Right-to-left shunt and risk of decompression illness with cochleovestibular and cerebral symptoms in divers: Case control study in 101 consecutive dive accidents

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Objective: **We investigated the role of right-to-left shunt with standardized transcranial Doppler ultrasonography in a large population of divers referred for symptoms of decompression illness.**

Design: **Case series compared with a control group.**

Setting: **Military teaching hospital, hyperbaric unit.**

Patients: **Patients were 101 consecutive divers with clinical evidence of decompression illness and a control group of 101 healthy divers.**

Intervention: **Specification of the type of decompression illness involved and detection/evaluation of right-to-left shunt by standardized transcranial Doppler. The degree of right-to-left shunt was defined as major if the number of high-intensity transient signals in the middle cerebral artery was >20.**

Measurements and Main Results: **We evaluated the odds ratios by logistic regression analysis with vs. without right-to-left shunt for subjects with cochleovestibular symptoms, cerebral decompression illness, spinal decompression illness, and Caisson sickness. Of the 101 divers presenting with decompression illness, transcranial Doppler detected a right-to-left shunt in 59 (58.4%), whereas control subjects demonstrated a right-to-left shunt in 25 cases (24.8%; odds ratio, 4.3; 95% confidence interval, 2.3–7.8; $p = .09$). When a right-to-left shunt was detected, the right-to-left shunt was major in 12 of 25 patients in the control group and in 49 of 59 patients in the decompression illness group (odds ratio, 8.7; 95% confidence interval, 4.2–18.0; $p < .001$). Within the decompression illness group, the proportion of major right-to-left shunt was 24 of 34 (odds ratio, 29.7; 95% confidence interval, 10.0–87.2; $p < .0001$) in the cochleovestibular subgroup, 13 of 21 (odds ratio, 24.1, 95% confidence interval, 6.8–86.0, $p < 0.0001$) in the cerebral decompression illness subgroup, ten of 31 (odds ratio, 3.9; 95% confidence interval, 1.5–10.3; $p < .01$) in the spinal decompression illness subgroup, and two of two (odds ratio, 1.1; 95% confidence interval, 0.2–5.7; $p = .9$) in the subgroup of divers with Caisson sickness.**

Conclusion: **Based on our results, we conclude that major right-to-left shunt was associated with an increased incidence of cochleovestibular and cerebral decompression illness, suggesting paradoxical embolism as a potential mechanism. (Crit Care Med 2003; 31:84–88)**

KEY WORDS: patent foramen ovale; decompression illness; paradoxical embolism; transcranial Doppler; cochleovestibular decompression illness

Decompression illness (DCI) may occur in recreational or professional divers, astronauts, and aviators and may cause severe neurologic damage. The mechanism of DCI is thought to involve venous gas emboli, as a result of the continuous release of inert gas in the form of a free gas phase from peripheral tissues during decompression (1, 2). Prevention of DCI is implemented by performing standardized and accepted decompression procedures, using dive computers or dive tables. Because dive tables allow micronucleation, bubbles and DCI may occur. Furthermore, individual susceptibility variations may influence the outcome. Right-to-left shunt (RLS) of venous gas emboli from a patent foramen ovale or intrapulmonary shunting has been reported to increase the risk of developing clinical manifestation of DCI (3–5) such as cochleovestibular DCI symptoms, cerebral DCI symptoms (6), and high spinal DCI symptoms in recreational and professional divers. However, it is unknown whether the degree of RLS influences the risk. Detection of arterialized microbubbles in the middle cerebral artery by standardized transcranial contrast Doppler ultrasonography (TCD) is a noninvasive and highly sensitive method to assess clinically significant RLS. A sensitivity and a specificity as high as 100 and 82%, respectively, when compared with transesophageal echocardiography, were reported (7–9).

We hypothesized that paradoxical embolism across a patent foramen ovale with major RLS might be involved in the pathogenesis of cochleovestibular and cerebral DCI. To test this hypothesis, we designed the present study by using a large series of affected DCI divers to examine a) the presence and the degree of RLS, detected by TCD; and b) the association between RLS and cochleovestibular and cerebral DCI.

