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A critical review of physiological bubble formation in hyperbaric decompression

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ABSTRACT

Bubbles are known to form in the body after scuba dives, even those done well within the decompression model limits. These can sometimes trigger decompression sickness and the dive protocols should therefore aim to limit bubble formation and growth from hyperbaric decompression. Understanding these processes physiologically has been a challenge for decades and there are a number of questions still unanswered. The physics and historical background of this field of study is presented and the latest studies and current developments reviewed. Heterogeneous nucleation is shown to remain the prime candidate for bubble formation in this context. The two main theories to account for micronuclei stability are then to consider hydrophobicity of surfaces or tissue elasticity, both of which could also explain some physiological observations. Finally the modeling relevance of the bubble formation process is discussed, together with that of bubble growth as well as multiple bubble behavior.

Contents

1. Introduction

Decompression Illness (DCI) is a pathophysiology affecting divers, astronauts, pilots and compressed air workers. It is caused by bubbles which grow in the body during or after a reduction in ambient pressure (decompression). DCI encompasses both arterial gas embolism (AGE) and decompression sickness (DCS) which can be difficult to distinguish and require the same treatment [1]. AGE which can also have iatrogenic causes results from gas emboli in the arterial circulation, either from a pulmonary over expansion which ruptures the alveolar capillaries or through cardiac shunts that allow venous gas emboli to enter the arterial circulation. DCS, also referred to colloquially as "the bends", is caused by bubble formation from dissolved inert gas in the tissues during decompression.

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In the case of scuba diving, pressurized air (or another breathing mixture) is breathed by the divers at ambient pressure throughout the dive. As pressure increases with depth the partial pressures of oxygen and inert gases breathed are also increased. This results in a pressure gradient from the inspired gas in the lungs to the rest of the tissues in the body which are saturated for sea level. As the divers descend and stay at depth, inert gases, not utilized by the body will dissolve in the tissues until these become saturated. The uptake of gas happens with different rates for different tissue types. Once the divers start to ascend, the pressure gradient reverses and the tissues start "off gassing" creating bubbles that go from the tissues into the blood stream. Normally these bubbles diffuse from the alveolar capillaries into the lungs to be expired out of the body through respiration. Doppler Ultrasound findings have shown repeatedly that bubbles are formed routinely on dives [2–7] and only sometimes does it result in DCS. This can happen when the ascent is too fast for instance, yielding big bubbles which get stuck in a blood vessel and/or too many bubbles which overload the filtering capacity of the lungs. Another mechanism proposed is that of very small bubbles passing through the lungs into the arterial circulation and being subsequently excited to growth by gas diffusion from nervous tissues [8]. It is the process of bubble formation in this context of hyperbaric decompression that is of interest in this review.

There are an estimated 7 million active recreational scuba divers worldwide and the world's biggest training agency, PADI, certifies over 500,000 new divers every year [9], with annual certifications tripling in the last 20 years [10]. Additionally, diving is also key for environmental and scientific monitoring, construction and maintenance work, offshore oil exploitation, forensic, rescue, military and filming purposes. In the USA over 1100 cases of DCI are reported every year, a 100 of which are fatal [9]. In the absence of complications relating to asthma, shunts and lung infections or diseases, AGE can be prevented effectively by adhering to slow ascents and to the golden rule of diving "never hold your breath". Occurrences have decreased dramatically from 18% of total DCI occurrences in 1987 to 8% in 1997 [11]. In a study of DCI data from 1998 the Divers Alert Network (DAN) classified as AGE only 3.9% of 441 cases [12]. In contrast to AGE, DCS risk is inherently dependent on the dive profile and most importantly on the ascent profile. It is managed by adhering to decompression schedules dictated by tables or dive computers which allow for stops at different depths for controlled off gassing of tissues so that bubbles can be effectively eliminated by respiration. DCS occurrence is also relatively rare, with rates of 0.01–0.1% per dive, the higher end of the spectrum reflecting rates for commercial diving and the lower rates for scientific and recreational diving [13–16]. DAN's study on a population of 135,000 dives made well within the current limits for decompression by 9000 recreational divers showed a DCS rate of 0.03% [12,17]. Some studies with different decompression procedures show significantly higher risk, for instance 1.3% for some US Navy dives in the 70s [18] or 4.4% in US Navy trials for long exposures under increased exercise and thermal stress [19]. The definition of acceptable risk also varies widely depending on the diving purpose, commercial diving setting it at 0.1% for mild and 0.025% for serious cases, and the US Navy at 2% for mild and 0.1% for serious cases [20].

