 80 min (dive A). The descent and ascent rate was equivalent to 9 m/min; the decompression stop was performed at 3 m for 7 min. Thirteen divers performed a dive to 50 m with a bottom time of 20 min (dive B). The descent and ascent rate was 9 m/min; decompression stops were performed at 6 m for 4 min and at 3 m for 15 min.

Bubble detection. Venous and arterial nitrogen bubbles were assessed within 60 min after surfacing (20). In both dives, the occurrence of venous and arterial bubbles and the incidence of symptoms were compared between the PFO and closure groups.

Venous bubbles were assessed by experienced echocardiographers (J.H. and J.J.) using transthoracic echocardiography (TTE). An ultrasound system, Philips HD-10, with a 2 to 3.7 MHz multifrequency probe (Philips, Amsterdam, the Netherlands) was used. Bubbles were visualized by pulse-wave Doppler in the right ventricular outflow tract from the parasternal short-axis view, and their detection was performed for 1 min. The test was considered positive if 1 or more bubbles were detected.

Arterial bubbles were detected by means of TCCS in the medial cerebral artery (21). An experienced neurologist (M.S.) who was blinded to whether the diver was in the closure or PFO group performed the examination. The same ultrasound equipment as for the echocardiographic examination was used. Bubbles were detected for 1 min during native breathing and subsequently 3× for 40 s after a Valsalva maneuver. The test was considered positive if 1 or more bubbles were detected.

The divers were observed and questioned for any DCS symptoms, with special attention to any neurological or cutaneous manifestations. If symptoms occurred, immediate treatment in a hyperbaric chamber was administered. Treatment Table 5 of the U.S. Navy Diving Manual Revision 6 (18) was used as the treatment protocol. The primary endpoint was the occurrence of arterial bubbles.

Definitions. Arterial bubbles were defined as high-intensity transient signals in the Doppler spectrum detected by TCCS in the medial cerebral artery (21). Venous bubbles were defined as high-intensity transient signals in the Doppler spectrum detected by TTE in the right ventricular outflow tract. Neurological symptoms of DCS were defined as headache, unusual fatigue, visual problems, limb weakness or paralysis, dizziness, and paresthesia reported by the patient ≤24 h after the simulated dive. A history of unprovoked DCS was defined as any DCS symptoms that originated ≤24 h after a dive performed within the limits of any commercially-available diving table or computer used by the diver.

Statistical analysis. Normally distributed data are presented as mean ± SD and non-normally distributed data as median (interquartile range). The distribution of data was evaluated by the Kolmogorov-Smirnov test. Fisher exact test and the Mann-Whitney *U* test were used when appropriate. A p value of ≤0.05 was considered to indicate a statistically significant difference.

Results

A total of 47 divers (age 35 ± 8.6 years, 81% men) were examined after a single air dive in a hyperbaric chamber.

Table 1. Baseline Characteristics of PFO and Closure Groups for Dive A

	PFO Group (n = 19)	Closure Group (n = 15)	p Value
Age, yrs	33.0 ± 7.6	40.6 ± 8.5	0.02
Male	80	79	1.00
BMI, kg/m^2	26.0 (22.2–29.7)	27.4 (24.7–30.9)	0.27
Logged dives	100 (39–150)	500 (100–1,880)	0.02
Logged decompression dives	2 (0–15)	150 (5–400)	0.01
DCS history	53	100	<0.01
Time between PFO closure and experimental dive, months	—	36 (17–81)	—

Values are mean ± SD, %, or median (interquartile range). — = data are not available.
BMI = body mass index; DCS = decompression sickness; PFO = patent foramen ovale.

TTE and TCCS were used to assess the occurrence of bubbles. In all divers, adequate visualization of the medial cerebral artery during the TCCS examination was possible. The occurrence of arterial and venous bubbles was compared between the PFO and closure groups separately for dives A and B. The baseline characteristics for dives A and B are shown in Tables 1 and 2, respectively.

Dive A. Dive A was a dive to 18 m for 80 min of bottom time. Thirty-four divers (19 in the PFO group [age 32 years, range 21 to 51; 74% men], 15 in the closure group [age 38 years, range 28 to 55; 80% men]) performed this dive. Venous bubbles were detected in 74% of divers in the PFO group versus 80% in the closure group (p = 1.0) (Fig. 1). Arterial bubbles were detected in 32% versus 0% of divers, respectively (p = 0.02) (Fig. 1). In 21% of divers with PFO and detected arterial gas bubbles, neurological symptoms of DCS were present (headache, unusual fatigue, transitory visual disturbances). No divers (0%) reported DCS symptoms in the closure group (p = 0.11).

Dive B. Dive B was a dive to 50 m for 20 min of bottom time. Thirteen divers (8 in the PFO group [age 31.5 years, range 26 to 40; 100% men], and 5 in the closure group [age 34 years, range 18 to 51; 80% men]) performed this dive.

Table 2. Baseline Characteristics of PFO and Closure Groups for Dive B

	PFO Group (n = 8)	Closure Group (n = 5)	p Value
Age, yrs	32.9 ± 4.8	33.4 ± 12.1	1.00
Male	100	80	0.38
BMI, kg/m^2	25.5 (23.6–26.9)	30.7 (23.0–32.6)	0.23
Logged dives	55 (17.5–185)	300 (35–2,310)	0.23
Logged decompression dives	0 (0–75)	100 (10–315)	0.13
DCS history	38	100	0.08
Time between PFO closure and experimental dive, months	—	31 (7–67)	—

Values are mean ± SD, %, or median (interquartile range). — = data are not available.
Abbreviations as in Table 1.

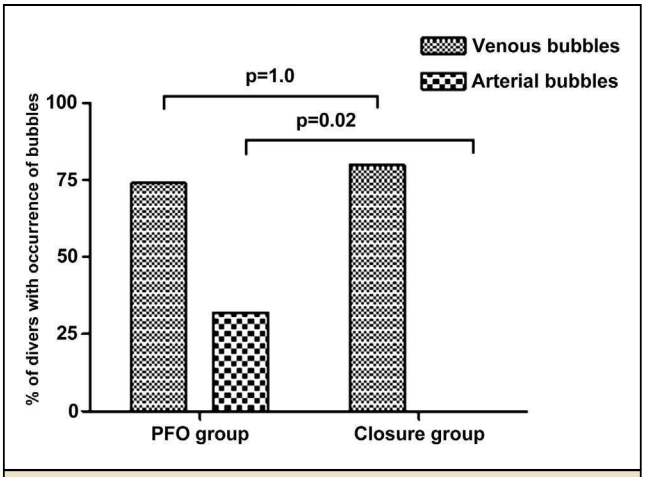

Figure 1. Occurrence of Bubbles After Dive A

The proportion of divers with the occurrence of venous and arterial bubbles after dive A in divers with patent foramen ovale (PFO group) and divers treated with a catheter-based patent foramen ovale closure (closure group). There was no difference in the occurrence of venous bubbles between the PFO and closure groups ($p = 1.0$), but no arterial bubbles were detected in the closure group ($p = 0.02$).

Venous bubbles were detected in 88% of divers in the PFO group versus 100% of divers in the closure group ($p = 1.0$) (Fig. 2). Arterial bubbles were detected in 88% versus 0% of divers, respectively ($p < 0.01$) (Fig. 2). In 25% of divers with PFO and detected arterial gas bubbles, mild neurological symptoms of DCS were present (headache, unusual fatigue, transitory visual disturbances, dizziness). No divers (0%) reported DCS symptoms in the closure group ($p = 0.49$).