METHODS

Subjects. We investigated a first cohort of consecutive divers (85 men and 16 women, mean age 35 ± 10.3 yrs) referred for DCI (n = 101) to the Hyperbaric Center from September 1997 to December 1999 and a second cohort of healthy unaffected control divers (n = 101). All subjects agreed to be evaluated by

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TCD ultrasonography for the presence of an RLS and gave their informed consent for the study. The protocol was approved by the Institutional Review Board.

Four types of manifestations were observed: a) cochleovestibular DCI; b) cerebral DCI; c) spinal DCI; and d) osteomyoarticular pain, that is, Caisson sickness, localized in the vicinity of a joint, associated with normal neurologic examination. Cochleovestibular DCI was diagnosed according to the description by Farmer et al. (10).The symptoms of cochleovestibular DCI were tinnitus, hearing loss, vertigo, nausea, and vomiting, beginning shortly after the dive. To avoid confusion between inner ear barotrauma and cochleovestibular DCI, we excluded patients with potential middle or inner ear barotrauma based on the presence of a) difficulties in middle ear pressure equalization during the dive; b) otoscopy abnormalities; c) Eustachian tube dyspermeability; or d) cochleovestibular symptoms beginning during descent or compression. The manifestations of cerebral DCI were visual blurring, hemiplegia, monoparesis or hemiparesis, focal weakness, hemiparesthesia, cerebellar signs, and headache, alone or in combination. Spinal DCI was diagnosed when the following symptoms occurred: a) paraparesis or paraplegia; b) bilateral hypesthesia or weakness; c) bilateral paresthesia, even without objective evidence of hypesthesia; d) bladder or bowel dysfunction; e) mid-dorsal pain, or f) any combination of these. We also defined severe DCI as a persistent neurologic dysfunction and an abnormal neurologic examination after hyperbaric oxygen treatment. Patients presenting with minor, vague, only subjective and transient symptoms, even if a hyperbaric oxygen treatment had been applied, were excluded from this category. Patients were also excluded if the dive profile, the clinical examination, or the chest radiograph suggested pulmonary barotrauma (n = 5). Patients who had multiple features of DCI were categorized according to the more pronounced symptoms. One patient presenting with complete paraplegia and a transient loss of consciousness possibly related to cerebral localization was classified in the spinal DCI group. Finally, divers showed clinical signs of cochleovestibular DCI in 34 patients, cerebral DCI in 21 patients, spinal DCI in 31 patients, and Caisson sickness in 15 patients. DCI was classified as severe in 81 patients, according to our definition, and required more than one hyperbaric oxygen treatment. The average number of hyperbaric oxygen treatments was 4.1. The depth of diving, the number of decompression table limit violations, and the number of repetitive dives are shown in Figure 1. The depth of diving was >30 m in 73% of all DCI patients, and the tables limits were violated in 54%; details of the dive profile vs. the type of DCI are reported in Table 1. The elapsed time between surfacing and the beginning of the hyperbaric oxygen treatment was as follows: <1 hr, n = 17; 1–2 hrs, n = 33; 2–6 hrs, n = 47; 6–12 hrs, n = 3; >12 hrs, n = 1.

The control group of 101 divers, who were healthy volunteers (77 men and 24 women) with a mean age of 33 ± 9.3 yrs, were recruited from local diving clubs and military diving groups following advertisement. The inclusion criteria were as follows: a) no experience of DCI at any time; and b) a normal clinical examination. There were no significant differences in age and gender between the two groups.

Evaluation by TCD Ultrasonography. Standardized TCD was performed at the end of the therapeutic recompression in a hyperbaric chamber by using an EME Pioneer (Nicolet, UK) with a 2-MHz probe. The probe was attached to the patient's head, and the M1 segment (first segment from the internal carotid artery bifurcation to the first middle cerebral artery bifurcation) of the right middle cerebral artery was monitored at a depth of 50–60 mm. The Doppler spectrum was continuously recorded and stored on a hard disk. Patients received a 20-mL bolus injection of agitated oxypolygelatin via an antecubital vein (18-gauge catheter). TCD ultrasonography was considered as positive (indicating the presence of an RLS) when we recorded at least five typical high-intensity transient signals (HITS) of the Doppler spectrum, 5–15 secs after injection. After the injection at rest, during normal breathing, the test was repeated in association with provocative maneuvers: at release

