Isobaric inert gas supersaturation: observations, theory, and predictions

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Collins, Jerry M. Isobaric inert gas supersaturation: observations, theory, and predictions. J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 44(6): 914-917, 1978.—An isobaric inert gas supersaturation model incorporating both diffusion and perfusion properties of biological tissue is presented in a form which allows ready comparison with experimental observations. This model requires only measurement of inert gas flux and blood gas solubility in order to evaluate "counterdiffusion potential." Inert gas flux across the skin of Yorkshire piglets anesthetized with pentobarbital was measured for He, Ne, CH₄, C₂H₆, N₂O, and SF₆. Model predictions based upon these data compare favorably with published reports of isobaric inert gas supersaturation, as well as several previously unpublished observations. The possibility of supersaturation resulting from the use of hydrogen as a breathing gas in a helium environment is also discussed, and extensive animal testing is recommended before potentially dangerous human exposure occurs.

METHODS
Experimental determination of transcutaneous inert gas flux. Female Yorkshire piglets (4-17 kg) were used for all experiments. Anesthesia was induced (40 mg/kg) and maintained (5-10 mg·kg⁻¹·hr⁻¹) with pentobarbital sodium. Blood pressure and pulse rate were monitored via a catheter in the right carotid artery, and intravenous fluids given as needed. Tracheostomy was performed, and d-tubocurarine was used in conjunction with volume-controlled ventilation (Harvard Respirator). Minute volume was adjusted to keep end-tidal carbon dioxide at about 5% (Beckman Lira infrared analyzer). Rectal temperature was controlled to 37 ± 0.3°C using a hot water blanket. All animals were killed with a rapid intravenous injection of 20 ml of saturated KCl solution.

The lower abdomen (midline region) was chosen as the site for the collection cup (borosilicate glass cylinder of volume 430 ml, skin contact area 42 cm²). Most animals had little hair in this region, and only a few required light shaving. The cup was sealed to the skin with alphacyanoacrylate glue (Permabond). Two temperature probes penetrated the top of the cup; one measured the gas temperature inside the cup, and the other was glued (<1 cm² surface area) to the skin before the cup was sealed. The skin temperature was controlled to the desired value by adjusting the temperature of the gas inside the cup. Temperature control was effected by circulating hot water (in a few cases, cold water) through a copper coil wound around the exterior surface of the cup. As soon as the cup was sealed in place, pure nitrogen was flushed (0.5 l/min for 20 min) through two sampling ports which were located on the cup wall 180° apart but at different heights from the base. At the end of this flush less than 0.1% oxygen remained. Large increases in the cup oxygen percentage in an isolated sample were a clear sign of contamination, and the sample was rejected. Continuous increase in cup oxygen percentage was a sign of a leaky seal.
and the experiment was deleted from this series.

When the cup flush was complete, the ports were sealed with two 20-ml glass syringes. These syringes were used to isobarically and isovolumetrically mix the gas inside the cup. The experimental period was begun by switching the pig's breathing gas from 28% oxygen in nitrogen to 28% oxygen in a mixture of the inert gases to be studied. A three-way, gas-tight Hamilton stopcock was interposed between one of the ports and its glass syringe. Either a 100-μl or a 1.0-ml gas-tight sampling syringe (Precision Sampling) was attached to the third orifice of the stopcock, and a sample of well mixed cup gas was obtained from the gas in the glass syringe with care taken to flush the dead space in the stopcock. Samples were taken at intervals of from 15 min to 1 h, depending upon the length of the experiment (4-13 h) and the complexity of the gas analysis (4-8 components).

Gas chromatography was used to analyze all samples. Ne, N₂, O₂, SF₆, CO₂, O₃, and N₂ were analyzed using helium carrier gas and a thermal conductivity detector (Varian) with a sensitivity of at least 100 ppm. Helium (sensitivity of 100 ppm), oxygen (0.1%), and nitrogen (0.1%) were determined using argon carrier gas and a thermal conductivity detector (Carle). Methane and ethylene were determined using a flame ionization detector (Carle).

After the cup was sealed, a continuous accumulation of gases from the breathing mixture was seen and a least-squares fit of the fractional composition of gas in the cup vs. time data was obtained. A minimum of five data points was utilized, and only data with a correlation coefficient \( r > 0.99 \) were accepted (\( r > 0.97 \) for SF, oxygen, and nitrogen data). The measured flux was directly proportional to the slope of the least-squares line

\[
q = \text{slope (fraction/h) } \times \text{ cup volume (ml)} \tag{1}
\]

These flux values were standardized to body temperature (37°C). Since the partial pressure of gas in the cup was always very small compared to the arterial partial pressure, specific fluxes (obtained by normalizing the measured fluxes by the partial-pressure driving force and skin transfer area) were calculated as

\[
F = \frac{q}{Pa (\text{ATA})/\text{cup surface area (m}^2\text{)}} \tag{2}
\]

Arterial partial pressure, \( Pa \), was calculated from the known inspired gas partial pressure, with correction for humidification and \( O_2-CO_2 \) exchange in the lung.

