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Potential Errors in the Measurement of Anesthetic Partial Pressure in Blood

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ALTHOUGH it is easy to measure anesthetic partial pressures in gas mixtures, it is not straightforward in blood. A single-step technique has been described,[1] but more commonly the sample is equilibrated in a water bath with a similar amount of air, and the partial pressure of the anesthetic in the gas phase is measured. The equilibration reduces the partial pressure of anesthetic in the blood, but the initial value can be calculated if the solubility of the anesthetic is known. The solubility can be determined by flushing the headspace with air and repeating the equilibration. The first descriptions of the method performed the equilibrations at constant pressure in glass syringes,[2,3] but others have used glass vials, which provide a constant volume.[4,5] The samples of equilibrated gas are analyzed at ambient pressure, preserving the anesthetic concentration but reducing the partial pressure if the vial has been pressurized by heat and humidification. An appropriate pressure correction factor can be calculated, but if the blood sample is deoxygenated, then the pressure within the vial will be reduced by oxygen uptake, and the calculated correction factor will be too large. Conversely, nitrous oxide can transfer into the gas phase and increase the pressure; therefore, the correction factor will be too small unless nitrous oxide is absent or measured and included in the

factor. We report a simple way to prepare vials so that blood is oxygenated during equilibration, the vials are sampled at ambient pressure, and no correction factor is needed.

Materials and Methods

Vials of 2 ml nominal volume (1.95 ml by water displacement) are used with silicone, Teflon-faced septa (Phase Separations Ltd., Deeside, United Kingdom) in their caps. They are prepared shortly before sampling by first flushing with oxygen and then partially evacuating them to a pressure of approximately 150 mmHg using a needle and syringe. This provides sufficient oxygen to saturate any sample, but the pressure within the vial will remain subatmospheric even after warming, humidification, or movement of nitrous oxide. Exactly 1 ml blood is injected through the septum, and the vial is placed in a motorized roller in a water bath at 37°C. After 30 min, the vial contents are brought to atmospheric pressure by penetrating the septum with a hollow needle and entraining air. This reduces the concentration of anesthetic in the headspace, but its partial pressure is unaffected and remains in equilibrium with the blood. The vial is rotated in the water bath for another minute to disrupt bubbles in the headspace, and then the headspace is sampled and analyzed in a gas chromatograph. A portion (0.5 ml) of the blood is transferred to a second prepared vial that is then processed in the same way. We calculate the blood gas coefficient ($\lambda_{B:G}$) for each anesthetic from the second vial equilibration using a relationship derived from conservation of mass during equilibration:

$$P_1 \cdot \lambda_{B:G} \cdot V_{blood} = P_2 \cdot \lambda_{B:G} \cdot V_{blood} + P_2 \cdot$$
$$(V_{vial} - V_{blood}) \quad (1)$$

where P_1 and P_2 are, respectively, the partial pressure of the anesthetic in blood before and after the equilibration (these are assumed to be equal to the partial pressures in the corresponding headspace sample and are derived

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Table 1. The Composition of the Tonometers after Equilibration

Hb (g/dl)	Saturation (%)	DeO$_2$ Hb (g/dl)	Tonometer (%)			Measured by Old Method (* if N$_2$O unknown)						Measured by New Method			
			N$_2$O	des	iso	n	N$_2$O	des	*	iso	*	n	N$_2$O	des	iso
13.8	100	0	44.4	1.71	0.96	3	46.0	1.77	(1.44)	0.97	(0.80)	4	41.6	1.63	0.89
14.2	100	0	14.0	1.26	1.04	5	14.1	1.25	(1.17)	1.00	(0.94)	5	13.3	1.21	0.96
14.1	100	0	21.9	1.82	0.98	5	23.1	1.91	(1.72)	1.01	(0.92)	5	20.6	1.75	0.92
14.7	6	13.8	6.1	0.69	—	5	7.5	0.82	(0.79)	—	—	4	6.3	0.69	—
12.7	21	9.5	7.0	1.32	0.41	6	8.0	1.49	(1.44)	0.44	(0.43)	4	6.9	1.26	0.38
13.9	3	13.1	43.2	1.23	0.83	3	53.4	1.52	(1.21)	0.99	(0.81)	3	40.9	1.17	0.76
10.7	7	10.0	7.4	0.86	—	5	9.0	1.05	(1.00)	—	—	5	7.3	0.85	—

Hb = hemoglobin; DeO$_2$ Hb = deoxygenated hemoglobin; des = desflurane; iso = isoflurane.

