The alveolar gas equation

Steven Cruickshank BA MB BS FRCA
Nicola Hirschauer MD(Munich) FRCA

Steven Cruickshank BA MB BS FRCA

Consultant Anaesthetist
Department of Anaesthesia
Newcastle General Hospital
Newcastle upon Tyne
NE4 6BE
Tel: 0191 256 3198
Fax: 0191 256 3154
E-mail: stevencruickshank@hotmail.com
(for correspondence)

Nicola Hirschauer MD(Munich) FRCA

Specialist Registrar
Department of Anaesthesia
Newcastle General Hospital
Newcastle upon Tyne

The alveolar gas equation (AGE) is well known and relates the alveolar concentration of oxygen $F_A O_2$ (or equivalently partial pressure $P_A O_2$) to three variables: $F_I O_2$, $F_A CO_2$ and the respiratory quotient (R). However, the AGE predicts an absurdity: if we input a $F_I O_2$ sufficiently low, say 0.05 (*i.e.* a $P_I O_2$ of about 5 kPa), into the equation

$$F_A O_2 = F_I O_2 - \frac{F_A CO_2}{R}$$

then for typical values of $F_A CO_2 = 0.05$ and $R = 0.8$, a negative value for $F_A O_2$ is predicted. Therefore, it is plain that the AGE is not true for all conditions. Where does the AGE come from, and will the derivation explain the problem and define the conditions under which it is true?

Derivation of the AGE

Carbon dioxide

The metabolic minute production of carbon dioxide ($\dot{V}CO_2$) is approximately 200 ml (0.20 litre min^{-1}) in a resting adult. We will assume this value is constant. Under steady-state conditions where the $P_a CO_2$ is unchanging with time, this amount must be removed by alveolar ventilation each minute. The alveolar membrane is thin and carbon dioxide is highly diffusible and we may therefore assume that $P_A CO_2 = P_a CO_2$ to a close approximation (*i.e.* that there is a negligible $P CO_2$ gradient between blood and alveolar space).

Partial pressures

The concentration of a component gas in a mixture of gases is related to the partial pressure by Dalton's law of partial pressures. This states that an individual gas such as carbon dioxide in the mixture of gases in the alveolar space will be present in a concentration (or fraction) that is the same proportion as $P_A CO_2$ is of the total pressure (*i.e.* approximately P_I at the end of inspiration). For typical values of $P_I = 100$ kPa and $P_a CO_2 = P_A CO_2 = 5$ kPa, we have $F_A CO_2 = 0.05$ or 5%. The quantity of carbon dioxide removed from the alveolar

space in 1 min is simply the alveolar ventilation ($\dot{V}_A$) multiplied by $F_A CO_2$. Since, for steady-state conditions, this must be the same as $\dot{V}CO_2$, we have

$$\dot{V}CO_2 = F_A CO_2 \times \dot{V}_A$$

$$\dot{V}CO_2 = \frac{P_A CO_2}{P_I} \times \dot{V}_A$$

Rearranging and using our assumption that $P_A CO_2 = P_a CO_2$, we obtain the following (Fig. 1):

$$P_A CO_2 = \frac{\dot{V}CO_2 \times P_I}{\dot{V}_A} = P_a CO_2$$

Oxygen

The input of oxygen into the alveolar space, and the output from it, must, in steady-state conditions, be equal.

Input is by alveolar ventilation and using the same arguments as for carbon dioxide:

$$\text{Input} = \dot{V}_A \times F_I O_2$$

Output, on the other hand, is in two directions:

(i) across the alveolar membrane into the blood – in steady-state conditions, the oxygen consumption $\dot{V}O_2$; and
(ii) in the expired gas ($\dot{V}_A \times F_A O_2$):

$$\text{Output} = \dot{V}O_2 + \dot{V}_A \times F_A O_2$$

So, for steady-state conditions, we can write

$$\text{Input} = \text{Output}$$

$$\dot{V}_A \times F_I O_2 = \dot{V}O_2 + \dot{V}_A \times F_A O_2$$

which rearranges as

$$\dot{V}O_2 = \dot{V}_A \times [F_I O_2 - F_A O_2]$$

We are now ready to complete the derivation by noting that

$$R = \frac{\dot{V}CO_2}{\dot{V}O_2}$$

so that

$$R = \frac{\dot{V}CO_2}{\dot{V}O_2} = \frac{F_A CO_2 \times \dot{V}_A}{\dot{V}_A \times [F_I O_2 - F_A O_2]}$$