A number of predisposing factors have been identified for DCS, hydration levels being one of the most important [21,22]. A lot of studies have been done with regards to a potential link between a PFO (Patent Foramen Ovale) and an increased DCI risk [23,24]. The idea of a systematic PFO screening for all divers is not implemented due to the prevalence of the condition in the general population (roughly one in four people) and the debatable benefits of having it surgically closed versus the risk of the operation itself [25]. The general consensus remains however that in the event of a previous DCI case, then a PFO screening should be undertaken. Obesity, temperature, smoking, age, repetitive diving, flying after diving, reverse or toothpick diving profiles, as well as previous injuries are also nowadays considered to be risk factors [26,27].

The role of exercise has also been debated [28] and depending on its timing and intensity can increase or decrease risk [29–32]. Additionally, an adaptive response to diving has been hypothesized and the susceptibility to DCS seems to be very different from individual to individual [33].

The bubbles can cause problems through mechanical effects directly (blocking or distorting vessels) but also from the associated inflammatory response they trigger [34]. DCS severity can vary from skin itching and marbled appearance to excruciating pain, convulsions, paralysis, coma and death. Over 60% of symptoms present in the first 3 h post dive, with some presenting as late as 48 h post dive [35,36], and can be localized (joint pain in a particular articulation) or involve multiple systems. Historically classified as Type I or II for severity, with the second type referring to neurological symptoms, more recently emphasis has been on the progression (or lack thereof) of the disease [35]. In addition to first aid treatment, pure oxygen and intravenous fluids are administered if possible [37,38]. DCS treatment is to recompress the diver in a recompression chamber to alleviate the symptoms and shrink the bubbles formed, breathing oxygen at high partial pressure to achieve optimal denitrogenation, then bring him back to normobaric conditions. The outcome depends largely on the delay to recompression treatment, in addition to the severity of the hit (for instance cerebral or spinal cord involvement) [39–43]. In a review of 1763 cases, 80% of cases were completely resolved [43].

The study of bubble formation and growth in hyperbaric physiology and the factors which influence them is of prime importance for understanding the pathophysiology of DCS and improve its prevention and treatment. Echographic recording and imaging of bubbles has shown bubble number post dive to be an indicator of decompression stress. It is as such a good way of improving DCS prevention by devising decompression schedules which control the number and size of bubbles formed, instead of relying solely on the outcome DCS/no DCS to quantify success of the decompression schedule [1,3,7].

The study of bubble formation can improve preventive measures against DCS risk in two ways. Firstly by improving the decompression algorithms which rely on bubble modeling and secondly through predive conditioning [44,45] that would target bubble growth itself. Together with DCS studies, it is also relevant in physiology, in particular to understand the processes of adaptation to extreme environmental stress, but also for hyperbaric oxygen (HBO) treatment and as a study of tolerated embolism to the circulation which can have medical applications (ultrasound microbubble contrast agents or surgical and mechanical ventilation embolism risks).

This review aims to cover the literature on physiological bubble formation during decompression, primarily in the context of scuba diving. This complex research area links a variety of disciplines with drastically different methodologies ranging from mathematical modeling to physiological studies. As such, a comprehensive study of where these agree and disagree would be useful in summarizing the limits between theory and observations from experiments in vitro, ex vivo and in vivo. This critical review provides an up to date list of references for this field of study. The current consensus and disagreements in the field are pointed out and the successes and limitations of the studies included are discussed. Where appropriate, suggestions for further studies to be undertaken are also included. The relevant physics background of bubble formation (nucleation) is also included.

2. Background

2.1. Fundamental physics

Supersaturation can be viewed as a tissue's tendency to produce bubbles and as such depends on the difference between the gas tension in the tissue and the ambient pressure. Supersaturation normally results from a saturated solution being subjected to a thermodynamic change which increases its concentration further (thus bringing it beyond saturation) such as an increase in temperature, decrease in volume or decrease in ambient pressure. In the scuba diving context,

pressure is the main variable of interest. The diver's tissues become saturated in inert gas at depth. For a diver breathing pressurized air, this inert gas is nitrogen since most of the oxygen is being used by the body through metabolism [14]. During ascent, the tension of the dissolved gas in the tissues is greater than its partial pressure in the lungs.

Nucleation is the localized formation of a new thermodynamic phase out of a solid, liquid or gas phase. The case of interest here is the formation of bubbles (gas phase) from tissues (assumed "liquid" phase). There are two types of nucleation: homogeneous and heterogeneous. The most common nucleation process is heterogeneous nucleation where nucleation happens at specific sites between two phases or around microscopic impurities. Homogeneous nucleation happens where nucleation does not have preferential sites for the bubbles to grow from. The random fluctuations of the molecules in the liquid are statistically likely to form microscopic regions where molecules are more closely packed together and voids where the bubbles grow from. As this process is random such sites are created throughout the liquid and thus no preferential sites exist [46]. This process is actually not very common since bubbles are normally observed to nucleate from preferential sites and homogeneous nucleation usually involves supercooling or superheating. It seems therefore unlikely that homogeneous nucleation is at the origin of the venous gas emboli observed in these conditions.

