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CLINICAL STUDY

Risk stratification of neurological decompression sickness in divers

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ABSTRACT

INTRODUCTION: Patent foramen ovale (PFO) is a risk factor of decompression sickness (DCS). However, data on risk stratification of divers with a PFO are sparse. This study sought to evaluate the risk of neurological DCS (DCSneuro), based on the presence and grade of a right-to-left shunt (RLS).

METHODS: A total of 640 divers were screened for a RLS using TCD between 1/2006 and 4/2017. RLS was graded as low, medium, or high grade with two subgroups - after a Valsalva maneuver or at rest. Divers were questioned about their DCS history. Survival analysis techniques were used to assess risk factors for unprovoked DCS.

RESULTS: A RLS was found in 258 divers (40.3 %). 44 (17.1 %) divers with a RLS experienced DCSneuro compared to 5 (1.3 %) divers without a RLS ($p < 0.001$). The proportion of DCSneuro increased from 4.6 % in the low-grade RLS subgroup to 57.1 % in the subgroup with high-grade RLS at rest. The hazard ratio for DCSneuro and RLS was11.806 ($p < 0.001$).

CONCLUSIONS: Divers with a RLS had a higher risk of DCSneuro and the risk increased with RLS grade. We suggest that TCD is an appropriate method for RLS screening and risk stratification in divers *(Tab. 4, Fig. 2, Ref. 29).* Text in PDF *www.elis.sk*

KEY WORDS: decompression sickness, right-to-left shunt, transcranial sonography.

Introduction

Scuba diving is an activity attracting millions of amateurs and professionals worldwide. During submersion, the diver breathes air or other gas mixture under elevated pressure.This change in environment has physiological effects and may lead to specific disorders associated with raised ambient pressure, the most common of them being decompression sickness (DCS) (1).

Decompression sickness is caused by nitrogen bubbles that form in supersaturated tissues during the diver's ascent. These bubbles can cause either local tissue damage or embolize through the blood (2). Small quantities of venous gas bubbles are common after recreational scuba diving (3, 4). The occurrence of these bubbles is usually not associated with any clinical manifestation. Symptoms may occur either due to high bubble load, or paradoxical embolism (arterialization of bubbles) in a diver with a transient or permanent right-to-left shunt (RLS) (1).

Several forms of DCS are recognized, reflecting the localization of bubble formation and embolisation. According to symptoms, DCS is classified as cutaneous, musculoskeletal, neurological or pulmonary. The musculoskeletal form, manifesting as severe joint pain is caused by local bubble formation in the avascular joint cartilage (5). The pulmonary form is caused by massive air embolism in the pulmonary vasculature (2). Neurological symptoms are caused by injury to the brain or spinal cord (6, 7). Cutaneous DCS is manifested by a localized skin rash and its precise pathophysiology is still discussed (8). Nevertheless, data from case-control studies show that paradoxical embolization of gas bubbles through a RLS might play an important role in the cutaneous and neurological forms (9–12). Moreover, multiple brain lesions appearing as possible chronic sequelae of repeated subclinical embolizations through an RLS have also been reported (13).

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Transcranial Doppler sonography (TCD) is a safe screening method with comparable or higher sensitivity and lower specificity for RLS detection compared to the gold standard – transesophageal echocardiography (TEE) (14–17). As this detection method does not directly display the PFO but its effect – microbubbles by-passing the lung-capillary filter and detected in the brain circulation, we preferred the term RLS in this article to the less accurate term PFO.

The prevalence of patent foramen ovale (PFO) in the adult population is high (20–4 %) (18). Nevertheless, many questions including optimal screening method, risk stratification and management strategy in divers remain unclear (1). The aim of our study was to establish the risk of different types of DCS (especially the most severe form with neurological impairment) in relation to the presence of a RLS and its grade determined by transcranial sonography.

