



Original article

High-grade patent foramen ovale is a risk factor of unprovoked decompression sickness in recreational divers



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ABSTRACT

Background: Patent foramen ovale (PFO), male sex, age, and body mass index (BMI) were all identified as potential risk factors of decompression sickness (DCS). It has been debated whether PFO might cause unprovoked DCS (i.e. without violation of decompression procedure) due to paradoxical embolization of venous gas emboli. To date, there are no data on the incidence or risk factors of unprovoked DCS. This study sought to evaluate the risk factors of unprovoked DCS in recreational divers.

Methods: A total of 489 consecutive divers were screened for PFO between January 2006 and January 2014 by means of transcranial Doppler. All patients were prospectively included in the study registry. Survival analysis techniques were used to assess for risk factors for unprovoked DCS. Age, sex, BMI, PFO presence, and grade were analyzed. The total sum of dives was used as a measure of time.

Results: The group performed a total of 169,411 dives (mean 346 ± 636). Thirty-six (7%) of the divers suffered from an unprovoked DCS. The frequency 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, BMI, or total number of dives between the respective groups. In the adjusted Cox proportional hazards model, PFO grade 3 was a major risk factor for unprovoked DCS; there was a slight protective effect of increasing age.

Conclusions: We demonstrated that a high-grade PFO was a major risk factor for unprovoked DCS in recreational scuba divers.

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Introduction

Patent foramen ovale (PFO) has been associated with an increased risk of decompression sickness (DCS) in divers due to paradoxical embolization of nitrogen bubbles that form during the diver's ascent [1]. However, this hypothesis has been widely debated. The prevalence of PFO in the general population is high

(27%) [2]. Therefore, it remains to be determined whether other factors, such as risky diving behavior, body mass index (BMI), age, or sex, play a more important role [3–6]. On the other hand, reports that nitrogen bubbles can be detected in venous blood, even after a single conservative dive, raised the concern that divers with a right-to-left shunt might suffer from DCS even without violating decompression regimen [7,8]. These unpredictable events have been termed unprovoked DCS and are a potential threat to millions of recreational divers worldwide. Yet, to date, there are no data on the incidence and risk factors for unprovoked DCS. The aim of our study was to assess the risk factors for unprovoked DCS in recreational divers.

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Methods

A total of 489 consecutive divers were screened for PFO at our center between January 2006 and January 2014 by means of transcranial color-coded sonography (TCCS). All patients were prospectively included in the study registry. The screening was offered to all registered Czech diving clubs and was regularly promoted through diving magazines, websites, instructor courses, and diving and hyperbaric medicine meetings. Baseline data (i.e. demographic data, diving experience, and DCS history) were collected from all divers at the time of the screening examination. Divers with a history of DCS filled in a detailed questionnaire in order to reveal any violation of the rules of safe recreational diving. The questions included the number and timing of all preceding dives, maximum depth, bottom time, and any violation of regimen advised by a diving computer or table, such as exceeding the maximum ascent rate or shortening the advised safety stop. The study was approved by the local ethics committee and all study subjects gave written informed consent to participate in the study.

Transcranial color-coded sonography was used for the detection of a right-to-left shunt, as described previously [9]. The shunt was graded according to the International Consensus Criteria: grade 1, 1–10 bubbles; grade 2, >10 bubbles but no curtain (uncountable number of bubbles); and grade 3, curtain [10]. The TCCS was performed by experienced neurologists (MS and AT), blinded to the diver's DCS history. The method used to define the presence of a PFO and its grade in this study was TCCS. In patients considered for catheter-based PFO closure (divers with a history of unprovoked DCS and right-to-left shunt detected on TCCS), a transesophageal echocardiography was performed to assess the anatomy of the interatrial septum and surrounding structures [11,12]. Transesophageal echocardiography was also offered to all other symptomatic divers (provoked and unprovoked DCS regardless of the result of the TCCS examination) and to divers with a high-grade shunt on TCCS and no previous history of DCS.

