Hyperbaric oxygen therapy: oxygen and bubbles.

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Recompression using oxygen is the accepted treatment for decompression injury. As early as 1877 Paul Bert stated that recompression using oxygen is the optimal treatment for decompression problems (2). He also pointed out that this treatment was very effective for getting rid of the gas from the vascular system but much less effective against paralysis and the serious types of decompression sickness.

A list of some of the treatments that are used presently is shown in Table 1. They vary quite significantly both in pressure and in oxygen content, going from 190 kPa (9 msw,30 fsw) on air to 780 kPa (68 msw, 204 fsw) using nitrox. Treatments to depth of relief or saturation tables are also used. Even if there is considerable clinical experience with other procedures than the standard US Navy Table 6 (280 kPa using oxygen), there is really little published data to support use of the other treatments. However, it is probably true that the available evidence suggests that treatment at depths shallower than 60 feet runs the risk of failure and that treatments deeper than 60 feet offers no particular benefit in the majority of cases (23).

Table 1. Treatments Used Today

- 190 kPa Air or O_2 (In-water recompression)
- 200 kPa O_2 (Boussuges et al)
- 220 kPa O_2 (Comex 12)
- 240 kPa O_2 (Ørnhagen)
- 280 kPa O_2 (USN 5 & 6, Kindwall)
- 400 kPa 50/50 Heliox of nitrox
- 600 kPa air or nitrox (USN 6A, RN 71)
- 780 kPa air and nitrox (USN 8, Hawaian)
- Depth of relief and saturation tables

It is commonly accepted that supplemental oxygen should be administered immediately after a decompression accident, and continued until the patient reaches the hyperbaric chamber. Generally, this will significantly reduce symptoms. A large number of patients will reach the chamber without any symptoms at all (14; 16). Still, there is general consensus that even if no symptoms are observable, the patient should be recompressed.

Studies have shown that while the majority of the commercial divers are treated within fifteen minutes after they develop symptoms, for amateur divers there is a considerably longer

time delay, many hours in most cases (15). Delay in starting treatment may influence results significantly (16), however, it seems that after some hours, a further holdup of treatment does not significantly influence outcome (14; 22). A study by McIver and McIver (15) showed that 61% of the divers who were treated within two hours were fit to dive after one treatment, while only 44% of those treated later were fit.

When gas is formed, the initial effect of the bubbles will be related to volume expansion and the mechanical effects of the bubble surface. Following this, bubbles will initiate a number of secondary biochemical effects, mostly related to inflammation. The secondary effects are not determined by bubbles as such but by how the body reacts to them.

The purpose of the initial treatment is primarily to diminish the mechanical effects of the bubbles, while the later treatments, which I have arbitrarily defined as those performed one to two hours after the insult, is HBO_2 treatment for both primary and secondary bubble effects. This critical time interval is difficult to define, and no one knows how long it is. One consequence of this approach is that it is beneficial for the final outcome to eliminate bubbles rapidly.

So what are these primary bubble effects? If we only consider the vascular bubbles (see later), my opinion is that the bubbles mainly damage the endothelium (18; 19) and only rarely do they lead to flow obstruction and ischemic effects. Total occlusion of flow is probably rare unless excessive amounts of gas are present

There are a number of secondary effects which I will not go through in detail, like activation of leukocytes, aggregation of thrombocytes, initiation of coagulation (21; 26). The body regards bubbles as foreign surfaces and responds to them some time after the gas bubbles have been formed. Rapid removal of the bubbles can perhaps prevent some of these secondary effects.

The question of the location of the decompression bubbles is of some significance. Behnke pointed out that the matter of bubble location was of the greatest importance since, if bubbles form extravascularly in the nervous tissue, any decompression poses the probability of serious consequences (1). It is well documented that bubbles can be observed in the venous system in nearly all decompressions (7; 17). Very little data actually show that there are many bubbles in other tissues, with the possible exception of fat (17) (1). Bubbles are not seen in flowing blood (10). Bubbles are usually formed at hydrophobic surfaces (27), where bubble precursors (nuclei) are stable. Following severe experimental decompressions, we did not observe bubbles in the muscles themselves, but on tendons and fascia (unpublished data).

