Reliability of Right-to-Left Shunt screening in the prevention of Scuba diving related-decompression sickness.

Emmanuel Gempp[1], Marianne Lyard[2], Pierre Louge[3]

[1] French Navy Diving School, Toulon, France

[2] Department of diving and hyperbaric medicine, Sainte Anne's military hospital, Toulon, France

[3] UIISC 7, Brignoles, France

The authors take the responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Corresponding author: Emmanuel Gempp, gempp@netc.fr

French Navy diving School, BP 311, 83800 Toulon cedex 9, France

No source funding

Conflict of interest: none declared

Key words: scuba diving; right-to-left shunt; persistent foramen ovale; decompression sickness; transcranial Doppler ultrasonography.

Abstract

Objectives: The aim of this study was to investigate the relationship between right-to-left shunt (RLS) and the clinical features of decompression sickness (DCS) in scuba divers and to determine the potential benefit for screening this anatomical predisposition in primary prevention.

Methods: 634 injured divers treated in a single referral hyperbaric facility for different types of DCS were retrospectively compared to 259 healthy divers. All subjects had a RLS screening by contrast Transcranial Doppler (TCD) ultrasound according to a standardized method. The number of bubbles detected defined the degree of RLS (small if 5-20 bubbles, large if >20 bubbles).

Results: 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 musculoskeletal DCS. There was in increased risk of DCS with the size of RLS. The determination of diagnostic accuracy of TCD testing through the estimation of likelihood ratios revealed that predetermination of RLS did not change significantly the prediction of developing or not a DCS event.

Conclusion: The assessment of RLS remains indicated after an initial episode of spinal cord, cerebral, inner ear and cutaneous form of DCS but this approach is definitely not recommended in routine practice.

Introduction

Scuba diving can lead to specific injuries such as decompression sickness (DCS), resulting from nitrogen bubble formation in supersaturated tissues during divers' ascent. These bubbles can cause local tissue damage or be released into the venous circulation from peripheral tissues. Paradoxical embolization of venous bubbles through a right-to-left shunt (RLS), either intrapulmonary or cardiac (i.e. persistent foramen ovale or PFO), with subsequent passage in the arterial blood, is commonly recognized as a pathological condition that may promote the development of certain types of DCS including spinal cord, cerebral and inner ear injuries [1-6]. It has been demonstrated that the prevalence of RLS (with a feature of atrial shunt > 93% [7]) was greater in DCS divers, ranging from nearly 50% (spinal cord) [2,4] to 80% (inner ear) [3] compared to 22-36% in asymptomatic divers [1,7] and 25-34 % in the general population from autopsy studies [8]. The increased relative risk of DCS with this anatomical predisposition was estimated between 2.5 and 6.5 from previous meta-analysis [9,10]. For that reason, the great majority of divers transferred in our facility for DCS are screened for RLS before discharge by contrast enhanced-transcranial Doppler (TCD) ultrasonography, a minimally invasive method which has proven to have a high sensitivity and good accuracy compared with other techniques [11,12]. However, the discrepancy between the low incidence of DCS (between 0.01% and 0.03% per dive according to the diving population) [13] and the high prevalence of RLS in healthy individuals raises the question among military and professional diving authorities to establish a routine RLS screening during the medical examination for dive recruitment. Therefore, the aim of this controlled study was 1) to investigate the relationship between RLS and the clinical features of DCS and 2) to evaluate the reliability of RLS screening as a strategy of primary prevention for reducing the risk of DCS.

