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Short-acting NO donor and decompression sickness in humans

Z. Valic, I. Palada and Z. Dujic

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Nitroglycerine: relief from the heartache of decompression sickness?

DECOMPRESSION SICKNESS (DCS) was first described in the early 19th century in compressed-air workers and divers who, after decompressing from increased ambient pressure, developed joint pain, paresthesias, and sometimes spinal cord injury or death. In animal experiments, Paul Bert (1) in Paris was able to demonstrate bubble formation after decompression, which he confirmed as due to inert-gas (nitrogen) supersaturation. Acceptable limits for pressure (depth)-time exposure have been identified, and staged decompression schedules have been developed that allow inert gas to wash out of tissues before unacceptable degrees of supersaturation occur. Early methodology used mathematical models to design prototype decompression profiles, which were then modified by field testing using as an end point clinical DCS. A more sensitive method incorporates ultrasound to detect circulating bubbles as a marker of decompression stress in both experimental animals and human divers (10). Guidelines based on such methodologies have largely reduced the risk of DCS to acceptable levels.

What can one do, however, when confronted with the need to decompress more quickly than is called for by a proven decompression schedule? Such a need might arise, for example, in a damaged, disabled submarine. Ingress of water would increase the ambient pressure within the vessel, where submariners might be trapped for several hours or days. Successful rescue to the surface might then be followed by severe or even fatal DCS.

Strategies thus far have focused on facilitation of tissue inert-gas washout. Exercise during decompression may help by augmenting tissue blood flow (14). Alternatively, breathing enriched O₂ mixtures before decompression reduces tissue inert-gas partial pressure, whereas, because of local consumption of O₂, tissue Po₂ rises only minimally. Another approach is the intravenous injection of a perfluorocarbon emulsion, which can provide an inert-gas sink (3, 11).

In this issue of the *Journal of Applied Physiology* Møllerlækken and colleagues (8) from Trondheim, Norway, have described another technique: administration before decompression of a nitric oxide (NO) donor, glycerol trinitrate [nitroglycerine (NTG)]. In their study, anesthetized pigs were compressed to 500 kPa (40 m of sea water equivalent depth) where they remained while breathing 7% O₂. After the inspired Po₂ was raised, the pigs were then decompressed to atmospheric pressure over 2 h. Bubbles in the right ventricular outflow tract were assessed using transesophageal echocardiography. Toward the end of the decompression, bubbles were easily detected in the control animals, of which two of seven died within 15 min of reaching atmospheric pressure. In the experimental group, NTG was infused at 0.4 μg·kg⁻¹·min⁻¹ for 30 min immediately before decompression and then stopped. In this group during and after decompression, there were significantly fewer bubbles and no deaths.

Ultrasonic bubble detection has its limitations as a predictive tool for bubble-induced illness: present technology is only practical for bubble detection in flowing blood; bubbles are usually only detectable on the venous side of the circulation, from which most are removed by the pulmonary capillaries. Nevertheless, high levels of venous bubbles can overwhelm the

filtration abilities of the pulmonary capillary network and have been shown to correlate with clinical DCS in humans (9).

What could be the explanation for the ameliorative effect of nitrate on bubble formation and mortality in the study of Møllerlækken et al. (8)? One hypothesis is that NTG induced an increase in cardiac output and hence tissue blood flow that was maintained for part of the decompression, thus shortening inert-gas half times. Indeed, in the animals treated with NTG heart rate was significantly higher immediately after NTG infusion and 30 min into decompression. NTG metabolites 1,2- and 1,3-glyceryl dinitrate are pharmacologically active (5) and have longer half-lives than the parent compound (7). In this experiment, neither cardiac output, regional tissue perfusion, nor inert-gas elimination rate was measured, so it is impossible to discount such a mechanism. However, in clinical use after discontinuation of a short infusion of NTG, its hemodynamic effect wears off within minutes. Therefore, a hemodynamic explanation, although conceivable, seems unlikely.

Could it be that there is another explanation, unrelated to hemodynamics? Although little is known about the biophysics of bubble formation, it is likely that they evolve from micronuclei. Platelet or neutrophil adhesion to endothelium might also provide nuclei for bubble formation. As NO donors, nitrates have other effects that may explain the results, such as inhibition of platelet aggregation (12) and leukocyte adhesion (6). Indeed, NO synthase inhibition enhances decompression-induced bubble formation (15), and in both this study and an earlier one NO donors attenuate it (16). Exercise many hours before a dive, in both animals (16) and humans (2, 4), also attenuates decompression-induced bubble formation, conceivably due to shear stress-induced upregulation of endothelial NO synthase (13).

With regard to decompression-induced bubble formation, the prerequisite condition for decompression-induced bubble formation has been known for many years: tissue inert-gas supersaturation. However, there is almost no knowledge of the local microcirculatory conditions necessary to facilitate gas leaving solution and forming bubbles or of the cellular or molecular mechanisms that modulate it. Whereas small animals are often poor surrogates for humans with regard to decompression effects, the study of Møllerlækken et al. (8) has demonstrated that nitrates have a protective effect in large animals. Although it would be premature to recommend nitrates for human use in diving, this study points the way for future investigations of decompression-induced bubbles to go beyond models of tissue gas tension and bubble growth and to examine biochemical mechanisms involved in both their generation and their pathophysiological effects.

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