Our hypothesis is that serious decompression problems, e.g. neurological decompression illness, are caused by the reaction of the body to intravascular bubbles. Bubbles in tissue may be involved and obviously are an issue in musculoskeletal DCS. The main role for tissue bubbles (or stationary vascular bubbles) is the effect on gas dynamics, as they slow down the elimination of inert gas (12). While of possible importance, there is little evidence that is contributes to disease process. One example comes from a study in goats done by Palmer published in 1998 (20). When staining for endothelium in the spinal cord he always saw endothelium surrounding the gas. He could never find gas bubbles that were not inside a vessel. Even if extravascular bubbles can not be wholly discounted as the source for serious decompression sickness, an hypothesis assuming that the main cause are vascular bubbles can be useful and testable.
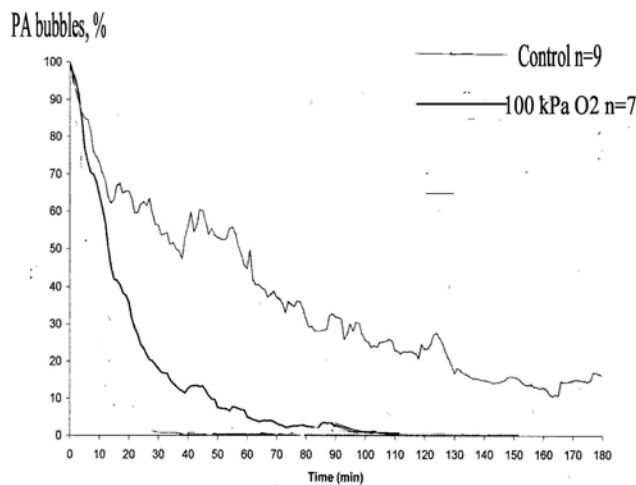
Bubbles formed on the venous side of the circulation can go through the pulmonary vasculature (24) or through an open Foramen Ovale (25). There is also a potential for bubble formation in the arterial circulation. Several studies have shown that bubbles can be observed on the arterial side before they are seen on the venous side following decompression (1)**.** As early as

1900 it was observed that if animals were killed under pressure and then decompressed, bubbles were found in equal amounts both in arteries and veins. If they were decompressed alive, the bubbles were mainly seen in the veins, indicating that the potential to form bubbles was just as great on the arterial side as on the venous side (11). If we assume that the mechanism of injury in DCI is similar to the one seen following ischemia and reperfusion, then the mechanism for the treatment effect of HBO_2 would be similar to what has been presented at this symposium.

When we use oxygen at increased pressure, it has effects that may influence the actual dosage of oxygen reaching the organs. We did a study in anesthetized pigs, demonstrating that there is a significant increase in shunt fraction in the lung even after five minutes of 100 kPa oxygen and that this fraction increased nearly three times following 200 kPa oxygen breathing (8). It is conceivable that the effect is considerably less in active man.

Another important factor is that oxygen has an effect on nitrogen elimination. In the same study, we looked at nitrogen elimination measured in the central venous blood. We were able to demonstrate that breathing 200 kPa oxygen significantly slowed down the washout of nitrogen by a factor of three (9).

We have performed a series of experimental studies where we have looked at the effect of pressure and oxygen on the elimination of gas bubbles in the pulmonary artery (13). In Figure 1, we see the effect of breathing oxygen compared to breathing air following a standard dive (500 kPa, 40 minutes breathing air, 200 kPa/minute decompression). The maximum amount of bubbles produced was set equal to 100%. Breathing air, the bubbles were eliminated rather slowly. Extrapolating this curve to zero will give an elimination time in the order of three to four hours. If 100 kPa oxygen was breathed, the bubbles were eliminated significantly faster. In this and the following studies, the treatment was started as soon as maximum bubble production was observed, usually 20 – 40 minutes after decompression.

Fig. 1. The effect of air and 100 kPa oxygen on elimination time for gas bubbles in the pulmonary artery.

