THE CONTROL OF VENTILATION IN HYPOXIA I

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Normal Adjustments

This article is mainly concerned with the initial respiratory mechanisms which come into play on exposure to mild and moderate hypoxia at altitude and with the normal adjustments made in arterial blood gas tensions when acclimatization is complete. The range of hypoxia is that occurring between sea level and 18000 feet (5500 m approx) tolerated, after suitable acclimatization, by most normal subjects from sea level and inhabited up to this level by high altitude residents. It is proposed here that important lessons (clinical and physiological) can be learned from mild hypoxia and that these affect our interpretation of the events occurring in more severe hypoxia. The theoretical framework given here points towards high altitude studies which may facilitate earlier detection of acute mountain sickness (AMS). Choice and development of improved measurement methods will be recommended in a future edition.

Alveolar and arterial PCO_2 and ventilation under natural, air breathing, conditions
Perhaps suprisingly, measurement of alveolar or arterial PCO_2 (P_ACO_2 or P_aCO_2 respectively) give a better idea of the normality or otherwise of ventilation under most, resting, conditions than does formal measurement of ventilation. This is because, even at rest there is enough variation of the CO_2 production rate (VCO_2) for very different ventilations to be appropriate for PCO_2 constancy. The product of alveolar ventilation (VA) and $PACO_2$ divided by the baromentric pressure (P_B) gives the CO_2 production rate (VCO_2). From this, of course, P_ACO_2 is equal to VCO_2 x P_B / V_A. This shows that (for constant P_ACO_2) alveolar ventilation (and hence total ventilation) has to change in direct proportion to metabolism (VCO_2 - strictly, VCO_2 x P_B, which is convertible to moles; (1). Alveolar PCO_2 (P_ACO_2) measurement also shows whether the value represents normal or abnormal respiratory control.
End-tidal PCO_2 ($P_{et}CO_2$ is a good guide to P_ACO_2 at rest and is used to determine hypo- or hyper-ventilation. Low $P_{et}CO_2$ and arterial PCO_2 (P_aCO_2) signify hyperventilation (2). High $P_{et}CO_2$ and P_aCO_2 signify underventilation, as occurs with CO_2 retention in chronic obstructive airways disease (3,4). PCO_2 (without an 'A' or 'a' suffix) will often be used from here on for general purposes in discussion of P_ACO_2, $P_{et}CO_2$ and P_aCO_2.

PCO_2 in acute mild hypoxia - lack of change
With acute exposure to moderate or severe hypoxia (rather than mild hypoxia) there is a fall in PCO_2, but in the mildest range PCO_2 does not fall. Correspondingly, there is no increase in ventilation in the mildest range (fig 1A) (5). There can therefore be no respiratory alkalosis inhibiting ventilation in the mildest range in air breathing subjects, even though isocapnic studies (5,6) show ventilation increasing progressively throughout hypoxia. The lack of ventilatory response to mild hypoxia at first seems curious in view of the numerous studies showing that sinus nerve discharge begins to increase (fig 1C) as soon as even the mildest hypoxia is

introduced (7, 8)

Furthermore, there is probably no adaptation (decay) in sinus nerve firing with time during hypoxia (9). We therefore have a ventilatory drive from the peripheral arterial chemoreceptor without the expected ventilatory response. This difficulty is commonly ignored but it is suggested here that it is well worth resolving because it unlocks clues as to normal function.

Support for the idea that there is no ventilatory response in the mildest range of acute hypoxia comes from the classic high altitude study of Rahn and Otis (10). In their study (where they include findings from several others studies) alveolar PCO_2 ($PACO_2$) was unaltered in the mildest range of acute hypoxia. $PACO_2$ only began to fall when alveolar PO_2 (PAO_2) fell below 60 mm Hg. Again, for the mildest hypoxia it is difficult to see why, there is no ventilatory or $PACO_2$ change in the face of a presumed increase in peripheral arterial chemoreceptor drive. It is proposed that the answer to the dilemma (peripheral chemoreceptor stimulation without a ventilatory response) is that there is an equal and opposite inhibition of ventilation from another source.