Tribonucleation [47] is the formation of new gas bubbles in a solution where two adhesive surfaces are rapidly separated from one another due to the resulting negative pressure that ensues momentarily [47–49].

In the context of this review, cavitation is defined as the process of bubble formation from a nucleus. This can occur either when the pressure in the fluid drops below the saturation vapor pressure (boiling cavitation), or due to the desorption of dissolved gases (degassing cavitation) which can happen at a higher pressure than the saturation vapor pressure [46].

For a bubble to form "spontaneously" in a solution with dissolved gas a supersaturation greater than 10.0 MPa is required which is reached at about 900 m sea water (msw). However bubbles have been observed by ultrasound imaging in divers after dives as shallow as 3.6 m (equivalent to about 40 kPa of pressure) [50]. De novo bubble formation by homogeneous nucleation does not seem possible from the pressure excursions of human decompression [13,51].

Heterogeneous nucleation however can account for bubble formation in relatively low supersaturation levels such as the ones observed in the scuba diving context. This is at the origin of the concept of "micronuclei" which are hypothesized to act as gas nuclei or "seeds" for the bubbles to grow from [13,51]. Their current definition is small gas filled bubbles whose size does not exceed 10 μm [52]. For bubbles to grow from micronuclei, the dissolved gas in the supersaturated tissues entering the micronuclei needs to overcome its surface tension. The smaller the bubble is, the strongest its surface tensile strength. For a given pressure gradient there will therefore be a critical size radius above which the bubbles will be excited to growth.

2.2. Early studies

The postulate for micronuclei has actually been around for a long time, with little direct experimental evidence to support it in vivo. Leonard Hill described how bubbles need weak "points" to grow from a fluid as early as 1912 [53]. In the 1960s and 1970s Brian Hills developed an approach to prevent decompression sickness (which he described as "thermodynamic and kinetic") focused on tracking both dissolved and free phase gas [54]. Hempleman and Hennessy suggested that a certain degree of embolism is tolerated by the body and suggested a new definition of DCS as a volume threshold of total gas bubbles circulating [55].

In 1954, Herzfeld and Fox [56] discussed the necessity of nuclei to induce bubble formation via ultrasonic cavitation, arguing that pressures in the order of hundreds of atmospheres (tens of MPa, i.e. below 900 msw) would be needed otherwise. These bubble seeds in turn need to be stabilized since their surface tension alone would otherwise dissolve them. To account for this they suggested bubbles with organic skins [56]. These stabilized bubbles may then act as cavitation nuclei. This is also supported from Harvey's work [51] whose experiments showed that undissolved gases play a key role in such cavitation. No cavitation could be ultrasonically induced for some time after subjecting water to 1000 atm for 15 min and rapidly decompressing it. Harvey explained this observation saying that the high pressures forced the gas into complete solution and today would be called a "denucleation procedure".

In addition to Harvey who showed that fissures in solids could support growth of free phase gas, stabilization through geometrical considerations, looking at contact angles of the growing bubble from a non-flat surface, was also considered by Greenspan and Tschiegg [57] who showed that the acoustic cavitation threshold in water could be raised by passing samples through membrane filters.

In 1968, Campbell evaluated quantitatively the theory that tribonucleation in liquid solutions happens in areas of reduced pressures as two attractive surfaces are rapidly separated, and discussed the role of the solid surface composition in such homogeneous nucleation [47]. He found that to induce bubble growth to a macroscopic size, gas in solution had to be present, similarly to the cavitation conditions described by Harvey and Herzfeld. Contact angles that would yield bubble formation were also discussed as surface crevices of the separating surfaces were considered geometrically.

Stability analysis of gas bubbles in liquid solutions were analytically treated by Epstein and Plesset in the 80s [58], first using diffusion theory and then more systematically in full thermodynamic considerations, resulting in the well known Raleigh–Plesset equation.