Methods

Study settings and design

A total of 640 divers were enrolled in the DIVE-PFO (Decompression Illness prevention in Divers with a Patent Foramen Ovale) registry between January 2006 and April 2017 (19). All divers were examined for the presence of an RLS with transcranial Doppler sonography (TCD). The screening was offered to all registered Czech diving clubs as well as police and firefighter divers. It was regularly promoted through diving magazines, websites, instructor courses, and diving and hyperbaric medicine meetings. All divers signed informed consent to participate in the study and the study protocol was approved by the local ethics committee.

Prior to the TCD examination, all divers filled in a detailed questionnaire about their health status, number of dives and prior DCS accidents.We also inquired about possible risk factors for DCS such as repetitive dives, decompression dives, dehydration, diving in cold water, and exercise after diving (20). The study was not limited to recreational diving and included also professional and technical divers.

Right-to-left shunt examination

Transcranial Doppler sonography was performed to detect the presence of a RLS. The examination was performed by experienced neurologists blinded to the diver's DCS history. Divers were examined in a supine position. Blood flow in the right middle cerebral artery (MCA) was monitored through the temporal window. An echocontrast agent (hydroxyethyl starch activated with air) was given three times at rest and three times after a Valsalva maneuver. The number of microbubble signals (MBS) in the MCA was counted after each application and the highest number of three was taken for each condition – rest breathing and Valsalva maneuver. The effectiveness of the Valsalva maneuver was verified by at least a 33 % decrease in the MCA peak flow velocity compared to the basal spectrum.

The shunt was graded as follows: 0: no shunt – 0 MBS, 1: low-grade shunt – one to ten MBS, 2: medium grade – more than 10 MBS and no curtain (uncountable number of MBS), and 3: high grade – a curtain of MBS (21). Two other categories were defined according to the presence of a high-grade shunt after a Valsalva maneuver or at rest.

Patients were divided into two main categories: 1 – without a RLS (RLS-) and 2 – with a RLS (RLS+). In the RLS+ group, we defined four subgroups: 1 – low-grade shunt (RLS+1); 2 – medium grade shunt (RLS+2); 3 – high-grade shunt after provocation with Valsalva maneuver (RLS+3Vals); and 4 – a high-grade shunt at rest breathing (RLS+3rest).

Outcomes

According to the symptoms described, DCS events drawn from the subject questionnaire, were ranked in one or more of the following categories as defined previously in the literature (1, 2, 6):

1) Neurological decompression sickness (DCSneuro) was defined as an occurrence of focal or general neurological symptoms (e.g. hemiparesis or paraparesis, hemihypesthesia, loss of consciousness, visual loss, extreme fatigue).
2) Cutaneous decompression sickness (DCSskin) was defined as an itchy rash or cutis marmorata.
3) Musculoskeletal decompression sickness (DCSjoint) was defined as new onset of severe joint pain.
4) Constitutional form of decompression sickness (DCSmild) was defined by mild, general symptoms such as fatigue, malaise or headache.

The study focused only on unprovoked DCS, thus episodes that were caused by violation of decompression regimen were excluded. The endpoint was the occurrence of DCSneuro event within 24 hours after diving.

Statistical analysis

Baseline characteristics were compared between the groups using the $\chi 2$ test for categorical variables and the Mann-Whitney U test or independent samples t-test for continuous variables as appropriate. The associations between variables and the endpoints were evaluated using survival analysis techniques. We used the Cox proportional hazards models to compute a hazard ratio (HR) with 95% confidence interval (CI), both unadjusted and adjusted for potential confounding covariates. A total sum of dives value was used as a measure of time. Variables with a $p \leq 0.1$ on univariate testing were included in the elimination algorithm. Additionally, Kaplan-Meier survival curves were created and log-rank statistics were calculated. We calculated the HR (adjusted and unadjusted) for the occurrence of the primary and secondary outcomes. All statistical analyses were done using IBM SPSS Statistics 25.0 (IBM Corp., Armonk, USA).

