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HIGHLIGHTED TOPIC | *The Physiology and Pathophysiology of the Hyperbaric and Diving Environments*

Selective vulnerability of the inner ear to decompression sickness in divers with right-to-left shunt: the role of tissue gas supersaturation

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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* 106: 298–301, 2009. First published September 18, 2008; doi:10.1152/japplphysiol.90915.2008.— Inner ear decompression sickness has been strongly associated with the presence of right-to-left shunts. The implied involvement of intravascular bubbles shunted from venous to arterial circulations is inconsistent with the frequent absence of cerebral symptoms in these cases. If arterial bubbles reach the labyrinthine artery, they must also be distributing widely in the brain. This discrepancy could be explained by slower inert gas washout from the inner ear after diving and the consequent tendency for arterial bubbles entering this supersaturated territory to grow because of inward diffusion of gas. Published models for inner ear and brain inert gas kinetics were used to predict tissue gas tensions after an air dive to 4 atm absolute for 25 min. The models predict half-times for nitrogen washout of 8.8 min and 1.2 min for the inner ear and brain, respectively. The inner ear remains supersaturated with nitrogen for longer after diving than the brain, and in the simulated dive, for a period that corresponds with the latency of typical cases. It is therefore plausible that prolonged inner ear inert gas supersaturation contributes to the selective vulnerability of the inner ear to short latency decompression sickness in divers with right-to-left shunt.

diving; decompression illness; patent foramen ovale

DECOMPRESSION SICKNESS (DCS) is caused by formation and growth of bubbles from excess dissolved gas in body tissues following reduction in ambient pressure. It is a complex multisystem disorder whose pathophysiology remains incompletely understood (9). This is particularly true of DCS involving the vestibulocochlear apparatus, commonly referred to as "inner ear DCS" (IEDCS). Symptoms referable to inner ear involvement, such as nausea, vertigo, and hearing loss, may occur in association with other DCS manifestations or as an isolated clinical entity (18). Cases of "isolated" IEDCS have long been associated with decompression from deep dives using breathing gases based on helium and oxygen. Some of these involve onset of symptoms during the ascent. We previously reported such a case and proposed a physiological compartmental model of inner ear inert gas kinetics that predicted that the conditions necessary for bubble growth would arise during ascent from the dive, despite adherence to a decompression protocol (5). We concluded that inappropriate matching of inner ear gas elimination and ascent rate appeared to be a plausible cause for isolated IEDCS during decompression from deep dives.

Subsequently, two studies have described isolated IEDCS arising early after surfacing in divers visiting more modest depths (50 m or less) and, in most cases, using air rather than mixed gas (2, 13). Interestingly, both studies utilized transcranial Doppler sonography after administration of venous bubble contrast to demonstrate an unexpectedly high prevalence of right-to-left shunting among their cases. The case series by Klingmann et al. (13) reported 11 cases of IEDCS in 9 divers, all of whom proved to have a "major" shunt (based on number of bubbles detected). The case-control study by Cantais et al. (2) reported 34 cases of IEDCS, of whom 24 (70.6%) and 4 (11.8%) had major and minor shunts, respectively, compared with the finding of major shunts in only 12 (11.9%) of 101 control divers who had never suffered DCS. Neither study specifically looked for a patent foramen ovale (PFO), but both posited this lesion as the most likely cause of the observed right-to-left shunting.

Venous inert gas bubbles are commonly formed during or after decompression from dives (20), and the only plausible link between right-to-left shunt and IEDCS is the transfer of these bubbles into the arterial circulation. Thus the studies by Klingmann et al. (13) and Cantais et al. (2) have been interpreted as suggesting that in divers with such a shunt, IEDCS may be caused by arterial bubbles acting as emboli. This logic is sound, but a purely embolic cause fails to explain why in many cases the inner ear can be affected while the brain appears not to be. If bubbles are entering the labyrinthine artery from the basilar artery, they must also be distributing widely in the brain, yet in cases of isolated IEDCS we see no evidence of this.