A series of experiments that supported the gas nuclei concept were performed in the late 70s and early 80s by the Tiny Bubble Group (Yount et al.) in which they pressurized and then decompressed transparent gelatin to study bubble formation [59–61]. The motivation for this was the simple observation that DCS can present in almost any part of the body. They hypothesized that this is due to the properties of water relating to cavitation. Gelatin was chosen as an aqueous medium because it is conveniently transparent and the bubbles produced in it stationary which makes it easy to count and size them optically. Their series of experiments in 1976 concluded with the hypothesis that bubbles form out of pre existing nuclei. Bubble formation in humans and in supersaturated distilled water was shown even for pressures below 1 atm, whereas the calculated tensile strength of water should exceed 1000 atm [59,62]. This cannot be explained by "solid impurities with smooth surfaces" [63]. Moreover the cavitation threshold was shown to increase significantly after degassing procedures, a specific test for gas nuclei. A similar technique was tried on the gelatin samples where static pressure was applied and the cavitation threshold for gelatin was shown to increase. Yount et al. concluded from these observations that gas nuclei were probably at the origin of bubble formation in scuba divers and they went as far as suggesting denucleation procedures from pressure excursions or via drugs. They hypothesized that the acclimatization observed in many caisson workers [64] might be due to micronuclei population depletion. They also urged for new decompression algorithms that would incorporate bubble dynamics directly (instead of compartment ratio considerations only) to be developed in light of these findings. They suggested asymptomatic bubble outcome of a dive measured ultrasonically as a way to measure the success of the decompression schedule since all dives result in some degree of bubbling [5,65].

Some of the early experimental "evidence" for the micronuclei concept in vivo came from Evans who in 1969 showed that decompressing

shrimp after compressing them to 400 atm resulted in significantly less bubbles [66], presumably from "crushing" the micronuclei population pre decompression. Other animal experiments included the decompression of rats breathing air after a very short pressure excursion to 3 MPa (305 msw) before leaving them at 0.7 MPa (73 msw) for 2 h. This experiment showed significantly less DCS occurrence for the rats which went to 3 MPa with respect to those which didn't [67]. Both studies seem consistent with the idea of shrinking gas bubble precursors before decompression to account for less bubble formation, thus supporting the micronuclei theoretical basis. They also show potential for preventing DCS by developing procedures to target micronuclei pre dive.

2.3. The micronuclei stability problem

The concept of micronuclei is not without its problems. The most important one is accounting for the long term existence of these gas filled microbubbles since from their tiny size it would be expected that they spontaneously shrink in the absence of other stabilizing forces, for instance surface active coatings. A stabilization process to account for non negligible half lives therefore needs to be discussed [50,51]. To understand the problem let us consider the three forces acting on a single bubble. Those will be the gas content pressure pushing outwards, the ambient pressure pushing inwards and the Laplace surface tension of the bubble. For a bubble to be stable they need to equilibrate. The surface tension force is inversely proportional to the radius so becomes dominant for very small bubbles that should have a tendency to dissolve below a critical radius at ambient atmospheric pressure. Micronuclei, of the order of a couple of micrometers, need to be stable for ambient atmospheric pressure but without invoking an additional stabilization mechanism they would dissolve immediately. Mechanical stability is a necessary but not sufficient condition for bubble stability. For a microbubble to be stable, it also needs be thermodynamically stable or in other words in chemical equilibrium with its surroundings. Since micronuclei are hypothesized to exist independently of diving, they should be stable at atmospheric pressure. However in the absence of a stabilizing mechanism, their surface tension would shrink them to dissolution [68].

One way of overcoming this issue is to invoke surfactants which are amphilic organic compounds that lower the surface tension of bubbles [60,69,70]. The Tiny Bubble group first looked at surfactant molecules as stabilizers [60,63]. The permeability of the membrane of the bubble which depends on the diffusivity across the bubble then also dictates the rate of bubble growth. However, a surfactant that would lower the surface tension term of the Young Laplace equation has not yet been identified in vivo [13]. In addition, in vitro studies showed the opposite effect with known surfactant, as an increase in surfactant induced a decrease in bubble formation after decompression [71]. Another stabilization mechanism comes from geometrical considerations to find contact angles that would permit bubble growth. For instance hydrophobic crevices have been suggested.

Yount et al. proposed a stability mechanism [60] for gas nuclei. This is needed to explain why stable nuclei seem to exist which is a priori counter intuitive since large gas phases with a radius above 1 μm should rise to the surface of a standing liquid and smaller ones should diffuse outwards due to surface tension effects. Herzfeld and Fox's idea of an organic impermeable skin to stabilize bubble nuclei was abandoned after Strasberg showed that a cyclic change in pressure did not leave the nuclei unaffected [72]. In addition the counter diffusion that seems to happen where multiple gases are involved [73] also goes against impermeable skins. To overcome the problem encountered with impermeable skins, Yount et al.'s hypothesis was a stabilization mechanism based on surface active skins of varying gas permeability. The idea is that the surface of the bubbles must be initially permeable for the gas to diffuse inwards, then should progressively become effectively impermeable above a threshold static pressure applied rapidly. These properties were found in practice to be similar to having surfactant skins so this model became the surfactant stabilization theory.

