

## VIEWPOINT |

## Why predominantly neurological decompression sickness in breath-hold divers?

J. D. Schipke<sup>1</sup> and K. Tetzlaff<sup>2</sup><sup>1</sup>Research Group Experimental Surgery, University Hospital Düsseldorf, Düsseldorf Germany; and <sup>2</sup>Sportmedizin Tübingen Universitätsklinikum Tübingen, Tübingen, Germany

Submitted 1 October 2015; accepted in final form 20 January 2016

*Signs and Symptoms Consistent with DCS in Breath-Hold Diving*

It has been widely believed that human free divers were immune to decompression sickness because the only inert gas added during a breath-hold dive is the nitrogen (N<sub>2</sub>) that remains in the lungs from the inhalation before submerging. However, there has been anecdotal evidence from case reports of divers suffering neurological symptoms after repeated free dives. In breath-hold divers of the Tuamotu Archipelago a neurological syndrome called *taravana* had been described as early as 1958 (33). Paulev in 1965 reported symptoms such as nausea, dizziness, progressive visual disturbances, and unilateral paresis after repetitive free dives to 20 m (66 ft.) depth, and modeling of N<sub>2</sub> tissue saturation supported the idea of reaching critical tissue nitrogen concentrations after frequent repetitive free dives with short surface intervals (31). These observations led to the hypothesis that decompression stress would be possible in humans performing extreme repetitive breath-hold dives (20). The possibility that free-diving humans could accumulate enough (N<sub>2</sub>) in the body tissues to suffer DCS after single deep breath-hold dives remained a controversial topic (29). More cases of stroke-like incidents after repeated shallow-water dives were reported more recently from professional Japanese breath-hold divers (Ama). Kohshi et al. (17) described a case of right homonymous hemianopsia in a 33-yr-old man whose magnetic resonance imaging (MRI) of the brain showed signal intensities in the left occipital lobe and right basal ganglia. Another 39-yr-old man suffered right-sided motor weakness and sensory numbness, with his MRI showing increased signal intensities in the left parietal lobe and basal ganglia (17). These divers had neither vascular diseases nor risk factors for stroke, and the MRI findings were consistent with a vascular pathogenesis of the lesions, i.e., occlusion of cerebral arteries. Remarkably, in both cases the symptoms occurred in the afternoon during the second diving shift, performing repeated breath-hold dives to 20–25 m depth with 1-min surfacing intervals for several hours. More cases of acute neurological injury in Ama divers were published subsequently (18, 19), and a recent survey among professional Japanese Ama divers revealed that 6.9% of divers reported stroke-like neurological events during or immediately after repetitive breath-hold diving (38). A neuroimaging study in-

vestigated asymptomatic Japanese breath-hold divers using MRI (19). In that study, 11 of 12 divers displayed abnormalities of the brain consistent with ischemic lesions, indicating that even in the absence of overt neurological symptoms long term breath-hold diving can cause damage to the brain, probably through accumulation of repeated transient injury (19). Another study supports possible underestimation of the true damage to the brain. In that study elite breath-hold divers (≥30 m; 5 yr experience) with normal neurologic exams and normal brain MRIs, exhibited abnormal brain SPECT images in all five divers (32). Finally, stroke-like neurological events have been reported in competitive free divers after deep breath-hold dives >100 m depth (35). Remarkably, these cases occurred in young healthy subjects without a history of cardiovascular disease or pertinent risk factors.