Methods

Participants

All the medical forms of divers referred for DCS and treated at Sainte Anne's Military Hospital (Toulon, France) from 1998 to 2013 were retrospectively consulted by two hyperbaric physicians (EG, PL). Exclusion criteria were: incomplete clinical data, lack of TCD results and patients with cerebral air embolism resulting from pulmonary barotrauma. After analysing the results of the physical examination and the radiological findings, injured divers were classified in subgroups depending on the topography of the lesions and the final diagnosis, i.e. spinal cord, cerebral, inner ear, musculoskeletal and cutaneous forms of DCS. Ambiguous DCS were separately reported. This latter category corresponded to divers with an uncertain diagnosis of DCS because of the atypical presentation of neurological symptoms and the inconclusive radiological investigations. Patients who had multiple features of DCS were categorized according to the more pronounced symptoms. The spinal cord DCS subgroup was divided into two outcome categories: patients with sequelae and those with complete recovery. Sequelae were defined as a significant residual deficit (urinary disorders, ataxia, motor or sensory symptoms), three months after the initial insult. The control group consisted on asymptomatic divers without history of DCS recruited from local diving clubs and military diving groups that were volunteers to participate in the study during the same period. The study design was approved by the local institutional ethics committee (Sainte Anne's military hospital) and all participants gave their written informed consent.

TCD ultrasonography examination

The presence and functional size of RLS were assessed with a pulsed TCD ultrasonography (Explorer CVS, Diagnostic Medical Systems, Perols, France) using a standardized protocol routinely performed in our facility by experimented operators since many years. This technique was found to have a good inter-and intra-investigator reproductibility (kappa values > 0.8) (Sastry).

A mixture of 19ml saline and 1ml air is agitated 6 times between two 10ml syringes, connected to a 3-way stopcock, to create microbubbles as sonographic contrast. The emulsion is then injected into a 18-gauge catheter placed in the antecubital vein of the patient laid in supine position. Middle cerebral artery flow is monitored through the temporal bone window using a 2-Mhz probe set at 50-60mm depth for detecting circulating microbubbles on the Doppler spectrogram in real time. For each diver, the test was repeated twice: the first time at rest, during normal breathing and, the second one, followed by a provocative manoeuver consisting on blowing into a manometer and maintaining a pressure of 40mmHg during 5 seconds before the release of the forced expiration. TCD was considered as positive (indicating the presence of an RLS) when we recorded at least five typical high intensity transient signals called "hits", 15 seconds after the injection at normal breathing, and 10 seconds after the end of the provocative manoeuver. RLS was classified into three grades according to the current literature [7,11]: absence of RLS if <5 hits, small RLS if 5-20 hits, large RLS if >20 hits. Doppler signals recorded onto digital tape were analysed later by 2 trained observers (EG,PL).

Statistical analyses

Data were expressed as mean +/- SD. Comparisons between groups were completed using the Student's *t* test for a continuous variable and the Chi squared test or Fisher's exact test for categorical variables. A p value of <0.05 was considered to indicate a statistically significant difference. The performance of RLS testing was estimated through the calculation of sensitivity, specificity, negative and positive predictive values and the likelihood ratios. Predictives values of RLS screening are referring to the probability of having DCS once the results of test are known. The positive likelihood ratio (LR+) summarizes how many times more likely divers victims of DCS are to have a RLS than asymptomatic divers. The prediction is considered enough high if LR+ is greater than 10. Conversely, the negative likelihood ratio (LR-) describes how many times less likely injured divers are to have a negative screening of RLS compared to divers without DCS. Thus, a very low LR- (below 0.1) virtually rules out the risk that a diver without RLS will develop DCS. Statistical analyses were done using either Graphpad Prism 6.00 (GraphPad Software, San Diego, CA) or internet program to calculate odd ratios (OR) and likelihood ratios for 2x2 tables with 95%CIs around them [14].