One possible explanation for this discrepancy arises from our previous work on inner ear inert gas kinetics and our consequent ability to predict gas supersaturation conditions in the inner ear after diving. "Supersaturation" refers to the sum of tissue gas partial pressures being greater than ambient pressure, a condition necessary for bubble growth (22). Bubbles introduced to tissue that is supersaturated with inert gas

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have been shown to grow (11), and it follows that small arterial bubbles, either shunted from the venous circulation or introduced to the arterial circulation by pulmonary barotrauma, would grow and be more likely to cause both microvascular obstruction and mechanical disruption if carried into a tissue that was significantly supersaturated with inert gas. Although not previously raised in relation to the inner ear, this concept has been discussed in relation to spinal DCS, albeit without any attempt at validation (19, 23).

Thus, to explain the selective vulnerability of the inner ear to DCS in divers with a right-to-left shunt, we hypothesize, first, that the rate of inert gas elimination from the inner ear may be slower than that for the brain; and, second, that this would provide a longer time interval within which the arrival of any bubbles shunted from the veins would be more likely to result in bubble growth and symptoms. The aim of this study was to investigate this hypothesis by modeling and comparing gas washout from the inner ear and brain after a hypothetical dive.

METHODS

The inner ear model of inert gas kinetics is a physiological model based on parameters in the literature, the structure and validation of which have been detailed previously (3). Three well-stirred compartments represent the membranous labyrinth (the vascular compartment), the perilymph, and the endolymph. Inner ear gas uptake and washout occur via perfusion equilibration of the membranous labyrinth with arterial blood and, negligibly, by diffusion across the round window. Within the inner ear, gas diffuses between the membranous labyrinth and each of the labyrinthine fluid compartments across diffusion-limited membranes of zero volume. The diffusion time constants across these membranes were formulated to reflect the geometry of the inner ear. Such compartmental diffusion models provide a first-order approximation of diffusion kinetics.

A well-established model of cerebral inert gas kinetics (4–6) was used to represent the brain. This model was constructed by estimating the volume of a single, well-stirred compartment by fit of the model to the arterial and sagittal sinus inert gas concentrations and sagittal sinus blood flows measured during sequential breathing of different inert gases and changes in cerebral blood flow in anesthetized sheep. Similar compartment volumes are estimated from nitrous oxide, helium, and nitrogen kinetic data and from actual measurement of tissue weight. The single, well-stirred compartment model fits inert gas kinetic data well except at artificially lowered cerebral blood flow. For the present simulations a normal cerebral blood flow of 55 ml·100 g^{-1}·min^{-1} was assumed, which resolves to a compartmental half-time of 1.2 min.

Inner ear and brain inert gas tensions were simulated for a hypothetical air dive to 30 m of seawater gauge (4 atm absolute, 405.3 kPa), a depth typical of the dives reported in Klingmann et al. (13). Model inputs comprised arterial inert gas tensions and middle ear inert gas partial pressures, both considered to equilibrate instantly with inspired inert gas partial pressures adjusted for vapor pressure at 37°C. For the brain model, nitrogen concentrations (C) and nitrogen tensions (C/α) were converted using a value of nitrogen solubility (α) in tissue and blood of 0.016 (15).

RESULTS

Figure 1 shows the calculated gas tensions in the brain and membranous labyrinth of the inner ear for a hypothetical air dive to a pressure of 4 atm absolute for 25 min followed by direct ascent to the surface (1 atm absolute) at a rate of 1 atm/min. For clarity, only the compartment representing the membranous labyrinth is shown. Gas tensions in the compartments representing the endolymph and perilymph follow similar time courses. It is the membranous labyrinth that is vascularized, and it is this gas tension to which arterial gas emboli entering inner ear would be exposed. It is clear from Fig. 1 that there is a prolonged period of supersaturation in the inner ear immediately after surfacing when compared with brain tissue.