*Possible Mechanisms of (Transient) Neurological Injury in Breath-Hold Diving*

Surprisingly, DCS-like phenomena associated with breath-hold diving are primarily of the neurological type (12, 19). Although the underlying mechanisms of brain damage in breath-hold diving remain to be elucidated, N<sub>2</sub> bubbles passing through the heart (= extrapulmonary shunt) or the lungs (= intrapulmonary shunt) so as to become arterialized may be a factor contributing to stroke-like clinical presentations in elite breath-hold divers after deep dives (18). In fact, the ultrasonic detection of gas bubbles in the right ventricle (34) and in the pulmonary infundibulum (22) points at the possibility that inert gas microbubbles can develop in divers after breath-hold dives. Normally, such bubbles should be filtered by the lung capillaries. However, small VGE may spill over to become arterialized but would dissolve in the arterial system, because of high surface tension causing the bubble to shrink. However, if arterialized gas bubbles do not dissolve, because of their enlarged size, and lodge in the cerebral capillary network, they may further increase in size because of nitrogen influx from contiguous temporarily supersaturated tissue. For repetitive shallow water breath-hold dives as carried out by Japanese Ama and other indigenous divers it can be expected that N<sub>2</sub> supersaturation will occur in brain tissue if surface intervals are short enough, i.e., about 1 min (13). For single deep dives with no prior residual nitrogen it has been estimated from probabilistic models designed for predicting the percent likelihood of DCS that DCS risk is negligible until breath-hold depth reaches 100 m but would increase nonlinearly from that depth (11). These theoretical considerations are consistent with clinical

Address for reprint requests and other correspondence: J. D. Schipke, Research Group Experimental Surgery, Univ. Hospital Düsseldorf, Wildenbruchstrasse 10, D-40545 Düsseldorf, Germany (e-mail: j.schipke@gmx.org).

observations of DCS-like symptoms after single deep breath-hold dives (11, 35).

Hence DCS-like symptoms and signs associated with extreme repetitive or single deep breath-hold diving may indicate DCS (42). DCS might in fact explain some fatal accidents in humans after repetitive deep breath-hold dives with short surface intervals (38). There are cases of DCS that have been reported to resolve spontaneously. One option suggests a transient hyperpermeability in the microvasculature as a possible cause of cerebral DCS in breath-hold divers (27). A transient ischemic attack (TIA) is a transient episode of neurologic dysfunction caused by ischemia that might be induced by an embolus that occludes an artery in the brain (10). TIA is characterized by an abrupt onset of focal neurological symptoms that resolves within 24 h (3). These attacks cause symptoms such as contralateral paralysis or sudden weakness or numbness. A TIA may also cause sudden dimming or loss of vision, aphasia, slurred speech, and mental confusion. But unlike a stroke, the symptoms of a TIA can resolve within a few minutes or 24 h. Therefore the possibility exists that TIA after breath-hold diving may be a clinical presentation of DCS.

Hypoxia per se could be the cause of DCS-like symptoms and signs after breath-hold diving. However, whether single extended apnea or repetitive bouts of apnea are associated with a risk for hypoxic brain damage has not been established. Yet it is suggested that prolonged exposures to apnea leading to severe hypoxia may be a risk even for long-term brain damage (23). Thus alterations seen in MRI could be due to immediate hypoxic damage, because free diving is associated with extreme hypoxia (16). In fact, a protein marker of injured CNS cells, S100 calcium binding protein B (S100B), was increased after breath-holding in trained breath-hold deep divers, likely indicating a temporary opening of the blood-brain barrier (2). Entrapped bubbles may also lead to cellular injury, thus releasing S100B (14). We do not favor the concept that hypoxia alone would induce the neurological disorders reported in breath-hold divers, because individuals performing any static or dynamic breath-holds in shallow water have not reported DCS-like symptoms, although these divers can sustain breath-hold durations of more than 10 min.

#### *Pulmonary Shunts as a Route for Arterialization of VGE*

Intrapulmonary arteriovenous (IPAV) anastomoses in humans were first described 65 years ago (39). Such pathways with 25 and 50  $\mu\text{m}$  diameter were more recently confirmed to exist in baboon and adult healthy human lungs (24). IPAV anastomoses were described as large diameter connections allowing blood flow to bypass the lung capillaries and to provide a route for right-to-left embolus transmission (5). Bates and colleagues (5) report the passage of albumin particles with a mean diameter of 29  $\mu\text{m}$ ; maximum diameter was up to 120  $\mu\text{m}$ . Doppler ultrasound permits the detection of bubbles  $>19$   $\mu\text{m}$  (15). IPAV anastomoses may represent breaches in the pulmonary filter (1), allowing an embolus passing such a shunt to reach the heart or the brain. From their study on patients with a cerebrovascular accident or with a TIA, the same authors conclude that intrapulmonary shunts present potentially unrecognized facilitators of cerebrovascular accidents and TIA (1). Several factors being present during breath-hold diving may facilitate the opening of intrapulmo-