A history of unprovoked DCS was defined as any DCS symptom that originated less than 24 hours after a dive or series of dives that complied with all the rules advised to recreational divers. For the definition of recreational diving, we reviewed the rules advised by the largest international scuba (self-contained underwater breathing apparatus) diving agencies (Professional Association of Diving Instructors, Confédération Mondiale des Activités Subaquatiques, Scuba Schools International, National Association of Underwater Instructors) at the level of open water diver, and advanced open water diver or their equivalent [13–16]. For the DCS event to be considered unprovoked the divers had to comply with the adopted decompression algorithm [17]. Technical diving, such as diving with mixtures containing helium or decompression diving, was excluded. For an unprovoked DCS, the diver had to perform a non-decompression air dive, according to any commercially available recreational diving table or computer, to a maximum depth of

40 m, with a maximum ascent rate 10 m/min with a safety stop performed as advised by the computer or table. For consecutive dives, a minimum 2 h surface interval between dives and a maximum of 3 consecutive days of diving were required. Also, if the diver reported inadequate hydration or severe exhaustion (e.g. due to technical problems, problems with orientation or strong currents), the DCS was considered provoked.

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

We analyzed age, sex, BMI, and PFO (each grade of PFO in a separate analysis compared to divers without PFO). Due to the possibility of numerically unstable estimates and large standard errors, 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. The goodness of fit of the model was tested. Additionally, Kaplan–Meier survival curves were created, and log-rank statistics were calculated. All statistical analyses were carried out using IBM SPSS Statistics 25.0 (IBM, Armonk, NY, USA).

Results

A total of 489 divers were screened for the presence of a right-to-left shunt between January 2006 and January 2014 by means of TCCS. The mean age was 35.5 ± 9.0 years, and 87% were men. A PFO was found in 40% of the divers. Thirty-six (7%) of the divers suffered from an unprovoked DCS. The divers had performed a total of 169,411 dives (mean 346 ± 636) and experienced a total of 54 unprovoked DCS episodes (occurrence rate per dive 0.03%). The prevalence of PFO was 97% in divers with a history of unprovoked DCS and 36% in controls ($p < 0.001$); for PFO grade 3, the prevalence was 86% versus 18%, respectively ($p < 0.001$). There was no difference in sex, age, BMI, or the total number of dives between the respective groups. The results are summarized in Table 1.

PFO presence, age, and sex were included in the final adjusted model (unadjusted HR for unprovoked DCS by individual variables are summarized in Table 2). The adjusted HR for unprovoked DCS in divers with a PFO, compared to divers without a PFO, was 60.0 (95% CI 8.2–438.5, $p < 0.001$). Divers with PFO grade 3 had a higher risk of unprovoked DCS ($HR_{adj} = 93.0$, 95% CI 12.5–688.7, $p < 0.001$). The adjusted HR for unprovoked DCS in divers with a PFO grade 1, compared to divers without a PFO, was not significant but was numerically higher ($HR_{adj} = 10.8$, 95% CI 1.0–121.8, $p = 0.054$). Two

Table 1
Results.

Group	All divers (n = 489)	Controls (no unprovoked DCS) (n = 453)	Unprovoked DCS (n = 36)	p-Value
Dives – total, mean (+/-SD)	169,411, 346.4 (635.6)	156,693, 345.9 (647.7)	12,718, 353.3 (463.2)	0.17
Age (years) – mean (+/-SD)	35.6 (9.0)	35.5 (9.1)	36.4 (7.7)	0.22
Male sex, total (%)	423 (86.5%)	393 (86.8%)	30 (83.3%)	0.61
BMI (kg/m ²) – mean (+/-SD)	26.1 (3.2)	26.1 (3.1)	26.2 (3.6)	0.99
PFO	196 (40.1%)	161 (35.5%)	35 (97.2%)	<0.001*
PFO grade 1	65 (13.3%)	63 (13.9%)	2 (5.6%)	0.21
PFO grade 2	20 (4.1%)	18 (4.0%)	2 (5.6%)	0.65
PFO grade 3	111 (22.7%)	80 (17.7%)	31 (86.1%)	<0.001*

BMI, body mass index; DCS, decompression sickness; PFO, patent foramen ovale; +/-SD, standard deviation.

