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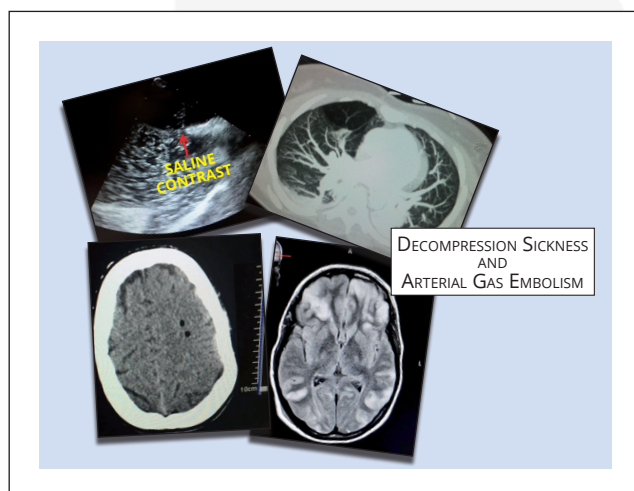
OFFICIAL JOURNAL OF ITALIAN SOCIETY OF ANESTHESIOLOGY, ANALGESIA, RESUSCITATION AND INTENSIVE CARE (SIAARTI)



## SIAARTI

PRO VITA CONTRA DOLOREM SEMPER

VOLUME 85 · No. 10 · OCTOBER 2019



E D I Z I O N I · M I N E R V A · M E D I C A

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## EXPERT'S OPINION

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# Diving physiopathology: the end of certainties? Food for thought

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### ABSTRACT

Our understanding of decompression physiopathology has slowly improved during this last decade and some uncertainties have disappeared. A better understanding of anatomy and functional aspects of patent foramen ovale (PFO) have slowly resulted in a more liberal approach toward the medical fitness to dive for those bearing a PFO. Circulating vascular gas emboli (VGE) are considered the key actors in development of decompression sickness and can be considered as markers of decompression stress indicating induction of pathophysiological processes not necessarily leading to occurrence of disease symptoms. During the last decade, it has appeared possible to influence post-dive VGE by a so-called “preconditioning” as a pre-dive denitrogenation, exercise or some pharmacological agents. In the text we have deeply examined all the scientific evidence about this complicated but challenging theme. Finally, the role of the “normobaric oxygen paradox” has been clarified and it is not surprising that it could be involved in neuroprotection and cardioprotection. However, the best level of inspired oxygen and the exact time frame to achieve optimal effect is still not known. The aim of this paper was to reflect upon the most actual uncertainties and distil out of them a coherent, balanced advice towards the researchers involved in gas-bubbles-related pathologies.

(Cite this article as: Balestra C, Germonpré P, Rocco M, Biancofiore G, Kot J. Diving physiopathology: the end of certainties? Food for thought. *Minerva Anestesiologica* 2019;85:1129-37. DOI: 10.23736/S0375-9393.19.13618-8)

KEY WORDS: Diving; Decompression sickness; Physiopathology.

Our understanding of decompression physiopathology has slowly improved during this last decade and some uncertainties have disappeared. The aim of this paper was to reflect upon the most actual uncertainties and distil out of them a coherent, balanced advice towards the researchers involved in gas-bubbles-related pathologies.

### On the cardiologic side

In medicine, few things change as slowly as anatomy. However, even though the anatomy of the

heart has not changed in many years, understanding the consequences of certain anatomic traits has, in diving medicine, generated quite some discussion.<sup>1</sup> Consider the case of the Patent Foramen Ovale (PFO) to illustrate this<sup>2</sup> (Figure 1).

Simply think of how for years it was considered that a foramen ovale, whether closed or open (patent) would be a permanent condition.<sup>3</sup> Nowadays, we know that this it is not so. Indeed, after suspecting this from “transversal” anatomic dissection studies, we have shown that on divers examined with the exact same technique (rans

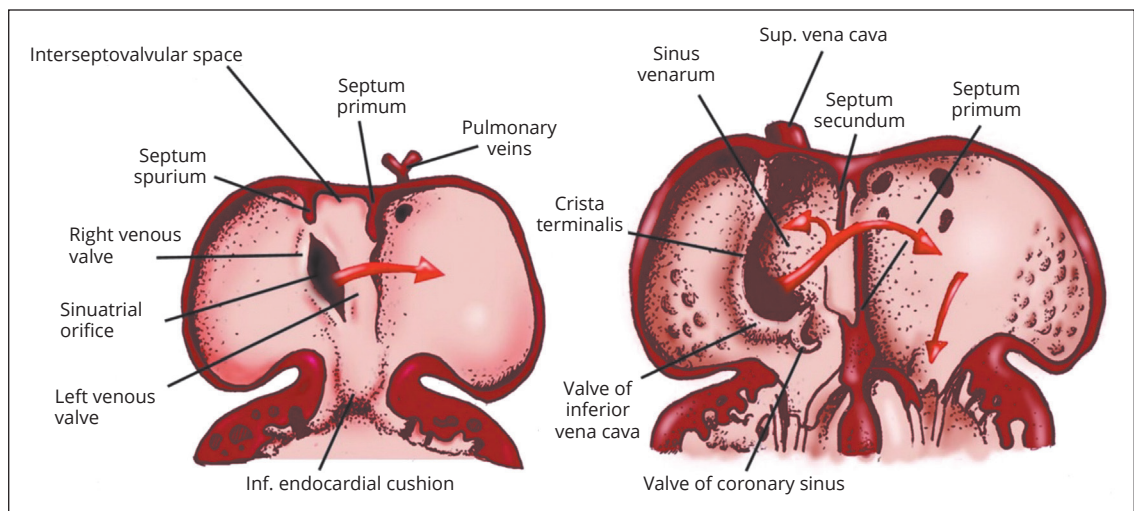


Figure 1.—Embryonic development of the heart.