nary shunts, including body positioning (39), submaximal to maximal exercise (25), and hypoxia (21). Elliott et al. (9) recently found a 28% prevalence of transpulmonary passage of contrast at rest in a group of 174 healthy, young, asymptomatic subjects; that rate was reduced to 5% by breathing 100%  $\text{O}_2$  and assuming an upright body position. In contrast to resting positions, more than 95% of healthy humans show shunting through IPAV anastomoses during exercise (8, 37). Interestingly, breathing 100% oxygen prevented arteriovenous shunting during submaximal exercise and dramatically reduced it at maximal exercise (26). Moreover, the transpulmonary passage of bubbles was shown to increase and occur at lower relative workloads when breathing hypoxic gas compared with breathing air (25). Laurie et al. (21) found that a 30-min exposure to a gas mixture with a reduced inspired oxygen tension of 10% opened IPAV anastomoses in all healthy adult subjects at rest.

During breath-hold diving, hypoxia is present and increases with breath-hold duration. Arterial  $\text{Po}_2$  values may reach levels as low as 19 to 28 mmHg, whereas venous  $\text{Pco}_2$  values might increase up to 40 to 50 mmHg (2, 30). Thus hypoxia may be a key factor in deep breath-hold diving to allow transpulmonary passage of venous gas microbubbles. It is yet unknown whether acute severe hyperbaric hypoxia would have the same effect on IPAV anastomoses as prolonged normobaric hypoxia, but current evidence is increasing that oxygen is playing an important role in the regulation of IPAV anastomoses. Hypercapnia is known to act synergistically to the effects of hypoxia on the pulmonary circulation. However, during breath-hold diving a substantial rise in  $\text{PaCO}_2$  is prevented by the large amount of highly soluble  $\text{CO}_2$  taken up by the blood with increasing pressure, thereby blunting the compression effect on blood-gas tension (28). Additionally, results from a recent study indicate that pulmonary pressure, pH, and  $\text{Pco}_2$  are unlikely regulators of IPAV anastomoses blood flow (40). The contribution of exercise during the dive could similarly be excluded, because very few exercise-induced arterialized gas bubbles reach the cerebral vasculature (4).

Blood flow through IPAV anastomoses is increased by acute hypoxia at rest by mechanisms that are still poorly understood. These shunts offer an alternative pathway for VGE to bypass the capillary filter and thus may lead to arterial gas embolism in the central nervous system. As the prevalence of both neurological injury with DCS-like symptoms and cerebral ischemic lesions among Japanese Ama breath-hold divers cannot be explained by the presence of cardiac right-to-left shunts or other factors—in fact none of the Japanese cases of acute stroke had a patent foramen ovale—the recruitment of IPAV anastomoses due to hypoxia during breath-hold diving may be a potential mechanism of injury. This pathophysiology may also explain cerebral arterial gas embolism and stroke-like phenomena in humans performing extreme breath-hold dives. An interesting aspect within the context of the physiology of diving is that the  $\text{N}_2$  gas bubble will increase in size during ascent, and, additionally, coalesce with other bubbles, which may allow a greater sized bubble to be present on the outflow side than what originated on the inflow and hence not be restricted by the diameter of the shunting vessel. In fact, it was postulated recently that  $\text{N}_2$  microbubbles after multiple breath-hold dives may be retained or trapped in small pulmonary arteries but will be compressed during descent, thus allowing these bubbles to become small enough to pass through pulmo-

nary capillaries (19). However, this hypothesis may not be valid for elite breath-hold divers who usually perform single deep dives, i.e., start the dive without possible N<sub>2</sub> supersaturation from a prior dive. Because there is still gas exchange in the human lung at great depth, venous gas bubbles may be formed along the extreme N<sub>2</sub> gradient between tissues and the alveolar space, and eventually these bubbles may arterialize through opened IPAV anastomoses. However, the mechanisms of N<sub>2</sub> gas bubble formation and their vascular passage during extreme human breath-hold dives remain to be elucidated.