Results

A cohort of 640 divers was examined and divided into two groups according to the result of the TCD examination: RLS present (RLS+ group) or absent (RLS– group). A right-to-left shunt was found in 258 divers (40.3 %). Divers in the whole cohort performed a total of 188,621 dives, the RLS+ group performed 80,969 dives

Tab. 1. Demographics and clinical characteristics. Using the χ2 test, independent samples t-test or Mann–Whitney U test as appropriate.

Variable	All patients	RLS+	RLS-	p
Subjects, No. (%)	640	258 (40.3%)	382 (59.7%)	–
Men, No. (%)	529 (82.7%)	201 (77.9%)	328 (85.9%)	0.01*
Age, mean (SD), years	35.6 (9.7)	36.2 (9.6)	35.2 (9.7)	0.20
Height, mean (SD), cm	179.2 (8.5)	179.1 (8.1)	179.3 (8.8)	0.80
Weight, mean (SD), kg	83.8 (14.6)	83.9 (15.7)	83.8 (13.9)	0.91
BMI, mean (SD)	26 (3.4)	26 (3.7)	25.9 (3.1)	0.78
Number of dives, median (IQR)	114.5 (40–300)	120.0 (49–300)	103.5 (33–300)	0.31
Number of decompression dives, median (IQR)	5 (0–40)	10 (0–50)	5 (0–30)	0.07
Hypertension, No. (%)	20 (3.1%)	6 (2.3%)	14 (3.7%)	0.34
Migraine, No. (%)	22 (3.4%)	12 (4.7%)	10 (2.6%)	0.17
Coronary heart disease, No. (%)	3 (0.5%)	2 (0.8%)	1 (0.3%)	0.35
Smoking, No. (%)	101 (15.8%)	42 (16.3%)	59 (15.4%)	0.83

RLS+ – group with a right-to-left shunt; RLS– – group without a right-to-left shunt; BMI – body mass index; SD – standard deviation; IQR – interquartile range; * indicates a statistically significant difference

Tab. 2. Incidence of decompression sickness subtypes.

Variable	All divers	RLS+	RLS-	p
Subjects, No. (%)	640 (100%)	258 (40.3%)	382 (59.7%)	–
Any DCS	152 (23.8%)	111 (43%)	41 (10.7%)	< 0.001*
DCSmild	36 (5.6%)	19 (7.4%)	17 (4.5%)	0.12
DCSskin	84 (13.1%)	70 (27.1%)	14 (3.7%)	< 0.001*
DCSjoint	34 (5.3%)	21 (8.1%)	13 (3.4%)	< 0.01*
DCSneuro	49 (7.7%)	44 (17.1%)	5 (1.3%)	< 0.001*

RLS+ – group with a right-to-left shunt; RLS– – group without a right-to-left shunt; DCS – decompression sickness; DCSmild – form of DCS with constitutional symptoms only; DCSskin – cutaneous form of DCS; DCSjoint – musculoskeletal form of DCS; DCSneuro – neurological form of DCS

Tab. 3. Circumstances in dives with neurological decompression sickness.

	All	RLS+	RLS–	Groups differed significantly (p<0.05)*
Number	49	44	5	
Physical exertion after submersion	3 (6.1%)	3 (6.8%)	0 (0%)	> 0.99
Repetitive dives	31 (63.3%)	27 (61.4%)	4 (80%)	0.64
Decompression dive	13 (26.5%)	12 (27.3%)	1 (20%)	> 0.99
Dehydratation	4 (8.2%)	3 (6.8%)	1 (20%)	0.36
Cold water	9 (18.4%)	8 (18.2%)	1 (20%)	> 0.99
Any of the above	37 (75.5%)	33 (75%)	4 (80%)	> 0.99

RLS+ – group with a right-to-left shunt; RLS– – group without a right-to-left shunt

Tab. 4. Subgroups according to the grade of right-to-left shunt.