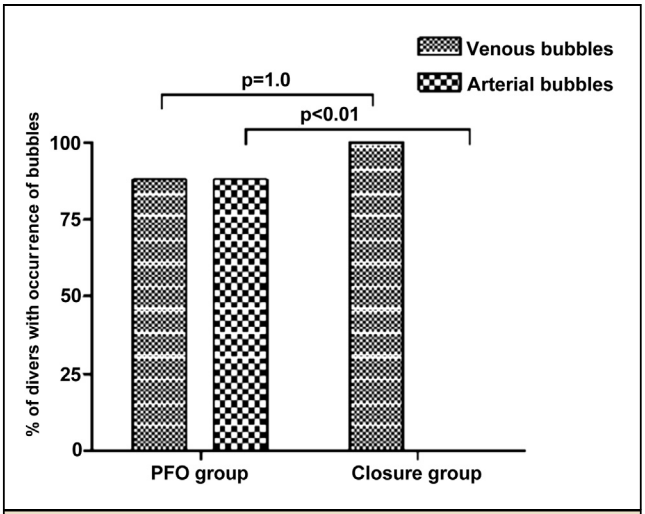

Figure 2. Occurrence of Bubbles After Dive B

The proportion of divers with the occurrence of venous and arterial bubbles after dive B in divers with patent foramen ovale (PFO group) and divers treated with a catheter-based patent foramen ovale closure (closure group). There was no difference in the occurrence of venous bubbles between the PFO and closure groups ($p = 1.0$), but no arterial bubbles were detected in the closure group ($p < 0.01$).

The typical appearance of post-dive venous bubbles in the right heart chambers and no arterial bubbles in the left heart chambers in a diver with a PFO closure device is shown in Figure 3.

Discussion

The present study is the first to our knowledge to demonstrate the effect of catheter-based PFO closure on the occurrence of arterial bubbles after simulated dives. In our study, no difference was found in the occurrence of venous bubbles between the PFO and closure groups. However, in the closure group, no arterial bubbles were detected. It is plausible, therefore, that the presence of a PFO plays a key role in paradoxical embolization of venous bubbles after scuba dives. Additionally, because PFO occlusion led to elimination of bubble occurrence in the medial cerebral artery, this closure strategy should have a role in the prevention of unprovoked DCS recurrence in divers.

Decompression sickness. DCS is caused by nitrogen bubble formation during the diver's ascent (3). The diver is exposed to an elevated pressure of nitrogen when breathing compressed air during the submersion (nitrogen can be exchanged for other inert gases such as helium or hydrogen in the breathing mixtures used by professional or technical divers). This excess nitrogen dissolves in all tissues at a rate dependent on their chemical composition and the density of capillaries (22). The total nitrogen load is determined by the depth profile (i.e., the partial pressure of nitrogen the diver is exposed to) and the duration of the dive (i.e., the duration of

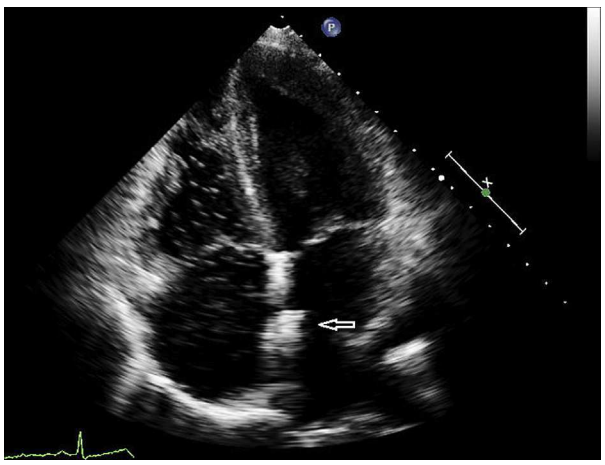

Figure 3. Post-Dive Venous Bubbles in a Diver After Foramen Ovale Closure

Transthoracic echocardiography (apical 4-chamber view) in a diver with a catheter-based patent foramen ovale (PFO) closure device after surfacing from a simulated dive. Venous bubbles are apparent in the right atrium and ventricle; no bubbles are visible in the left heart chambers. The PFO closure device is indicated by an **arrow**.

the exposure). During the ascent and hours after the dive, the excess gas is transported from the tissues back to the alveoli and exhaled. If the diver reaches the surface too early, the tissues get hypersaturated and intravascular and extravascular bubbles form and increase in size (3). To prevent DCS, divers perform the ascent according to decompression tables or a decompression algorithm implemented in a diving computer.

Small numbers of intravascular bubbles form in the capillaries and the venous blood even during a properly performed ascent (4). These bubbles are usually asymptomatic because most of the time, they are effectively filtered by the pulmonary circulation (3). If the bubble load is massive (in case of violation of the decompression regimen), the embolization manifests as a pulmonary DCS. In divers with PFO, a paradoxical embolization to the systemic circulation may occur and cause various, mostly neurological or cutaneous DCS symptoms even after a dive with an appropriate decompression regimen (unprovoked DCS) (3).

Paradoxical embolization results from increased right atrial pressure due to hemodynamic changes that occur in divers. After submersion, blood redistributes from the periphery to the thorax, which results in an increased right atrial pressure (23). Moreover, divers perform a Valsalva maneuver frequently during the dive (to equalize pressure in the middle ear), which further contributes to the increased right atrial pressure and leads to transient right-to-left shunting through the PFO.

PFO in divers. The connection between PFO and DCS was first described in the 1980s (6,7). Since then, a high prevalence of PFO has been repeatedly reported in divers with the neurological or cutaneous form of DCS (8,9). The possible chronic sequelae of repeated exposure to asymptomatic arterial embolisms have also been discussed. Knauth et al. (10) reported an association of PFO with multiple brain lesions in a follow-up study using magnetic resonance imaging. However, we have to bear in mind that these studies have several inherent limitations and are not generalizable.

PFO or other right-to-left cardiac shunt is present in about 27% of the normal population (11). However, the management of divers with PFO remains unresolved. Routine screening for PFO in divers is currently not recommended in most countries (24,25). Suggested recommendations for divers with diagnosed PFO and a history of DCS include the cessation of diving, a conservative approach to diving (26), and PFO closure.

It has been suggested by several investigators that a catheter-based PFO closure in divers might eliminate the arterialization of bubbles and prevent unprovoked DCS (12–14). No divers had arterial bubbles after PFO closure in this study; both the Amplatzer septal occluder and the Occlutech Figulla PFO Occluder N were highly effective. In the deeper dive, where the nitrogen load was greater, arterial gas bubbles were observed in all divers with a PFO and venous bubbles were detected. Moreover, 29% of these had cerebral DCS symptomatology. This is in agreement with the landmark case-controlled study by Germonpré et al. (27), who found high prevalence of high-grade PFO in divers suffering from unprovoked cerebral DCS. No divers in the closure group had DCS symptoms after either the 20-m or 50-m dive.

It has been suggested that the transpulmonary passage might also play an important role in the occurrence of post-dive arterial gas emboli. Ljubkovic et al. (28) observed arterial bubbles in 9 of 34 divers who tested negative for PFO and argued that transpulmonary arterialization would occur if a large amount of bubbles were produced and an individual exhibited a higher susceptibility for the transpulmonary passage. This was not observed in the closure group in our study, where no arterial emboli were detected, despite the fact that the occurrence of venous bubbles was not different from the PFO group. Also, clinical studies support the fact that PFO might be the major route of paradoxical embolization in divers. Torti et al. (8) reported that the odds of suffering a major DCS were 5× higher in divers with PFO and that the risk paralleled PFO size. Wilmhurst et al. (9) found that the incidence of PFO was 77% among 61 divers who had suffered the cutaneous form of DCS, compared with 28% in control subjects.

Study limitations. The absence of symptom-based clinical endpoints is the main limitation of this observational study. A randomized prospective follow-up trial would be necessary to assess the clinical efficacy of catheter-based PFO closure in divers. The primary endpoint was the occurrence of arterial bubbles, defined as 1 or more bubbles present. The binary grading of bubbles (none or any) might not have revealed a picture with enough differentiation. Another potential limitation is the experimental setting of the study. There is some evidence that wet dives generate more venous bubbles than dry dives do (29). In our study, only dive A was a dry dive, in dive B, the divers were submersed in a water reservoir inside the hyperbaric chamber using their usual scuba equipment.

Conclusions

We have demonstrated that in conditions of 2 simulated dives, catheter-based PFO closure was associated with the elimination of arterial bubbles. These results suggest that PFO occlusion might lead to a reduction of unprovoked DCS incidence in divers.

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Key Words: catheter-based closure ■ decompression sickness ■ paradoxical embolization ■ patent foramen ovale.

Attachment 3

Effect of Conservative Dive Profiles on the Occurrence of Venous and Arterial Bubbles in Scuba Divers: a Pilot Study.