* Statistically significant difference.

Table 2
Hazard ratio for unprovoked decompression sickness by univariate and multivariate analysis.

Variable	Univariate analysis HR (95% CI, p)	Multivariate analysis HR (95% CI, p)
Age (years)	0.955 (0.916–0.995, p = 0.030)	0.941 (0.902–0.981, p = 0.004)
Sex (male)	0.383 (0.158–0.933, p = 0.035)	0.557 (0.223–1.396, p = 0.212)
BMI	0.930 (0.824–1.050, p = 0.243)	0.970 (0.851–1.105, p = 0.645)
PFO	52.371 (7.173–382.382, p < 0.001)	59.959 (8.199–438.483, p < 0.001)
PFO 1	10.817 (0.978–119.682, p = 0.052)	10.806 (0.959–121.772, p = 0.054)
PFO 2	28.114 (2.536–311.642, p = 0.007)	–
PFO 3	78.124 (10.662–572.418, p < 0.001)	92.943 (12.544–688.663, p < 0.001)

BMI, body mass index; CI, confidence interval; HR, hazard ratio; PFO, patent foramen ovale.

Final model included adjustments for age, sex, and PFO presence. PFO grades 1–3 were compared to controls, for PFO grade 2 the HR was numerically unstable and not statistically significant.

out of twenty divers with a PFO grade 2 had unprovoked DCS, the HR was numerically unstable and not statistically significant. The results of the multivariate analysis are summarized in Table 2. Also according to the results of the log-rank test of the Kaplan–Meier analysis the risk of unprovoked DCS was significantly higher in divers with a PFO (Fig. 1) and with PFO grade 3 (Fig. 2).

Discussion

We screened a total of 489 divers, who performed a total of 169,411 dives, and found that unprovoked DCS occurred in 7% of the divers, the occurrence rate per dive was 0.03%. The prevalence of PFO and, importantly, PFO grade 3 was high in patients with a history of unprovoked DCS. There was no difference in sex, age, BMI, or the total number of dives between the respective groups. PFO grade 3 was found to be the major risk factor of unprovoked DCS, using the Cox proportional hazards model.

Decompression sickness is caused by nitrogen bubbles that form in supersaturated tissues during the diver’s ascent. These bubbles cause either local tissue damage or embolize through venous blood [18]. The clinical manifestation is heterogeneous from severe neurological impairment to a localized skin rash [18]. Clearly, if a diver severely violates the decompression regimen and reaches the

surface too early, the bubble load may be massive and cause a fatal pulmonary gas embolism. On the other hand, a small number of venous gas emboli (VGE) might be effectively filtered by pulmonary circulation and, thus, remain subclinical. It is of note, that even after a properly performed recreational dive a small number of VGE may be detected. Ljubkovic et al. found VGE after 80% of single no-decompression air dives [8]. It has been debated whether an unprovoked DCS might occur in some of these divers.

To our knowledge, this is the only study to date to assess for risk factors for unprovoked DCS in recreational divers. However, some previous studies have focused on the risk factors of DCS in general. Traditionally, age, BMI, and repetitive diving were considered risk factors for DCS. Carturan et al. monitored 50 divers after two dive profiles and found ascent rate, age, aerobic fitness, and adiposity to be associated with a higher post-dive VGE occurrence [4]. In a study performed by the Divers Alert Network (DAN), 67 recreational divers were monitored for two years for Doppler-detected VGE. The incidence of high-bubble grade was approximately 20% higher for repetitive dives than for first dives and approximately 20% higher for males than females, which also increased with age (25% in male and 55% in female divers) [7].