PCO_2 in acute mild hypoxia – central chemoreptor inhibition

At least some central chemoreceptor inhibition would be expected as a result of the increase in cerebral blood flow which occurs with even mild hypoxia (11). This is illustrated by the experimental work of Van Beek (12,13) where the responses of the brain and peripheral arterial chemoreceptors to blood gas changes were studied separately (14,15). By perfusing the brain in cats independently of the rest of the circulation Van Beek was able to show that, when peripheral arterial chemoreceptor stimulation was kept constant and cerebral perfusate was made hypoxic ventilation decreased. On the other hand peripheral arterial chemoreceptor stimulation (with cerebral gas tensions constant) caused an increase in ventilation as soon as PaO_2 fell, as would be expected from the increase in chemoreceptor firing (16,17). Over the mild range in Van Beek's study the separate peripheral stimulatory effect and central inhibitory effect were equal, thereby explaining the lack of ventilatory response in the intact animal. Furthermore, central PCO_2 was reduced as expected from hypoxic increases in cerebral blood flow and the fall in ventilation was directly as expected from separate tests of sensitivity. We can conclude that the lack of acute ventilatory or PCO_2 change in intact animals and man in the mild range is likely to be due to central inhibition from lowered central PCO_2 due to increased cerebral blood flow.

In man increased cerebral blood flow is well documented in hypoxia at high altitude (see box 1, 18). This will reduce PCO_2 in the cerebral extracellular fluid in mild hypoxia despite the lack of alveolar or arterial PCO_2 change. It is the resulting alkalosis around the central chemoreceptor which causes central chemoreceptor inhibition of ventilation, as in Van Beek's experiment, opposing peripheral chemoreceptor stimulation. This is the likeliest reason for the lack of ventilatory change in the mild range. Indeed, in another model without central hypoxia (and therefore no central chemoreceptor alkalosis causing inhibition of ventialtion), Bisgard has shown that awake goats exhibit rapid ventilatory acclimatisation to isolated carotid body hypoxia, providing further supportive evidence (28).

After this traverse through the lowlands of hypoxia it is apparent that the ventilatory changes seen on acute exposure are small or absent as a result of central chemoreceptor inhibition opposing peripheral chemoreceptor drive. Respiratory alkalosis is not operative in mild hypoxia and probably of only minor importance in moderate hypoxia.

Box 1 Cerebral blood flow, measured by Severinghaus and his colleagues (18) at 12500 feet (3810 m), was increased acutely (6-12 hours) by 24% which would reduce the difference between cerebral venous (and cerebro-spinal fluid CSF) PCO_2 and arterial PCO_2 to about 1/1.24 times its original value (almost 10 mmHg, 1.3 kPa). The new central PCO_2 would therefore be only 8.1 mm Hg (1.1kPa) above arterial (instead of 10 mm Hg, 1.3 kPa). PCO_2 at the central chemoreceptor would therefore be nearly 2 mm Hg (0.26 kPa) less than expected from the arterial PCO_2 value.

Prolonged mild hypoxia at altitude

Hypoxic studies on cats and man, involving acute exposure to hypoxia in the laboratory, give us clues as to mechanisms operating in acute hypoxia, but the usual form of hypoxic exposure in man is far less abrupt than in the laboratory. An initial flight from Kathmandu to Lukhla (9300 ft, 2800 m; on the route to Everest) does involve fairly rapid ascent and the hypoxia is mild enough for there to be no fall in PCO_2 in most cases. The same hypothesis applies at these altitudes; that in acute hypoxia there is an increase in peripheral arterial chemoreceptor stimulation of ventilation opposed by a centrally mediated inhibition and no net change in ventilation. The range where these equal and opposite effects occur, according to Rahn and Otis (10) corresponds with altitudes up to 10000 feet (3048 m, barometric pressure about 530 mm Hg).

Central opposition to peripheral drive will also apply during higher ascents (above 3048m) but peripherial arterial chemoreceptor stimulation now exceeds central inhibition, so ventilation increases and arterial PCO_2 falls. The point at which peripheral stimulation overcomes central inhibition and ventilation begins to increase occurs at a PaO_2 of about 50mmHg (see Fig 1.A).