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Letter to the Editor

Effect of conservative dive profiles on the occurrence of venous and arterial bubbles in divers with a patent foramen ovale: A pilot study ☆

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Patent foramen ovale (PFO) is a risk factor for decompression sickness (DCS) in divers due to paradoxical embolization of nitrogen bubbles formed in peripheral blood during decrease of ambient pressure [1]. In our previous study we have demonstrated that catheter-based PFO closure prevented right-to-left shunting of bubbles and might prevent DCS recurrence [2]. However, the question of PFO closure is still debatable [3]. Also, randomized clinical data are lacking in this field. Therefore, the majority of divers are currently not referred for PFO closure, and various conservative dive profiles (CDP) are recommended to prevent unprovoked DCS (i.e., without violation of decompression regimen) [4]. Unfortunately, to date, the safety of these CDP has not been tested in divers with PFO. The aim of this study was to test the effect of dive time and ascent rate restrictions on the occurrence of venous and arterial bubbles in divers with PFO after simulated dives. We compared a standardly recommended no-decompression dive [5] and a stricter regimen with slower ascent to the same control dive, which was previously used to test the efficacy of catheter-based PFO closure [2].

We screened a total of 532 consecutive divers for PFO using transcranial color coded sonography (TCCS). The diagnosis of PFO was confirmed by transesophageal echocardiography. Forty-six divers (36.4 ± 10 years; 72% men) with a significant PFO (grade 3 according to the international consensus criteria [6]) who had previously not undergone PFO closure were enrolled in this pilot study. All divers performed a simulated dive to 18 m in a hyperbaric chamber. Divers were randomized into three groups: group A (n = 13; 36.5 ± 9 years; 77% men) performed a standard Bühlmann regimen no-decompression dive (dive time 51 min, ascent rate 10 m/min), group B (n = 14, 40.9 ± 12 years; 64% men) performed the same regimen with a slower ascent (51 min, 5 m/min), and a control group (n = 19; 33.0 ± 8 years; 74% men) performed a staged-decompression dive according to the US Navy decompression regimen (80 min, 9 m/min, decompression stop 7 min at 3 m). Within 60 min of surfacing, the presence of venous and arterial bubbles was assessed. Venous bubbles were assessed by pulse wave Doppler in the right ventricular outflow tract (RVOT), and arterial bubbles by TCCS during native breathing and after Valsalva maneuvers, as described previously [2]. The study was approved by the local ethics committee and all patients signed an informed consent.

In all divers, visualization of RVOT and the middle cerebral artery was possible. The occurrence of arterial and venous bubbles is summarized in Fig. 1. There was significantly lower occurrence of venous bubbles in groups A and B compared to controls (for group A, 31% vs. 74%, $p = 0.03$; for group B, 14% vs. 74%, $p < 0.01$). The reduction in arterial bubble occurrence was not significant in group A compared to controls, but there was elimination of arterial bubbles in group B (for group A, 8% vs. 32%, $p = 0.42$; for group B, 0% vs. 32%, $p = 0.03$). There was no significant difference in venous or arterial bubble occurrence between groups A and B (venous, 31% vs. 14%, $p = 0.38$; arterial, 8% vs. 0%, $p = 0.48$). All divers were observed for any DCS symptoms 24 h after the simulated dive. In the control group transient neurological symptoms (headache, unusual fatigue, and transitory visual disturbances) were present in 21% of divers, no DCS symptoms were observed in group A ($p = 0.13$) or B ($p = 0.12$).

Generally, the aim of our research is to stratify the risk of DCS in divers with PFO and to find the optimal management strategy for symptomatic divers, including potential catheter-based PFO closure. In our

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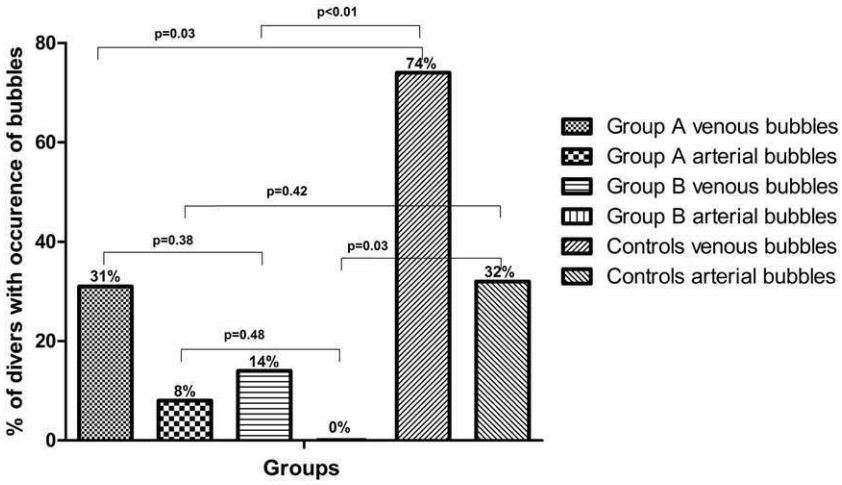

Fig. 1. Summary of the occurrence of post-dive venous and arterial bubbles.

previous study we have demonstrated that catheter-based PFO closure prevented the arterialization of bubbles after simulated dives [2]. In this pilot study we sought to find a safe diving regimen for divers with a significant PFO. A standard decompression regimen failed to eliminate post-dive arterial emboli (bubbles). However, this was achieved when the standard decompression regimen was combined with a slower ascent. Therefore, we suggest that a stricter diving regimen might be necessary to minimize the risk of the paradoxical embolization of bubbles and prevent unprovoked DCS in divers with PFO. We feel that further cardiological research in this field should focus on the management of divers with previous unprovoked DCS. The safety of any conservative diving measures should be studied prior to routine clinical use. Similarly, randomized clinical data are needed to determine the role of catheter-based PFO closure.

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Attachment 4

Patent foramen ovale: transcatheter closure or conservative dive profile in decompression sickness prevention in divers?

Patent foramen ovale: transcatheter closure or conservative dive profile in decompression sickness prevention in divers?

Foramen ovale patens: katetrizační uzávěr nebo konzervativní profil ponoru jako prevence dekompresní choroby potápěčů?

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Novotny S, Honek J, Januska J, Sefc L, Horvath M, Fiedler J, Sramek M, Veselka J, Honek T, Tatar M. **Patent foramen ovale: transcatheter closure or conservative dive profile in decompression sickness prevention in divers?** Cardiology Lett. 2014;23(3):223–227

Abstract. *Aim:* The aim of this study was to compare the influence of transcatheter patent foramen ovale (PFO) closure and safe diving recommendations limiting bottom time and depth on the occurrence of arterial bubbles after simulated dives in a hyperbaric chamber.

Methods: Forty-seven divers with a PFO were enrolled in this observational trial. Nineteen divers with PFO performed a decompression dive to 18m for 80 min (control group), 15 divers after a transcatheter PFO closure performed the same dive (group 1) and 13 divers with PFO performed a dive to the same depth for a non-decompression time of 51 min (group 2). In all divers venous and arterial bubbles were screened, venous bubbles by means of transthoracic echocardiography, arterial by means of transcranial Doppler ultrasonography.

Results: Venous bubbles were detected in 74% divers in the control group, in 80% in group 1 (p=1.0) and in 31% in group 2 (p=0.03); arterial bubbles in 32% divers in control group, in 0% in group 1 (p=0.02), in 15% in group 2 (p=0.42).