esophageal with bubble contrast echocardiography, 10 sec Valsalva maneuver, same cardiologists, same echograph) but six to seven years apart, some of those PFOs become more permeable with time. Others can become smaller, or in the case of a small patency, can close over time.<sup>4</sup>

The “semi-lunar groove,” lying next to the *fossa ovalis* where the PFO is located, needs to be appreciated as the source of turbulent blood flow which may impact the passage of blood through the PFO. Venous contrast “bubbles” injected into a large blood vessel in the elbow may be swept away from the inter-atrial septum by these turbulences and thus be prevented from becoming “paradoxical gas emboli.” This frequently causes a “false-negative” result and makes the detection of a PFO by contrast echocardiography a challenging task. Knowledgeable cardiologists are aware of this possibility and they perform so-called respiratory “provocation maneuvers” to reliably diagnose a PFO. These maneuvers, by first increasing the intrathoracic pressure and then suddenly releasing it, cause a reversal of the pressures between the left and right atria.<sup>5</sup> Sometimes referred to as a “Valsalva maneuver”, this is a completely different maneuver than the one used by the divers to equalize pressure in their ears during descent in the water. It needs a conscious, collaborating diver, some prior practice and a perfect timing of injection of contrast fluid. A procedure not easy to master.<sup>6</sup>

The understanding of these anatomical and functional aspects of patency of the foramen ovale have slowly resulted in a more liberal approach toward the medical fitness to dive for those bearing a PFO, even after a decompression sickness incident. Fears that a PFO may be responsible for “silent” brain lesions, even if the diver never had decompression sickness, are largely unfounded.<sup>7</sup> For further reading, the European guidelines<sup>6</sup> clearly approach how to manage diving with PFO both from a physician’s and a diver’s perspective discussing both the need to detect and to close it.

These observations lead to the conclusion that while the anatomy of the heart remains unchanged, it is our understanding of its biomechanical properties and of the variable impact of these, that has changed.

### On the bubble side

Even more has our understanding of the physiopathology of decompression changed over the course of the last ten years. It is no longer required to consider a bubble an “occluding” object in the blood vessel in order to explain the decompression disorders.

The relation between saturation of tissues with inert gas and decompression sickness is more complicated than only physical relations (Figure 2). While the extensive analysis of relationships

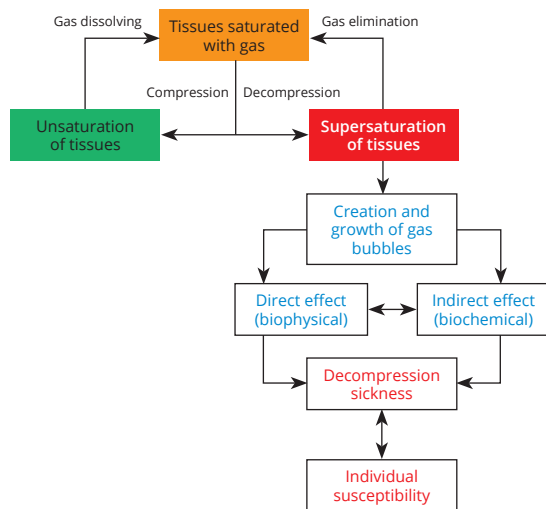


Figure 2.—Relation between saturation of tissues with inert gas and decompression sickness.

between inert gases, gas bubbles, disturbances in blood flow in capillaries and induction of biochemical reactions by irritated endothelium deserves dedicated review, hereby the factors previously recognized as secondary to the decompression sickness are discussed as emerging in most current descriptions of the decompression physiopathology.

We now know that gas emboli are frequently found in the blood of divers after surfacing from a dive and are frequently completely “asymptomatic.” Large amounts of bubbles have been reported on divers during their journey flying back to Europe after a week’s diving in the Indian Ocean, respecting the recommended “24 hours pre-flight interval.” Many bubbles could be seen in the right heart’s cavities. In some cases, the right atrium and ventricle were full of bubbles, corresponding to a “grade 4” in the well-known Spencer scale (where grade 0 reflects no Doppler bubble signal and the highest grade 4 describes bubble signals sounding continuously throughout the systole and diastole, obscuring normal cardiac signals). Yet the diver is completely free of symptoms.<sup>8,9</sup> Even though it is exceptional to find such large amounts of bubbles, lesser degrees of vascular gas embolism (VGE) have been found in about 20% of divers following the currently recommended pre-flight interval after diving. This observation is valid also for compressed

air (caisson) workers,<sup>10</sup> high altitude exposures<sup>11</sup> and saturation dives.<sup>12</sup>

Even if the presence of circulating bubbles by itself cannot be used to predict decompression sickness,<sup>13</sup> a statistical correlation between the degree of bubbling and the risk of decompression sickness has been clearly established.<sup>14</sup> Circulating VGE are nowadays considered the key actors in both development of decompression sickness, a disease that can still have lethal consequences,<sup>15, 16</sup> and markers of decompression stress (DCS), meaning the status of being out of the comfort zone. In some observations of experimental dives DCS was observed in 2% of cases, but at the same time VGE was detected in 56% of cases (DCIEM data 1979-1991). No wonder that if the current rate of DCS is around 0.015% for scientific diving and 0.1% for commercial diving, the predominant studies on safety of decompression are oriented to monitoring of VGE.