3. Recent studies and discussion

3.1. Bubble formation mechanisms

In 2008 Goldman revised and lowered the pressure threshold needed for homogeneous nucleation. Applying a similar approach to Abraham's thermodynamic study of liquid droplets surrounded by vapor phase [74], Goldman derived Gibbs free energy expressions for gas bubble formation from supersaturation [75]. The nucleation energy threshold was shown lower than previously thought resulting in the theoretical possibility for homogeneous nucleation to occur for human decompression situations (less than 5 atm, roughly equivalent to 40 msw) in very particular tissues with very low surface tensions. The Gibbs free energy expressions obtained are based on the assumption that the system under consideration is "closed". Physiological tissues however are perfused by blood and exchange dissolved gas. Therefore this study can only be applied to physiological tissues under the assumption that this exchange with the circulatory system is slow enough to be ignored during the nucleation process. In other words there is a "separation of time scales" between perfusion and nucleation processes. As pointed out by Goldman however, even if homogeneous nucleation did actually occur physiologically it would still only account for a very small percentage of the venous gas emboli observed ultrasonically, especially since bubbles are detected with pressure exposures far smaller than 5 atm [1]. Therefore the conclusion of this study in the scuba diving context, assuming that the approximations hold, still maintains that heterogeneous nucleation, tribonucleation and bubble growth from stabilized pre existing micronuclei are definitely more important processes than homogeneous nucleation.

A potential candidate for micronuclei was discovered, as atomic force microscopy has shown that gas nanobubbles of 5–30 nm form spontaneously on smooth flat hydrophobic surfaces submerged in water [76–80]. As suggested by Arieli in 2011 [81], hydrophobic surfaces in the body, for example in large blood vessels and fat, might therefore be where micronuclei are formed, without necessarily having crevices. To support this hypothesis they looked at the formation of bubbles on hydrophobic and hydrophilic smooth silicon wafers in degassed water compressed to 90 m for 15 h then decompressed. The results showed bubbles only on the hydrophobic surface. The possibility for these nanobubbles to act as nucleation sites was discussed in other studies, showing them to be so stable ("superstable") as to exclude the possibility they would act as gas nuclei for bubbles to grow from them. Their stability was demonstrated not only for ambient pressure but also for a reduction in ambient pressure down to 6 MPa [82]. These nanobubbles have therefore been shown to be stable for hours, despite the expectation that they would dissolve in much less than a second due to their large Laplace pressures. This superstability has not been explained theoretically as yet. However it should be noted that this stability during huge pressure fluctuation does not exclude growth by gas diffusion from a supersaturated tissue and in Arieli's et al. study, probably mainly due to the very high supersaturation of the tissues, the nanobubbles do appear to act as micronuclei. The critical radius of curvature of these bubbles is 100 nm above that for which they can evolve as bubbles [79]. This seems to be in agreement with the evolution on hydrophobic crevices. Higher percentage of adipose tissue is a known predisposition to DCS. This was traditionally explained through the fact that, being more aqueous, it was a medium in which nitrogen dissolved better. This theory might offer an additional if not alternative explanation: that hydrophobicity of adipose tissue makes it a preferential site for bubble growth from a larger micronuclei population from nanobubbles.

3.2. Stability

The stability issue of micronuclei was investigated further and an alternative solution, proposed by Goldman in 2010, avoids the issue of surfactants not having been identified in vivo [83]. Mathematically the Young–Laplace equation for a spherical stable gas bubble was generalized [84] to include effects of its surface tension and elastic forces from its surroundings, assumed to be a soft isotropic material. The resulting Generalized Young Laplace equation (GYL) is exact in the regime where these spherical bubbles are large enough (above 1 μm) to ignore microscopic behavior of the surface tension and the interface between the bubble and its surroundings. The Gibbs free energy of deformation of the elastic surrounding is also derived. Treating the tissues as soft deformable materials in a supersaturated state, the Gibbs free energy for the system and per bubble was derived using the GYL equation derived in 2009 [84]. For a material with a nonnegligible shear modulus, this demonstrated that free energy wells which would stabilize small gas bubbles exist. A new model for tissues as "isotropic elastic materials that have a surface tension and resist both compression and shear forces" is thus proposed, which would account for the micronuclei hypothesis while solving their stabilization problem. Tissue elasticity is therefore considered here as a potential explanation for micronuclei stability that accounts for both mechanical and thermodynamic stabilities. The derivation shows that bubbles below a certain radius and above a certain radius will be mechanically stable, whereas any radius size in between will be unstable, because of the opposite forces acting on the bubble pressure due to the surface tension and shear resistance. These thresholds depend on the relative magnitude of the shear modulus of the elastic material under consideration, but they correspond in size roughly to radii below 0.8 μm and then above 6 μm. This interesting property could explain why very small bubbles (bubble nuclei) need the dissolved inert gases to trigger their growth above the radius for the second mechanically stable region. Another study combining this mechanical stability to chemical stability considerations found that elastic materials with non negligible shear modulus can indeed yield stable micronuclei for the bubbles to grow from [83]. The main potential for criticism in this study comes from the relatively small stabilizing potential wells which can account for bubble stability over finite periods of time (short times, but actual timescale not given). However assuming that tribonucleation happens in the body from muscle movement for instance, which has been suggested as a mechanism to explain the higher DCS occurrence after exercise [13], this could account for a nonnegligible population of micronuclei at any one time as new micronuclei are formed by tribonucleation.