Conclusion: Safe diving recommendations avoiding decompression procedure led to the decrease in occurrence of venous bubbles but not the elimination of arterial bubbles in divers with PFO. Transcatheter PFO closure led to elimination of arterial bubbles. The results suggest that transcatheter PFO closure might be an effective treatment in prevention of DCS: the effectivity of the up-to-date safety recommendations used needs to be further tested, especially in longitudinal clinical studies. Fig. 1, Tab. 1, Ref. 18, Online full text (Free, PDF) www.cardiology.sk

Key words: patent foramen ovale – decompression sickness – simulated dive – transcranial Doppler ultrasonography – paradoxical embolism

Novotný Š, Honěk J, Januška J, Šefc L, Horváth M, Fiedler J, Šrámek M, Veselka J, Honěk T, Tatár M. **Foramen ovale patens: katetrizační uzávěr nebo konzervativní profil ponoru jako prevence dekompresní choroby potápěčů?** Cardiology Lett. 2014;23(3):223–227

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Abstrakt. *Cíl:* Cílem této práce bylo srovnat vliv katetrizačního uzávěru foramen ovale patens (PFO) a bezpečnostních doporučení omezujících dobu a hloubku ponoru na výskyt arteriálních dusíkových bublin po simulovaném sestupu v hyperbarické komoře.
Metodika: Této observační průřezové studie se zúčastnilo celkem 47 potápěčů s PFO. Kontrolní skupinu tvořilo 19 potápěčů s PFO, kteří se zúčastnili dekompresního ponoru do 18 m na 80 min. Skupinu 1 představovalo 15 potápěčů, kteří v minulosti podstoupili katetrizační uzávěr PFO a provedli stejný ponor jako kontrolní skupina. Skupinu 2 tvořilo 13 potápěčů s PFO, kteří provedli ponor do stejné hloubky po maximální doporučenou bezdekompresní dobu 51 min. U všech byla do 60 min od vynoření provedena detekce venózních bublin pomocí transtorakální echokardiografie a arteriálních bublin pomocí transkraniální dopplerovské ultrasonografie.
Výsledky: Venózní bubliny byly detekovány u 74 % potápěčů v kontrolní skupině, ve skupině 1 u 80 % (p = 1,0), ve skupině 2 u 31 % (p = 0,03). Arteriální bubliny byly detekovány u 32 % potápěčů v kontrolní skupině, ve skupině 1 u 0 % (p = 0,02), ve skupině 2 u 15 % (p = 0,42).
Závěr: Bezpečnostní doporučení omezit ponor tak, aby nevyžadoval dekompresní zastávku, vedlo k snížení počtu venózních bublin u potápěčů s PFO, k eliminaci arteriálních bublin ale nedošlo. Katetrizační uzávěr PFO vedl k eliminaci arteriálních bublin. Výsledky naznačují, že katetrizační uzávěr PFO by mohl být efektivní léčbou v prevenci dekompresní choroby potápěčů, efektivitu v současnosti užívaných bezpečnostních doporučení bude nutno dále ověřit zejména v longitudinálních klinických studiích. Obr. 1, Tab. 1, Lit. 18, Online full text (Free, PDF) www.cardiology.sk
Klíčová slova: foramen ovale patens – dekompresní nemoc – simulovaný ponor – transkraniální dopplerovská sonografie – paradoxní embolizace

Přístrojové potápění je populární sport přitahující miliony zájemců po celém světě. V České republice je v současné době registrováno přes 250 potápěčských klubů a potápění provozuje aktivně 50 – 100 tis. lidí. Obecně lze potápění považovat za velmi bezpečný sport (0,0005 % úmrtí na ponor) (1). Na druhou stranu je pobyt pod vodní hladinou spojen se specifickými riziky, se kterými je veřejnost včetně zdravotníků stále málo seznámena.

Dekompresní nemoc (DCS) je způsobená vznikem dusíkových bublin v přesycených tkáních při výstupu potápěče k hladině. V průběhu ponoru dochází k sycení tkání dusíkem, který je pod vodní hladinou dýchán pod zvýšeným parciálním tlakem. Při příliš rychlém výstupu na hladinu (dekompresi) pak může dojít k překročení kritické hladiny a vzniku intravaskulárních a extravaskulárních bublin. Intravaskulární bubliny vznikají, vzhledem k tlakovým poměrům, především ve venózní krvi. Tyto bubliny následně embolizují do plic. Pro zamezení výskytu DCS probíhá vynoření potápěče podle dekompresních postupů omezujících rychlost výstupu a v případě potřeby dodržováním tzv. dekompresních zastávek v definovaných hloubkách, aby se umožnila bezpečná eliminace přebytečného dusíku z krve a tkání. Přesto i při dodržení těchto postupů v některých případech dojde k rozvoji DCS (nevyprovokovaná dekompresní příhoda). Malé množství dusíkových bublin vzniká běžně ve venózní krvi i po jednom ponoru při dodržení bezpečnostních předpisů (2, 3). Většina takových příhod probíhá subklinicky, protože plicní kapilární filtr zachytí přítomné bubliny a umožní jejich postupné rozpuštění. U potápěčů s foramen ovale patens (PFO) dochází k pravo-levému (paradoxnímu) zkratu přes mezisíňovou přepážku a bubliny, které projdou do velkého oběhu, mohou vést ke vzniku DCS (nejčastěji neurologické a kožní). K intermitentnímu pravo-levému zkratu přes PFO přitom dochází při přístrojovém potápění často. Jednak potápěč pravidelně provádí Valsalvův manévr k vyrovnání tlaku ve středním uchu, navíc dochází v průběhu ponoru k redistribuci krve z periferie do hrudníku a ke zvýšení tlaku v pravé síni (4).

Souvislost mezi PFO a DCS byla poprvé popsána v 80. letech 20. století (5, 6). Od té doby byla opakovaně zaznamenána vyšší prevalence PFO u potápěčů s neurologickou a kožní formou DCS (7, 8). Knauth et al. (9) popsali také chronické následky opakovaných asymptomatických embolizací do CNS v podobě mnohočetných lézí na magnetické rezonanci mozku. Přesto není dosud vyřešena otázka screeningu a dalšího postupu u potápěčů s PFO. Výskyt PFO v populaci je přitom vysoký (27 %) (10).

V naší předchozí práci jsme prokázali vysoký výskyt venózních i arteriálních bublin po simulovaných dekompresních ponorech potápěčů s PFO (11). Cílem této práce bylo porovnat výskyt arteriálních bublin po dekompresním ponoru potápěčů s PFO, po katetrizačním uzávěru PFO a po bezdekompresním ponoru dle současných bezpečnostních doporučení pro potápěče s PFO.

Materiál a metodika

V této průřezové observační studii bylo zařazeno celkem 47 potápěčů s PFO či po jeho katetrizačním uzávěru. Potápěči absolvovali simulované ponory v hyperbarické komoře a po výstupu byly sonograficky sledovány žilní a arteriální bubliny.

Kritéria pro zařazení do studie byly: věk ≥ 19 let, diagnostikované PFO nebo stav po provedení katetrizačního uzávěru PFO v minulosti a souhlas s účastí ve studii. Kritéria pro vyloučení ze studie byly: provedení jiného ponoru < 24 hod před simulovaným sestupem a nesouhlas se zařazením do studie. Studie byla schválena Etickou komisí Fakultní nemocnice Motol a všichni potápěči podepsali informovaný souhlas s účastí ve studii.

Katetrizační uzávěry byly prováděny ve dvou centrech mezi únorem 2006 a dubnem 2013. U 5 (25 %) potápěčů byl použit okluder Amplatzer septal occluder (AGA Medical Corporation, Golden Valley, USA) u 15 (75 %) byl použit okluder Occlutech Figulla PFO Occluder N (Occlutech GmbH, Jena, SRN). Výkon byl prováděn, jak bylo dříve popsáno (12). U všech potápěčů byl uzávěr indikován na základě proběhlé nevyprovokované DCS (příznaky DCS po provedení ponoru bez porušení předepsaných dekompresních pravidel).

Kontrolní skupina byli potápěči s PFO, kteří se účastnili dekompresního simulovaného ponoru v dekompresní komoře (HAUX Life Support, Karlsbad-Ittersbach, Německo) do 18 m na 80 min podle tabulek US Navy Air Decompression Procedure 1996, s výstupovou i sestupovou rychlostí 9 m/min a s dekompresní zastávkou po dobu 7 min v 3 m. Skupina 1 byli potápěči po katetrizačním uzávěru PFO, kteří se účastnili stejného ponoru. Skupina 2 byli potápěči s PFO, kteří se účastnili ponoru do 18 m podle dekompresní tabulky Bühlmann na maximální čas nevyžadující dekompresní zastávku (51 min), se sestupovou a výstupovou rychlostí 10 m/min a bezpečnostní zastávkou 1 min v 3 m.