Recent research has indicated that the presence of bubbles and/or microparticles and other circulating agents are, at least in part, responsible for changes in the characteristics of the wall of blood vessels after diving. This “endothelial dysfunction,” even if completely asymptomatic, can be detected and measured by means of flow-mediated dilation (FMD) — a technique which also permits evaluation of the “health” of our coronary vessels.<sup>17</sup> The changes in FMD amplitude after the dive cannot be directly correlated with the risk for decompression sickness to occur, but rather can act as a marker for the “oxidative stress”,<sup>18</sup> which can be induced by bubbles and/or circulating microparticles<sup>19</sup> and by the increased oxygen pressure in the lungs and blood during diving.<sup>20</sup> Pre-dive administration of antioxidant drugs only partially reverses the post-dive FMD changes, indicating that the oxidative stress is not the only culprit here.<sup>21, 22</sup>

Which mechanisms exactly underpin these phenomena are not known. It appears that the presence of post-decompression VGE is rather unpredictable for an identical dive profile. There is a large inter-individual variability,<sup>23</sup> but sometimes also a variability within the same diver. At one time many VGE are present, whereas at another time (with the same dive profile) much less VGE can be detected.<sup>24</sup> Therefore, in div-

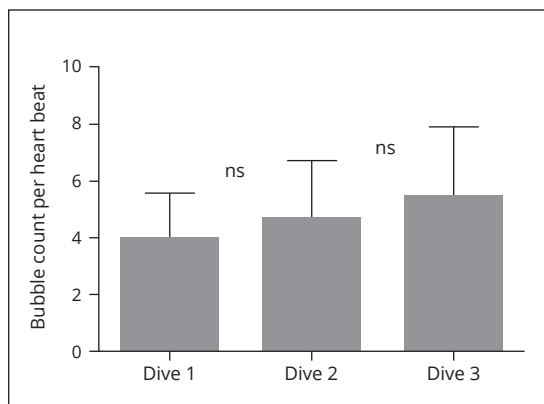


Figure 3.—VGE counts in “reliable bubbleers” or consistent bubbleers chosen among a larger sample; the number of bubbles per heartbeat is non significantly different for this selected group of divers after a standard dive - 33m/20 min in deep pool (Nemo33, Brussels) - one week apart repeated three times; these divers will allow to analyze the preconditioning effect.

ing research exploring the presence of VGE, it is important to make sure that the test subjects are reliable “bubbleers”, meaning that they constantly bubble in the same conditions, in other terms, the same mean number of bubbles per heartbeat after the same diving conditions.

Figure 3 shows the result of three standard dives performed before doing any research intervention. These divers showed a similar VGE level during the three same dives, making them reliable “bubbleers.” Note that 15 other divers had significant variation in their VGE levels and were not selected for further analysis.

Why some divers are reliable bubbleers, and others are not, is not known. Several factors have been proposed, such as age, sex (gender), body mass index, and lean body mass as opposed to fat mass. None of these, however, has been able to predict the “bubbling behavior,” even if in rodents, this may be the case.<sup>25</sup> Young and fit divers seem to have a lesser risk for high VGE counts after decompression than older divers or divers in poorer physical condition.<sup>26</sup> On one hand, these uncertainties still severely limit the practical application of results obtained from post-dive bubble studies. On the other hand, defining personal factors influencing creation of gas bubbles will offer in the future the option for having individually oriented decompression schedules fully optimized to each diver.

## On the preconditioning side

A large number of these studies aimed at reducing VGE counts by modifying decompression procedures or gas mixes, thus trying to reduce the risk of decompression sickness. During the last decade, it has appeared possible, perhaps surprisingly, to influence post-dive VGE by performing interventions before the dive (so-called “preconditioning”). This includes oxygen pre-breathing, exercise, some drugs, heat exposure and whole-body vibration.

Oxygen pre-breathing is a routinely used procedure to reduce the incidence of altitude decompression sickness in aviators and astronauts. Castagna *et al.*<sup>27</sup> found that oxygen pre-breathing provides a significant reduction in decompression-induced bubble formation, regardless of the experimental conditions. This is confirmed by the work of Bosco *et al.*,<sup>28</sup> who showed that pre-breathing oxygen under increased pressure is more effective.