which, in turn, with cancellation and rearrangement, becomes

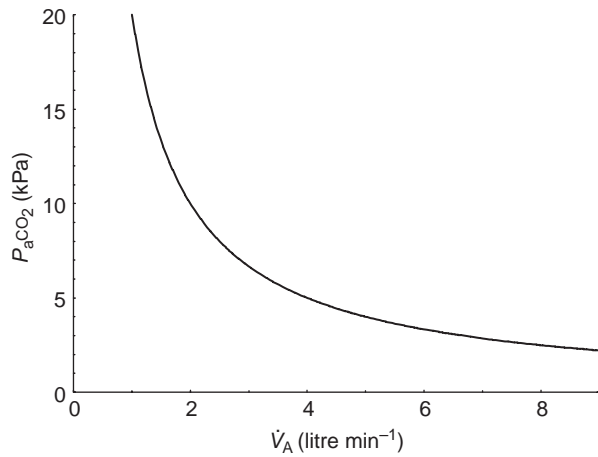$$R = \frac{F_A CO_2}{[F_I O_2 - F_A O_2]}$$

Fig. 1 The relationship of alveolar ventilation ($\dot{V}_A$) to the resulting P_aCO_2 for constant $\dot{V}CO_2$ is a non-linear one. It is a rectangular hyperbola.

$$[F_IO_2 - F_AO_2] = \frac{F_ACO_2}{R}$$

$$F_AO_2 = F_IO_2 - \frac{F_ACO_2}{R}$$

which is almost the familiar version of the AGE. Converting to partial pressures (Dalton) and using our assumption that $P_ACO_2 = P_aCO_2$, this finally becomes the familiar 'short' AGE:

$$P_AO_2 = P_IO_2 - \frac{P_aCO_2}{R}$$

What does the AGE say?

We have derived the usual 'short' AGE using the assumption of steady-state conditions. The AGE will only be valid so long as the assumptions upon which we constructed it remain true. It is evident that, at low F_IO_2, the steady-state assumption will be violated – the required $\dot{V}O_2$ cannot be supplied at the lowered F_AO_2 – and therefore we cannot expect the AGE to describe the resulting F_AO_2 accurately. In fact, F_AO_2 then becomes a time-dependent variable rather than a constant equilibrium quantity, since more is being taken up than supplied and the AGE relationship breaks down at some ill-defined (*i.e.* not defined by our simple model) F_IO_2; the patient becomes progressively hypoxic.

F_AO_2 is dependent upon three variable quantities: P_IO_2, P_ACO_2 and R. Although all are variables, they are not equally easily engineered. P_IO_2 is very easily manipulated, of course. P_ACO_2, on the other hand, is quite easy to manipulate in the intubated, ventilated patient but much less so in the spontaneously breathing subject. R is alterable by manipulation of the diet but not in any rapid, simple and predictable manner.

$$P_AO_2 = P_IO_2 - \frac{P_aCO_2}{R}$$

• With P_IO_2 as the input variable and P_ACO_2 and R fixed, we have a linear relationship of the type $y = mx + c$, where $y = P_AO_2$,
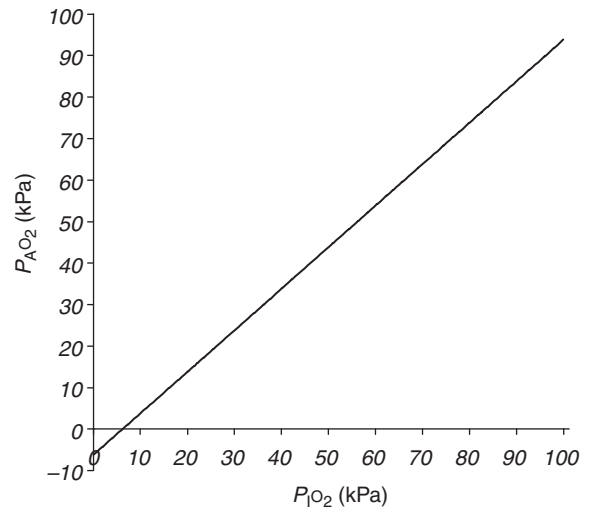