Sonografické vyšetření bylo provedeno u všech potápěčů do 60 min od vynoření. Venózní bubliny byly detekovány pomocí transtorakální echokardiografie. Byl použit přístroj Philips HD 10 (Philips, Amsterdam, Nizozemsko) s multifrekvenční sondou s rozsahem 2 – 3,7 MHz. Bubliny byly sledovány po dobu jedné minuty pulzním dopplerovským vyšetřením ve výtokovém traktu pravé komory v parasternálním zobrazení na krátkou osu. Arteriální bubliny byly detekovány pomocí stejného přístrojového vybavení. Po dobu jedné minuty byl při nativním dýchání sledován pulzním dopplerovským vyšetřením výskyt bublin v arteria cerebri media. Poté byly bubliny sledovány stejným způsobem třikrát po dobu 40 sekund po provedení Valsalvova manévru. Testy byly považovány za pozitivní při výskytu ≥ 1 bublin.

Data byla testována na normalitu pomocí Kolmogorovova-Smirnovova testu. Parametrická data byla statisticky zhodnocena pomocí jednosměrné analýzy rozptylu, neparametrická data pomocí Kruskalova-Wallisova testu a Mannova-Whitneyho testu. Nominální proměnné byly zhodnoceny pomocí Fischerova testu a Chí-kvadrátu. Primárním cílem byl výskyt arteriálních bublin.

Výsledky

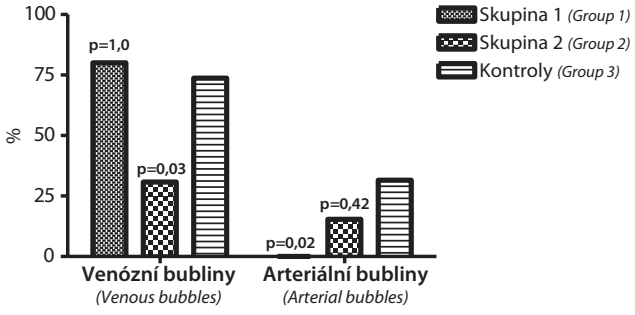
Celkem 47 potápěčů bylo sonograficky vyšetřeno na přítomnost arteriálních a venózních bublin po simulovaném sestupu v hyperbarické komoře. Kontrolní skupina (n = 19) byli potápěči s PFO, kteří provedli dekompresní sestup do 18 m na 80 min. Skupina 1 (n = 15) byli potápěči po katetrizačním uzávěru PFO, kteří provedli identický sestup jako potápěči v kontrolní skupině. Skupina 2 (n = 13) byli potápěči s PFO, kteří provedli bezdekompresní ponor do 18 m na 51 min. Charakteristika skupin je uvedena v **tabulce 1**.

Venózní bubliny byly detekovány u 74 % potápěčů v kontrolní skupině, ve skupině 1 u 80 % potápěčů (p = 1,0), ve skupině 2 u 31 % potápěčů (p = 0,03). Arteriální bubliny u 32 % potápěčů v kontrolní skupině, ve skupině 1 u 0 % (p = 0,02) a ve skupině 2 u 15 % (p = 0,42). Výskyt arteriálních a venózních bublin je přehledně srovnán na **obrázku 1**. U dvou potápěčů ze 6 (33 %), kteří manifestovali v kontrolní skupině arteriální bubliny, byly zaznamenány příznaky DCS. Oba potápěči byli úspěšně léčeni rekompresí v hyperbarické komoře s promptní úlevou obtíží. Ve

Tabulka 1 Základní charakteristika skupin
Table 1 *Baseline characteristics of study groups*

	Skupina 1 *(Group 1)* (n = 15)	Skupina 2 *(Group 2)* (n = 13)	Kontroly *(Controls)* (n = 19)
Věk (roky) *(Age in years)*	40,6 ± 8,5*	36,5 ± 9,0	33,0 ± 7,6
Mužské pohlaví *(Male sex)* (%)	79	77	80
BMI (kg/m^2)	27,4, 24,7 – 30,9	25,2, 24,0 – 30,7	26,0, 22,2 – 29,7
Počet ponorů *(Number of dives)*	500, 100 – 1 880*	127, 40 – 364	100, 39 – 150
Počet dekompresních ponorů *(Number of decompression dives)*	150, 5 – 400*	3, 1 – 50	2, 0 – 15
DCS v *anamnéze (DCS history)* (%)	100	62	53

BMI – index tělesné hmotnosti *(body mass index)*, DCS – dekompresní nemoc *(decompression sickness)*. Data jsou uvedena jako průměr ± směrodatná odchylka respektive medián, interkvartilní rozsah; *p < 0,05 *(Data are shown as mean ± standard deviation or median, interquartile range); * p<0.05*



Obrázok 1 Výskyt arteriálních a venózních bublin
Figure 1 *Occurrence of arterial and venous bubbles*
Srovnání výskytu venózních a arteriálních bublin u skupiny 1 (potápěči po katetrizačním uzávěru foramen ovale patens, dekompresní sestup), skupiny 2 (potápěči s foramen ovale patens, bezdekompresní sestup) a kontrol (potápěči s foramen ovale patens, dekompresní sestup). *(Comparison of venous and arterial bubbles occurrence in group 1 (divers after transcatheter patent foramen ovale (PFO) closure, decompression dive), group 2 (divers with a PFO, non-decompression dive) and controls (divers with a PFO, decompression dive).*

skupině 1 ani skupině 2 nebyly zaznamenány projevy DCS u žádného potápěče.

Diskuse

PFO je u potápěčů spojeno se zvýšeným rizikem vzniku DCS zejména s kožní a neurologickou symptomatologií a to i tzv. nevyprovokovaných příhod, kdy potápěč neporuší doporučený dekompresní režim (7, 8). Diskutovány jsou i možné trvalé následky opakovaných asymptomatických arteriálních embolizací do mozku (9). Prevalence PFO v populaci je přitom velmi vysoká, kolem 27 % (10). Tato situace právem vzbuzuje obavy potápěčské veřejnosti a často i lékařů, kteří jsou stále s problematikou DCS málo seznámeni. Ve většině zemí včetně České Republiky zatím neexistují doporučené postupy, které by tuto problematiku řešily. Spolehlivou prevencí opakovaných DCS je ukončení potápěčské činnosti, ale toto řešení je z našich zkušeností pro většinu potápěčské veřejnosti nepřijatelné. Někteří autoři navrhují v této indikaci katetrizační uzávěr PFO a zejména u profesionálních potápěčů, kde by jinak hrozila ztráta zaměstnání, je již tento výkon individuálně prováděn (13, 14). Jinou možností je doporučit konzervativní přístup k potápění, tedy soubor bezpečnostních doporučení s omezením maximální hloubky a doby ponoru, který by vedl k snížené tvorbě a paradoxní embolizaci bublin (15). Problémem takových doporučení je nedostatek důkazů, které by podporovaly dlouhodobý efekt jak katetrizačního uzávěru, tak konzervativního přístupu k potápění.

V naší studii jsme na malé skupině potápěčů po simulovaném sestupu v barokomoře přímo srovnali výskyt venózních a arteriálních bublin. Jako model dekompresního sestupu byl u kontrolní skupiny využit sestup do 18 m na 80 min (s dekompresní zastávkou po dobu 7 min v 3 m), který v naší práci generoval venózní bubliny u 74 % potápěčů a u 32 % potápěčů byly detekovány i bubliny arteriální. To je ve shodě s dříve popsaným faktem, že ke vzniku bublin dochází již po jednom ponoru i při dodržení dekompresního režimu (2, 3). V kontrolní skupině došlo u jedné třetiny potápěčů s arteriálními bublinami k rozvoji příznaků DCS. U potápěčů po katetrizačním uzávěru byl podle očekávání nalezen stejný počet venózních bublin, nicméně došlo k eliminaci bublin arteriálních a žádný potápěč neměl příznaky DCS. Zkrácením doby ponoru na bezdekompresní čas, doporučený Buehlmannovými tabulkami určenými pro rekreační potápěče, došlo k významnému snížení počtu venózních bublin, ale k úplné eliminaci arteriálních bublin u potápěčů s PFO nedošlo.

Tvorba bublin je individuální a závisí na řadě faktorů jako je věk, index tělesné hmotnosti, pohlaví, či hydratace před ponorem (16, 17). Množství rozpuštěného dusíku závisí zejména na době expozice a hodnotě parciálního tlaku dusíku. Ke vzniku bublin pak dojde při hypersaturaci tkání při příliš rychlém výstupu na hladinu (18). Tvorba bublin tedy závisí také na výstupové rychlosti (17). Pomalejší výstup na hladinu by mohl u potápěče s PFO vést k další redukci výskytu arteriálních bublin.