In scuba diving, AGE may be caused by introduction of alveolar gas through barotrauma of the lung or VGE via cardiac shunts or via pulmonary vessels into the arterial circulation. Normally the capillary bed of the pulmonary vasculature is an effective filter for VGE (6); however, its capacity to effectively filter gas bubbles depends on size, location, and the amount of bubbles trapped in the pulmonary circulation and significant decompression stress is associated with an increased risk of a spillover of VGE into the arterial side of the circulation (7). VGE may bypass this filter through a cardiac right-to-left shunt such as patent foramen ovale (PFO). The presence of a PFO has been associated with the risk of decompression illness in scuba divers (41); this risk has been reported to be 4.5-fold higher in divers with a PFO compared with those without, and the incidence of ischemic brain lesions on cranial MRI was two times higher in divers with PFO (36). Thus, although the clinical presentation of DCS may be similar between scuba diving and breath-hold diving, the underlying pathophysiology of arteriovenous shunting of VGE can differ because hyperoxia is present during scuba diving and may in fact prevent spillover of VGE through IPAV anastomoses. This preventive mechanism may fail once a certain threshold of VGE is reached in the pulmonary arterial circulation. Of note, in breath-hold diving AGE may also be caused by introduction of alveolar gas through barotrauma of the lung or VGE via cardiac shunts. However, barotrauma of the lung is unlikely to occur during ascent, because, unlike scuba diving, there is no gas added to the lungs at depth. Cardiac shunts, in particular PFO, may be present in breath-hold divers as in the general diving population. However, it has been reported that in none of the Japanese cases of stroke and TIAs after breath-hold dives a PFO was present.

### Conclusion

IPAV shunts normally exist in humans, and hypoxia may contribute to the recruitment of these shunts. In breath-hold deep divers, the occurrence of neurological signs and symptoms compatible with DCS predominates over symptoms that would indicate “pain only” DCS. We suggest hypoxia to possibly induce recruitment of intrapulmonary AV shunts permitting venous N<sub>2</sub> bubbles to spill over to the arterial circulation. The arterialized bubbles will eventually travel to the cranial arteries and may occlude cerebral arterial blood vessels causing stroke-like phenomena, similar to the presentation of gas embolism in scuba diving. Because some of the neurological cases resolve spontaneously and because of similar symptoms, we draw attention to the possibility that neurological DCS in breath-hold divers and transient ischemic attacks in patients might relate to each other.

### ACKNOWLEDGMENTS

The authors are grateful to the reviewers for constructive comments that helped improving this manuscript.

### DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

### AUTHOR CONTRIBUTIONS

J.D.S. and K.T. drafted manuscript; J.D.S. and K.T. edited and revised manuscript; J.D.S. and K.T. approved final version of manuscript.