Denitrogenation *per se* does not seem preponderant in the effectiveness of oxygen pre-breathing.<sup>29</sup> On the contrary, the proposed mechanism is based on the ability of oxygen to replace nitrogen in the gas nuclei by diffusion. Reduction of tissue oxygen pressure after switching from oxygen to air would then enhance the consumption of oxygen from the gas nuclei, thus eliminating it completely.<sup>30</sup> Another possibility is that oxygen administration induces an increased lymphatic uptake of the micronuclei. Recently it has been confirmed that diving several days in a row decreases the number of VGE observed,<sup>31</sup> which represents some kind of adaptation. Inheritability of DCS protection is also considered in murines.<sup>32</sup>

Experimental studies with rats have shown that a single session of treadmill exercise, 20 hours before diving, reduced bubble levels and also mortality in a dramatic way.<sup>33</sup> In human divers also, pre-dive exercise has been shown influential<sup>34</sup> and, depending on the timing and intensity, seems to reduce or augment VGE counts.<sup>35-37</sup> Interestingly, significant effects of exercise on post-dive VGE can be observed when work is conducted either two hours before or 24 hours before the dive. This two-peak phenomenon has been also proposed in ischemic preconditioning for altitude exposures,<sup>38</sup> where protection shortly

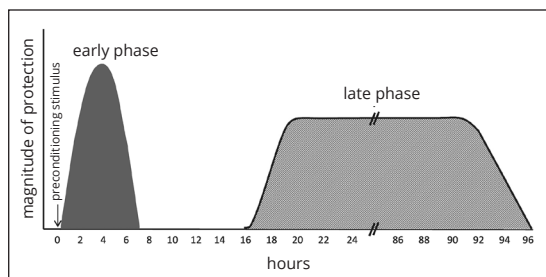


Figure 4.—The different theoretical time courses of protection after a preconditioning stimulus.

before the event seems more powerful than the protection of the 2nd phase, which becomes apparent 12-24 hours later and can last several days. The different time courses of protection can be explained by the different mechanisms underlying both phases. The early phase is assumed to be caused by rapid post-translational modification of pre-existing substances; the late phase is most likely caused by the synthesis of new protective substances (Figure 4). One explanation could be a change in the nitric oxide (NO)-producing properties of the endothelial surface of the blood vessel wall, changing its properties so that gas micronuclei become less adherent (and are swept away) or shrink in volume, thus reducing the VGE counts during decompression.<sup>39</sup> Indeed, we know that 45 minutes of exercise increases the activity of the enzyme NO-synthetase. Also, increasing NO levels by taking so-called “NO-donor drugs” reduces bubble counts.<sup>40</sup>

Yet another interesting pharmacological preconditioning for decompression has been reported while using simvastatin. Its use decreased both death and DCS rate in the animal model.<sup>41</sup> It is not yet defined why this pharmacological agent, which modifies lipid content and metabolism, protects also against DCS. The potential correlation of DCS with high serum lipids content has been suggested in humans.<sup>42</sup>

Another way to increase NO availability could be to reduce oxidation of NO by providing antioxidants. Oral administration of black chocolate has been studied outside of the diving medicine context, to increase antioxidant activity. Indeed, it has been shown that the endothelial function is improved by high-cocoa-containing chocolate.<sup>43</sup> Recently, the effect of 30 grams of black choc-

olate, taken two hours before a dive, was measured. The study showed a favorable effect on the endothelial dysfunction post-dive (improvement of the FMD changes), however without a significant effect on bubble production.<sup>44</sup>

Exercise has been shown to be a pre-conditioning factor, but sustained exercise in order to increase the physical fitness is also related to the propensity to generate gas bubbles. It was shown that non-fit individuals (defined as having low maximal oxygen consumption [ $VO_{2max}$ ] <40 mL/min/kg) have higher gas bubble grades than those with high maximum oxygen consumption rate ( $VO_{2max}$  >40 mL/min/kg) after similar dives.<sup>45</sup> This protective effect (perhaps adaptation) persists for several weeks, and it was not present after three months of inactivity.<sup>46</sup>

NO seems to play an important role from these experiments. However, when NO is blocked by certain drugs, this increases VGE counts (as expected), but only in untrained (sedentary) rats and not in trained (fit) rats.<sup>33</sup> This suggests there are other factors at play. Possible candidates are heat shock proteins (HSPs), blood rheological properties or naturally present antioxidant defense mechanisms.

Heat exposure may offer some protection from decompression sickness in rats, and this has been linked to the production of HSPs. These may act as “guardian angels” of the cells, or rather, they are able to facilitate restructuring of proteins that are damaged by stress, whether heat-induced or otherwise. They thus increase the survival chances of the cell after such an aggression.<sup>47</sup> There are multiple types of HSPs. The most studied in humans are HSP70 (named after their molecular weight). It has been shown that a single infrared sauna session of 30 minutes’ duration, ending one hour before a dive (hyperbaric chamber, dry), significantly decreases post-dive bubble formation and increases HSPs in the blood plasma two hours after the sauna. HSPs appear to be able to interact with the metabolic pathways of NO production,<sup>48</sup> offering a possible explanation for their effect. Also, such a sauna session induces an extracellular dehydration, causing a slight decrease in circulating blood volume as well as a significant improvement of FMD changes post-dive.

Dehydration by itself, in analogy with the effect of high temperature exposure (sauna), and comparable with dehydration induced by physical exercise, reduces post-dive VGE.<sup>49</sup> In contrast, preventive hyperhydration (extra hyperosmotic solutions before the dive) also has been shown to offer some benefit in decompression.<sup>49</sup> It is thought that ensuring an optimal plasma volume before the dive prevents the post-dive dehydration (and decrease of the cardiac “pre-load”) that is commonly observed at the end of the dive, and which may be responsible for a slowing of the off-gassing process.<sup>49</sup> A simple advice for divers could be to hydrate well keeping an optimal plasmatic volume before dive to be safer.

