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# *Expansion of Gas Bubbles by Nitrous Oxide and Xenon*

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***Background:*** **Nitrous oxide is well known to expand gas bubbles trapped in enclosed spaces and is contraindicated in situations where this may occur. Xenon, an anesthetic gas with similar physical properties to nitrous oxide, is also likely to expand gas bubbles, and it has been predicted that microbubbles in the circulation may expand dramatically when exposed to xenon. Because of the possibility that xenon will be used during cardiopulmonary bypass surgery, a procedure that is likely to introduce microbubbles into the circulation, the authors reinvestigated the extent to which xenon expands gas bubbles in aqueous solution.**

***Methods:*** **Gas bubbles of either air or oxygen were formed in an aqueous solution, and their size was monitored using optical microscopy when they were exposed to a rapidly flowing solution of xenon, nitrous oxide, or a xenon–oxygen mixture.**

***Results:*** **Both nitrous oxide and xenon rapidly expanded air bubbles, although nitrous oxide caused a much larger expansion. The observed expansion was not greatly dependent on the initial size of the bubble but was significantly greater at lower temperatures. Under conditions relevant to cardiopulmonary bypass surgery (50% xenon–50% oxygen, 30°C), the increase in diameter was modest (9.7 ± 0.8%).**

***Conclusions:*** **Although xenon does expand small air and oxygen bubbles, the extent to which this occurs under clinically relevant conditions of concentration and temperature is modest.**

IT is well known that nitrous oxide should not be used as a general anesthetic in situations where enclosed gas spaces may be present, because such gas spaces are likely to expand, creating pathophysiologic disturbances. This can occur, for example, in patients who have intraocular gas bubbles after vitreoretinal surgery[1] or in patients who have trapped air bubbles after craniotomy[2] or epidural injections.[3] Gas bubble expansion is due to nitrous oxide's low potency (which results in high blood concentrations of nitrous oxide) and low blood/gas partition coefficient (and hence a high propensity for nitrous oxide to partition into the gas phase from the blood). Therefore, nitrous oxide will move into an air space faster than air moves out, and the bubble will expand.

The blood concentration of nitrous oxide is approximately 13 mM when 70% of an atmosphere is breathed and the gas/blood partition coefficient at 37° is 2.1.[4] The only other anesthetic with comparably unfavorable characteristics in this regard is xenon. When 70% xenon is breathed, the blood concentration is approximately 3.2 mM, and the gas/blood partition coefficient is 8.7.[5]

Because of a renewed interest in xenon as a general anesthetic,[6] the question as to whether it will also expand gas bubbles has been raised.[7] In particular, because xenon has been shown to have neuroprotective properties,[8–11] it has been proposed[10] that it might be useful during cardiopulmonary bypass (CPB) surgery to ameliorate the cognitive deficits that are known to occur.[12] However, cardiac surgical procedures, especially those requiring CPB, are capable of introducing microbubbles into the circulation[13]; therefore, an understanding of the extent to which xenon may expand these bubbles is of critical importance. Unfortunately, published estimates vary widely. At one extreme, a set of theoretical calculations predicts that a spherical 50-nl bubble of oxygen will expand indefinitely when exposed to 70% xenon–30% oxygen, with the volume increasing fivefold in approximately 20 min,[7] and then will continue to increase at an accelerated rate. At the other extreme, much smaller expansions are seen[14] after 10 min when relatively large (400 μl) gas bubbles are injected into animals exposed to xenon. A third study[15] observed an intermediate increase in volume when 10-μl bubbles of air were exposed to xenon in water over 3 min. We have directly determined the rate and extent of gas bubble expansion when air bubbles are exposed to xenon in aqueous solution and compared these to the situation with nitrous oxide.

## Materials and Methods

Gas solutions were prepared by bubbling pure gases (air, oxygen, nitrous oxide, or xenon) through fine sintered-glass bubblers in Dreschel bottles filled with water. During bubbling, the solutions were continuously stirred at room temperature (which could be set between 20° ± 0.2° and 30° ± 0.2°C). The solutions were bubbled at a rate of 30 ml/min for 20 min, and gas chromatography measurements showed that the gases would saturate a solution bubbled in this way within 10 min. Generally, two solutions saturated with gas at 1 atmosphere (atm) were used. The first, usually an air-saturated solution, was used to equilibrate the bubble, and the second (test) solution contained nitrous oxide or xenon, or a combination of xenon and oxygen. For example, if the xenon-saturated solution and the oxygen-saturated solutions were combined in the ratio of 1:1, this provided a xenon