All	RLS-	RLS+			
		RLS+1	RLS+2	RLS+3Vals	RLS+3rest
640	382	87	26	131	14
100%	59.7%	13.6%	4.1%	20.5%	2.2%

RLS+ – group with a right-to-left shunt; RLS– – group without a right-to-left shunt. RLS+ divers were divided into four groups: with low grade (RLS+1); medium grade (RLS+2); and high grade. The high grade was divided into groups with high grade at rest (RLS+3rest) or after Valsalva maneuver (RLS+3Vals).

and the RLS- group performed 107,652 dives. Baseline characteristics of both groups are summarized in Table 1.

In the RLS+ group, 44 (17.1 %) divers had a history of DCSneuro, in the RLS– group DCSneuro occurred only in 5 (1.3 %) divers (p <0.001). The incidence of DCSneuro was 7.16/10,000 dives in the RLS+ group and 0.65/10,000 dives in the RLS– group. Groups also differed significantly in the occurrence of any subtype of DCS (111 vs 41, 43 % vs 10.7 %, p <0.001), the occurrence of DCSskin (70 vs 14, 27.1 % vs 3.7 %, p < 0.001) and DCSjoint (21 vs 13, 8.1 % vs 3.4 %, p <0.01) . The groups did not differ in the history of DCSmild (19 vs 17, 7.4 % vs 4.5 %, p = 0.12). It should be noted, that some divers, 26 (10.9 %) in the RLS+ and 4 (1%) in the RLS– group, had a history of more than one type of DCS (Tab. 2).

The groups did not differ in the circumstances observed around dives with DCSneuro. The most common were repetitive dives: in 27 (61.4 %) cases in the RLS+ group and 4 (80 %) cases in the RLS– group. Other frequent conditions were decompression dives (27.3 % and 20 %f or RLS+ and RLS–, respectively) and submersion in cold water (18.2 % and 20 % for RLS+ and RLS–, respectively) (Tab. 3).

Survival analysis was performed to compare DCSneuro occurrence between the groups. The unadjusted hazard ratio (HR) for DCSneuro and RLS+ is 11.806 (CI 4.670–29.843, p <0.001), the highest of all recorded variables in univariate analysis. The Cox model adjusted for the number of decompression dives and male sex found the hazard ratio adjusted (HRadj) for DCSneuro and RLS+ 12.062 (CI 4.759–30.573, p <0.001). Among other types of DCS, only DCSskin had significant HR 2.763 (CI 1.538–4.964, p = 0.001) for DCSneuro development. From 84 divers with DCSskin 20 divers also suffered from DCSneuro. The Kaplan-Meier survival curve was created using the number of dives as a measure of time. The survival distributions of DCSneuro were significantly different; log-rank test p < 0.001 (Fig. 1).

The size of RLS+ subgroups (a total of 258 RLS+ divers) according to the grade of RLS was 87 divers with RLS+1, 26 with RLS+2, 131 with RLS+3Vals and 14 with RLS+3rest (Tab. 4). The number of divers who had suffered from DCSneuro was highest in the RLS+3rest subgroup – 8 (57.1 %) and decreased with