### REFERENCES

1. Abushora MY, Bhatia N, Alnabki Z, Shenoy M, Alshaher M, Stoddard MF. Intrapulmonary shunt is a potentially unrecognized cause of ischemic stroke and transient ischemic attack. *J Am Soc Echocardiogr* 26: 683–690, 2013.
2. Andersson JP, Linér MH, Jönsson H. Increased serum levels of the brain damage marker S100B after apnea in trained breath-hold divers: a study including respiratory and cardiovascular observations. *J Appl Physiol* 107: 809–815, 2009.
3. Barak OF, Madden D, Lovering AT, Lambrechts K, Ljubkovic M, Djucic Z. Very few exercise-induced arterialized gas bubbles reach the cerebral vasculature. *Med Sci Sports Exerc* 47: 1798–1805, 2015.
4. Bates ML, Jacobson JE, Eldridge MW. Transient intrapulmonary shunting in a patient treated with  $\beta_2$ -adrenergic agonists for status asthmaticus. *Pediatrics* 133: e1087–1091, 2014.
5. Butler BD, Hills BA. Transpulmonary passage of venous air emboli. *J Appl Physiol* 59: 543–547, 2009.
6. Butler BD, Katz J. Vascular pressures and passage of gas emboli through the pulmonary circulation. *Undersea Biomed Res* 15: 203–209, 1988.
7. Eldridge MW, Dempsey JA, Haverkamp HC, Lovering AT, Hokanson JS. Exercise-induced intrapulmonary arteriovenous shunting in healthy humans. *J Appl Physiol* 97: 797–805, 2004.
8. Elliott JE, Nigam SM, Laurie SS, Beasley KM, Goodman RD, Hawn JA, Gladstone IM, Chesnutt MS, Lovering AT. Prevalence of left heart contrast in healthy, young, asymptomatic humans at rest breathing room air. *Respir Physiol Neurobiol* 188: 71–78, 2013.
9. Ferro JM, Rodrigues G, Canhao P, Melo TP, Oliveira V, Pinto AN, Crespo M, Salgado AV. Diagnosis of transient ischemic attack by the nonneurologist. A validation study. *Stroke* 27: 2225–2229, 1996.
10. Fitz-Clarke JR. Risk of decompression sickness in extreme human breath-hold diving. *Undersea Hyperb Med* 36: 83–91, 2009.
11. Gempp E, Blatteau JE. Neurological disorders after repetitive breath-hold diving. *Aviat Space Environ Med* 77: 971–973, 2006.
12. Goldman S, Solano-Altamirano JM. Decompression sickness in breath-hold diving, and its probable connection to the growth and dissolution of small arterial gas emboli. *Math Biosci* 262: 1–9, 2015.
13. Havnes MB, Hjelde A, Brubakk AO, Møllerlökken A. S100B and its relation to intravascular bubbles following decompression. *Diving Hyperb Med* 40: 210–212, 2010.
14. Hills BA, Butler BD. Size distribution of intravascular air emboli produced by decompression. *Undersea Biomed Res* 8: 163–170, 1981.
15. Kjeld T, Jattu T, Nielsen HB, Goetze JP, Secher NH, Olsen NV. Release of erythropoietin and neuron-specific enolase after breath holding in competing free divers. *Scand J Med Sci Sports* 25: e253–7, 2015.
16. Kohshi K, Katoh T, Abe H, Okudera T. Neurological accidents caused by repetitive breath-hold dives: Two case reports. *J Neurol Sci* 181: 137–139, 2000.
17. Kohshi K, Wong RM, Abe H, Katoh T, Okudera T, Mano Y. Neurological manifestations in Japanese Ama divers. *Review Undersea Hyperb Med* 32: 11–20, 2005.
18. Kohshi K, Tamaki H, Lemaitre F, Okudera T, Ishitake T, Denoble PJ. Brain damage in commercial breath-hold divers. *PLoS One* 9: e105006, 2014.
19. Lanphier EH. Application of decompression tables to repeated breath-hold dives. In: *Physiology of Breath-Hold Diving and the Ama of Japan*, edited by Rahn H, Yokoyama T. Washington, DC: National Academy of Science, National Research Council Publication, p. 227–236, 1965.
20. Laurie SS, Yang X, Elliott JE, Beasley KM, Lovering AT. Hypoxia-induced intrapulmonary arteriovenous shunting at rest in healthy humans. *J Appl Physiol* 109: 1072–1079, 2010.