In a retrospective observational study, male divers were also at a higher risk of DCS, although this might have been influenced by

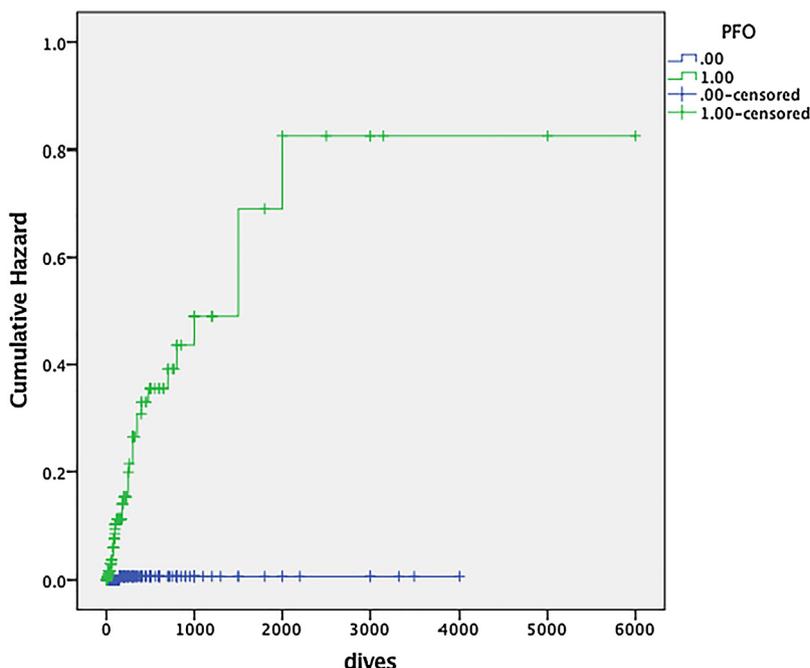


Fig. 1. Kaplan–Meier analysis: cumulative hazard of unprovoked decompression sickness in divers with and without a patent foramen ovale. Log-rank test for equality of survivor function was $\chi^2 = 49.068$, $p < 0.001$. PFO, patent foramen ovale.

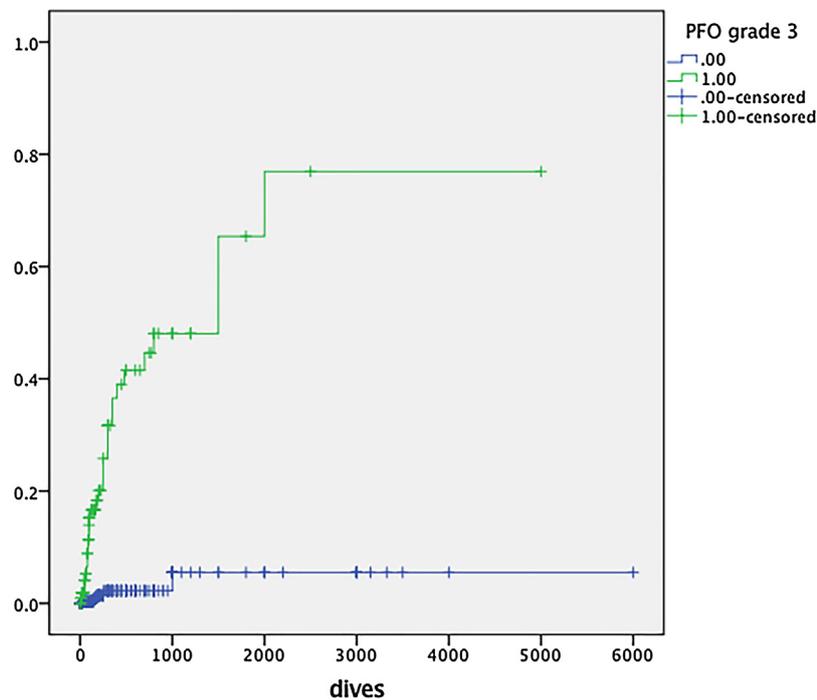


Fig. 2. Kaplan–Meier analysis: cumulative hazard of unprovoked decompression sickness in divers with and without a patent foramen ovale grade 3. Log-rank test for equality of survivor function was $\chi^2 = 76.835$, $p < 0.001$. PFO, patent foramen ovale.