A further preconditioning method, whole body vibration, has been shown to be extremely effective in reducing VGE production after the dive. In those divers who consistently produced bubbles, 30 minutes of vibration while lying down on a vibrating mattress, before the dive, reduces VGE count by a factor ten or more.<sup>50</sup> Interestingly enough, this effect was not accompanied by significant change in FMD, which suggests that the protective effect is not primarily NO-dependent but rather a simple mechanical action, dislodging and eliminating gas pockets (microbubbles, micronuclei) from the endothelial wall or eliminating them by increased lymphatic drainage. It has been shown that vibrations can change the endothelial spatial relationships and increase lymphatic transport.<sup>51, 52</sup>

### On the future side... mixing uncertainties to conclude

Now that we have summarized the changes in our understanding of the physiology of the heart and of decompression phenomena, we can begin to explore the combination of these new findings in a single group of divers, using identical dives — thus “combining our uncertainties.”

One such experiment is described here (Figure 5): preconditioning, either with pre-dive oxygen breathing (30 minutes), pre-dive whole body vibration (30 minutes) or the combination of both. Surprisingly, the combination of both techniques has a lesser effect than vibration

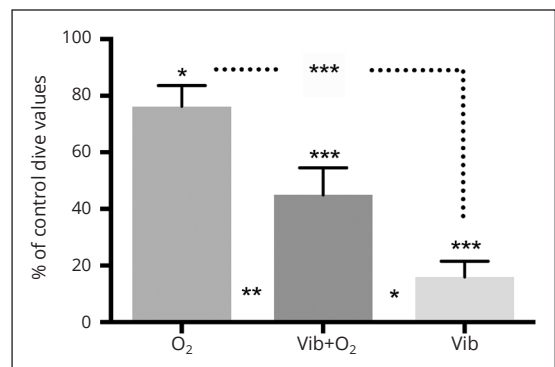


Figure 5.—Effects of two different methods of preconditioning and their combination on vascular gas emboli on the same divers (N.=6) after a standardized dive in a pool (33 m/20 min).

O<sub>2</sub>: pre-dive oxygen breathing (30 minutes); Vib: pre-dive whole body vibration (30 minutes); Vib+O<sub>2</sub>: the combination of both.

\*P<0.05; \*\*P<0.01; \*\*\*P<0.001.

alone. This suggests that desaturation (denitrogenation) is less effective than gas nuclei reduction, and may even decrease the effect of vibration, for example by reducing the blood flow in the tissues (oxygen-induced vasoconstriction). Sometimes “more” seems to be “less.” A similar antagonistic effect of oxygen with other factors was observed when measuring the elimination of nitrogen during negative-pressure breathing in a sitting position, immersed, with head above the water surface.<sup>53</sup> It seems that oxygen is the single most important factor in eliminating inert gas and decreasing VGE and other factors that are antagonistic due to some other physiological (biophysical or rather biochemical) pathways.

Let us not forget that oxygen (both its presence and absence) acts as a potent signaling mechanism in many, if not most, of the cellular processes. Oxygen has been used therapeutically mainly to alleviate or correct hypoxia, and has been administered in supra-atmospheric doses in the form of hyperbaric oxygen (a method which had been derived from the diving medicine practice, but has been applied for non-diving diseases since the 1960s). Hyperbaric oxygen is, by definition, given in an intermittent way, and in recent years, the effects of intermittent oxygen administration at non-hyperbaric doses have been investigated. As an example, we have shown that intermittent “normobaric” hyperoxia,

using doses of oxygen only slightly higher than the normally breathed air, may stimulate erythropoietin (EPO) production, much like observed in hypoxia. It is postulated that the cessation of cellular hyperoxia may induce an acute state of “relative hypoxia” — hence the name given of “normobaric oxygen paradox” or NOP.<sup>54-56</sup> The HIF-1 $\alpha$  (hypoxia inducible factor 1 alpha)-dependent gene regulation is responsible for many different genetic expressions including EPO and vascular endothelial growth factor (VEGF), and possibly other cytokines. Therefore, it is not surprising that the (cytokine) effects of EPO have been demonstrated to increase based on the NOP, as in neuroprotection and cardioprotection.<sup>57-59</sup> The best level of inspired oxygen and the exact time frame to achieve optimal effect is not known. N-Acetyl-L-Cysteine (NAC) supplementation has been shown to help. All the reported data demonstrate how hyperoxic and hypoxic states can potentially be manipulated if oxygen is considered as a multifaceted molecule more than just a gas.<sup>60</sup>

The abovementioned factors are important, but this list cannot be treated as exhaustive now, and perhaps less so in the future. For example, quite recently, the influence of diet and gut content on DCS both in animal models and in human observations has been investigated.<sup>61</sup> In those publications, the main factor affecting decompression outcome is hydrogen, produced in the digestive system by some bacteria. Interestingly, the possibility of using bacterial inoculation in human guts for enhancing hydrogen elimination in hydrogen-based breathing mixtures for deep dives has been proposed and patented many years ago.<sup>62</sup> Some other pharmacological agents protecting endothelium also seem promising in protection against DCS.<sup>63</sup> For sure, more experiments must be planned and conducted.