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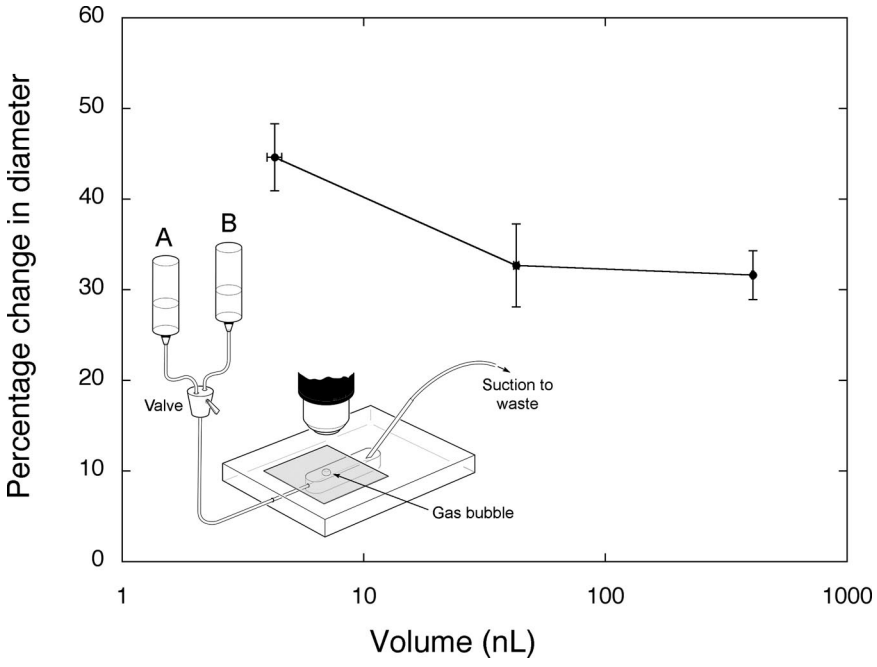


**Fig. 1. The percentage increases in the diameter of air bubbles of different sizes when exposed to an aqueous solution of xenon (1 atm) at 20°C. Each point is the mean of measurements on four different bubbles with sizes 4.3 ± 0.3, 42.8 ± 1.1, and 408 ± 5 nl. The *inset* shows a schematic diagram of the experimental setup. A gas bubble is trapped under a glass coverslip and exposed to a rapidly flowing solution while its size is monitored using a microscope and video camera (see Materials and Methods for more details). A valve allows solution A to be switched with solution B and *vice versa*.**

test solution with the equivalent of 50% atm xenon and 50% atm oxygen. Xenon (99.9%, research grade) was provided by Air Products (Basingstoke, United Kingdom), and nitrous oxide was obtained from BOC (Guildford, Surrey, United Kingdom).

A bubble of chosen size (between 4 and 400 nl), initially of air, was introduced into a narrow channel (3.8 by 1.5 mm in cross-section) attached beneath a glass coverslip (see inset to fig. 1) using an airtight syringe. A solution flowed through this channel at the rate of approximately 2 ml/min, providing rapid exchange (< 10 s) of the water surrounding the bubble. First, the bubble was equilibrated at a chosen temperature with the gas of choice (usually air), and the diameter of the bubble was measured over time using a microscope (Nikon Eclipse 80 microscope; Kingston upon Thames, Surrey, United Kingdom), digital video camera, and software (Micropublisher 3.3 RTV camera and QCapture Pro software; Burnaby, British Columbia, Canada). The bubble was then observed for approximately 15 min until its size stabilized. A second gas solution was then introduced into the chamber, and the change in bubble size was recorded over the next 25 min. Finally, the test solution was replaced with the initial solution until a final equilibrium was reached. Because most bubbles tended to reduce in size slowly, changes in bubble size were corrected for any slow changes in baseline by fitting the baseline segments before and after bubble expansion with a decaying exponential function and calculating the size changes with respect to this continuous baseline. Multiple measurements were made using, typically, four different bubbles for each experiment.

## Results

Because the discrepancies in the literature regarding expansion of bubbles by xenon might be due to different initial bubble volumes, we first investigated whether bubble expansion depended on this parameter. For convenience, these experiments were conducted using 100% xenon at 20°C. Figure 1 shows the results of these experiments that demonstrate that the percentage increase in diameter was roughly the same over two orders of magnitude in bubble volume (4–400 nl). We did notice, however, that all air bubbles tended to reduce in size over time, even when equilibrated with a solution saturated with air, and that, below a volume of approximately 0.5 nl, the bubble disappeared rapidly (< 20 min). For all subsequent experiments, we used bubbles with a volume of 40 nl, which is close to estimates based on *in vivo* measurements of bubble size in the microcirculation[16] and close to the volume used (50 nl) for the most extensive theoretical simulations that have been made.[7] We then investigated the effects of temperature and measured bubble expansion at 20° and 30°C. Figure 2 shows typical results for xenon. The percentage increase in diameter at 20°C was approximately 1.3 times larger than that observed at 30°C. The time course of bubble expansion was well fitted by a double exponential. The time constant for the initial rapid expansion was approximately 2 s, and although there was a tendency for the expansion to be faster at lower temperatures, this did not reach statistical significance. We next compared the extent of bubble expansion by 100% nitrous oxide, 100% xenon, and a 50:50 mixture of xenon and oxygen (fig. 3). The expansion due to nitrous oxide was mark-

