# Micro-nucleation in supersaturated oxygen solution injection

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## 1. Introduction

We present here an example of an important biomedical technique in which it is critical to understand and avoid bubble nucleation in supersaturated aqueous solutions of oxygen. By doing so it is possible to inject highly supersaturated oxygen solutions through a small capillary without the formation of significant gas bubbles. The potential medical benefits of a successful technique of this kind are substantial and multi-faceted. Deprivation of oxygen even for brief periods of time such as occur during heart attacks or strokes results in cell damage or death - and is a primary cause of permanent physiological damage. Consequently rapid therapeutic oxygen delivery systems could substantially enhance the treatment, for example, of acute myocardial infarction or acute cerebral stroke.

The strategy discussed here has been described previously (Brereton *et al.* 1998). It involves the preparation of a highly concentrated solution of oxygen in an aqueous solution under very high pressure and the injection of this liquid into the bloodstream through a small capillary tube or tubes. Recent experiments performed at TherOx, Inc., in Irvine, California, have clearly demonstrated that the nucleation, when it does occur, results from heterogeneous nucleation (Brennen 1995) on the interior surface of the distal end of the capillary and that treatment of this interior surface of the capillary can be remarkably successful in suppressing nucleation. Brereton *et al.* (1998) suggested that the potential nucleation was homogeneous. On the contrary, the present experiments clearly show that heterogeneous nucleation is the dominant phenomenon and a recent heterogeneous nucleation theory by Creech *et al.* (2002) yields results consistent with the observations.

Two basic strategies mitigate for success. The first of these is to prepare and treat the interior surface of the capillary in a way that minimizes the occurrence of nucleation sites. The second of the strategies is that of high fluid velocity. Inside the capillary tube this leads to a high longitudinal pressure gradient which implies a short distal length of tube for which the fluid pressure is below the saturation pressure. Minimizing the interior surface area below the saturation pressure minimizes the chance of a nucleation site being activated. A second benefit of high fluid velocity is that it maximizes the rate of mixing in the jet external to the capillary. Nevertheless, given the uncertainities naturally associated with the occurrence of micron and sub-micron nucleation sites on the interior surface it is inevitable that some of the capillaries will happen to have one or more nucleation sites close enough to the distal end to produce bubbles. A well-regulated testing procedure has been developed by TherOx to eliminate these defective capillaries. However, the fact that this testing procedure can achieve acceptable success rates is one of the most remarkable and promising aspects of this research.

## 2. Experiments

In parallel with the development of a heterogeneous nucleation theory (Creech *et al.* 2002), experiments were conducted at TherOx to investigate the onset of nucleation in highly super-saturated liquid jets emerging from small capillary tubes. Most were drawn silica capillaries with internal diameters ranging from $75\mu m$ to $325\mu m$ though tests were also performed with some polymer (PEEK and Teflon) capillaries. The smoothness and cleanliness of the interior and posterior surfaces of the capillaries were critical in minimizing nucleation. The interior surface of some of the capillaries were coated with benzalkonium heparin (BKH for short), a biocompatible treatment designed for medical devices.

The experiments themselves were simple. Using a special high pressure delivery system (US Patent 5,893,838) in which the flow rate could be carefully adjusted, highly concentrated solutions of oxygen and carbon dioxide in distilled water (filtered down to $2\mu m$) were pumped through the capillary tube whose distal end was submerged in a large beaker of water. Visual observation of the emerging jet determined whether or not nucleation was occuring; sometimes a microscope was used. The saturated pressures of oxygen employed varied from 0.17 to $6.41Mpa$. Experiments were also conducted with carbon dioxide because its much higher solubility would provide information on the importance of that parameter; the $CO_2$ saturated pressures ranged from 0.41 to $3.37MPa$.

Early in the testing it was discovered that the nature of the flow within the capillary tube (whether it was laminar or turbulent) could have a significant impact on whether or not nucleation occurred. In the current experiments this transition could be readily investigated by using alcohol rather than water as the host liquid in the receiving beaker and thus observing the emerging jet whose spreading angle demonstrated whether the internal flow was laminar or turbulent. All the transitional Reynolds numbers were in a range close to 2000.

All experiments were initiated by flushing the capillary with distilled water to removed any trapped air bubbles, before connecting to the high pressure $O_2$ or $CO_2$ solution supply. If nucleation was going to occur it would happen almost instantaneously and persist as long as the flow continued. In cases in which nucleation occurred, the capillary was subsequently disconnected from the supply and several $ml$ of ethanol forced through it with a syringe (for convenience we refer to this as "ethanolization"). Then the capillary was reconnected to the supply and the nucleation test repeated. In the majority of the cases in which this was done, the nucleation was completely suppressed - and the capillary would run indefinitely without nucleation. This was a most remarkable and dramatic phenomenon. Sometimes nucleation could be initiated by increasing the flow rate until the internal flow became turbulent. In such cases, the nucleation would