Results

A total of 722 patients were admitted and 634 (87%) were finally included. 259 healthy divers served as controls. Both groups were matched with respect to gender and diving experience. There was, however, a significant difference in age between DCS divers and controls (43.6 +/- 11.3 vs 34.6 +/- 9.0, respectively, p<0.0001). TCD examination revealed that 398 RLS (63%) were present in the group of divers affected by DCS while 82 cases only (32%) were tested positive for RLS in the control group ($p<0.0001$) (Table 1). the global odd of suffering a DCS was 3.6 [95%CI, 2.7-4.9] in divers with RLS and the relative risk increased in parallel with RLS size with an odd at 4.1 [95%CI, 2.9-5.7] for only high-grade RLS (Figure 1). When considering the different clinical features, the prevalence of RLS (including the small ones) was higher in divers presenting with cerebral, spinal cord, inner ear DCS and cutaneous forms of DCS compared to the control group. Conversely, the proportion of RLS in divers suffering from musculoskeletal DCS and in those with ambiguous presentation was comparable to that of control group.

Additional analysis revealed that residual deficit following spinal cord DCS was not associated with the presence of RLS (OR, 0.7[95%CI,0.4-1.3]; $p=0.3$). The accuracy indices of TCD ultrasonography regarding the different features of DCS are displayed in table 2. The data show that the reliability of RLS screening is not enough to correctly identify the divers at risk of DCS development or not with numerical values of LRs always above 0.1 or below 10.

Discussion

The role of RLS in DCS has been largely debated [1-6]. In a recent study, Wilmshurst showed that the risk of a diver suffering shunt-related DCS was closely related to the dimensions of the PFO rather than just the presence of the defect [7]. Other studies have also demonstrated that the functional characteristics of the RLS, i.e. shunting at rest or after Valsalva maneuver and amount of vascular bubbles crossing atrial defects, may be associated with a greater likelihood of DCS development [1, 15, 16]. In the present work based on the largest cohort of injured divers ever studied before, 63% of TCD-tested DCS patients were found to a have a RLS. These data are in accordance with the findings of other series examining PFO with echocardiogram in DCS divers [5, 6, 16] and also consistent with previous reports showing that RLS is associated with all types of DCS, except for the musculoskeletal and ambiguous forms [1, 17, 18]. More specifically, it appears that divers with RLS have an increased odd of DCS involving skin tissues and inner ear. The mechanisms postulated by several authors are based on the concept of peripheral gas bubbles amplification in supersaturated tissues with longer perfusion half-time caused by venous gas emboli entering the arterial circulation through RLS (Mitchell et doolette 2015, Wilmshurst 2015).

We further confirmed the trend that there was an association between the degree of RLS and the risk of DCS since higher ORs were found after exclusion of the small grades from the data: This finding corresponds roughly to the results of a previous meta-analysis [9] and support the fact that the clinical impact of small shunts is likely insignificant, as evidenced in figure 1. Our results found no major differences in the neurological outcome between spinal cord DCS patients with or without RLS suggesting that this condition was not predictive of a more severe presentation or incomplete recovery. This finding did not correlate with another investigation demonstrating a higher prevalence of PFO in divers that experienced a major episode of DCS and required a longer course of hyperbaric treatment compared to those with minor symptoms [17]. However, in that latter study, the clinical definition of symptoms severity appeared inconsistent and too broad if we consider the existing diagnostic classifications [19] thus qualifying the assertion that PFO could influence the outcome of DCS presentation.

By using likelihood ratios as alternative statistics for summarizing the performance of TCD testing, our data illustrate that RLS determination does neither contribute significantly to the prediction of DCS nor firmly reduce its a posteriori incidence. Our finding are unique although many authors have already suggested that there was no rationale that the average recreational diver need to be routinely screened for RLS since DCS is a rare event while PFO is a common anatomic finding existing in a quarter of normal subjects [10, 9, 20]. The error of associating a common factor with an uncommon disease, referred to as "referral bias", is well known and has been discussed elsewhere [21]. For example, a recent prospective study examining the incidence of DCS in a group of 132 divers initially tested for RLS revealed that the relative risk of DCS was 2-3 times as high in positive-tested subjects (germonpre), a preliminary result in line with previous retrospective reports dealing with this [10,16]. However, when considering the overall incidence of DCS in this diving population, the absolute increase remained small (from nearly 2 to 6 per 10 000 dives) confirming that systematic RLS screening was not useful for reducing significantly DCS risk. Moreover, although it is conceivable that

RLS represents an identifiable contributor to DCS, there are other critical factors such as vascular bubble load [22, 23] or biological markers [24] that may be involved in susceptibility to DCS.