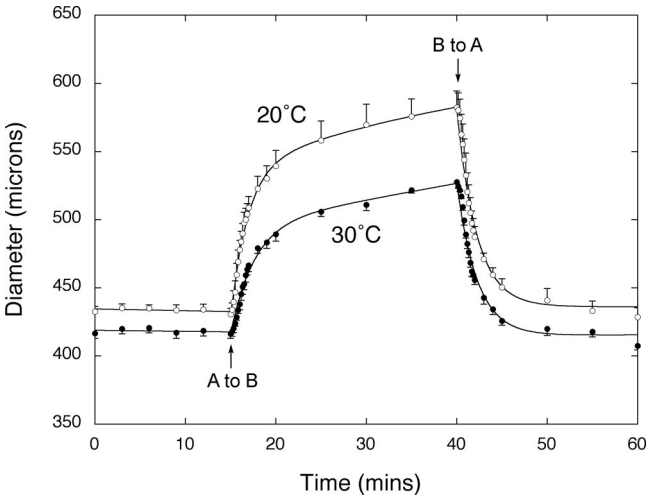


**Fig. 2. Bubble expansion is greater at lower temperatures. The expansion of air bubbles of about 40 nl when exposed to an aqueous solution of xenon (1 atm). Each *point* is the mean of four independent measurements. The *lines* during bubble expansion and contraction are biexponential fits to the data points. The *vertical arrows* indicate the solution changes.**

edly greater than that observed with xenon, and the expansion observed with 50% xenon–50% oxygen was approximately half that observed with 100% xenon. Finally, to mimic the situation that might pertain if xenon were to be used in CPB surgery, we measured the expansion of 40-nl air and oxygen bubbles when exposed to a mixture of 50% xenon and 50% oxygen at 30°C (fig. 4). The percentage increases in diameter were 9.7 ± 0.8 and 7.4 ± 0.3%, respectively, corresponding to percentage increases in volume of 32 ± 3 and 29 ± 1%, respectively.

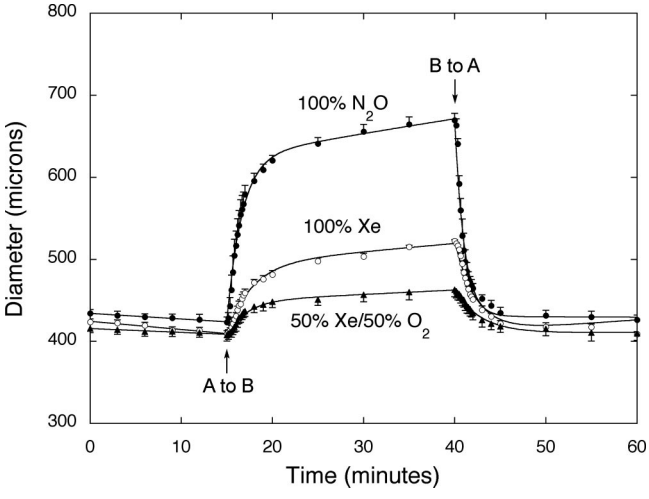


**Fig. 3. A comparison between the expansions observed with different gases. The data are for air bubbles of approximately 40 nl, exposed to nitrous oxide (1 atm), xenon (1 atm), and a 50:50 xenon–oxygen mixture at 30°C. The *vertical arrows* indicate the solution changes.**

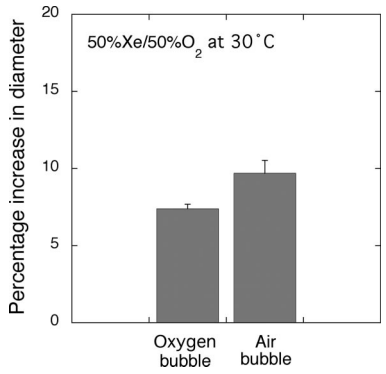


**Fig. 4. The expansion of air bubbles and oxygen bubbles (approximately 40 nl in volume) exposed to a solution containing a 50:50 xenon–oxygen mixture at 30°C, conditions relevant to the use of xenon during cardiopulmonary bypass surgery.**