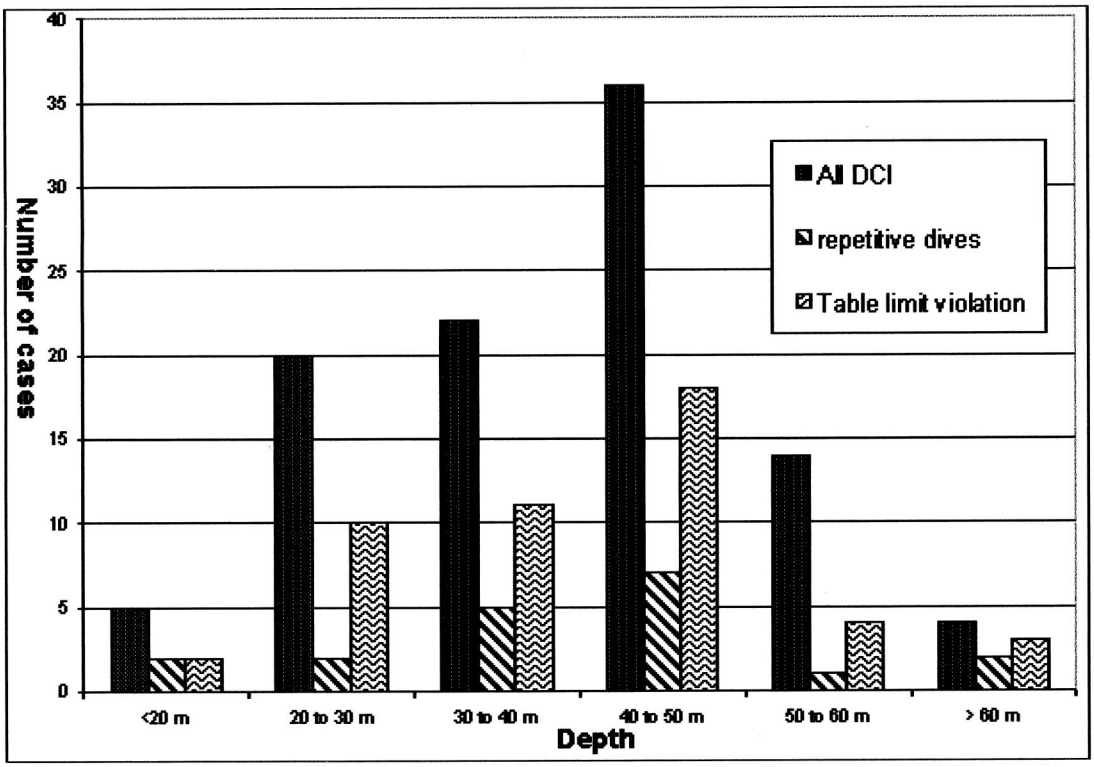

Figure 1. Number of divers with decompression illness (*DCI*) vs. depth in meters of sea water. Table limit violations are calculated according to French Navy MN90 tables. For the repetitive dives, we indicated the depth of last dive.

Table 1. Depth of diving and number of table limits violations vs. type of decompression illness (DCI)

	Total No. of Cases	Depth <30 (%)	Depth 30–60 (%)	Depth >60 (%)	No. of Table Limits Violations (%)
Cerebral DCI	21	4 (19)	12 (57)	5 (24)	11 (52)
Spinal DCI	31	8 (26)	20 (64)	3 (9.6)	18 (58)
Caisson sickness	15	4 (26)	10 (66)	1 (6.6)	9 (60)
Cochleovestibular DCI	34	11 (32)	22 (65)	1 (3)	17 (50)
Total	101	27 (27)	64 (63)	10 (10)	55 (54)

Table limit violations according to French navy MN90 tables. Depth in meter of sea water. Results in number of cases (% of total).

of the Valsalva maneuver with the contrast injection immediately before the maneuver, and while the subject was coughing. The Valsalva maneuver was documented based on the decrease of blood velocity in the middle cerebral artery. A cerebral velocity increase was also observed at the release of Valsalva maneuver (Fig. 2). The Valsalva maneuver was repeated once, when no HITS was observed, and at least four boluses were injected to conclude that TCD ultrasonography was negative (one at rest, two during Valsalva maneuver, and one while the subject was coughing). We estimated semiquantitatively the difference between a slight and important contrast passage as follows. A minor RLS was defined if <20 HITS were detected solely during provocation maneuvers, with no contrast passage at rest. An RLS was major for >20 HITS (6), observed within 15 secs after the injection of the agitated solution during normal breathing.