An alternative stabilization mechanism, from geometrical considerations, was considered. A bubble growth model from hydrophobic conical crevices inside vessels was tested with realistic tissue parameters by Chappell and Payne [85]. They looked at their behavior under compression [86], showing that the geometry would resist the compression via slight deformation and change of radius of curvature. They then investigated how bubbles could grow from these crevices under decompression [87]. The model was developed to account for a single inert gas and gas transfer happened through the walls of the crevice. Incorporating metabolic gases (in this case oxygen) was shown to have a measurable impact in making the surface tension less significant in the nucleation rate. This was explained through the high diffusivity of metabolic gases. Since hypobaric decompression yields bubbles with a greater percentage of metabolic gases as observed in astronauts [88,89], it would be interesting to check this theory by applying the model to a hypobaric decompression scenario. The cavity geometry was also looked at and four different geometries analyzed [90], while neglecting gas transfer. The nucleation behavior was found to depend mainly on the size of the mouth of the cavity after initial growth were the bubble reaches the opening. At this point the flow conditions also play an important part, as one might expect.

3.3. Single and multiple bubble behavior

Single bubble growth on a solid surface was studied by generating a single bubble on a submerged heater. As heat is applied the liquid becomes supersaturated locally. This procedure is somewhat different to the traditional way to study these phenomena by degassing supersaturated liquid through decompression, where a single bubble alone cannot be produced. Thermal degassing which involves mass transfer but also heat transfer is thus achieved (as opposed to decompression degassing which only involves mass transfer in theory). To study the bubble generation and growth separately from the gravitational effects on them, the experiments where performed in microgravity conditions (ESA parabolic fights) [91,92]. The experimental observations were compared to a theoretical model [93] derived considering spherical bubbles in a uniformly cooled liquid that were heated from the inside. The initial stage of growth was shown to agree with a parabolic diffusion law, after which a linear growth model was more appropriate. The lateral motion of the bubbles along the heater as they are first generated was also looked at and discussed with respect to the surface of the heaters used [94]. Multiple bubble growth and detachment showed competition for the dissolved gas available in the supersaturated solution amongst bubbles growing closely together [95]. The final size of bubbles was shown to be smaller than that of a single bubble, and a critical temperature could be found above which any increase in temperature did not result in faster bubble growth.

Karapantsios et al. have argued for the necessity to study the characteristics of bubbly flow (multiple bubbles flowing with the liquid) in addition to single bubble generation, since it is this abundance of bubbles which is at the origin of DCS above some threshold. An impedance spectroscopy technique, In Vitro Embolic Detector (IVED), was developed to detect bubbles in the blood stream by measuring the gas fraction. The in vitro phase of this project showed very good resolution as well as sensitivity to variations in gas fraction and bubble size in bubbly flows [96], and the in vivo phase, currently animal testing, is in progress. The results were validated through acoustic spectroscopy and electrical impedance tomography measurements. An in vitro experiment to simulate a realistic bubbly flow in the human vena cava was devised to investigate the effect of surfactant and/or electrolyte concentrations on the bubble size distribution (measured both by the IVED and electrical impedance tomography for validation purposes) to continue the improvement of these techniques but sized optically in this study [97]. The study found no correlation between the bubble size and the radial position of the tube or viscosity of the liquid. The size distribution was however found dependent on the flow rate and lower for higher surfactant and electrolyte concentrations and when both were added together this effect was amplified. An assumption throughout the paper is that the addition of surfactants will not affect the radial distribution of different bubble sizes in the tube, and all measurements for sizing were done near the surface of the tube. Another limitation of the study is the high bubble count needed for sizing.

A mathematical study to look at the interaction between blood born bubbles and tissue bubbles was conducted, assuming that bubbles can form in tissues and in the wall of vessels [98]. Once again competition for dissolved gas was pointed out. It was also shown that the number of tissue bubbles will influence the number of blood bubbles, whereas the opposite effect is very unlikely. The main variable of interest is obviously perfusion of tissues.