## Discussion

This work was motivated by a concern that, if xenon were to be used in cardiac surgical procedures requiring CPB to ameliorate the cognitive deficit that this surgery can cause,[12] it might do more harm than good if any microbubbles that were introduced during the procedure expanded to a pathologic extent. It has been predicted that a dramatic expansion will occur, with bubbles of 50 nl increasing to an unlimited size.[7] The rate at which gas bubbles will expand (or contract) when they are surrounded with an aqueous solution containing another gas is dependent on a number of variables. The most important of these are the concentration of the gas in solution, the rate the gas solution is presented to the bubble, the relative gas/water partition coefficients of the two gases, and their relative diffusion coefficients in solution. In addition to these critical variables, the rate will also depend on temperature, viscosity, surface tension, and any other additional pressures on the bubble, such as tissue elasticity and hydrostatic pressure, as well as a number of even more minor factors. Although some of these parameters are known or can be estimated with reasonable certainty, others are much less certain and can only be approximated. Consequently, we wished to directly determine bubble expansion in aqueous solution under well-defined conditions where bubbles were exposed to high rates of solution exchange that would maximize any bubble growth. We found, consistent with previous workers, that 100% nitrous oxide expanded air bubbles to a far greater extent than xenon and that expansion was greater at lower temperatures.[15] In both cases, we surmise that this is due to the increased concentration of gas in solution and the consequently greater rate of diffusion of the xenon or nitrous oxide into the air bubble. Under conditions that are likely to be encountered clinically during CPB (50% xenon–50% oxygen, 30°C), the expansions of air and oxygen bubbles were modest, with the diameters changing by less than 10%.

There are two limitations to our study that are worth addressing. First, we studied gas bubbles formed in wa-

ter rather than blood. We made this choice because of the impracticality of passing fine gas bubbles through blood, which causes frothing and protein denaturation. However, we believe that using water rather than blood made no material difference to the study. Although it is true that gas bubbles might be slightly more likely to form in the first place (because of the lower surface tension of blood compared to water), there is little reason to suppose that their expansion by xenon or nitrous oxide would be greatly affected. Second, we studied bubble expansion for a limited time (25 min), and bubbles might be present for longer periods under clinically relevant circumstances. Nonetheless, it is clear from our data that the major expansion occurs rapidly and subsequent expansion is relatively slow (figs. 2 and 3).

Our results are comparable to the expansions found with much larger air bubbles in water[15] or injected into animals[14] when exposed to xenon, and very much smaller than the expansions predicted from theoretical simulations.[7] The possibility that the experimental results and those of theoretical calculations are due to differences in initial bubble size can now be excluded on the basis of our measurements, which were from bubbles ranging from 4 to 400 nl, and cover the range investigated theoretically.

Therefore, although xenon will expand bubbles in the circulation or any trapped air spaces, this effect (< 10% increase in diameter) is relatively small and certainly considerably smaller than that found with nitrous oxide. Moreover, a recent study concluded that the presence of xenon in the ventilatory gases had no effect on the likelihood of bubble formation.[17] Nonetheless, if air bubbles are present and exposed to xenon, they will definitely expand, but whether these expansions would present a clinically significant problem is difficult to determine. For very small microbubbles that might easily pass through blood capillaries, it seems that a change in diameter would be the most relevant parameter and the changes we have observed are small. However, for bubbles that occlude a capillary, the volume increase might be the more relevant parameter, although again, the changes we observe at clinically relevant gas compositions are not large (approximately 30%).

In the past, nitrous oxide has been extensively used in patients undergoing cardiac surgery but seems to have been discontinued because of the adverse effects that it exerts on myocardial performance in patients after CPB[18] rather than an adverse effect on neurologic outcome through putative cerebral air bubble expansion; in fact, no adverse neurologic consequence was observed in the only trial that directly sought this effect in patients who were randomly assigned to receive either nitrous oxide (50% in oxygen) or oxygen during CPB.[19] Although nitrous oxide is not currently advocated for use in the peri-CPB period, this proscription probably has more to do with its adverse effect on myocardial performance[17] than on putative neurocognitive dysfunction that may follow expansion of cerebral air bubbles,[18] although the possibility of gas bubble expansion is nonetheless perceived as a potential problem.[19,20] When considering the use of xenon in lieu of nitrous oxide in patients on CPB, not only is bubble expansion likely to be considerably smaller, but its beneficial neuroprotective properties[9–11] might outweigh any possible adverse cerebral effects, especially if xenon is administered under hypothermic conditions.[19] Furthermore, unlike nitrous oxide, xenon has a salubrious effect in patients with poor myocardial performance.[20]

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