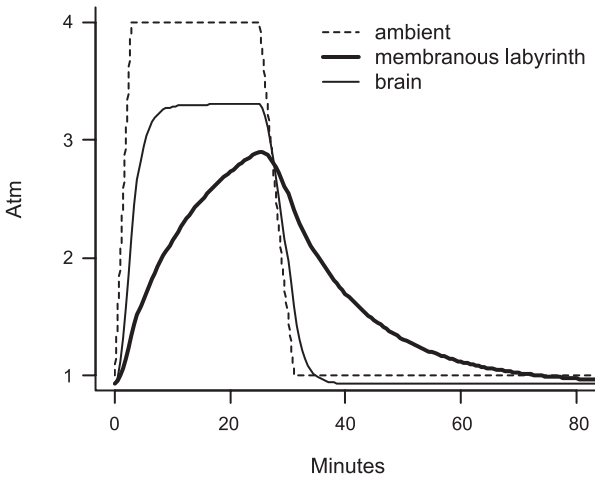

Fig. 1. Time course of gas kinetics in the brain and membranous labyrinth of the inner ear during and after a no-stop dive. Absolute ambient pressure (dashed line) and compartment gas tensions (solid lines) are shown in atm. Compartment gas tensions include a fixed contribution of 0.19 atm representing oxygen, carbon dioxide, and water vapor. Note the prolonged supersaturation of the membranous labyrinth after decompression.

The extent of supersaturation in each of the regions depicted in Fig. 1 will depend on the dive profile, increasing with depth, time at depth, and rate of ascent, but the same pattern of a longer-lasting supersaturation in the inner ear than in the brain would always be present. For instance, this simulated dive is a "no-stop" profile, and although the decompression schedules of the dives reported by Klingmann et al. (13) are not provided in the paper, many likely included decompression stops. Although any decompression stops would reduce the magnitude of supersaturation in the brain and inner ear, the same pattern of a longer-lasting supersaturation in the inner ear than in the brain would manifest with each ascent.

DISCUSSION

DCS may occur when a reduction in environmental pressure, such as ascent from a dive, allows the pressure of dissolved gas in tissues to exceed ambient pressure, resulting in bubble formation. Bubbles can form within the tissues themselves, and they also appear in venous blood (9). Venous bubbles appear after many dives without causing symptoms (7), and this is attributed in part to them being "filtered" from the circulation by the pulmonary capillary bed (1). However, over the last two decades, evidence has accumulated that the presence of a right-to-left shunt (such as a PFO) that bypasses the pulmonary circulation is associated with an increased risk of DCS in certain organs, including the brain, spinal cord, and skin (17). Recently, IEDCS, including "isolated" cases in which there are no symptoms referable to other organ systems, has also been strongly associated with the presence of a major right-to-left shunt (2, 13). The only plausible mechanism that explains these associations is that a shunt allows bubbles to pass from venous to arterial circulations and be carried to the target organ.

This association between isolated IEDCS and right-to-left shunts is intriguing because the inner ear derives its blood supply from the labyrinthine artery, a tiny branch of either the basilar artery or the anterior inferior cerebellar artery (itself a branch of the basilar artery). The basilar artery distributes solely to the brain, and so if vascular bubbles are reaching the inner ear, then they must also be distributing widely (and in much larger numbers) to the brain. It is unclear why the inner ear can be injured under these circumstances while the brain may remain apparently unaffected. One explanation might be that the vascular labyrinth represents an end-arterial territory supporting a delicate signal transducer that is selectively vulnerable to injury by small vascular bubbles. However, it can be argued that end-artery territories are found in functionally important tissue loci throughout the brain (8) and that these should also be affected by concomitant exposure to any bubbles large enough to disturb inner ear function. In fact, in open-chamber cardiac surgery, another situation in which many small arterial bubbles are known to distribute to the cerebral vessels (16), patients often develop postoperative cognitive dysfunction indicating brain injury, but inner ear problems are never reported. Thus the association between right-to-left shunt and isolated IEDCS may not be satisfactorily explained solely on the basis of venous bubbles entering the arteries and being carried to the inner ear.

We have demonstrated that the half-time for nitrogen elimination from the inner ear after decompression is slower than that for the brain. The inner ear nitrogen washout in Fig. 1 is multiexponential but can be approximated by a monoexponential with an 8.8-min half-time (3). This is compared with the brain nitrogen half-time of 1.2 min. These findings provide a potential explanation for the selective vulnerability of the inner ear to injury by vascular bubbles after diving. Thus, after a dive, the inner ear remains supersaturated with inert gas for longer than brain tissues, and the window of opportunity for growth of small vascular bubbles distributing to the labyrinthine artery territory is correspondingly longer. This expectation that bubbles would grow when introduced to a tissue already supersaturated with inert gas is well supported (11, 12), and the short postdive latency of most cases reported in one series (13) also reflects the short period of elevated risk from persistent supersaturation predicted by this study. In dives of the type reported by Klingmann et al. (13), venous bubbling may not peak until 1 h after surfacing, and the bubbling may be sustained for hours (20). Despite this, the vast majority of their cases developed symptoms within 30 min of surfacing, which supports the proposition that another risk factor present early after the dive has a role to play.