Fig. 2 The alveolar gas equation predicts a relationship of inspired oxygen partial pressure (P_IO_2) to the resulting alveolar partial pressure (P_AO_2) that is linear. It also predicts a nonsensical negative P_AO_2 at low P_IO_2. The equation is valid only at values of P_IO_2 sufficient to allow normal oxygen uptake $\dot{V}O_2$.

$m = 1$, $x = P_IO_2$ and $c = [-P_ACO_2/R]$. The graph of P_AO_2 *vs* P_IO_2 is linear with unity gradient (Fig. 2). The intercept on the vertical axis is negative, as we have noted. This is a graph of the *equation*, not of the physiology. In the physiological range (above, say, 8–9 kPa), it will describe the physiology reasonably well.

• With P_IO_2 fixed and P_ACO_2 as the input variable, we also have a linear relationship. However, if we ask how P_AO_2 is related to $\dot{V}_A$ – which, with $\dot{V}CO_2$, determines P_ACO_2 – then the relationship is non-linear. We have from before

$$P_ACO_2 = \frac{\dot{V}CO_2 \times P_I}{\dot{V}_A} = P_aCO_2$$

Substituting for P_aCO_2 in the AGE:

$$P_AO_2 = P_IO_2 - \frac{\dot{V}CO_2 \times P_I}{\dot{V}_A \times R}$$

$$P_AO_2 = P_IO_2 - \frac{1}{\dot{V}_A} \times \left[\frac{\dot{V}CO_2 \times P_I}{R}\right]$$

This is an equation of the form

$$y = m \times \frac{1}{x} + c$$

with $y = P_AO_2$ as before,

$$m = -\left[\frac{\dot{V}CO_2 \times P_I}{R}\right]$$

$x = \dot{V}_A$ and $c = P_IO_2$. This is an equation of inversely related quantities whose graph is a rectangular hyperbola, but the negative sign before the coefficient modifying the x-term turns the hyperbola of Figure 1 upside down so that we subtract it from the (assumed

constant) P_IO_2. The hyperbola is also amplified by division by R if it is less than unity. The effect of the scaling for various values of R is shown. A P_IO_2 of 20 kPa is taken to represent breathing air with allowance for water vapour (Fig. 3). It is apparent from the graph that a reduction in $\dot{V}_A$ to levels which allow very high levels of P_aCO_2 similarly predict a negative value for P_AO_2 as before. Once again, we have to be careful to use the equation only in circumstances where it is valid; if the steady-state condition is violated, the equation does not apply.

It is evident from these graphs that P_AO_2 is much more effectively raised by increasing the inspired concentration than it is by hyperventilation. However, in the spontaneously breathing patient in air, hyperventilation is the only option.

Refining the AGE

In the appendix to West's *Respiratory Physiology*, and in other texts, a more elaborate version of the AGE is given:

$$P_AO_2 = P_IO_2 - \frac{P_aCO_2}{R} + \left[F_IO_2 \times P_aCO_2 \times \left(\frac{1-R}{R}\right)\right]$$

Where does the fearsome-looking extra term in the expression come from, and is it important?

In our derivation of the AGE, we obtained expressions for $\dot{V}O_2$ and $\dot{V}CO_2$ and substituted these into the definition of R. This is actually not a valid procedure, since we need to look at input and output volumes in the functional residual capacity (FRC). The FRC volume is constant in our model, and yet when the R-value is not unity, more gas is extracted from the FRC by oxygen uptake $\dot{V}O_2$ (say 0.25 litre min^{-1}) than is added to it by $\dot{V}CO_2$ (0.20 litre min^{-1}, when $R = 0.8$). This is plainly incompatible with a constant FRC volume; the 50 ml discrepancy must be made up by an additional passive inflow of gas. Even at end-inspiration or expiration, there must be a small difference in pressure between atmosphere and alveolus such that this volume