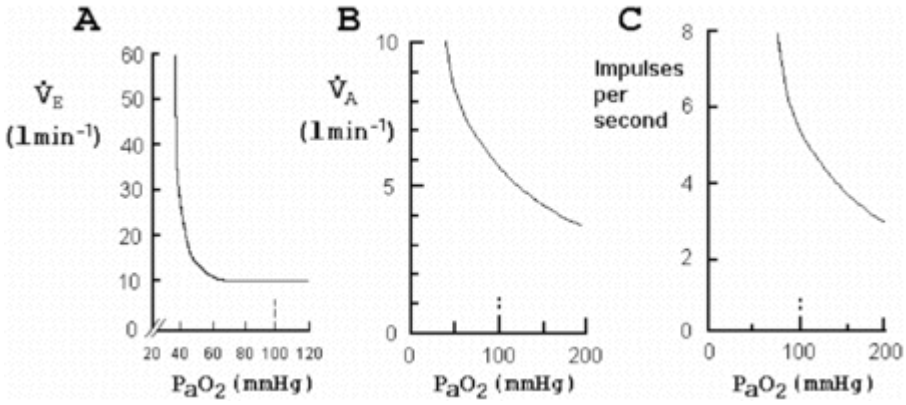

Figure 1. A. shows the acute ventilatory response to hypoxia (5,17) with no increase in ventilation in the mildest range despite increased peripheral arterial chemoreceptor drive. B. shows the ventilatory response to chronic hypoxia; i.e. after acclimatization. The response here is shown as alveolar ventilation (approximately 2/3 total ventilation). C. shows the peripheral arterial chemoreceptor response (sinus nerve chemoreceptor discharge (8) increasing with even the mildest hypoxia. The ventilatory response is now simply related to peripheral arterial chemoreceptor discharge, compatible with acclimatization having eliminated central inhibition (see text). [Vertical dotted lines at 100 mmHg (13.3 kPa) signify normal sea level PaO_2].

Adjustments occurring in the first 2 to 3 days of acclimatization

It is proposed here that acclimatization involves this 'removal of central inhibition' exposing the unopposed ventilatory response to the peripheral arterial chemoreceptors. In the acclimatised state even mild hypoxia results in an increase in ventilation (Fig 1.B).

As outlined above, with acute mild hypoxia, there is initial alkalinity of the cerebral extracellular fluid due to the increased cerebral blood flow. Removal of central inhibition of ventilation could either be caused by a reduction in cerebral blood flow, thus returning the central chemoreceptor pH to normal or some other process of pH normalisation. Cerebral extracellular pH is normally controlled close to 7.32 (19) and will be corrected toward this by the choroid plexus and blood-brain barrier (cerebral microvessels) (20). Since, in Severinghaus' study (18) ventilatory acclimatisation had taken place by 3 days (72 hours) despite no reduction in cerebral blood flow , it seems likely that removal of the inhibitory central alkalinity results from homeostatic regulation of central hydrogen ion rather than attenuation of cerebral blood flow. It would be useful to have experimental evidence for this in mild hypoxia. By five days there appears to be a clear reduction of the cerebral blood flow (18) but it is not clear what mechanisms are involved at this stage.

Figure 1 illustrates the points made here. It shows the lack of acute ventilatory response in the mild range of hypoxia (A), despite the response of the peripheral arterial chemoreceptors (C). In contrast, after acclimatization has occurred (B) alveolar ventilation is similar to the peripheral arterial chemoreceptor response. This is compatible with the central inhibition in A having been removed in B.