There are several limitations to our hypothesis that must be acknowledged. First, while the gas kinetic modeling undertaken here serves as a "proof of concept" for our proposed mechanism, we do not claim that it explains isolated IEDCS across the entire range of diving depths, durations, breathing gas combinations, and latency of onset. Not all divers who suffer IEDCS have a PFO, and even in those who do, other mechanisms may be responsible. For example, as previously mentioned, isolated IEDCS can occur during decompression (before surfacing) from deep mixed-gas dives, and our previous work suggests that this might be explained by bubble formation within the labyrinth itself because of high local supersaturation (3). This latter mechanism is consistent with the pathophysiology proposed by Landolt et al. (14) and entirely independent of the shunting of venous bubbles across a PFO. Second, the treatment of the brain as a homogeneous organ from a gas kinetic perspective does not account for small suborgan structures whose kinetics might be different. We cannot exclude the possibility that there are other vascular territories within the brain, sensitive to bubble injury, whose inert gas kinetics might be substantially slower than other brain regions. However this is unlikely since slow kinetics of the inner ear, which we predict to be one-seventh that of the brain average, are due to the substantial diffusion limitation imposed by the inner ear's unique anatomy. Inert gas kinetics elsewhere in the brain are determined primarily by tissue perfusion, and only about a threefold difference in half-times between the fastest and slowest regions would be expected (6). Third, our explanation for selective vulnerability of the inner ear appears almost contradictory when it is considered that "cerebral DCS" can occur in the absence of inner ear manifestations. However, cerebral DCS symptoms without inner ear involvement could be explained on the same basis that almost certainly accounts for the lack of inner ear injury in cardiac surgery, that is, that few or no bubbles reach the inner ear via the tiny labyrinthine artery despite their presence in the much larger basilar artery.

Finally, although our focus was on the selective vulnerability of the inner ear to DCS, this study circumstantially supports the suggestion that tissue supersaturation is also relevant to other organ systems whose vulnerability to DCS is associated with right-to-left shunts. Wilmshurst and Bryson (23) speculatively raised this hypothesis in relation to spinal DCS without conducting any gas kinetic model simulations to validate the idea. They pointed out, logically, that if a shunt and the consequent presence of arterial bubbles were the only important pathophysiological factors in spinal DCS, then patients undergoing bubble contrast echocardiography for detection of a PFO could be expected to exhibit the relevant symptoms or signs when the test is strongly positive and large numbers of small bubbles are shunted into the arterial system. In practice, this is never reported despite the fact that the size range of bubbles produced in agitated saline bubble contrast (21) overlaps significantly with those formed in venous blood after decompression from experimental dives by dogs (10). We contend that our comparison of the inner ear and brain provides objective support (that hitherto has been lacking) for the concept of tissue vulnerability to adverse effects of small arterial bubbles based on prevailing inert gas tensions. It is an ideal comparison for this purpose because the vascular anatomy overwhelmingly favors embolization of the brain, yet IEDCS without cerebral symptoms is frequently reported.

Thus it is possible that after surfacing there may be a window of risk for growth of intravascular bubbles entering any of the relevant tissues. Whether symptoms actually arise may depend on a chain of events that include venous bubble formation, right-to-left shunting of venous bubbles, and passage of those bubbles into a functionally important tissue at a time when it is supersaturated with inert gas, the latter depending on the tissue's gas washout kinetics and the nature of the dive and decompression. A complicated sequence of interdependent events like this would help explain Moon and Bove's observation that PFO is prevalent among divers, yet those forms of DCS strongly associated with shunts remain relatively rare (17).

In conclusion, despite the stated limitations of our hypothesis, it is plausible that prolonged inner ear inert gas supersaturation contributes to the occurrence of short-latency IEDCS in divers with PFO who do not concomitantly suffer cerebral symptoms.

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