The columns marked * show the anesthetic partial pressure that would have been calculated using the old method had nitrous oxide not been measured (the new method does not use nitrous oxide results in its calculations of volatile anesthetic concentrations). Mean values are shown; the SD of the measurements for the tonometer, the old and the new methods, was in every case less than 2%, 5%, or 7%, respectively, of the measured value.

from the areas of the peaks on the chromatogram without recourse to correction factors), V_{blood} is the volume of blood in the vial, and V_{vial} is the vial volume. The partial pressure of each anesthetic in the original sample is determined by using $\lambda_{B:G}$ in the same equation applied to the first vial equilibration.

The method differs from our previous description[5] in three respects: vial preparation, pressure equalization of the headspace after equilibration, and absence of a correction factor. Other methods could be modified similarly. We have tested the new method using blood equilibrated in a tonometer. With the approval of the chairman of the local ethics committee and verbal consent of volunteers and patients, blood samples were drawn, heparinized, and placed in a tonometer flask of nominal volume (250 ml). The air above the blood was flushed with nitrogen or oxygen, up to 50% nitrous oxide, and approximately 1% desflurane and 0.5% isoflurane. The tonometer flask was then sealed with a Teflon-faced silicone septum and rolled in a water bath at 37°C for several hours. Pressure equalization during equilibration was performed meticulously. Three samples of the gas phase were analyzed, and then blood samples were drawn and processed alternately by either the new method or our previous method.[5] All gas samples were processed the same way, with details of the gas chromatograph method being incidental to the methods' principles. Gas samples (20 μl) were injected into a gas chromatograph (Hewlett-Packard 6890; Hewlett-Packard Chemical Analysis Group, United Kingdom) fitted with two columns of different retentive characteristics. An automated switching system allowed the volatile anesthetics to traverse only the less retentive column, keeping the run time short (2.4 min), while the gases traversed both columns, allowing separation of nitrous

oxide from oxygen.[6] Because many gas chromatographs cannot measure volatile and gaseous anesthetics simultaneously, we calculated the old method a second time, ignoring the nitrous oxide results.

Results

Nine tonometers were prepared with different samples of blood (table 1). Completely desaturated blood did not affect the results of the new method but caused the old method to overestimate anesthetic concentrations by 20% (fig. 1). If nitrous oxide was not included in the old method's calculations, volatile anesthetic concentrations were underestimated by up to 20% (fig. 2).

Discussion

We have drawn a known volume of a gas sample from the headspace of a closed vial and injected it into a gas chromatograph at atmospheric pressure. The area under each peak of the chromatogram correlates with the amount of anesthetic present, which can be related to a concentration in the injected sample, but the partial pressure of anesthetic in the headspace depends on the total pressure within the vial. When there is no gas exchange between the sample and the headspace, the pressure increase within the vial can be calculated from basic physical principles. However, because a 1-ml sample could take up as much as 0.2 ml oxygen or liberate a greater amount of nitrous oxide, there is no longer a simple way to calculate or measure the pressure within the vial, and consequently no way of knowing the correction factor to apply. A very deoxygenated sample could take up enough oxygen to make the pressure
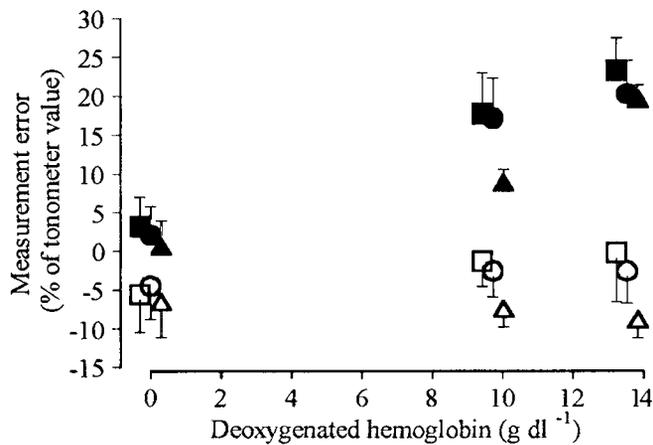
Fig. 1. The effect of deoxygenated hemoglobin on the error in measurement of blood partial pressure of nitrous oxide (*closed squares*), desflurane (*closed circles*), and isoflurane (*closed triangles*) when using the standard vials, expressed as a percentage of the tonometer value. The errors when using the evacuated vials are shown (*open symbols*). The results for nitrous oxide are offset slightly to the left, and for isoflurane to the right, for clarity. The error bars indicate the SD. The results from more than one tonometer are pooled, but the range of the deoxygenated hemoglobin was no more than 0.7 g/dl in each case.

within the vial subatmospheric, but with a fully saturated sample, the pressure within the vial could be greater than atmospheric because of warming, humidification, or movement of nitrous oxide. In the latter case, it would not be appropriate to puncture the septum and allow pressure equalization because anesthetic would be lost from the vial, giving falsely low results. These considerations apply to any method using vial headspace analysis.