Z výsledků usuzujeme, že katetrizační uzávěr vedl k eliminaci arteriálních bublin po simulovaném sestupu v barokomoře a mohl by tak být efektivní léčbou rekurentní nevyprovokované DCS u potápěčů s PFO. Aplikace současných bezpečnostních doporučení pro potápěče s PFO vedla k nižšímu výskytu venózních bublin, ale nezabránila jejich paradoxní embolizaci do systémového oběhu a je tedy potřeba k takovým doporučením přistupovat obezřetně zejména s ohledem na klinické obtíže potápěče. Otázkou zůstávají dlouhodobé následky asymptomatických paradoxních embolizací. Odpověď na dlouhodobou efektivitu obou postupů by měly přinést výsledky longitudinálních studií s klinickým sledováním potápěčů s PFO.

Závěr

PFO může ohrožovat potápěče vznikem takzvané nevyprovokované dekompresní příhody s výskytem akutních symptomů i při dodržení dekompresních pravidel. Bezpečnostní doporučení pro potápěče s PFO by měly omezovat zejména maximální hloubku a dobu ponoru a nejspíše i doporučit delší bezpečnostní zastávky, pomalejší výstupovou rychlost a dostatečnou hydrataci před ponorem. Jejich efektivitu je nutno ověřit v longitudinálních klinických studiích. Katetrizační uzávěr PFO se zdá být možnou vysoce efektivní alternativou. Přístup k potápěči s PFO by měl být individuální, základem prevence DCS nadále zůstává zejména důkladná edukace potápěče. Simulovaným sestupem lze ověřit individuální riziko vzniku bublin.

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Attachment 5

Patent Foramen Ovale in Recreational and Professional Divers: An Important and Largely Unrecognized Problem.

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Review

Patent Foramen Ovale in Recreational and Professional Divers: An Important and Largely Unrecognized Problem

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ABSTRACT

Patent foramen ovale (PFO) is associated with an increased risk of decompression sickness (DCS) in divers that results from a paradoxical embolization of nitrogen bubbles. The number of scuba divers worldwide is estimated in the millions, and the prevalence of PFO is 25%-30% in adults. It is interesting that despite these numbers, many important issues regarding optimal screening, risk stratification, and management strategy still remain to be resolved. Recently published data suggest the possible effectiveness of both PFO closure and conservative diving measures in preventing arterial gas embolization. This review aims to introduce the basic principles of physiology and the pathophysiology of bubble formation and DCS, summarize the current literature on PFO and diving, and review the possibilities of diagnostic workup and management.

RÉSUMÉ

Le foramen ovale perméable (FOP) est associé à une augmentation du risque du mal de décompression (MDC) chez les plongeurs et résulte d'une embolisation paradoxale de bulles d'azote. Dans le monde entier, on estime que le nombre de plongeurs en scaphandre autonome s'élève à plusieurs millions, et que la prévalence du FOP est de 25 % à 35 % chez les adultes. Il est intéressant de constater qu'en dépit de ce nombre, il reste de nombreuses questions importantes à résoudre concernant le dépistage optimal, la stratification du risque et la stratégie de prise en charge. Les données récemment publiées suggèrent l'efficacité possible de la fermeture du FOP et des mesures préventives traditionnelles de plongée pour éviter l'embolisation gazeuse artérielle. Cette revue a pour but de présenter les principes de base de la physiologie et de la physiopathologie de la formation des bulles et du MDC, de résumer la littérature actuelle sur le FOP et la plongée, et de passer en revue les possibilités de bilan diagnostique et de prise en charge.

Scuba (self-contained underwater breathing apparatus) diving is a popular sport that attracts millions of participants worldwide.[1] Exposure to the hyperbaric environment is associated with unique effects on human physiology and specific disorders. Much attention has been paid to the risks related to patent foramen ovale (PFO).[2] In divers, PFO is associated with an increased risk of decompression sickness (DCS).[3] Despite the high prevalence of PFO (25%-30% in adults),[4] many issues—including optimal screening, risk stratification, and management strategy—remain to be resolved. This review aims to introduce the basic principles of physiology and the pathophysiology of bubble formation and DCS, summarize current literature on PFO and diving, and review the possibilities of diagnostic workup and management.

Background

With the development of professional and recreational diving in the 20th century, the knowledge of DCS progressed. DCS was first described in an animal model in 1670 by Robert Boyle.[5] The first clinical cases of divers experiencing DCS were reported much later in 1841.[6] The description of 110 cases (14 divers died) during the construction of the Brooklyn Bridge in 1873 is more well known. Five years later, in his classic work *La Pression Barometrique*, French zoologist and physiologist Paul Bert postulated that DCS is caused by nitrogen gas bubbles and showed the advantages of breathing oxygen after DCS develops.[7] In 1908, after a series of animal decompression experiments, John Scott Haldane developed the first dive tables that advised staged decompression for the British Admiralty.[8] This marked the development of further decompression models that are routinely used today by recreational and professional divers to prevent DCS.

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DCS: Physiology and Pathophysiology

The diver is exposed to a hyperbaric environment during submersion. In scuba diving, air (or other breathing mixture of oxygen and inert gases) is breathed at ambient pressure. According to Henry's law, the amount of gases dissolved in tissues is proportional to their partial pressures. Thus at depth, the concentration of gases in tissues increases over time. The rate of gas saturation is dependent on the chemical composition and density of capillaries in a particular tissue.[9] As the diver ascends to the surface, a pressure gradient drives the dissolved gases back from peripheral tissues to venous blood and ultimately to the alveolar space from which it is expired out of the body. If the pressure drops too quickly, the tissues become supersaturated with gases not used by the body (nitrogen and inert gases), and a gas phase forms.[10]

The process of bubble formation has attracted the interest of researchers for more than a century, but many aspects remain unclear. Although still controversial, it is generally agreed that an a priori presence of some form of micronuclei is required for bubbles to form in divers.[10] It is important that the rate of saturation and desaturation differs among tissues. Mathematical models incorporating several tissue compartments are used to characterize whole-body gas kinetics.[11] To prevent DCS, divers routinely use specialized dive computers or tables that are based on these models.

DCS is caused by the formation and growth of gas bubbles in supersaturated blood or tissues during the diver's ascent (Fig. 1). These bubbles cause either local tissue damage or embolize through venous blood.[12] Small quantities of venous gas emboli (VGE) have been confirmed by Doppler studies in 80%-91% of scuba divers.[13,14] Most divers with VGE, however, remain asymptomatic, because these bubbles are effectively filtered by the pulmonary circulation. Symptoms may occur either with high bubble load (ie, pulmonary gas embolism in case of violation of the decompression regimen) or from paradoxical embolization (arterialization of bubbles) in a diver with a permanent or transient right-to-left shunt. If paradoxical embolization occurs in a diver with a PFO, arterialized bubbles lodge in peripheral capillaries. Furthermore, excess gas from supersaturated tissues promotes further growth of these bubbles. The resulting obstruction of capillaries causes local ischemia.[12]

The clinical picture of DCS is heterogeneous and reflects the number of bubbles and the sites of their formation and embolization. Based on symptoms, cutaneous, musculoskeletal, neurologic, and pulmonary forms of DCS are recognized. The musculoskeletal form, manifesting as severe joint pain, is thought to be caused by local bubble formation in the avascular joint cartilage.[15] On the other side of the spectrum are diverse and potentially severe neurologic manifestations in which it seems that bubble embolization through a PFO might play an important role.