Statistical Analysis. The ratio of probabilities of disease with vs. without a contributing factor (such as presence or degree of RLS) cannot be estimated without bias from a case-control study, because the distribution of the sample-based risk ratio depends on the unknown sampling fractions (proportions of diseased and disease-free subjects who are represented in the study) (11). However, when the probability of disease is small, the risk ratio is approximately the same as the odds ratio (OR), which can be estimated from such studies (11). In particular, we were able to estimate the ratio of the odds of each type of DCI for a person with vs. without RLS by using data from our DCI case-control study. Because of the small incidence of DCI in the population of divers, each estimated OR is regarded as being a valid estimate of the corresponding risk ratio. Using logistic regression analysis, we obtained point estimates and 95% confidence intervals (CIs) for each OR. All calculations were done with Stata statistical software (release 6.0; Stata, College Station, TX).

RESULTS

Potential Associations Between RLS and Types of DCI. Of the 101 divers presenting with DCI, TCD detected an RLS in 59 (58.4%), whereas control subjects

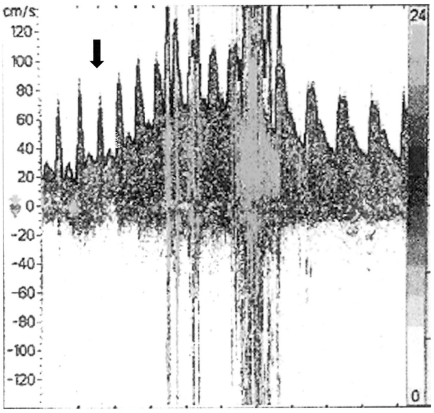

Figure 2. Transcranial Doppler ultrasonography of the right middle cerebral artery: depth 56 mm, mean velocity 66 cm/sec. Increase of the systolic velocities following the release of Valsalva maneuver. The *black arrow* represents the release of the Valsalva maneuver. Patent foramen ovale with minor right-to-left shunt (<20 high-intensity transient signals after provocative maneuvers).

demonstrated an RLS in 25 (24.8%) cases (OR, 4.3; 95% CI, 2.3–7.8; $p = .09$). The prevalence of RLS was higher in the divers presenting with cochleovestibular DCI (82.4%; OR, 14.2; 95% CI, 5.3–38.2; $p < .001$) and cerebral (81.0%; OR, 12.9; 95% CI, 4.0–42.0; $p < .001$) compared with 24.8% in the control group. These two types of DCI showed the highest association with RLS. However, the incidence of spinal DCI and Caisson sickness was not significantly associated with RLS. More specifically, the proportion of RLS patients with spinal DCI was 38.7% (OR, 1.9; 95% CI, 0.8–4.5; $p = .13$). For Caisson sickness, the proportion of RLS was only 13.3% (OR, 0.5; 95% CI, 0.1–2.2; $p = .3$), less than that observed in the control group (see Table 2).

Effects of the Degree of RLS. When a RLS was detected, the RLS was major in 12 of 25 patients in the control group and in 49 of 59 patients in the DCI group (OR, 8.7; 95% CI, 4.2–18.0; $p < .001$). Within the DCI group, the proportion of major RLS was 24 (OR, 29.7; 95% CI, 10.0–87.2; $p < .0001$) of a total of 28 RLS in the cochleovestibular subgroup (n = 34), 13 of 17 (OR, 24.1; 95% CI, 6.8–86.0; $p < .0001$) in the cerebral DCI subgroup (n = 21), ten of 12 (OR, 3.9; 95% CI, 1.5–10.3; $p = .013$) in the spinal DCI subgroup (n = 31), and two of two (OR, 1.1; 95% CI, 0.2–5.7; $p = .9$) in the subgroup of divers with Caisson sickness (n = 15). The highest association between major RLS and DCI was observed among cochleovestibular cases. The effect of major RLS was also highly significant for cerebral DCI. A lower but still significant association was observed for spinal DCI. The estimated risk of Caisson sickness was not significantly different between divers with and without major RLS. The effect of major RLS as an explanatory variable was compared with the no-RLS condition (see Table 3). In addition, in a separate analysis, we found that minor RLS was not associated with any type of DCI.