When 1 ml blood is injected into one of the prepared vials, the displacement causes the total pressure within the headspace to increase to approximately 300 mmHg. This represents approximately 0.4 ml oxygen at standard temperature and pressure, of which up to 0.2 ml could be absorbed into the sample before the partial pressure reduced to a level associated with continued desaturation. Because only artificially desaturated and polycythemic blood will absorb more oxygen than this, the sample will be fully oxygenated after the first equilibration and could, in fact, be handled conventionally for the second equilibration. On the other hand, 1 ml blood cannot carry > 0.5 ml nitrous oxide; therefore, even if no oxygen were absorbed into the blood, the pressure within the vial would remain less than atmospheric. Thus, the pressure can be brought to a known amount (atmospheric) without loss of anesthetic from the vial by entraining air through a needle, reducing the concentra-

tion but not the partial pressure of anesthetic within the vial.

Our results imply that measurements of anesthetic tensions in jugular bulb blood could be overestimated by almost 15%. This would be an important error in Kety-Schmidt's method of measuring cerebral blood, because it is based on differences between arterial and venous blood contents of nitrous oxide. The problem is conventionally overcome by injecting a small blood sample into a relatively large vial (10 ml).[7,8] The changes in pressure are then negligible, but the solubility coefficient cannot be measured because insufficient nitrous oxide remains in the blood to repeat the equilibration. Nitrous oxide causes the partial pressure of a volatile anesthetic to be underestimated, and it will have more effect than hypoxia in clinical samples. Its effect may explain the apparent magnitude of the end-expired to arterial anesthetic gradient without invoking intraalveolar inhomogeneity.[4]

Finally, the increasing errors in isoflurane measurement in more desaturated samples is an unexpected result that may be a chance event, but could be explained if the solubility of isoflurane is decreased by approximately 5% in fully desaturated blood. The left-hand side of equation 1 correctly determines the content of isoflurane in desaturated blood, but the use of $\lambda_{B\text{-}G}$
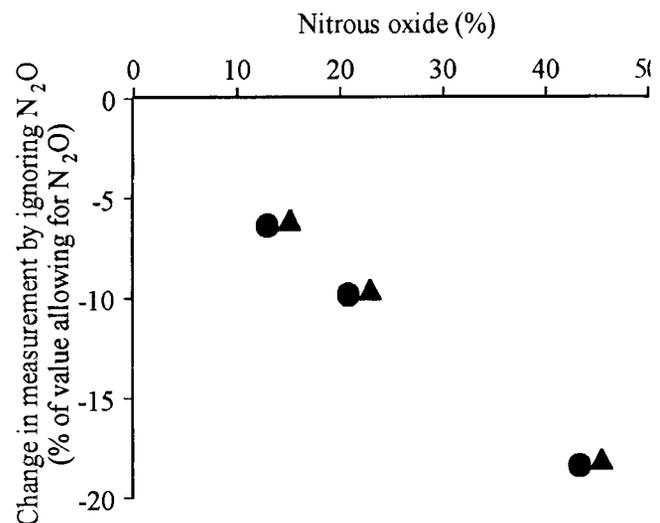

Fig. 2. The effect of excluding nitrous oxide from the correction factor used in the calculation of blood partial pressure of desflurane (*circles*) and isoflurane (*triangles*) when using the standard vials. The errors introduced to the results from the three fully oxygenated tonometers are expressed as a percentage of the value calculated with nitrous oxide in the correction factor. The results for desflurane are offset slightly to the left, and for isoflurane to the right, for clarity. The SDs of the errors are less than the size of the symbols.

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derived from the second equilibration, when the blood has been reoxygenated, would then underestimate the partial pressure in the original, deoxygenated sample.

In summary, we have demonstrated that some methods of measuring anesthetic partial pressures in blood give erroneous results with desaturated blood or in the presence of nitrous oxide, and we offer a simple, cost-free solution.

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