The normal PCO_2 after acclimatization depends on the PaO_2

After acclimatization is completed in normal man, the increase in ventilation (fig 1B) lowers PCO_2 (both alveolar and arterial). A PCO_2 value of 40 mm Hg (5.3 kPa) is only normal at sea level in normal subjects. A lower PCO_2 is normal in chronic hypoxia, since it is the normal outcome in acclimatized normal subjects. Normality of PCO_2 is an important criterion of normal respiratory control. It is important to decide what precisely is the normal PCO_2 in chronic hypoxia. It seems reasonable to use the values found in acclimatized subjects, relating normal PCO_2 to arterial (rather than to alveolar) PO_2. This is because it is arterial PO_2 which is detected at the receptor. Calculations from high altitude studies show that the normal acclimatized PCO_2 is approximately:

$$PaCO_2 = O.25\ PaO_2 + 15, \text{ or } 2,$$

depending on whether mm Hg or kPa are used (21,22,23,1). Cochrane, Prior and

Wolff (24) found that 29 patients at sea level with chronic stable asthma, whose P_aO_2 values ranged between normal and 50 mm Hg. (6.7 kPa), showed this same relationship. The fact that their P_aCO_2 was appropriate to their arterial PO_2 suggests that their respiratory control was normal (at least in this respect) despite their abnormal arterial oxygen tension. Hence, the equation above expresses an expanded definition of the normal PCO_2 which takes long term P_aO_2 into account. The expanded definition is important because it tells us whether PCO_2 values, and hence respiratory control, are normal in hypoxic subjects, both at sea level and at altitude. We will show how the equation is used shortly and, in the next issue, how it may be used clinically. More details of the origin of the equation are given in two reviews (16,17).

We can apply the equation at the upper limit of full altitude acclimatization where barometric pressure is close to half the sea level value). Here arterial PO_2 is around 40 mm Hg (5.3 kPa). The equation yeilds a normal PCO_2 of 25 mm Hg (see Box 2). Values of P_aO_2 and P_aCO_2 from subjects acclimatized at a slightly lower level 17800 feet (5430m; (25) were 43.6 and 25.9 mm Hg (5.81 and 3.45) respectively. The calculated normal PCO_2 is 27.0 mm Hg (3.6 kPa) a little higher than the measured PCO_2.

Box 2 The normal PCO_2 at a P_aO_2 of 40 mm Hg is calculated from the equation for normal PCO_2 as follows: Expected normal PCO_2 is 0.25 x 40 + 15 = 25 mm Hg or 0.25 x 5.3 + 2 = 3.3 kPa). Hence, we expect normal PCO_2 values for a P_aO_2 of 40 mm Hg to be 25 mm Hg (2.7 kPa corresponding to 18000 feet, 5486 m; where barometric pressure is half the value at sea level). Alveolar PO_2 is calculated from what is known as the alveolar air equation and arterial PO_2 is then around 7 mm Hg (0.93 kPa) less (26,27).

In Conclusion

The earliest, acute, stage of mild hypoxia presents a problem: why is there little or no ventilatory response despite an increase in peripheral arterial chemoreceptor firing. It is pointed out that the increase in cerebral blood flow which occurs in hypoxia washes out CO_2 from the brain. This will alkalinize the brain which will inhibit breathing via the central chemoreceptor, counterbalancing the peripheral arterial chemoreceptor drive. If, as seems likely, the effects are of equal magnitude this will account for there being no increase in ventilation. With more severe hypoxia where there is an increase in ventilation peripheral drive presumably exceeds central inhibition. During acclimatisation, central inhibition of ventilation is probably abolished by normalisation of central chemoreceptor pH.

The second area of discussion concerns the acclimatized state where hypoxia is chronically sustained. The definition of normal arterial PCO_2 should be expanded relating the expected normal PCO_2 to the extent of hypoxia in the acclimatised state. The equation (Normal P_aCO_2 = 0.25 x P_aO_2 + 15 for mm Hg, or 2 for kPa gives the expected normal P_aCO_2 derived from high altitude studies on normal subjects. This equation has also been shown to apply at sea level to patients with chronic stable asthma. Normality, or otherwise, of the P_aCO_2 shows us whether an important aspect

of respiratory control is normal or abnormal as will be discussed in the next edition.

Chris B Wolff
Deparments of Thoracic Medicine, King's College Hospital, and Clinical Pharmacology, St Bartholomew and The Royal London School of Medicine, London.

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