Editorial

Decompression sickness, fatness and active hydrophobic spots

Since decompression sickness (DCS) in humans was first described,[1] mankind has embarked on an odyssey to prevent it. The demonstration that decompression releases bubbles, which mainly contain inert gas (nitrogen, helium),[2] into the circulation and that the slower the decompression rate the lesser the incidence of DCS, resulted in 1908 in the publication of the first, reasonably safe diving tables.[3]

Besides the development of proper diving tables, the selection of divers is also of importance. A relationship between body composition and DCS was observed in dogs as long ago as the nineteenth century,[2] an observation supported early in the twentieth century: "*Really fat men should never be allowed to work in compressed air, and plump men should be excluded from high pressure caissons…or in diving to more than about 10 fathoms, and at this depth the time of their exposure should be curtailed. If deep diving is to be undertaken…. skinny men should be selected.*"[4]

Alas, nothing is that simple! From my own experience it was not always the fat diver who ended up in the treatment chamber with DCS. Therefore, other factors must be at play; gender,[5,6] age,[5,7] physical fitness,[7] and the existence of a persistent foramen ovale (PFO)[8] have all been studied as possible factors for the development of vascular gas bubbles and, therefore, for DCS. However, none of these factors, alone or in combination, explain why there are intra-individual or intra-cohort differences in bubble grades (BG). In other words, why does a dive I did today led to a high BG but the same dive next week lead to a low one? Or, why is there such a difference in BG amongst divers of more or less the same age, gender, body composition and physical fitness? In a letter in this issue, a novel hypothesis is postulated that may fill in these gaps; active hydrophobic spots (AHS).[9]

These AHS can be found at the luminal side of capillary, venous and arterial walls and have an oligolamellar lining. In an *in vitro* experiment, nanobubbles developed on AHS after a 'dive' to 1,000 kPa (90 msw).[10] It appears that AHS consist of dipalmitoylphosphatidylcholine (DPPC), which is the main component of surfactant.[11] It is proposed that DPPC may leak from the alveoli into the alveolar capillary and be transported to veins and arteries where it precipitates and forms AHS.[11] Based on these ideas, it is hypothesized that AHS generate nanobubbles that can grow into microbubbles. When these microbubbles detach from the AHS they might also take along pieces of the AHS membrane making the AHS smaller or even disappear.[10] This phenomenon could explain some of the earlier findings regarding the formation of microbubbles in divers. The fact that the presence of microbubbles differs between younger and older divers, after repetitive dives, and between experienced divers and novice divers can be explained by this model,[10] and AHS may be the missing link we are looking for in our quest to understand and treat DCS.

However, some reservations must be made. Firstly, these observations are derived from *in vitro* and animal experiments and whether or not they reflect a similar process in man remains unclear. Secondly, it appears that female divers have lower bubble grades after similar dives compared to male divers, suggesting lower decompression stress.[5,6] If AHS is the main generator for microbubbles, there should be a difference in the presence of AHS between men and women. We do not know from these animal experiments whether there is a gender difference, neither does a literature search in PubMed provide us with an answer.

Thirdly, as said before, DPPC is the main component of surfactant. All alveolar surfactant phospholipids, such as DPPC, are secreted to the alveolar space via exocystosis of the lamellar bodies (LB) from alveolar type II (ATII) cells.[12] To form a functional air-blood barrier, alveolar type I and ATII cells are connected to each other by tight junctions. These tight junctions constitute the seal of the intercellular cleft and in that way form a true barrier between the alveolus and the capillary.[13] Only small molecules like oxygen, carbon dioxide, etc. can penetrate through this barrier by themselves due to passive diffusion. All other (macro) molecules, including DPPC, need intermediate processes such as ion transport proteins,[14] channels,[12] metabolic pumps,[14] etc. to gain access to the pulmonary capillary lumen. To my knowledge, no such mechanisms for DPPC or LB are known.

A theoretical explanation might be the fact that the production of DPPC and the exocytosis of DPPC-containing LBs into the alveolar space can be stimulated by stretch.[12,15] Stretch of the alveoli can switch on Ca^{2+} entry by either mechanosensitive channels, store-operated channels or second messenger-operated channels, which induces LB exocystosis.[12] Furthermore, an ATP-release mechanism might also be responsible for the pulmonary alveolar mechanotransduction of LB.[12] During diving, transpulmonary pressure changes[16] occur which might induce additional alveolar stretch and thus, theoretically, an extra release of LB. However, whether or not such exocystosis of LB is vascularly orientated remains unclear. Besides which, the leakage of DPPC from the alveolus to the pulmonary capillary might also be as simple as a malfunction of the tight junction due to epithelial membrane damage as a result of diving. Finally, it is also possible that DPPC is produced in other non-ATII cells in our body of which we are currently unaware.

To conclude, this is an interesting hypothesis regarding the origin of microbubbles. Whether or not DPPC and LB are the main reason for individual sensitivity to DCS remains

unclear. Further research will hopefully identify if DPPC and LB are indeed the missing link or just another branch on the big tree of the genesis of decompression sickness.

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