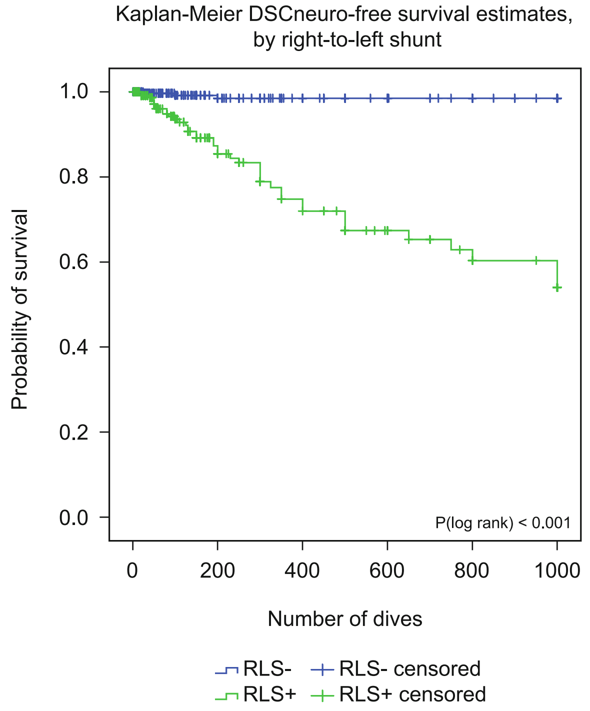

Fig. 1. Cumulative Kaplan–Meier estimates of the probability of neurological decompression sickness in the groups with and without a right-to-left shunt. The horizontal axis displays the number of dives. The cut off value of 1,000 dives covers 95% of the cohort. The vertical axis displays the probability of surviving without neurological decompression sickness. RLS+ group with a right-to-left shunt, RLS– group without a right-to-left shunt. The log-rank test gave p < 0.001.

lesser RLS severity: 30 (22.9 %) in the RLS3+Vals, 2 (7.7 %) in the RLS+2 and only 4 (4.6 %) in the RLS+1. The number of divers with repeated DCSneuro was highest in the RLS+3rest subgroup – 4 (28.6 %), 7 (5.3 %) in the RLS+3Vals, 1 (3.8 %) in theRLS+2 and 1 (1.1 %) in the RLS+1 subgroups.

Discussion

The results of the study may be summarized as follows: i) RLS was associated with DCSneuro occurrence; ii) the risk of DCSneuro development paralleled RLS grade; iii) DCSskin was associated with DCSneuro development; iv) a contributory cause was presenting 75.5 % of DSCneuro accidents, the most frequent were repetitive dives and decompression dives.

In a previous report from the DIVE-PFO, we have demonstrated that a high-grade PFO was a major risk factor for unprovoked DCS in 489 recreational scuba divers (22). This study specifically focused on recreational diving only and 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. In a multivariate analysis, PFO grade 3 was a major risk factor for unprovoked DCS. The present study includes 640 divers and a wide variety of diving activities including professional and technical diving and focuses specifically on the most feared neurological form of DCS. Also we have included a novel grading of a RLS dividing the high-grade category into the groups RLS+3Vals and RLS+3rest according to wether the shunting occurs at rest breathiong or after a Valsalva maneuver. Based on the results, the RLS+3rest subgroup was at highest risk of DCSneuro. However, a high-grade RLS shunt present at rest was not very common; it was present in only 14 of the 640 divers (2.2 %). More relevant for the diving population is the RLS+3Vals subgroup that comprised of 131 divers, of whom 30 (22.9 %) suffered from DCSneuro. Divers in this subgroup constituted 61.2 % of all DCSneuro cases.

We believe that TCD is an excellent tool for identification especially of this subgroup of divers, as the transcranial ultrasound probe does not limit the diver when performing the Valsalva maneuver as does the probe during a transesophageal echocardiography examination. Furthermore, the diver can practice this maneuver prior to the administration of the contrast agent and we can easily verify its effectiveness. Gempp et al. have performed TCD examination in 634 divers treated in a single referral hyperbaric facility for different types of DCS and compared them to 259 healthy divers (23). TCD detected 63 % RLS in DCS group versus 32 % in the control group (p <0.0001). The overall prevalence of RLS was higher in divers presenting a cerebral DCS (OR, 5.3 [95% CI, 3.2–8.9]; p <0.0001), a spinal cord DCS (OR, 2.1 [95% CI, 1.4–3.1]; p <0.0001), an inner ear DCS (OR, 11.8 [95% CI, 7.4–19]; p <0.0001) and a cutaneous DCS (OR, 17.3 [95% CI, 3.9–77]; p <0.0001) compared to the control group, but not in divers experiencing ambiguous symptoms or muscu-