## Conclusions

In conclusion, our understanding of decompression physiology is slowly getting out of its infancy. However, as in real life, with infancy also the certainties disappear. It is now our task, as researchers, to reflect upon these uncertainties and distil out of them a coherent, balanced advice to-

wards the divers. Let us not jump to conclusions too fast, as our new “certainties” may very well prove to be “not the whole story” again.

## Key messages

- Gas bubbles after decompression and reaction of the human organism to their presence depend not only on the dive profile, but also on before-exposure status, which can be influenced by some pre-conditioning maneuvers.
- Decompression sickness related to gas bubbles is in fact a systemic disease related to an individual response of the diver.
- Future research on diving and gas-bubble-related diseases, including decompression sickness and gas embolism, should be oriented to the personalized approach. Individual metabolism is also responsible for the so-called pre-dive static metabolic bubbles population, this new hypothesis opens new possibilities for decompression prevention by considering the diver’s individual susceptibility and recent history (life style, exercise) to mitigate the level of VGE during and after decompression.

## References

1. Germonpré P, Dendale P, Unger P, Balestra C. Patent foramen ovale and decompression sickness in sports divers. *J Appl Physiol* (1985) 1998;84:1622–6.
2. Balestra C, Germonpre P, Marroni A, Cronje FJ. PFO and the DIVER. Best Publishing, Flagstaff, AZ (USA); 2007.
3. Moon RE, Camporesi EM, Kisslo JA. Patent foramen ovale and decompression sickness in divers. *Lancet* 1989;1:513–4.
4. Germonpre P, Hastir F, Dendale P, Marroni A, Nguyen AF, Balestra C. Evidence for increasing patency of the foramen ovale in divers. *Am J Cardiol* 2005;95:912–5.
5. Balestra C, Germonpré P, Marroni A. Intrathoracic pressure changes after Valsalva strain and other maneuvers: implications for divers with patent foramen ovale. *Undersea Hyperb Med* 1998;25:171–4.
6. Pristipino C, Sievert H, D’Ascenzo F, Mas JL, Meier B, Scaciatella P, *et al.*; European Association of Percutaneous Cardiovascular Interventions (EAPCI); European Stroke Organisation (ESO); European Heart Rhythm Association (EHRA); European Association for Cardiovascular Imaging (EACVI); Association for European Paediatric and Congenital Cardiology (AEPC); ESC Working group on GUCH; ESC Working group on Thrombosis; European Haematological Society (EHA). European position paper on the management of patients with