$$\dot{V}_p = [\dot{V}O_2 - \dot{V}CO_2]$$

is delivered to the alveolar space each minute. This delivers a small extra amount of oxygen, which acts to boost the F_AO_2 a little. This is a bulk flow of gas caused by pressure difference which is not a result of diffusion; it follows from the general gas law PV = nRT, since n (the number of moles of, in this case, oxygen) is being continuously removed by uptake into the blood. RT and V are constant. This same process is at work in more dramatic fashion during apnoeic mass-transfer oxygenation, such as during brain death testing procedures or bronchoscopy. Details, for those with a head for algebra, are shown in the box.

Figure 4 shows the effect of taking the extra term into consideration on the linear relationship between P_IO_2 and P_AO_2. We can see that it is a pretty small modification. It is directly proportional to F_IO_2 and indeed is barely apparent at $F_IO_2 < 0.5$. Note that we cannot have both P_IO_2 and P_aCO_2 multiplied together in the

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Let us modify the AGE derivation according to the refined model:

$$O_2\text{-Input} = F_IO_2 \times \dot{V}_A + F_IO_2 \times \dot{V}_p = F_IO_2 \times [V_A + V_p]$$
$$O_2\text{-Output} = \dot{V}O_2 + F_AO_2 \times \dot{V}_A$$

Since O_2-Input = O_2-Output,

$$F_IO_2 \times \dot{V}_A + F_IO_2 \times \dot{V}_p = \dot{V}O_2 + F_AO_2 \times \dot{V}_A$$

Rearranging,

$$\dot{V}O_2 = \dot{V}_A[F_IO_2 - F_AO_2] + F_IO_2 \times \dot{V}_p$$

Now, using the expression for

$$\dot{V}CO_2 = F_ACO_2 \times \dot{V}_A$$

$$R = \frac{\dot{V}CO_2}{\dot{V}O_2} = \frac{F_ACO_2 \times \dot{V}_A}{\dot{V}_A[F_IO_2 - F_AO_2] + F_IO_2 \times \dot{V}_p}$$

$$\dot{V}_A[F_IO_2 - F_AO_2] + F_IO_2 \times \dot{V}_p = \frac{F_ACO_2 \times \dot{V}_A}{R}$$

$$[F_IO_2 - F_AO_2] + \frac{F_IO_2 \times \dot{V}_p}{\dot{V}_A} = \frac{F_ACO_2}{R}$$

$$F_AO_2 = F_IO_2 - \frac{F_ACO_2}{R} + \left[\frac{F_IO_2 \times \dot{V}_p}{\dot{V}_A}\right]$$

So we have a rather more complicated expression for the AGE. We can tidy this up a little further by manipulating the extra term in brackets:

$$\left[\frac{F_IO_2 \times \dot{V}_p}{\dot{V}_A}\right] = \frac{F_IO_2(\dot{V}O_2 - \dot{V}CO_2)}{\dot{V}_A}$$

But

$$\dot{V}O_2 = \frac{\dot{V}CO_2}{R}$$

from the definition of R,

$$\frac{F_IO_2 \times \dot{V}CO_2\left[\frac{1}{R} - 1\right]}{\dot{V}_A} = \frac{F_IO_2 \times \dot{V}CO_2\left[\frac{1-R}{R}\right]}{\dot{V}_A}$$

Finally, from before we have

$$F_ACO_2 = \frac{\dot{V}CO_2}{\dot{V}_A}$$

so the expression in brackets becomes

$$\frac{F_IO_2 \times \dot{V}CO_2((1-R)/R)}{\dot{V}_A} = F_IO_2 \times F_ACO_2 \times \left(\frac{1-R}{R}\right)$$

So we obtain the final form of our modified AGE:

$$F_AO_2 = F_IO_2 - \frac{F_ACO_2}{R} + \left[F_IO_2 \times F_ACO_2 \times \left(\frac{1-R}{R}\right)\right]$$

Put into partial pressure terms, this becomes

$$P_AO_2 = P_IO_2 - \frac{P_aCO_2}{R} + \left[F_IO_2 \times P_aCO_2 \times \left(\frac{1-R}{R}\right)\right]$$