Role of PFO

The connection between PFO and DCS was first described in the 1980s.[16,17] Since then, a high prevalence of PFO has been repeatedly reported in divers with the neurologic or cutaneous forms of DCS (Table 1). In an important study, Torti et al.[18] reported an incidence of major DCS per 10,000 dives of 1.5 with no PFO, < 1 with grade 1 PFO, 3 with grade 2 PFO, and 9 with grade 3 PFO. The associated odds would be 1 for a grade 1, 2 for a grade 2, and 6 for a grade 3 PFO compared with no PFO. However, this study had important limitations, including its retrospective nature and possible selection bias.[23] In another study, the incidence of PFO was 77% among 61 divers who had experienced the cutaneous form of DCS compared with 28% in controls. Additionally, besides the higher incidence of acute DCS, it has been suggested that repeated exposure to asymptomatic arterial embolisms could lead to chronic sequelae. Knauth et al.[24] reported an association of PFO with multiple brain lesions in a follow-up study using magnetic resonance imaging. There is, however, an ongoing debate regarding whether this finding has a pathophysiological link to PFO or any clinical significance.[25]

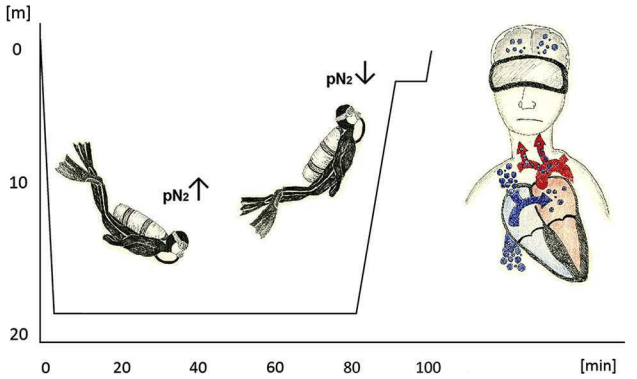

Figure 1. Pathophysiology of bubble formation and embolization in decompression sickness A dive profile of 18 m maximum depth and bottom time (time to ascent) of 80 minutes is depicted to demonstrate the pathophysiology of bubble formation and embolization in divers. During descent, the diver breathes air at elevated ambient pressure, and excess nitrogen dissolves in tissues. During ascent, the ambient pressure drops and a pressure gradient drives nitrogen from tissues to venous blood. If the pressure drops too quickly, the tissues become supersaturated and nitrogen bubbles form and embolize through venous blood. In a diver with a patent foramen ovale, a paradoxical right-to-left embolization of bubbles may occur and the bubbles lodge in peripheral capillaries. The resulting ischemia may manifest as decompression sickness. pN_2, partial pressure of nitrogen.

Bearing in mind the high prevalence of PFO,[4] these reports raise concern among divers and involved medical professionals. Moreover, in divers with PFO, a paradoxical embolization to the systemic circulation may cause various, mostly neurologic or cutaneous, DCS symptoms, even after a dive with an appropriate decompression regimen.[20] This unpredictable event has been coined "unprovoked DCS."

Paradoxical embolization results from increased right atrial pressure resulting from hemodynamic changes that occur in divers. After submersion, blood redistributes from the periphery to the thorax, which results in increased right atrial pressure.[26] Moreover, divers may perform a Valsalva manoeuvre during or after the dive (to equalize pressure in the middle ear or while lifting heavy diving equipment), which further contributes to the increased right atrial pressure and might lead to transient right-to-left shunting through the PFO. Conversely, it has been suggested that the transpulmonary passage might also play an important role in the

Table 1. Studies evaluating the presence of patent foramen ovale in divers with decompression sickness

Author	Year	Participants, type of study	Main findings
Torti et al.[18]	2004	Recreational divers (n = 230), cross-sectional study	Odds of experiencing major DCS event was 5 times higher in divers with PFO; the risk paralleled PFO size; overall risk was small (5 events per 10,000 dives)
Wilmhurst et al.[19]	2001	Divers with cutaneous DCS (n = 61) vs control divers (n = 123), case-control study	Right-to-left shunt present in 77% of cases vs 27.6% in controls ($P < 0.01$); large shunt present in 49.2% of cases vs 4.9% of controls ($P < 0.01$)
Germonpré et al.[20]	1998	Sports divers with neurologic DCS (n = 37) vs matched control divers (n = 37), case-control study	Prevalence of PFO was higher in subgroup of divers with cerebral DCS compared with matched controls (80% vs 25%, $P = 0.01$), but not in divers with spinal DCS (35% vs 50%, $P = 0.49$)
Cantais et al.[21]	2003	Divers with DCS referred for treatment in a hyperbaric chamber (n = 101) vs control divers (n = 101), case-control study	Prevalence of PFO higher in a series of consecutive DCS cases vs controls (59% vs 25%, $P < 0.01$); the proportion of major right-to-left shunts was higher in cochleovestibular and cerebral DCS subgroups but not in spinal and non-neurologic DCS
Gempp et al.[22]	2012	Divers with DCS referred for treatment in a hyperbaric chamber, recurrent cases (n = 24) vs single episode (n = 50), case-control study	Diving experience, the presence of Large right-to-left shunt, and the lack of changes in the way of diving after previous episodes of DCS were independently associated with a repeated episode

DCS, decompression sickness; PFO, patent foramen ovale.

occurrence of arterial gas emboli after a dive.[27] However, the estimated prevalence of large pulmonary arteriovenous malformations is low,[28] and the clinical significance of small functional shunts is doubtful.[29,30] Also, the numerous aforementioned clinical studies support the fact that a PFO might be the major route of paradoxical embolization in divers.[18-22] It is important to note that a small shunt probably does not impart risk, whereas a large shunt should be considered to increase the risk of DCS. The prevalence of large PFOs is estimated to be 6%-10% in the general population,[31] and the prevalence of a PFO was reported to decrease with age in a large autopsy study of normal hearts.[4] In contrast, there is some evidence for increasing patency of the foramen ovale in divers over years.[32]

Diagnostic Imaging

Three ultrasonographic techniques are available for imaging a PFO or detection of right-to-left intracardiac shunts: transthoracic echocardiography (TTE), transesophageal echocardiography (TEE), and transcranial color-coded ultrasonography. These methods may be used for screening, to plan and assist device closure, and to monitor the presence of venous and arterial bubbles after a dive.

TEE has traditionally been considered the gold standard of PFO diagnostics.[33] The proximity of the probe to the atrial septum ensures optimal resolution and enables quality 2-dimensional and 3-dimensional imaging of the PFO and surrounding structures. In the diagnostic work-up of cryptogenic stroke, TEE importantly enables the visualization of other potential sources of embolism, eg, a thrombus in the left atrial appendage or atherosclerotic lesions in the proximal aorta. However, in divers there are several disadvantages to take into account. Especially in the context of PFO screening, both the semi-invasiveness and the cost of the procedure need to be considered. Furthermore, patient positioning and sedation make it difficult to perform a sufficient Valsalva manoeuvre to visualize a shunt with the use of the contrast agent. In contrast, if PFO closure is considered, TEE is an optimal tool to confirm the intracardiac localization of a right-to-left shunt and to reveal the anatomy. TEE is generally used to assist transcatheter PFO closure, although intracardiac echocardiography may be used as an alternative.[34]

In several studies, contrast-enhanced TTE was shown to have similar sensitivity and specificity when compared with contrast-enhanced TEE.[35-37] However, in a study by Ha et al.,[38] the sensitivity and specificity of TTE was found to be 63% and 100%, respectively, when compared with TEE as a gold standard. This would suggest that TTE could generate a significant proportion of false-negative results. Also, the spatial resolution is inferior to that of TEE. However, the negative results from TTE may be caused by reduced sensitivity in detecting small shunts, which are not considered to be a risk. Conversely, a potential advantage is that it is easier for the patient to perform a Valsalva manoeuvre. Thus, it remains to be determined whether TTE could be used as a screening tool. Besides PFO detection, TTE may be used to monitor venous bubbles after a dive. In this setting, bubbles may be visualized in an apical 4-chamber view (Fig. 2) and quantified either on still images or by using pulsed-wave Doppler in the right ventricular outflow tract.[39,40]

Transcranial color-coded ultrasonography visualizes blood flow in the middle cerebral artery (MCA) through a temporal window in the skull. A pulsed wave Doppler study is used to detect gas bubbles (either nitrogen bubbles after the dive or microbubbles of ultrasonographic contrast material) as high-intensity transient signals (HITS) (Fig. 3). The presence of HITS confirms right-to-left shunting. The localization of the shunt may be intracardiac or transpulmonary. The transpulmonary passage is longer and the bubbles usually appear after > 15 cardiac cycles after the administration of ultrasonographic contrast medium.[30] When using standardized protocols, a sensitivity of 94%-100% and a specificity of 75%-100% compared with TEE has been reported.[30,41] This makes transcranial color-coded ultrasonography a valuable screening tool. A possible concern is that the temporal window may be inadequate to reliably visualize the MCA in 10%-12% of patients.[42] However, this is dependent on the examiner, the ultrasonographic equipment, and the age of the