- patent foramen ovale. General approach and left circulation thromboembolism. *EuroIntervention* 2019;14:1389–402.
7. Balestra C, Germonpré P. Correlation between patent foramen ovale, cerebral “lesions” and neuropsychometric testing in experienced sports divers: does diving damage the brain? *Front Psychol* 2016;7:696.
  8. Cialoni D, Pieri M, Balestra C, Marroni A. Flying after diving: in-flight echocardiography after a scuba diving week. *Aviat Space Environ Med* 2014;85:993–8.
  9. Cialoni D, Pieri M, Balestra C, Marroni A. Flying after diving: should recommendations be reviewed? In-flight echocardiographic study in bubble-prone and bubble-resistant divers. *Diving Hyperb Med* 2015;45:10–5.
  10. Gotoh Y, Nashimoto I. [Decompression bubbles in caisson workers (author’s transl)]. *Nippon Eiseigaku Zasshi* 1977;32:529–33. Japanese.
  11. Conkin J, Sanders RW, Koslovsky MD, Wear ML, Kozminski AG, Abercromby AF. A Systematic Review and Meta-Analysis of Decompression Sickness in Altitude Physiological Training. *Aerosp Med Hum Perform* 2018;89:941–51.
  12. Gardette B. Correlation between decompression sickness and circulating bubbles in 232 divers. *Undersea Biomed Res* 1979;6:99–107.
  13. Doolette DJ. Venous gas emboli detected by two-dimensional echocardiography are an imperfect surrogate endpoint for decompression sickness. *Diving Hyperb Med* 2016;46:4–10.
  14. Nishi R, Brubakk AO. Bubble Detection. In: Brubakk AO, Neuman, editors. *Bennett and Elliott’s physiology and medicine of diving*. Fifth Edition. Edinburgh: Saunders; 1986. p. 501–29.
  15. Møllerlækken A, Gaustad SE, Havnes MB, Gutvik CR, Hjelde A, Wisløff U, *et al.* Venous gas embolism as a predictive tool for improving CNS decompression safety. *Eur J Appl Physiol* 2012;112:401–9.
  16. Vann RD, Butler FK, Mitchell SJ, Moon RE. Decompression illness. *Lancet* 2011;377:153–64.
  17. Mazur A, Lambrechts K, Wang Q, Belhomme M, Theron M, Buzzacott P, *et al.* Influence of decompression sickness on vasoconstriction of isolated rat vessels. *J Appl Physiol* (1985) 2016;120:784–91.
  18. Germonpré P, Balestra C. Preconditioning to reduce decompression stress in scuba divers. *Aerosp Med Hum Perform* 2017;88:114–20.
  19. Arieli R, Arieli U, Marmur A. Bubble size on detachment from the luminal aspect of ovine large blood vessels after decompression: the effect of mechanical disturbance. *Respir Physiol Neurobiol* 2015;216:1–8.
  20. Thom SR, Bennett M, Banham ND, Chin W, Blake DF, Rosen A, *et al.* Association of microparticles and neutrophil activation with decompression sickness. *J Appl Physiol* (1985) 2015;119:427–34.
  21. Obad A, Marinovic J, Ljubkovic M, Breskovic T, Modun D, Boban M, *et al.* Successive deep dives impair endothelial function and enhance oxidative stress in man. *Clin Physiol Funct Imaging* 2010;30:432–8.
  22. Obad A, Valic Z, Palada I, Brubakk AO, Modun D, Dujic Z. Antioxidant pretreatment and reduced arterial endothelial dysfunction after diving. *Aviat Space Environ Med* 2007;78:1114–20.
  23. Papadopoulou V, Germonpré P, Cosgrove D, Eckersley RJ, Dayton PA, Obeid G, *et al.* Variability in circulating gas emboli after a same scuba diving exposure. *Eur J Appl Physiol* 2018;118:1255–64.
  24. Møllerlækken A, Breskovic T, Palada I, Valic Z, Dujic Z, Brubakk AO. Observation of increased venous gas emboli after wet dives compared to dry dives. *Diving Hyperb Med* 2011;41:124–8.
  25. Buzzacott P, Theron M, Mazur A, Wang Q, Lambrechts K, Eftedal I, *et al.* Age, weight and decompression sickness in rats. *Arch Physiol Biochem* 2016;122:67–9.
  26. Carturan D, Bousuges A, Burnet H, Fondarai J, Vanuxem P, Gardette B. Circulating venous bubbles in recreational diving: relationships with age, weight, maximal oxygen uptake and body fat percentage. *Int J Sports Med* 1999;20:410–4.
  27. Castagna O, Gempp E, Blatteau JE. Pre-dive normobaric oxygen reduces bubble formation in scuba divers. *Eur J Appl Physiol* 2009;106:167–72.
  28. Bosco G, Yang ZJ, Di Tano G, Camporesi EM, Faralli F, Savini F, *et al.* Effect of in-water oxygen prebreathing at different depths on decompression-induced bubble formation and platelet activation. *J Appl Physiol* (1985) 2010;108:1077–83.
  29. Gempp E, Blatteau JE. Preconditioning methods and mechanisms for preventing the risk of decompression sickness in scuba divers: a review. *Res Sports Med* 2010;18:205–18.
  30. Arieli Y, Arieli R, Marx A. Hyperbaric oxygen may reduce gas bubbles in decompressed prawns by eliminating gas nuclei. *J Appl Physiol* (1985) 2002;92:2596–9.
  31. Zanchi J, Ljubkovic M, Denoble PJ, Dujic Z, Ranapurwala S, Pollock NW. Influence of repeated daily diving on decompression stress. *Int J Sports Med* 2014;35:465–8.
  32. Lautridou J, Buzzacott P, Belhomme M, Dugrenot E, Lafère P, Balestra C, *et al.* Evidence of heritable determinants of decompression sickness in rats. *Med Sci Sports Exerc* 2017;49:2433–8.
  33. Wisløff U, Richardson RS, Brubakk AO. NOS inhibition increases bubble formation and reduces survival in sedentary but not exercised rats. *J Physiol* 2003;546:577–82.
  34. Dujic Z, Valic Z, Brubakk AO. Beneficial role of exercise on scuba diving. *Exerc Sport Sci Rev* 2008;36:38–42.
  35. Dervay JP, Powell MR, Butler B, Fife CE. The effect of exercise and rest duration on the generation of venous gas bubbles at altitude. *Aviat Space Environ Med* 2002;73:22–7.
  36. Blatteau JE, Bousuges A, Gempp E, Pontier JM, Castagna O, Robinet C, *et al.* Haemodynamic changes induced by submaximal exercise before a dive and its consequences on bubble formation. *Br J Sports Med* 2007;41:375–9.
  37. Castagna O, Brisswalter J, Vallee N, Blatteau JE. Endurance exercise immediately before sea diving reduces bubble formation in scuba divers. *Eur J Appl Physiol* 2011;111:1047–54.
  38. Berger MM, Macholz F, Mairbäurl H, Bärtsch P. Remote ischemic preconditioning for prevention of high-altitude diseases: fact or fiction? *J Appl Physiol* (1985) 2015;119:1143–51.
  39. Dujic Z, Palada I, Valic Z, Duplancic D, Obad A, Wisløff U, *et al.* Exogenous nitric oxide and bubble formation in divers. *Med Sci Sports Exerc* 2006;38:1432–5.
  40. Wisløff U, Richardson RS, Brubakk AO. Exercise and nitric oxide prevent bubble formation: a novel approach to the prevention of decompression sickness? *J Physiol* 2004;555:825–9.
  41. Zhang K, Wang D, Xu J, Li R, Cai Z, Liu K, *et al.* Simvastatin decreases incidence of decompression sickness in rats. *Undersea Hyperb Med* 2015;42:115–23.
  42. Kaczerska D, Siermoutowski P, Olszański R, Krefft K, Małgorzewicz S, Van Damme-Ostapowicz K. The influence of high-fat diets on the occurrence of decompression stress after air dives. *Undersea Hyperb Med* 2013;40:487–97.
  43. Flammer AJ, Hermann F, Sudano I, Spieker L, Her-

mann M, Cooper KA, *et al.* Dark chocolate improves coronary vasomotion and reduces platelet reactivity. *Circulation* 2007;116:2376–82.