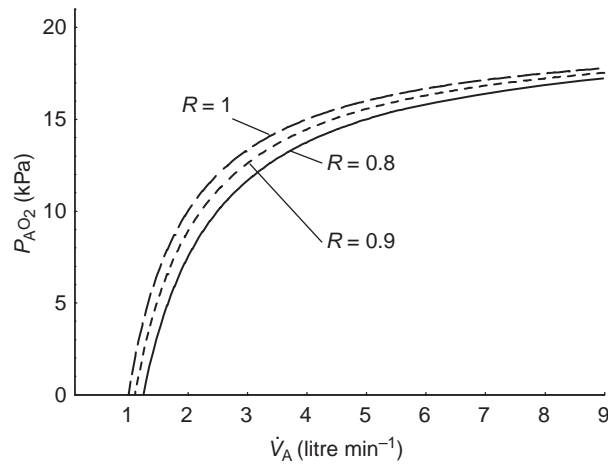**Fig. 3** The relationship of alveolar ventilation ($\dot{V}_A$) to the resulting P_AO_2 for constant P_IO_2 is non-linear.

Fig. 4 The extra term in the complete form of the alveolar gas equation (AGE), where R is less than unity, adds a small amount to the predicted P_AO_2. This is interesting but clinically trivial and may be neglected for practical purposes.

extra term in the brackets, since this would give a {pressure squared}; we must use F_IO_2 instead.

We can discard the extra term in the full AGE for any usual clinical purpose; it is complicated and simply too small to make a difference. By taking the discrepancy in the volumes entering the FRC into consideration, however, we have understood a minor detail of the physiology in this context which achieves major importance in another. In apnoea, P_aCO_2 increases by 0.3–0.7 kPa min^{-1}, say 0.5 kPa min^{-1}. If P_aCO_2 increases at this rate, then, by our assumption that $P_aCO_2 = P_ACO_2$, so does P_ACO_2. Since this is in the gas phase, we can apply Dalton's law and know that carbon dioxide is entering the FRC at 0.05×2 litre min^{-1} (*i.e.* about 10 ml of the 200 ml min^{-1} $\dot{V}CO_2$). The remainder of the $\dot{V}CO_2$ remains in the aqueous phase in the body water. Provided P_AO_2 is sufficient to saturate the Hb (preoxygenation), then uptake $\dot{V}O_2$ (say 0.25 litre min^{-1}) will proceed normally, and if the airway is filled with oxygen (flowing through catheter in trachea) this will be drawn into the FRC at a rate of 0.24 litre min^{-1} by bulk flow: this is apnoeic mass-transfer oxygenation.
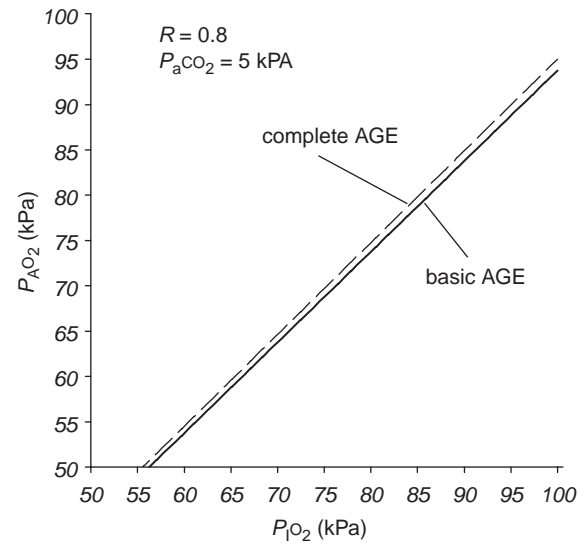
Under ideal circumstances (preoxygenation and normal gas exchange), this technique is limited by carbon dioxide toxicity and not hypoxia.

Key references

Cruickshank S. *Mathematics and Statistics in Anaesthesia*. Oxford: Oxford University Press, 1998

West JB. *Respiratory Physiology: The Essentials*, 6th edn. Baltimore: Lippincott Williams and Wilkins, 2000

See multiple choice questions 23–26.