Following this treatment, only one animal in the air recompression group had any signs of central nervous injury during a one week follow up period (6).

In Figure 2 the effect of various combinations of pressure and oxygen content are compared. If pressure is increased to 200 kPa, the bubbles are removed significantly faster compared both to the control and to the use of 100 kPa oxygen. However, neither the addition of oxygen up to 280 kPa, nor the increase of pressure up to 400 kPa significantly influences the elimination time of bubbles.

Fig. 2. The effect of pressure and oxygen on the elimination of pulmonary artery bubbles following decompression**.**
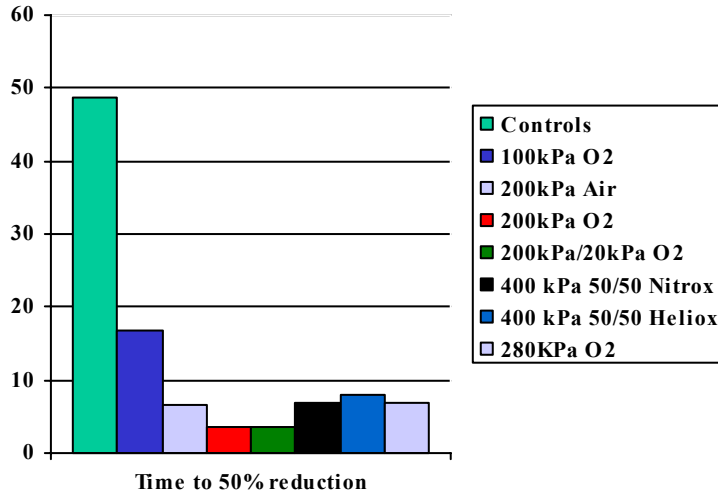
In order to try to understand the relative importance of pressure and oxygen on bubble elimination, further experiments were performed. The results can be seen from Figure 3.The effect of compressing to 200 kPa breathing either 100 % oxygen or a nitrogen/oxygen mixture containing 20 kPa oxygen is shown. The time it takes to eliminate the gas is exactly the same.
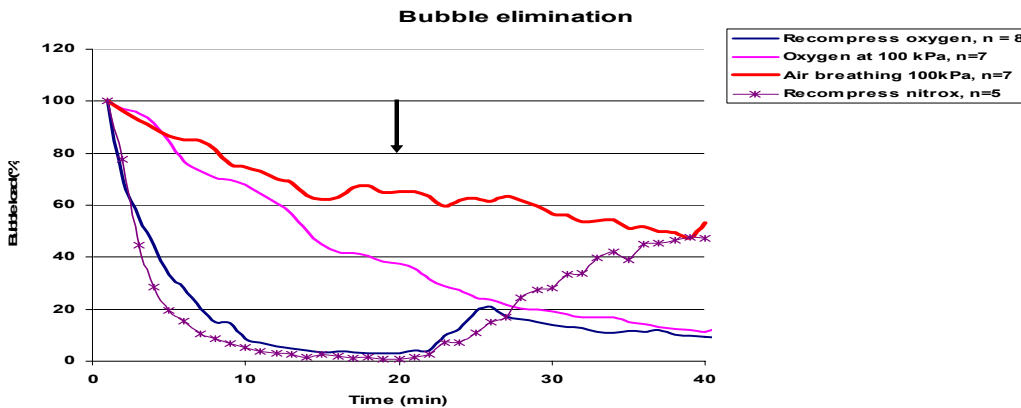

Fig. 3. The effect on pulmonary artery bubbles of recompression to 200 kPa breathing 200 kPa and 20 kPa oxygen. At the arrow, the animals are returned to 100 kPa breathing 100 kPa and 20 kPa oxygen respectively.