Our study has some limitations. Controls were partly selected from military divers. This may have accounted for the statistical difference in age between groups, thus creating a potential selection bias. However, this is unlikely because the frequency of PFO was reported to decrease with age [8]. Moreover, the small mean age interval observed between the 2 populations (i.e. 10 years) cannot explain an age-related variation of RLS patency. TCD ultrasonography with bubble contrast was the method chosen to detect RLS while transthoracic echocardiography (TTE), instead of transesophageal echocardiography (TEE), is now the most reliable technique to allow visualisation of atrial shunts with provocative manoeuvres being performed correctly without sedation [25]. In our study, the patients did not undergo a TTE or TEE after being detected by TCD in order to obtain an accurate picture of the septal anatomy. The reason was that TCD is a quick and easily reproducible technique with a high sensitivity for detecting clinically relevant RLS [12]. Indeed, the differentiation between cardiac and pulmonary sources of RLS is initially not useful for the diagnosis of shunt-mediated DCS, because both are believed to have the same pathophysiological effect (i.e. paradoxical bubble emboli to the systemic circulation). Thus, some authors recommend that divers being investigated for PFO would need only TCD and could avoid TEE if TCD is negative (Sastry 2).

Conclusion

The present study reinforces the notion that the presence of RLS is strongly associated with neurological, inner ear and cutaneous forms of DCS, leading to the general recommendation that injured divers should continue to have RLS examination following a DCS event, except for musculoskeletal localization and presence of atypical symptoms. However, our data have clearly demonstrated statistically for the first time that routine screening of RLS ~~in healthy divers~~ was not reliable ~~in primary prevention~~ to predict, and most importantly rule out DCS occurrence with confidence. These positions are in agreement with the recent consensus statement recently developed by a panel of experts coming from several scientific and medical diving organizations [25, DAN]

Diving physicians are also confronted to motivated divers who want to be declared fitness to dive again after undergoing transcatheter closure of PFO. This procedure may be considered in parallel with the conservative approach to resume diving [26], particularly for professional divers exposed to risky dives profiles [9, 27]. However, residual shunts in late follow-up after PFO closure (up to 45%) [28, 29] and procedural complications, though infrequent (< 3%), [28, 30] are a source of failure mitigating the potential efficacy of this alternative. Further investigations are needed to better clarify the selection criteria of divers eligible for PFO closure.

References

1 Cantais E, Louge P, Suppini A, Foster PP, Palmier B. Right-to-Left shunt and risk of decompression illness with cochleovestibular and cerebral symptoms in divers: case control study in 101 consecutive dive accidents. Crit Care Med 2003; 31:84–88.

2 Gempp, E, Blatteau JE , Stephant E, Louge P. Relation between right-to-Left shunts and spinal cord decompression sickness in divers. Int J Sports Med 2009; 30: 150–53.

3 Gempp E, Louge P. Inner ear decompression sickness in scuba divers. Eur Arch Otorhinolaryngol 2012;270:1831-7.

4 Wilmshurst P, Bryson P. Relationship between the clinical features of neurological DCI and its causes. Clin Sci 2000;99:65-75.

5 Germonpré, P, Dendale P, Unger P, Balestra C. Patent foramen ovale and decompression sickness in sports divers. J Appl Physiol 1998; 84: 1622–26.

6 Moon RE, Camporesi EM, Kisslo JA. Patent foramen ovale and decompression sickness in divers. Lancet 1989;333:513-4.

7 Wilmshurst PT, Morrison WL, Walsh KP. Comparison of the size of persistent foramen ovale and atrial septal defects in divers with shunt-related decompression illness and in the general population. Diving Hyperb Med 2015; 45: 89–93.