44. Theunissen S, Guerrero F, Sponsiello N, Cialoni D, Pieri M, Germonpré P, *et al.* Nitric oxide-related endothelial changes in breath-hold and scuba divers. *Undersea Hyperb Med* 2013;40:135–44.

45. Carturan D, Boussuges A, Vanuxem P, Bar-Hen A, Burnet H, Gardette B. Ascent rate, age, maximal oxygen uptake, adiposity, and circulating venous bubbles after diving. *J Appl Physiol* (1985) 2002;93:1349–56.

46. Pontier JM, Guerrero F, Castagna O. Bubble formation and endothelial function before and after 3 months of dive training. *Aviat Space Environ Med* 2009;80:15–9.

47. Medby C, Bye A, Wisløff U, Brubakk AO. Heat shock increases survival in rats exposed to hyperbaric pressure. *Diving Hyperb Med* 2008;38:189–93.

48. Blatteau JE, Gempp E, Balestra C, Mets T, Germonpré P. Pre-dive sauna and venous gas bubbles upon decompression from 400 kPa. *Aviat Space Environ Med* 2008;79:1100–5.

49. Gempp E, Blatteau JE, Pontier JM, Balestra C, Louge P. Preventive effect of pre-dive hydration on bubble formation in divers. *Br J Sports Med* 2009;43:224–8.

50. Germonpré P, Pontier JM, Gempp E, Blatteau JE, Deneweth S, Lafère P, *et al.* Pre-dive vibration effect on bubble formation after a 30-m dive requiring a decompression stop. *Aviat Space Environ Med* 2009;80:1044–8.

51. Leduc A, Lievens P, Dewald J. The influence of multi-directional vibrations on wound healing and on regeneration of blood- and lymph vessels. *Lymphology* 1981;14:179–85.

52. Balestra C. The lymphatic pathway for microbubbles. *Diving Hyperb Med* 2014;44:1.

53. Bodkin JJ, Curry TB, Lundgren CE. Negative pressure oxygen breathing and head-down tilt increase nitrogen elimination. *Undersea Hyperb Med* 2006;33:455–62.

54. Balestra C, Germonpré P, Poortmans JR, Marroni A. Serum erythropoietin levels in healthy humans after a short period of normobaric and hyperbaric oxygen breathing:

the “normobaric oxygen paradox”. *J Appl Physiol* (1985) 2006;100:512–8.

55. Rocco M, D'Itri L, De Bels D, Corazza F, Balestra C. The “normobaric oxygen paradox”: a new tool for the anesthetist? *Minerva Anestesiol* 2014;80:366–72.

56. Khalife M, Wiams K, Ben Aziz M, Balestra C, Sosnowski M. Effect of induced relative hypoxia on reticulocyte count in oncological abdominal surgery: a single-centre, controlled, randomized pilot study. *Int J Sci Res (Ahmedabad)* 2018;7:12–6.

57. De Bels D, Corazza F, Balestra C. Oxygen sensing, homeostasis, and disease. *N Engl J Med* 2011;365:1845.

58. De Bels D, Corazza F, Germonpré P, Balestra C. The normobaric oxygen paradox: a novel way to administer oxygen as an adjuvant treatment for cancer? *Med Hypotheses* 2011;76:467–70.

59. Lafère P, Schubert T, De Bels D, Germonpré P, Balestra C. Can the normobaric oxygen paradox (NOP) increase reticulocyte count after traumatic hip surgery? *J Clin Anesth* 2013;25:129–34.

60. Balestra C, Germonpré P. Hypoxia, a multifaceted phenomenon: the example of the “normobaric oxygen paradox”. *Eur J Appl Physiol* 2012;112:4173–5.

61. de Maistre S, Vallée N, Gaillard S, Duchamp C, Blatteau JE. Stimulating fermentation by the prolonged acceleration of gut transit protects against decompression sickness. *Sci Rep* 2018;8:10128.

62. Kayar SR, Fahlman A, Lin WC, Whitman WB. Increasing activity of H<sub>2</sub>-metabolising microbes lowers decompression sickness risk in pigs during H<sub>2</sub> dives. *J Appl Physiol* 1985;2001:2713–9.

63. Zhang K, Wang D, Jiang Z, Ning X, Buzzacott P, Xu W. Endothelial dysfunction correlates with decompression bubbles in rats. *Sci Rep* 2016;6:33390.

64. Imbert JP, Egi SM, Germonpré P, Balestra C. Static Metabolic Bubbles as precursors of vascular gas emboli during divers' decompression: a hypothesis explaining bubbling variability. *Front Physiol* 2019;10:807.

*Conflicts of interest.*—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Article first published online: June 20, 2019. - Manuscript accepted: June 14, 2019. - Manuscript revised: June 10, 2019. - Manuscript received: January 25, 2019.