Analysis. As presented by Hills (9), the steady-state flux of an inert gas across the skin (or other biological tissue) is

\[
q = \dot{Q}S\Delta p \tag{3}
\]

where \( q \) is the gas flux (ml/h), \( \dot{Q} \) is the blood flow (ml/h), \( S \) is the blood gas solubility (ml gas/ml blood \( \cdot \text{ATA}^{-1} \)), and \( \Delta p \) is the partial-pressure driving force (ATA). This equation can be rearranged to give pressure drop explicitly

\[
\Delta p = q/(\dot{Q}S) \tag{4}
\]

Supersaturation can occur in the blood only if the partial-pressure change of the inwardly diffusing gas is greater than outwardly diffusing gas (in absolute value)

\[
\Delta p_{\text{in}} > \Delta p_{\text{out}} \tag{5}
\]

The magnitude of this difference must exceed venous subsaturation, plus any nucleation pressure threshold. Substitution of the right side of Eq. 4 into Eq. 5 yields

\[
\frac{q_{\text{in}}}{(\dot{Q}S_{\text{in}})} > \frac{q_{\text{out}}}{(\dot{Q}S_{\text{out}})} \tag{6}
\]

or

\[
\frac{q_{\text{in}}}{S_{\text{in}}} > \frac{q_{\text{out}}}{S_{\text{out}}} \tag{7}
\]

Either theoretical expressions for inert gas transfer or experimental data may be substituted for \( q \) in Eq. 7. For a simple film model, Hills has shown (9), for equal gas solubility in film or blood phases, that Eq. 7 reduces to

\[
D_{\text{in}} > D_{\text{out}} \tag{8}
\]

where \( D \) is the diffusivity of the inert gas in the film layer.

Quinn (17) has presented a more detailed model for \( q \) through skin, but sufficient experimental data has not been generated to evaluate this model.

Our focus in this paper is on the application of experimental data for \( q \). To evaluate the likelihood of a specific gas combination generating supersaturation, all that is needed is a knowledge of the blood gas solubility and inert gas flux. Our measurements of inert gas flux have been normalized by the partial-pressure driving force and skin surface area to yield the specific flux, \( F \). Substitution of \( F \) (for \( q \)) into Eq. 7 gives

\[
\frac{(F/S)_{\text{in}}}{(F/S)_{\text{out}}} > 1 \tag{9}
\]

We refer to this ratio of specific flux to blood gas solubility \((F/S)\) as the counterdiffusion potential. This quantity further normalized with respect to helium as a reference is the relative counterdiffusion potential, or RCP (both quantities are presented in Table 1). If a gas with a high RCP is the environmental gas, while a low RCP gas is breathed, then supersaturation may develop. Viewing the situation in terms of Eq. 5, the partial-pressure driving force (from the gas entering the blood) is greater than the partial-pressure driving force (from the breathing gas).

| Table 1. Counterdiffusion potential, \( F/S \), and relative counterdiffusion potential, RCP |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Gas             | \( F \) (mol h\(^{-1}\) m\(^{-2}\) ATA\(^{-1}\)) | \( S \) (mol ml/gal ATA\(^{-1}\)) | \( F/S \) (mol ml/gal ATA\(^{-1}\)) | RCP |
| Ne              | 49.2            | 0.0088 (14)     | 5.591           | 100            |
| O₂             | 32.8            | 0.0100 (12)     | 3.280           | 59             |
| CH₄            | 24.3            | 0.0380 (14)     | 1.142           | 20             |
| N₂O           | 285             | 0.47 (13)       | 606             | 11             |
| C₂H₆          | 43.7            | 0.14 (13)       | 312             | 6              |
| SF₆            | 1.45            | 0.0079 (15)     | 193             | 3              |

\( F \) values measured for in vivo transcutaneous flux across pig skin (skin temperature, 34°C, except for SF₆, 41°C). Reference numbers for blood gas solubilities are in parentheses. Neon blood gas solubility not available, water gas solubility used.
DISCUSSION

The advantages of a model for isobaric inert gas counterdiffusion supersaturation which incorporates perfusion are both conceptual and operational. As Hills (9) has suggested, there are certain counterdiffusion supersaturation situations in which it is difficult to visualize two layers (e.g., the ear). In other situations (e.g., skin lesions), the two-layer model's arrangement of a lipid layer in contact with nitrogen and an aqueous layer in contact with helium is contrary to the perceived anatomic arrangement. The operational advantage of the model formulation presented in the previous section is basically the ability to explain known behavior and predict untried combinations on the basis of information now known: inert gas flux rates and blood gas solubility. The identity (or thickness or permeability) of the layer or layers is not required.