The phenomenon of competition for dissolved gas among growing bubbles was further investigated through numerical simulations [99]. A clamping phenomenon was demonstrated above a certain density of bubbles per unit tissue, after which the washout rate was considerably diminished, going from exponential to linear. This finding seems realistic since a number of decompression algorithms, the so-called exponential linear kinetics models, use a linear washout rate with

very good correlation to real dive data [100]. The main limitation of this study is the lack of information on in vivo bubble density in tissues which makes it very difficult to extrapolate the findings.

As an aside, the possibility for a single bubble to act as a "gas plug" was found possible [101], after calculating what size a bubble would need to be to block some of the capillaries in the body. For almost any driving pressure difference affecting bubble growth this was shown to be a possibility. The compliance of the vessels was not taken into account in the derivation of this model, however, and it would be expected that their contribution to this problem will be significant. It would be interesting to look at incorporating this, as a systematic analysis of the gas plug possibility resulting from a hyperbaric exposure was never investigated before Chappell and Payne's study.

3.4. Role in decompression modeling

Although this review has been primarily focused on bubble nucleation in the physiological context of human hyperbaric decompression, it is important to note that bubble growth is obviously also very relevant. To develop a decompression model based on physical parameters, both nucleation and growth have to be described, giving the rate of bubble "appearance" and that of "growth" respectively. Combined, they would allow for the precise calculation of bubble size distributions with respect to dive time, which could then be checked. In vitro physics experiments can thus be used to determine which parameters influence and dominate bubble number and size (nucleation and growth phases), as physiological studies can only observed their combined effects. In particular, exploiting the controlled set up from in vitro experiments can allow to study isolated phenomena, decoupling heat, mass transfer, gravitational and/or bubble competition effects as seen in the previous section.

Explicit bubble dynamics have been incorporated in the modeling of decompression to produce safer decompression procedures. They use Venous Gas Emboli (VGE) as a way of evaluating decompression models instead of only relying on the incidence of DCS. The Copernicus model [102,103] includes bubble considerations and assumes that bubbles grow from pre existing gas nuclei as Yount suggested in 1979, then relies on an approximate stabilization function from Yount 1979 and Chappell 2006. It also assumes that gas nuclei are attached to the endothelial layer [104].

A modification of the Srinivasan et al. model (1999) was presented in 2010 [105], where the concentration distributions around a tissue bubble at ambient pressure after decompression was solved analytically to find its growth rate. This was shown proportional to the ascent rate, tissue diffusivity, initial concentration differences and void fraction (dominant factor) and inversely proportional to the surface tension. The calculations were solved analytically for unsteady flow in tissue based on the three region model [106], showing how the concentration gradient decreases as the bubble grows.

A biophysical model specifically aimed at articular bends was developed recently [107]. The joint was separated into two compartments exchanging inert gas via blood perfusion and with one another via diffusion. The diffusion interface, along with relatively large diffusion coefficients, could account for the late onset of symptoms often observed. A critical volume of free phase gas was used as a definition for DCS. A clamping phenomenon was observed soon after the decompression onset. The model fitted the data and approximated well.

The need for a realistic biophysical model for bubble growth during hyperbaric decompression has been made clear with studies showing that the extrapolation region for dissolved gas models was not particularly good: if the models do not mimic biophysiological processes enough they cannot be extrapolated to situations different to their calibration dataset. However such a satisfactory model has yet to be developed [108]. In that respect using VGE counts instead of DCS/no DCS outcomes only is particularly important. This was made even clearer via a study on mild or "marginal" DCS events [109].

The difficulty arising from marginal DCS events (for instance skin rash) to calibrate probabilistic decompression algorithms to dive data has been discussed recently [109]. They were traditionally assigned fractional weights, resulting in more conservative models. A statistical analysis was performed to see whether these could be described as random occurrences, in which case they should not be included in model parameter fitting. Interestingly the study concluded that these should not be included in model fitting, since model calibration without them yielded the same correlation coefficient and similar extrapolation regions to real dive data. Analytically the calculated weighting that should be applied to these events was found to be 0. This highlights the difficulty of looking at DCS outcome as the sole indication for the calibration and validity of a model. Using VGE scores is much more powerful. The role of decompression models is no longer to limit DCS occurrences, it is to limit VGE scores post dive.