After 20 minutes (arrow) the animals were returned to pressure. Bubbles reappear and the number of bubbles increase until they reach the bubble elimination curve for air breathing and 100 kPa oxygen, respectively. This clearly indicates that it is the pressure that is the main determinant for the velocity whereby the bubbles disappear, while the oxygen increases the rate of elimination of the inert gas.(Brubakk et al, in manuscript)

Fig. 4. Bubble elimination following recompression breathing air. Own data and those of Branger et al.
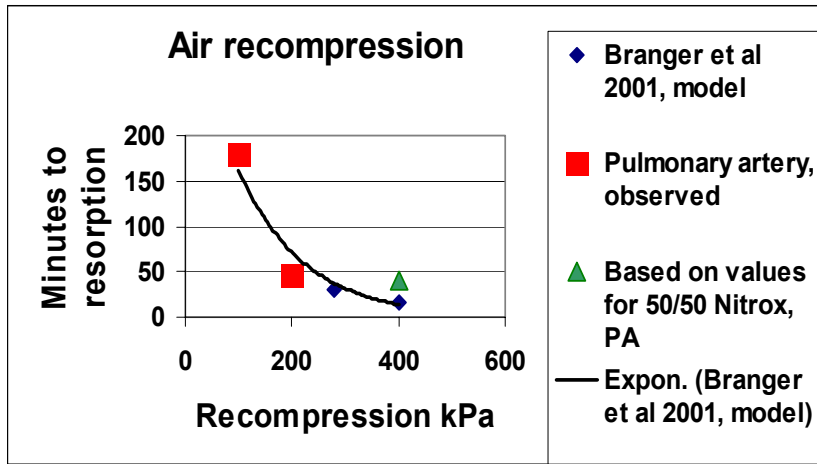
Our results have been compared to those from Lambertsen's laboratory (3; 4). In Figure 4 we can see a comparison between our data and the ones from Branger et al when air recompression is performed. There is an excellent fit both for the data and their model. If oxygen is added, however, their model predicts considerably shorter elimination times for bubbles than what is actually observed experimentally as demonstrated in Figure 5. Similar results are seen at 280 kPa.

Fig. 5. Effect of oxygen on bubble elimination time. Comparison between own data and model of Branger et al.
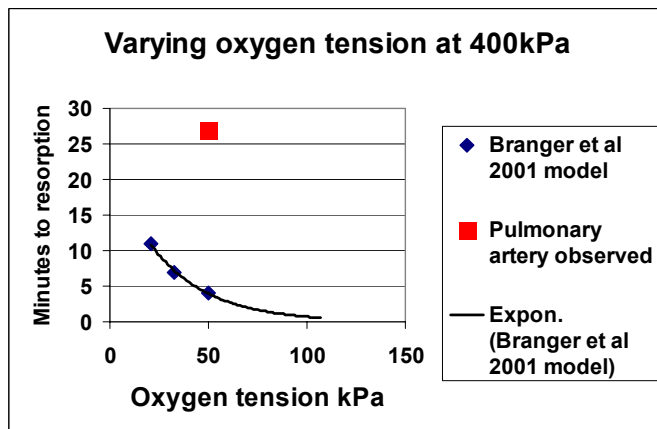
These data indicate that increasing pressure to 200 kPa significantly decreased elimination time for bubbles. Additional pressure up to 400 kilopascals will not influence elimination time. Increasing oxygen tension during recompression will have no additional effect on elimination time. However, increasing oxygen tension will increase the rate of inert gas elimination.

Rapid "treatment" of bubbles is actually used commercially in a procedure called surface decompression using oxygen (SurDO$_2$). In this method, the diver is returned rapidly to the surface and then recompressed within 5 minutes to 220 kPa breathing oxygen in a chamber. This method is considered quite safe and effective. However, if considerable number of bubbles are produced during ascent to surface, even oxygen breathing for 68 minutes is not able to eliminate all gas and a considerable amount of bubbles are still present following final return to surface (5).

In 1978 Barnard stated, "It is to be hoped that in the near future we will have at our disposal a system of treatment based on sound theory, on firm experimental evidence, and extensive clinical trials which are flexible enough to suit the many different types of cases which will continue to occur and that this would be a result of our efforts to understand the etiology of the disease and achieve its prevention."

I think we still have not reached this stage and there are many things we do not know. While 100kPa oxygen and USN6 remains the standard method of treatment, I hope that some of

the thoughts and results presented here may initiate further studies and improvement in treatment procedures.

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