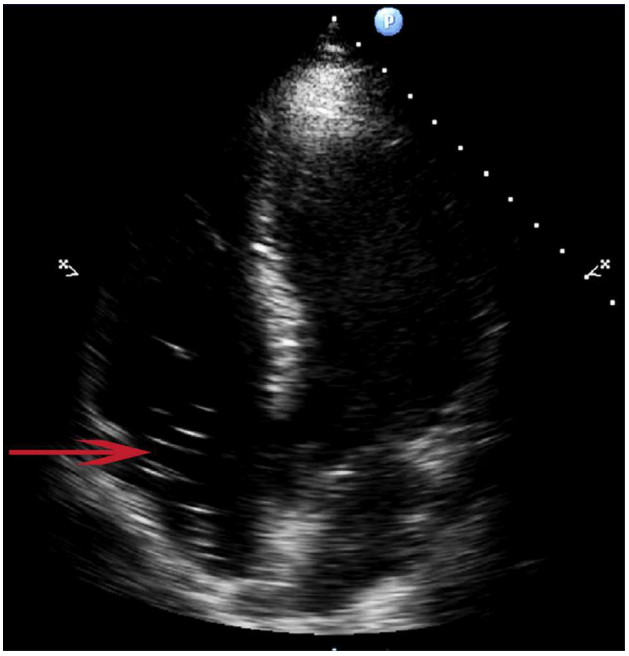

Figure 2. Echocardiographic appearance of venous bubbles after a dive. Transthoracic echocardiography apical 4-chamber view: nitrogen bubbles (**arrow**) after a dive are apparent in right-sided but not left-sided heart chambers in a diver with a patent foramen ovale and no right-to-left shunt during native breathing.

patient.[43] Therefore, this might not be a limitation in young healthy individuals, such as most recreational and professional divers.[39] For screening, agitated saline or hydroxyethyl starch solutions or a dedicated contrast agent may be used.[44] The monitoring for HITS should be performed according to a standardized protocol at rest and after a Valsalva manoeuvre.[45]

The shunt is graded as follows: 0 = no HITS, 1 = < 10 HITS, 2 = > 10 HITS but no curtain (uncountable number of bubbles), and 3 = curtain.[45] Arterial gas bubbles after a dive may be assessed in the same manner. However, to date there is no standardized protocol for this application. We suggest monitoring the MCA flow for 60 seconds during native breathing and subsequently 3 times for 40 seconds after a Valsalva manoeuvre.[39]

Therapeutic Options

There is still a large knowledge gap regarding the optimal risk stratification and management strategy in divers with PFO. Routine screening for PFO in divers is currently not recommended in most countries.[46,47] Suggested recommendations for divers with diagnosed PFO and a history of DCS include the cessation of diving, a conservative approach to diving, and PFO closure. The evidence for both conservative dive profiles (CDPs) and catheter-based PFO closure is still sparse.

It has been suggested by several authors that a catheter-based PFO closure in divers might eliminate the arterialization of bubbles and prevent unprovoked DCS.[48-50] So far, only 1 study has provided data on the effect of PFO closure on elimination of arterial gas emboli (AGE) after a dive.[39] In this study, VGE and AGE were assessed by means of ultrasonography in 47 divers after surfacing from a simulated dive in a hyperbaric chamber. All divers had a large PFO (grade 3 according to the International Consensus Criteria) and previously experienced DCS; in 20, the PFO was occluded with a catheter-based device (closure group), the other 27 divers did not undergo any closure procedure (PFO group).[45] The Amplatzer septal occluder (AGA Medical, Golden Valley, MN) and the Occlutech Figulla PFO Occluder N (Occlutech GmbH, Jena, Germany) were used. In this study, no divers in the closure group had AGE after a dive. Also, none of these

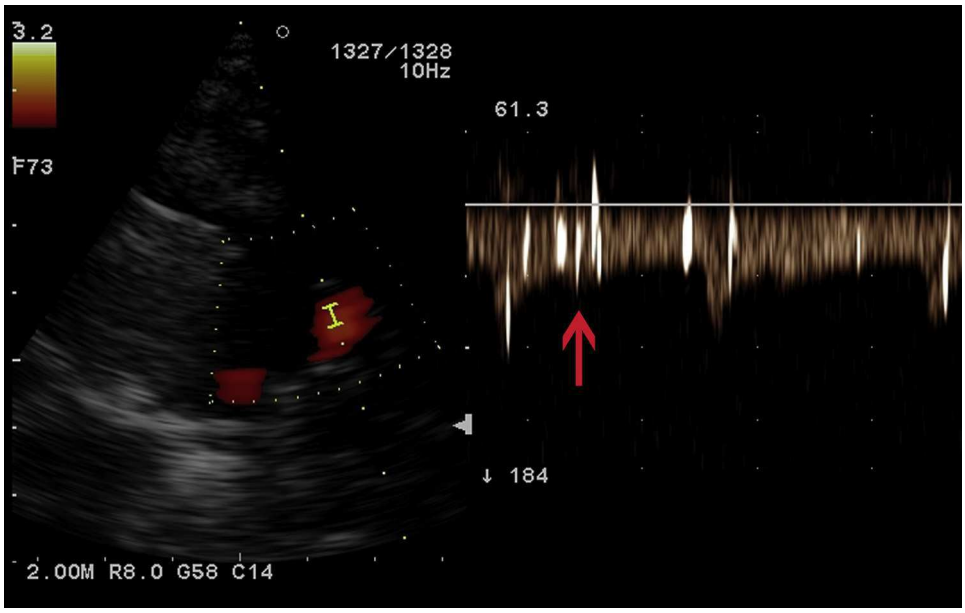

Figure 3. Arterial gas emboli visualized by transcranial color-coded ultrasonography. After a dive, arterial gas emboli are apparent as high-intensity transient signals (**arrow**) in the Doppler spectrum in the middle cerebral artery in a diver with a patent foramen ovale.

divers had DCS symptoms. However, the reduction in DCS incidence did not reach statistical significance. The lack of predefined clinical end points, the small scale of the study, and the experimental setting are important limitations that must be considered. Clearly, more clinical data are needed to obtain a definitive answer regarding DCS and PFO closure. Also, we must bear in mind that this is an invasive procedure with potential major complications, although the occurrence is generally low (< 1%).[51] The success rate of the procedure is high, but a moderate residual shunt may occur in about 10% of cases.[52] Furthermore, it is important to note that PFO closure might have the potential to decrease the risk of DCS to the level of divers without PFO, but not to zero.

It is often recommended that symptomatic divers diagnosed with PFO cease diving. This solution mostly is not accepted, and alternatives are sought. CDPs are measures aimed at lowering the probability of nitrogen bubble formation to decrease the risk of DCS. The probability of tissue supersaturation and subsequent bubble formation can theoretically be lowered by both minimizing tissue saturation (ie, limiting nitrogen exposure) and allowing more time for the desaturation of tissues. To lower nitrogen exposure, various CDP recommendations limit maximum depth, dive time, or number of dives per day or advise the use of mixtures with lower nitrogen content (enriched air nitrox).[22,51] Similarly, to allow more time for desaturation, a slower ascent rate and performing longer safety stops is recommended.[53] There is also some evidence that hydration and exercise before a dive reduce the risk of DCS.[54] Few data are available regarding the safety of these measures in divers with PFO. However, a recently published study suggested a significant decrease in the occurrence of arterial bubbles among divers with large PFOs by limiting the exposure time and reducing the ascent rate.[55]

Conclusions

It seems likely that the presence of a PFO is associated with an increased risk of DCS in recreational and professional divers as a result of paradoxical embolism of nitrogen bubbles. It is interesting that despite the high number of divers and the high prevalence of PFO, a large knowledge gap exists regarding optimal screening, risk stratification, and management strategy. It seems that catheter-based PFO closure might play a role in secondary DCS prevention in highly symptomatic divers in the future. Currently, however, there is a lack of clinical evidence to justify this approach. We assume that clinical studies will bring important pathophysiological and clinical insights in years to come.

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Disclosures

The authors have no conflicts of interest to disclose.

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