The current practice in VGE monitoring post dive relies on trained observers, usually clinicians, attributing a severity grade to the Doppler ultrasound video they have from the heart (or audio recording). Different scales exist (Spencer or Kisman-Masurel (KM) for sound recordings, and Ikeda, Eftedal–Brubakk (EB) for video) with 4 or 5 severity grades [1], but all rely on the frequency and amplitude of the signal, in other words number of observed bubbles per cardiac cycle as well as the relative intensity with respect to the cardiac sound in the case of audio recordings. However current grading methods have been shown to be inconsistent [110] as they are user dependent and the monitoring times post dive are not consistent between studies. In this respect having an objective, quantitative VGE scoring system, ideally a bubble counter and sizer (the latter part is not realized at the time of writing) per unit volume and time would be very useful, and indeed efforts are being made in this general direction [111–118].

Modeling considerations also include finding ways to explain physiologically the influence of known risk factors on bubble counts observed, such as exercise [119] and immersion [120].

An interesting modeling attempt in this direction to predict the median peak bubble grade post-dive evaluated by Doppler ultrasound in controlled physiological conditions [121] combines a dissolved gas phase model [122] with a bubble dynamics model for perfused tissues [99].

The evasive influence mechanism of exercise on bubble counts measured post dive was also investigated theoretically [119]. The bubbles were assumed to follow a Poisson distribution of formation with respect to time and their growth only dependent on pressure differences. Exercise was then factored in through an elevated consumption of oxygen and enhanced perfusion of tissues. This was shown to result in longer lifetimes for tissue bubbles and less bubble growth overall. However at the same time tissue motion could increase bubble formation through motion induced cavitation. To accurately predict outcome the relative rates of these processes would need to be calculated, which is in practice very difficult as there is no way of quantitatively characterizing these separately. Exercise timing and intensity, as well as the nature of exercise, which have all been shown to give particularly different results, were not considered systematically in this study.

A recent study showed that VGE bubble counts were significantly ($p < 0.0001$) higher for in water diving compared to the same dive profile in a dry chamber [120]. This is particularly important with respect to testing and parameterizing models which increasingly rely on venous gas bubble counts. In particular, deciding whether to use dry chamber data or real dive in cold water data for instance would yield different results if the same dive profile results in drastically different bubbles counts in those conditions. There are many interconnected factors that could explain the differences observed, including temperature, immersion, exercise, hydration, but also individual fitness. The wet/dry

differences can be due in part to temperature differences since diving with a wet suit would result in colder dive conditions. Hemodynamic distribution within the vasculature could also be at play since the microgravity effect of water submersion would result in a redistribution of blood volume [123]. In cold conditions this would be combined with vasoconstriction in the extremities to some degree [1]. Systematic studies looking at bubble counts in wet and dry diving whilst closely matching other conditions would be useful. For instance a study looking systematically at the same square dive profile could be devised for in water dives with drysuits and wetsuit exposures, and also in chamber conditions. The temperature and exercise conditions would need to match. Another factor as far as water diving is concerned could be the diver's orientation. In astronauts there is a known adaptive mechanism which happens due to the shift of fluids in the upper part of the body. A diver which would ascend on a line could be in upright position. In technical diving where decompression procedures can last for hours a diver is not likely to stay horizontal for the whole duration of the dive. To the best of our knowledge no study has been performed where the diver's position has been systematically investigated, either in chamber of water conditions.

4. Conclusion

Nanobubbles spontaneously forming on hydrophobic surfaces, observed via atomic force microscopy, constitute a potential candidate for micronuclei, although their capacity for growth is still debated as they are very stable. Heterogeneous nucleation and tribonucleation therefore still hold as the prime candidates for bubble formation in human hyperbaric exposures, homogeneous nucleation needing far greater pressure differences than those encountered.

Stabilization processes for micronuclei have been revised and some new ones proposed. Hydrophobicity of surfaces seems to be an important factor in crevice growth models and could potentially relate to some physiological studies where adiposity as a risk factor has been investigated. An alternative stabilization mechanism is that of stabilizing potential wells due to tissue elasticity, which combined with continuous degrees of tribonucleation from body movement could permit a constant supply of micronuclei and potentially explain some of the physiological studies on the role of exercise in bubble formation.

In any case, incorporating bubble formation and growth mechanisms in decompression models is important and the general direction of research in that area is an effort to make models more biophysical to allow better extrapolation. In that respect a consistent quantitative venous bubble monitoring system post dive, unambiguous and reliable needs to be developed to calibrate and verify these results.

The location of micronuclei or where bubbles form remains unanswered, with tissue bubbles (in situ) now having been presumably observed in vivo in addition to circulating bubbles [115,124]. The interaction between them, as well as between multiple bubbles has been shown to result in dissolved gas competition for growth where flow conditions and perfusion rates are dominant parameters. Furthermore the single gas plug possibility was shown to be worthy of more careful consideration as far as DCS is concerned. Finally, a closely controlled study looking at wet/dry dive differences would be useful to evaluate how many of the differences observed can be accounted for by other related parameters such as temperature and exercise.

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