8 Hagen PT, Scholz DG, Edwards WD. Incidence and size of patent foramen ovale during the first 10 decades of life: an autopsy study of 965 normal hearts. Mayo Clin Proc.1984;59:17-20.

9 Lairez O, Cournot M, Minville V, Roncalli J, Austruy J, Elbaz M, et al. Risk of neurological decompression sickness in the diver with right-to-left shunt : literature review and meta-analysis. Clin J Sport Med 2009;19:231-35.

10 Bove AA. Risk of decompression sickness with patent foramen ovale. Undersea Hyperb Med 1998;25:175-8.

11 Caputi L, Carriero MR, Falcone C, Parati E, Piotti P, Materazzo C, Anzola G. Transcranial Doppler and Transesophageal echocardiography: Comparison of both techniques and prospective clinical

relevance of transcranial Doppler in patent foramen ovale detection. J Stroke Cerebrovasc Dis. 2009;18: 343-48.

12 Kerut EK, Truax WD, Borreson TE, Van Meter KW, Given MB, Giles TD. Detection of right to left shunts in decompression sickness in divers. Am J Cardiol 1997;79:377-78.

13 Vann RD, Butler FK, Mitchell SJ, Moon RE. Decompression Illness. Lancet 2011; 377: 153–64.

Sastry S, Daly K, Chengodu T, McCollum C. Is transcranial Doppler for the detection of venous-to-arterial circulation shunts reproductible ? Cerebrovasc Dis 2007;23: 424-9.

14 Herbert R. Confidence interval calculator (last version, March 2011).http:/www.pedro.org.au/wp-content/uploads/CIcalculator.xls (accessed July 6, 2016)

15 Cartoni D, De Castro S, Valente G, Constanzo C, Pellicia A, Beni S, et al. Identification of professional scuba divers with patent foramen ovale at risk for decompression illness. Am J Cardiol 2004;94:270-73.

16 Torti SR, Billinger M, Schwerzmann M, Vogel R, Zbinden R, Windecker S, et al. Risk of decompression illness among 230 divers in relation to the presence and size of patent foramen ovale. Eur Heart J 2004;25:1014–20.

17 Liou K, Wolfers D, Turner R, Bennett M, Allan R, Jepson N, Cranney G. Patent foramen ovale influences the presentation of decompression illness in SCUBA divers. Heart Lung Circ 2015;24:26-31.

18 Wilmshurst PT, Pearson MJ, Walsh KP, Morrison WL, Bryson P. Relationship between right-to-left shunts and cutaneous decompression illness. Clin Sci 2001;100: 539–42.

Mitchell SJ, Doolette DJ. Selective vulnerability of the inner ear to decompression sickness in divers with right to left shunt: the role of tissue gas supersaturation. J Appl Physiol 2009;106:298-301.

19 Vann RD, Moon RE, Freiberger JJ, Denoble PJ, Dear GL, Stolp B, Massey EW. Decompression illness diagnosis and decompression study design. Aviat Space Environ Med 2008;79:797-8.

20 Cross SJ, Evans SA, Thomson LF, Lee HS, Jennings KP, Shields TG. Safety of subaqua diving with a patent foramen ovale. British Med J 1992;304:481-2.

21 Moon RE, Bove AA. Transcatheter occlusion of patent foramen ovale: A prevention for decompression illness? Undersea Hyperb Med 2004;31: 271-74.

22 Gawthrope IC, Summers M, Macey DJ, Playford DA. An observation of venous gas emboli in divers and susceptibility to decompression sickness. Diving Hyperb Med 2015;45:25-29.

23 Eftedal OS, Lydersen S, Brubbak AO.The relationship between venous gas bubbles and adverse effects of decompression after air dives. Undersea Hyperb Med 2007;34:99-105.

24 Thom SR, Bennett M, Banham MD, Chin W, Blake DF, Rosen A, et al. Association of microparticles and neutrophil activation with decompression sickness. J Appl Physiol 2015;119:424-34.