22. Lemaitre F, Kohshi K, Tamaki H, Nakayasu K, Harada M, Okayama M, Satou Y, Hoshiko M, Ishitake T, Costalat G, Gardette B. Doppler detection in Ama divers of Japan. *Wilderness Environ Med* 25: 258–262, 2014.
23. Liner MH, Andersson JP. Hypoxic syncope in a competitive breath-hold diver with elevation of the brain damage marker S100B. *Aviat Space Environ Med* 12: 1066–1068, 2009.
24. Lovering AT, Stickland MK, Kelso AJ, Eldridge MW. Direct demonstration of 25- and 50-microm arteriovenous pathways in healthy human and baboon lungs. *Am J Physiol Heart Circ Physiol* 292: H1777–H1781, 2007.
25. Lovering AT, Romer LM, Haverkamp HC, Pegelow DF, Hokanson JS, Eldridge MW. Intrapulmonary shunting and pulmonary gas exchange during normoxic and hypoxic exercise in healthy humans. *J Appl Physiol* 104: 1418–1425, 2008.
26. Lovering AT, Stickland Amann M, Murphy JC, O'Brien MJ, Hokanson JS, Eldridge MW. Hyperoxia prevents exercise-induced intrapulmonary arteriovenous shunt in healthy humans. *J Physiol* 586: 4559–4565, 2008.
27. Matsuo R, Kamouchi M, Arakawa S, Furuta Y, Kanazawa Y, Kitazono T. Magnetic resonance imaging in breath-hold divers with cerebral decompression sickness. *Case Rep Neurol* 24: 23–27, 2014.
28. Muth CM, Ehrmann U, Radermacher P. Physiological and clinical aspects of apnea diving. *Clin Chest Med* 26: 381–394, 2005.
- 28a. National Institute of Neurological Disorders and Stroke. Special Report from the National Institute of Neurological Disorders and Stroke: classification of cerebrovascular diseases III. *Stroke* 21: 637–676, 1990.
29. Olszowska A. Depth and time in relation to gas exchange. In: *The Physiology of Breath-Hold Diving*, edited by Lundgren CEG, Ferrigno M. Bethesda, MD: Undersea Hyperbaric Medical Society, p. 12–31, 1987.
30. Overgaard K, Friis S, Pedersen RB, Lykkeboe G. Influence of lung volume, glossopharyngeal inhalation and P(ET) O<sub>2</sub> and P(ET) CO<sub>2</sub> on apnea performance in trained breath-hold divers. *Eur J Appl Physiol* 97: 158–164, 2006.
31. Paulev P. Decompression sickness following repeated breath-hold dives. *J Appl Physiol* 20: 1028–1031, 1965.
32. Potkin RT, Uszler JM. Brain function imaging in asymptomatic elite breath-hold divers. 2006. In: *Breath Hold Diving. Proceedings of the UHMS & DAN Workshops*, edited by Lindholm P, Pollock NW, Lundgren CEG, Durham, NC, 2006, p. 135–137.
33. Rahn H, Yokoyama T. *Physiology of Breath-Hold Diving and the Ama of Japan*. Washington, DC: National Academy of Sciences, National Research Council Publication, 1965.
34. Schagatay E. Predicting performance in competitive apnea diving. Part III: deep diving. *Diving Hyperb Med* 41: 216–228, 2011.
35. Schipke JD, Gams E, Kallweit O. Decompression sickness following breath-hold diving: Review. *Res Sports Med* 14: 163–178, 2006.
36. Schwerzmann M, Seiler C. Recreational scuba diving, patent foramen ovale and their associated risks. *Swiss Med Wkly* 131: 365–374, 2001.
37. Stickland MK, Welsh RC, Haykowsky MJ, Petersen SR, Anderson WD, Dylan A, Taylor DA, Bouffard M, Jones RL. Intra-pulmonary shunt and pulmonary gas exchange during exercise in humans. *J Physiol* 561: 321–329, 2004.
38. Tamaki H, Kohshi K, Sajima S, Takeyama J, Nakamura T, Ando H, Ishitake T. Repetitive breath-hold diving causes serious brain injury. *Undersea Hyperb Med* 37: 7–11, 2010.
39. Tobin CE, Zariquiey MO. Arteriovenous shunts in the human lung. *Proc Soc Exp Biol Med* 75: 827–829, 1950.
40. Tremblay JC, Lovering AT, Ainslie PN, Stenbridge M, Burgess KR, Bakker A, Donnelly J, Lucas SJE, Lewis NCS, Dominelli PB, Henderson WR, Dominelli GS, Sheel AW, Foster GE. Hypoxia, not pulmonary vascular pressure, induces blood flow through intrapulmonary arteriovenous anastomoses. *J Physiol* 593: 723–737, 2015.
41. Wilmshurst PT, Byrne JC, Webb-Peploe MM. Relation between interatrial shunts and decompression sickness in divers. *Lancet* 2: 1302–1306, 1989.
42. Wong RM. Decompression sickness in breath-hold diving. *Diving Hyperbaric Med* 36: 139–144, 2006.