DISCUSSION

Intravascular bubbles may form during decompression, directly in venous blood or secondary to their formation in tissue. These bubbles are usually trapped in the lung, so that no clinical signs of DCI occur. DCI is initiated by small bubbles within the body, lying outside of normal gas-containing spaces and venous blood. These bubbles can provoke mechanical disruption of tissues, obstruct blood vessels, and activate coagulation, fibrinolysis, complement, or inflammatory cells or platelets. The site of bubble formation is not known, and three potential mechanisms have been postulated to explain the formation of pathologic bubbles: within the arterial blood, by arterialization of venous blood (through the pulmonary circulation, as a consequence of lung barotrauma, or through an RLS), and, last, directly *in situ*, designated as extravascular autochthonous bubbles. It has been suspected that these different mechanisms might be involved separately, depending on the location of bubbles in various target organs. In spinal cord disease, bubble accumulation in the epidural venous plexus, with activation of clotting mechanisms (2), and autochthonous bubble formation in the spinal cord white matter (12), have been suggested to induce spinal DCI.

Table 2. All shunts visualized by transcranial Doppler ultrasonography

	Yes	No	*p*	Odds Ratio for DCI With vs. Without Shunt (95% Confidence Interval)
Control group, n = 101	25 (24.8)	76 (75.2)		
DCI group, n = 101	59 (58.4)	42 (41.6)	.09	4.3 (2.3 < OR <7.8)
Cochleovestibular DCI, n = 34	28 (82.4)	6 (17.6)	<.001	14.2 (5.3 < OR <38.2)
Cerebral DCI, n = 21	17 (81)	4 (19.0)	<.001	12.9 (4.0 < OR <42.0)
Spinal DCI, n = 31	12 (38.7)	19 (61.3)	.13	1.9 (0.8 < OR <4.5)
Osteomyoarticular DCI, n = 15	2 (13.3)	13 (86.7)	.3	0.5 (0.1 < OR <2.2)

DCI, decompression illness; OR, odds ratio.

Table 3. Right-to-left shunting vs. no right-to-left shunting

	Major Shunts Visualized by TCD			
	Yes	No	*p*	Odds Ratio for DCI With Major Shunt vs. Without (95% Confidence Interval)
Control group, n = 101	12 (11.9)	89 (88.1)		
DCI group, n = 101	49 (48.5)	52 (51.5)	<.001	8.7 (4.2 < OR <18.0)
Cochleovestibular DCI, n = 34	24 (70.6)	10 (29.4)	<.0001	29.7 (10.0 < OR <87.2)
Cerebral DCI, n = 21	13 (61.9)	8 (38.1)	<.0001	24.1 (6.8 < OR <86.0)
Spinal DCI, n = 31	10 (32.3)	21 (67.7)	.013	3.9 (1.5 < OR <10.3)
Osteomyoarticular DCI, n = 15	2 (13.3)	13 (86.7)	NS	1.1 (0.2 < OR <5.7)

TCD, transcranial Doppler ultrasonography; DCI, decompression illness; OR, odds ratio.

We demonstrated that major right-to-left shunting was associated with an increased incidence of cochleovestibular and cerebral DCI, suggesting paradoxical embolism as a potential mechanism.

The cochleovestibular system may also be the site of autochthonous bubble formation, since this low-perfusion tissue is inadequate to rapidly remove the dissolved inert gas. But animal studies showed that cochleovestibular signs are of peripheral origin and tend to be vascular lesions (13). These lesions could be related to bubble blockage of microvessels, causing hemorrhage into labyrinthine spaces. This is likely to occur because capillary beds are very thin, without collateral circulation. Arterial bubble embolization is also the main mechanism postulated for cerebral lesions of DCI.