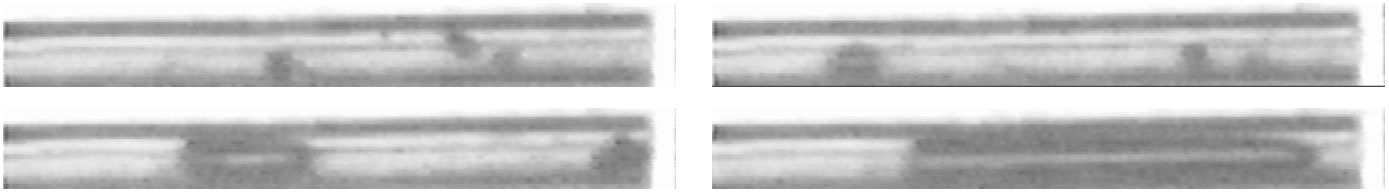

Figure 1: Four examples of high-speed video frames showing bubbles about to exit a particular $250\mu m$ capillary.

persist even when the flow rate was decreased so that the flow became laminar again. A similar regression was observed when the nucleation-free flow caused by ethanol was stopped, the capillary dried out and then reinstalled. It would then revert to its nucleation behavior prior to ethanolization. Thus, once nucleation sites became active again or were exposed to air, the benefit caused by the ethanol would disappear. However, another ethanolization would reinstitute the nucleation-free effect. While the explanation for this remarkable effect may be tentative, it appears that, even underwater, the ethanol preferentially wets the solid surface and dislodges the tiny gas bubbles (nuclei) in the crevices which constitute the nucleation sites. Clearly this is a consequence of ethanol preferentially wetting the solid surface. In addition, the solubility of all gases in ethanol is much greater than in water so the ethanol may also be eliminating nucleation sites by dissolving the gas.

**3. High Speed Video Observations**

A high-speed video camera was used to take $8000 fps$ videos of the bubbles in the flow. Figure 1 presents 4 examples of frames showing bubbles passing through the distal end of a $250\mu m$ silica capillary with a $3.45 MPa\ O_2$ solution flowing at $3.4 m/s$. The distal end of the capillary is on the left and the bubbles appear as black shadows through the transparent capillary wall. The two upper frames show smaller bubbles, one of which is of the $2.5d$ variety. The last frame shows one of the $10d$ bubbles discussed below. Analysis of the high speed videos revealed rather distinctive bubble production patterns best illustrated by the example of the $250\mu m$ capillaries. The largest number of bubbles were in a range between $0.2d$ (where $d$ is the tube I.D.) and about $1.6d$. Few bubbles smaller than $0.2d$ were observed, probably because smaller bubbles remain attached to the nucleation site until they have grown large enough for the drag to overcome the surface tension forces. In addition, the distribution contains several very distinctive peaks at larger sizes. At a speed of $3.4 m/s$, for example, almost all the larger bubbles had a size of either $2.5d$ or of $10d$. Creech *et al.* (2002) show that the $10d$ peak is consistent with the size and bubble production frequency of the most upstream nucleation site. When that site releases a bubble it grows by collection of gas from the other $10 - 15$ sites and thus achieves the $10d$ size by the time it reaches the exit. This explanation is supported by the fact that a bubble-free zone was observed to occur behind each $10d$ bubble and the duration of this bubble-free zone was in agreement with the model. Moreover the change in the size distribution when the flow velocity was decreased from $3.4 m/s$ to $1.7 m/s$ was also consistent with the model.

All of the high speed video analyses indicate that the number of potential nucleation sites in the $250\mu m$ and $325\mu m$ capillaries is small, between 8 and 15. This small number may help explain the effectiveness of "ethanolization", for that process need only eliminate a small number of sites in order to be effective.

**4. Concluding Remarks**

The experiments described in this paper confirm a remarbable phenomenon in which highly-supersaturated aqueous solutions of gas may be injected through a small capillary into an aqueous environment without the formation of significant and/or measurable gas bubbles. This technique has considerable potential therapeutic value in many medical treatments and could also prove valuable in other technologies. By comparing the experiments with a theoretical model which treats (1) the potential formation and growth of bubbles at nucleation sites inside the capillary at its distal end (2) the detachment and ejection of such bubbles from the capillary and (3) potential growth of the bubbles in the emerging jet, it is shown that the laboratory observations are consistent with such a heterogeneous nucleation model. Of particular note is the estimate that, in the successful silica capillaries, the number of potential nucleation sites is of the order of ten.

It is also clear that the treatment of the interior surface of the capillary is critical to the success or failure of the objective since it can effectively eliminate those nucleation sites, though perhaps only when they are so small in number. One simple technique that was deployed in the laboratory was to flush the capillary with ethanol after it had already been filled with an aqueous medium. Apparently, the ethanol strips out or dissolves the nucleation sites and causes them to be non-functional. This is an entirely reversible procedure; allowing the capillary to dry out re-establishes functioning nucleation sites; and "ethanolization" will then eliminate them. A medical device coating which has a similar though less dramatic effect is benzalkonium heparin (BKH).

**5. References**


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