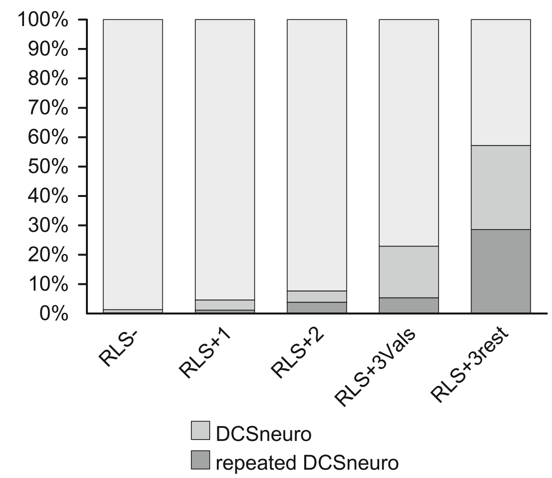

Fig. 2. Prevalence of the neurological form of decompression sickness and its recurrence in subgroups according to the grade of right-to-left shunt. RLS+, group with a right-to-left shunt; RLS–, group without a right-to-left shunt. RLS+ divers were divided into four groups: with low grade (RLS+1); medium grade (RLS+2); and high grade. The high grade was divided into groups with high grade at rest (RLS+3rest) or after Valsalva maneuver (RLS+3Vals). DCSneuro, neurological DCS.

loskeletal DCS. This is consistent with our findings. However, in our work we also included the number of dives, that enabled us to perform a survival analysis, and potential risk-behavior connected to DCS.

We discovered a higher proportion of RLS+ divers (258, 40.3 %) in our cohort compared to literary population data (18). This discrepancy cannot be explained by the higher sensitivity of the examination method used (TCD), as we discovered RLS in only 41 (33.9 %) of a concurrently examined group of 121 non-divers examination performed before participation in a diving course) following the same protocol. A possible explanation is that divers with a history of DCS (and presumably higher RLS incidence) were more interested in participating in the study and thus form a bigger proportion in our cohort. Therefore the incidence of DCS can only be applied with caution to the general diving population. However, a RLS was an independent risk factor of DCS and the risk paralleled the RLS grade.

Some DCSneuro incidents were also reported in the RLS- group, in 5 of 382 divers (1.3 %). A possible explanation is the shunt of gas bubbles through pulmonary arterio-venous anastomoses temporarily opened during increased physical activity, which were not detectable at the time of TCD investigation (24, 25). Another possible mechanism is the in-situ formation of bubbles (26). The cutaneous form of DCS was the only condition associated with DCSneuro. The subpopulation of divers with DCSskin had a nearly three times higher risk of DSCneuro. Therefore we suggest it might be reasonable to screen them for RLS presence. A higher prevalence of RLS in divers with cutaneous form of DCS has been reported previously (8, 10). Some authors suggest that marbling of the skin may be a symptom of embolization to autonomous areas of brain stem rather than the local effect of bubbles on skin vascularization (8). Nevertheless, 55.1 % of the divers with DCSneuro in our cohort experienced no previous diving-associated health problems.

Of note is that that there was a contributory cause presenting 75.5 % (37) of DSCneuro accidents; the most frequent were repetitive dives and decompression dives. Avoiding such conditions may make diving safe for divers with a RLS. Conservative diving was tested previously in divers with a PFO with favorable results (27, 28). Recently, we published a follow-up study from the DIVE-PFO registry and demonstrated that screening for a RLS with subsequent recommendation of conservative diving decreased the risk of DCS in divers with a PFO but did not completely eliminate it as did the catheter-based PFO closure (29).

This registry study with prospective patient enrolment is subject to inherent limitations, including selection bias. The prevalence of a RLS and the incidence of unprovoked DCS might not, therefore, be generalizable to the overall population of divers. The self-reporting of endpoints is another limitation of the study.

Conclusions

A right-to-left shunt was an independent risk factor of unprovoked DCSneuro development in divers with a wide range of diving activities. This risk paralleled the RLS grade as assessed by TCD. In the majority of divers a contributory cause was present, most frequently repetitive or decompression diving. The occurrence of DCSskin was associated with a higher risk of DCSneuro. Based on these results, we suggest that TCD is a useful tool in risk stratification of divers.

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