Patent foramen ovale probably represents the most frequent cause of RLS and is known to occur in 27.3% of the normal population (14). It is usually a channel through the interatrial septum, which forms a functional valve without significant blood shunting under normal hemodynamic conditions. A reversal of the normal left-to-right pressure gradient between right and left atrium may occur, as during a Valsalva maneuver, leading to a transient RLS. In contrast, a permanent LRS exists with an atrial septal defect, which is a contraindication for sport diving (5, 15). In recent years, several clinical studies have indicated a higher prevalence of patent foramen ovale in the divers who suffered from DCI (16–18). Patent foramen ovale could explain DCI by paradoxical gas bubble embolism, transient RLS allowing venous bubbles to cross into the arterial circulation rather than being eliminated by the lung.

Our results have demonstrated a significant increased risk of cochleovestibular and cerebral DCI in divers with RLS. The potential role of RLS in cochleovestibular DCI is a new finding, and we provide further evidence of its involvement in cerebral DCI. However, the noted effect on DCI was primarily caused only by major RLS and increased amounts of decompression venous gas emboli crossing into the arterial system. The weaker but still significant association between major RLS and spinal DCI suggests that paradoxical embolism may be an underlying mechanism in some types of spinal DCI. It also implies that mechanisms other than paradoxical embolism may be involved in spinal DCI. This is in accordance with the autochthonous bubbles or venous engorgement hypothesis. As expected, we found that the presence of a major RLS had no influence on the occurrence of Caisson sickness.

A limitation to the semiquantitative measurement is that the number of HITS detected correspond to an aggregation of bubbles and may underestimate the actual number of arterial gas emboli. Previous studies have used different criteria for semiquantitative results, all realized by counting the number of bubbles shunted during TCD. Occurrence of >20 HITS was regarded as an indicator of major shunts (6). In addition, it allows a comparison with transesophageal echocardiography, with an acceptable concordance for major RLS, whereas discrepancies seem to appear with minor RLS (9, 19–21). Whether the choice of the contrast solution and its dose influence the results is not known. However, very close sensitivities and sensibilities were reported when various contrast solutions were used.

The differential diagnosis of inner ear barotrauma and cochleovestibular DCI requires an accurate history and physical examination. In some instances this diagnosis is difficult to assess. Divers sometimes may not be aware when symptoms begin. Furthermore, inner ear barotrauma may occur even without signs of middle ear barotrauma. Therefore, in the present study, the patients with difficult differential diagnosis were excluded.

This technique, with provocative maneuvers, although not quite as sensitive in the detection of all shunt sizes, is a useful test, possibly superior to transesophageal echocardiography for detection of clinically significant RLS. It was compared with transesophageal echocardiography for the detection of a patent foramen ovale in patients with strokes (8, 9) and compared with transesophageal and transthoracic echocardiography in patients suffering from DCI (20). Indeed, positive and negative predictive values

were superior for TCD ultrasonography compared with transthoracic echocardiography, but the most sensitive technique was transesophageal echocardiography. Furthermore, it is usually faster to become competent with TCD ultrasonography than with echocardiography, and the equipment costs approximately ten times less. TCD ultrasonography is not as operator-dependent as transthoracic echocardiography. In most cases, the MCA waveform was readily obtained. The use of a headset supporting the probe allowed monitoring of the Doppler spectrum and made the procedure and the provocative maneuvers easier, the contrast agent being injected immediately before Valsalva maneuver (19). Although transesophageal echocardiography is a more sensitive method than TCD ultrasonography for detecting RLS, it is an invasive procedure, unsuitable for routine detection of RLS. There were no anatomical limitations for TCD ultrasonography in this study, but 5 to 15% of the patients may present a missing temporal bone window (22). TCD is a convenient, well-tolerated, and reliable technique to routinely screen divers for RLS.

CONCLUSIONS

We demonstrated that major RLS was associated with an increased incidence of cochleovestibular and cerebral DCI, suggesting paradoxical embolism as a potential mechanism. The weaker but still significant association between major RLS and spinal DCI suggests that paradoxical embolism might be involved in some cases.

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