their diving habits [19]. In contrast, Gempp et al. found results similar to ours in a small case-controlled study of divers with recurrent DCS [20]. They found a right-to-left shunt and lack of changes in the way of diving after a prior DCS as the only predictors of neurological DCS recurrence. Age, sex, and diving experience were not associated with recurrent neurological DCS. Together with the results of the present study, this suggests that the presence of a PFO might play a more important role in at least a subset of DCS, such as the neurological form or in unprovoked episodes.

Recreational divers are trained through several international diving organizations with a large emphasis on DCS prevention and diving safety in general. The use of dive computers (or tables) to prevent DCS is recommended for every dive. These devices use a multi-compartment model to calculate nitrogen desaturation in order to prevent bubble formation in all tissues. Furthermore, the divers are advised on other safety measures, such as proper pre-dive hydration or a maximum depth of 40 m [21]. Although recreational diving is generally considered a safe sport, none of the above-mentioned safety measures was ever validated in divers with a high-grade PFO [22]. Furthermore, it is known that, in spite of these preventive measures, small numbers of VGE still occur after a properly performed dive [7]. Theoretically, the paradoxical embolism of these bubbles could be responsible for unprovoked DCS.

The concept, that a small number of bubbles embolizing to the systemic circulation through a PFO could cause DCS, was mentioned already in the 1980s [23,24]. Several retrospective studies confirmed a higher incidence of PFO in symptomatic divers in the two following decades [20,25–28]. However, the role of PFO in the pathophysiology of DCS has been highly debated since then.

In a previous study, it was demonstrated that catheter-based PFO closure eliminated post-dive arterial gas emboli after simulated dives in a hyperbaric chamber [29]. In addition, after PFO closure, DCS was not observed in any of the divers. In another study, a conservative dive profile with a short exposure and a slower ascent rate decreased the occurrence of both venous and

arterial gas emboli [30]. Both studies suggest that gas bubbles embolize through the PFO in divers and might be responsible for a higher risk of DCS.

The present study demonstrates that this mechanism might cause unprovoked episodes in recreational scuba divers with a high-grade PFO. In a multivariate analysis, PFO grade 3 was a major risk factor for unprovoked DCS. We also observed a slight protective effect of increasing age. We could speculate that this might be due to more experience or a more conservative approach to diving. However, provocation of DCS by risky behavior was excluded by the strict definition of unprovoked DCS in this study. In the unadjusted analyses of individual variables, an increased risk was also observed for PFO grade 2 and males. However, this was not observed when adjusted to other covariates in the final Cox proportional hazards model.

This retrospective study is subject to inherent limitations, including selection bias. The prevalence of PFO and the incidence of unprovoked DCS might not therefore be generalizable to the overall population of recreational divers. However, the occurrence rate of DCS was comparable to previous reports [31,32]. Although this study is, to our knowledge, the largest available, the number of endpoints is still low. Another limitation is the self-reporting of endpoints, which is due to the fact that the majority of cases were not examined by a specialist at the time of divers' DCS events.

Conclusion

The present study is the first, to our knowledge, to demonstrate that a high-grade PFO is independently associated with unprovoked DCS in recreational scuba divers. The results suggest that the general safety diving recommendations for recreational scuba divers might be less safe for divers with a high-grade PFO.

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Conflicts of interest

The authors declare there is no conflict of interest.

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