Any combination of inert gases could be expected to yield supersaturation, if the total environmental pressure is large enough. The only restriction is that the gas which is breathed must have the lower F/S. Since this model development considers only the steady-state situation, no prediction can be made concerning the time necessary for supersaturation signs (e.g., lesions or embolism) to develop.

The ranking of gases in Table 1, together with 6 yr of accumulated observations of supersaturation phenomena, suggests that the greater the difference in RCP, the lower the environmental pressure required for manifestation of supersaturation. N,O and He have the greatest RCP difference, and symptoms are readily observed at 1 ATA (10). Ne and He have the smallest RCP difference of any combination for which supersaturation has been observed, and requires very high environmental pressure for supersaturation manifestation (11). This difference is even smaller when it is realized that the crude neon with which supersaturation was observed had 25% helium contamination. Since the combination of N., and He requires moderate pressure for supersaturation signs to develop, our model suggests that it would have a RCP intermediate between Ne and N,O. Finally, the model predicts that supersaturation cannot occur whenever the gas with higher RCP is breathed. In agreement with this prediction, no such observations have been reported, and we are familiar with no unpublished observations to the contrary.

After this theory had been developed and successfully compared to accumulated supersaturation observations, the next step was to test the model in a prospective sense. Since all previous demonstrations of supersaturation required nearly pure helium as the environmental gas, neon (25% helium contamination) was chosen as the environmental gas, since its RCP was next highest after helium. When a pig's hind limbs were surrounded by neon (flushed through a plastic bag), supersaturation signs (skin lesions and erythema and blood gas embolism) were observed in the neon-exposed areas during nitrous oxide breathing.

The possible future role of hydrogen as a diving gas (replacing helium) warrants a consideration of the counterdiffusion supersaturation potential for this gas. There is no measurement of the transcutaneous flux of hydrogen reported in the literature (and we chose not to study this gas for safety reasons), so only estimates can be made. Hydrogen has a slightly lower diffusivity than helium (8), and probably has a RCP between neon and helium. Piiper, Canfield, and Rahn (16) report flux data for both helium and hydrogen in rat subcutaneous tissue, and we estimate a RCP for H2 of 76, based upon He = 100. There are, of course, many differences between cutaneous and subcutaneous tissue. In most cases, it would seem appropriate (and slightly conservative) to expect the same counterdiffusion supersaturation behavior from environmental hydrogen as helium. An important difference ensues for hydrogen as a breathing gas. Our estimates suggest that breathing hydrogen in a high pressure helium environment may be as dangerous as breathing neon.

A recent report (5) on the HYDROX II experiments describes some pulmonary function tests which were designed to help assess the feasibility of hydrogen as a diving gas. These tests are ominously similar to those which led to the most severe human manifestations of isobaric inert gas supersaturation to date (1, 11). In a chamber pressurized with air to 7 ATA, the subjects breathed 97% H2 by mask. Although this particular combination should present no counterdiffusion dangers, the need can be anticipated to use a helium-filled chamber if testing is to be done at greater pressures, in order to avoid nitrogen narcosis. Since we consider that the combination of breathing H2 in a He chamber is likely to generate supersaturation signs, it would seem highly appropriate that any human exposure be preceded by extensive animal testing.

The final point of discussion concerns the scope of inert gas supersaturation. All documented cases to date have been related to pressurized chamber diving (except for pigs breathing N,O in a helium environment (10) or neon environment, as discussed above), although speculations have been raised concerning membrane oxygenators (18) and anesthesia (6, 9). While we recognize the need for vigilance in order to avoid episodes similar to the original human manifestations, it seems unlikely that nondiving manifestations of inert gas supersaturation in biological systems will be uncovered.

Anesthetic-related supersaturation can only occur with gases used in high inspired fractions, almost exclusively N2O. We have failed to observe supersaturation signs in pigs breathing 90% N,O in a chamber pressurized with 2 ATA of N2, so it seems unlikely that anesthetic situations will cause supersaturation signs.

In one artificially created situation, we were able to elicit counterdiffusion signs outside the context of diving. We have observed blood gas embolism in two pigs breathing N2O while the peritoneal cavity was flushed with helium. This counterdiffusion situation was similar to that encountered in laparoscopy, except that helium has not been used as a flushing gas, nor is there any basis for its selection in place of air, CO2, or N2O, which are most commonly used.

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