25 Smart D, Mitchell S, Wilmshurst P, Turner M, Banham N. Joint position statement on persistent foramen ovale (PFO) and diving. South Pacific Underwater Medicine Society (SPUMS) and the United Kingdom Sports Diving Medical Committee (UKSDMC). Diving Hyperb Med 2015;45:129-31.

Germonpre P. Incidence of DCS in divers with RLS-a prospective study. In: Patent foramen ovale and fitness to dive consensus workshop proceedings. Denoble PJ, Holm JR eds. Durham, NC, Diver Alert Network, 2015:47-56.

Sastry S, MacNab A, Daly K, Ray S, McCollum C. Transcranial Doppler detection of venous-to-arterial circulation shunts: Criteria for patent foramen ovale. J Clin Ultrasound 2009;37:276-80.

26 Gempp E, Louge P, Blatteau JE, Hugon M. Risk factors for recurrent neurological decompression sickness in recreational divers: a case-control study. J Sports Med Phys Fitness 2012;52:530-6.

27 Bove AA. The PFO gets blamed again…perhaps this time it is real. JACC Cardiovasc Interv 2014;7:409-10.

28 Pearman A, Bugeja L, Nelson M, Szantho GV, Turner MS. An audit of persistent foramen ovale closure in 105 divers. Diving Hyperb Med 2015; 45: 94–97.

29 Jerusum JT, Fuller CJ, Renz J, Krabill KA, Spencer MP, Reisman M. Diagnosis of secondary source of right-to-left shunt with balloon occlusion of patent foramen ovale and power M-mode transcranial Doppler. JACC Cardiol Intv 2009;2:561-7.

30 Wahl A, Praz F, Stirnimann J, Windecker S, Seiler C, Nedeltchev K, et al. Safety and feasibility of percutaneous closure of patent foramen ovale without intra-procedural echocardiography in 825 patients. Swiss Med Wkly 2008;138:567-72.

Table 1:

Association between RLS and each form of DCS. (In brackets the value corresponding only to the inclusion of large RLS).

	n	RLS -	RLS +	% RLS	OR	95% CI	p-value
Control group	259	177	82 (55)	32			
All DCS	634	236	398 (333)	63	3.6 (4.1)	2.7-4.9	<0.0001
Spinal cord DCS	255	128	127 (110)	50	2.1 (2.8)	1.4-3.1	<0.0001
Inner ear DCS	201	31	170 (148)	85	11.8 (15.4)	7.4-19	<0.0001
Cerebral DCS	97	28	69 (50)	71	5.3 (5.7)	3.2-8.9	<0,0001
Ambiguous DCS	47	35	12(9)	25	0.7 (0.8)	0.4-1.5	0.4
Musculoskeletal DCS	16	12	4 (3)	25	0.7 (0.8)	0.2-2.3	0.6
Cutaneous DCS	18	2	16 (13)	89	17.3 (21)	3.9-77	<0.0001

Table 2:

Accuracy indices of RLS screening by types of DCS

DCS presentation	Se	Sp	PPV	NPV	LR+	95% CI	LR-	95% CI
Spinal cord DCS	49%	68%	60%	58%	1.6	1.3-2	0.7	0.6-0.8
Inner ear DCS	85%	68%	67%	85%	2.7	2.2-3.2	0.2	0.16-0.3
Cerebral DCS	71%	68%	46%	86%	2.2	1.8-2.8	0.4	0.3-0.6
Ambiguous DCS	25%	68%	13%	83%	0.8	0.5-1.3	1.1	0.9-1.3
Musculoskeletal DCS	25%	68%	5%	94%	0.8	0.3-1.9	1.1	0.8-1.5
Cutaneous DCS	89%	68%	16%	99%	2.8	2.2-3.6	0.2	0.05-0.6

Se = sensitivity; Sp = specificity; PPV = positive predictive value; NPV = negative predictive value; LR+ = positive likelihood ratio; LR - = negative likelihood ratio.