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Alveolar P\textsubscript{CO\textsubscript{2}} oscillations and ventilation at sea level and at high altitude

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\textsuperscript{1}William Harvey Research Institute, Barts & The London Queen Mary School of Medicine & Dentistry, Charterhouse Square, London; \textsuperscript{2}Oxford Centre for Respiratory Medicine, Churchill Hospital, Oxford; \textsuperscript{3}Department of Respiratory Medicine, Northwick Park Hospital, Harrow, United Kingdom; \textsuperscript{4}Faculty of Human Movement Sciences, Vrije Universiteit, Amsterdam, The Netherlands; \textsuperscript{5}Pulmonary and Critical Care Medicine, University of Washington, Seattle, Washington; and \textsuperscript{6}York Hospitals NHS Foundation Trust, York, United Kingdom

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Alveolar P\textsubscript{CO\textsubscript{2}} oscillations and ventilation at sea level and at high altitude. \textit{J Appl Physiol} 104: 404–415, 2008. First published October 25, 2007; doi:10.1152/japplphysiol.00166.2007.—This study examines the potential for a ventilatory drive, independent of mean P\textsubscript{CO\textsubscript{2}}, but depending instead on changes in P\textsubscript{CO\textsubscript{2}} that occur during the respiratory cycle. This responsiveness is referred to here as “dynamic ventilatory sensitivity.” The normal, spontaneous, respiratory oscillations in alveolar P\textsubscript{CO\textsubscript{2}} have been modified with inspiratory pulses approximating alveolar P\textsubscript{CO\textsubscript{2}} concentrations, both at sea level and at high altitude (5,000 m, 16,400 ft.). All tests were conducted with subjects exercising on a cycle ergometer at 60 W. The pulses last about half the inspiratory duration and are timed to arrive in the alveoli during early or late inspiration. Differences in ventilation, which then occur in the face of similar end-tidal P\textsubscript{CO\textsubscript{2}} values, are taken to result from dynamic ventilatory sensitivity. Highly significant ventilatory responses (early pulse response greater than late) occurred in hypoxia and normoxia at sea level and after more than 4 days at 5,000 m. The response at high altitude was eliminated by normalizing P\textsubscript{CO\textsubscript{2}} and was reduced or eliminated with acetazolamide. No response was present soon after arrival (<4 days) at base camp, 5,000 m, on either of two high-altitude expeditions (BMEME, 1994, and Kanchenjunga, 1998). The largest responses at 5,000 m were obtained in subjects returning from very high altitude (7,100–8,848 m). The present study confirms and extends previous investigations that suggest that alveolar P\textsubscript{CO\textsubscript{2}} oscillations provide a feedback signal for respiratory control, independent of changes in mean P\textsubscript{CO\textsubscript{2}}, suggesting that natural P\textsubscript{CO\textsubscript{2}} oscillations drive breathing in exercise.

normal humans; respiratory control; dynamic CO\textsubscript{2} stimulus; altitude; oxygen supplementation; acetazolamide; P\textsubscript{CO\textsubscript{2}}; hypoxia

Respiratory control maintains near constancy of mean arterial P\textsubscript{CO\textsubscript{2}} (P\textsubscript{A\textsubscript{CO\textsubscript{2}}}), with scaling of ventilation in relation to the CO\textsubscript{2} production rate. Mean arterial P\textsubscript{CO\textsubscript{2}} changes very little over a wide range of activity and metabolic demand. The way in which control is sustained in the face of changes in demand is unknown. Although ventilation increases with inhalation of CO\textsubscript{2} enriched gas mixtures (static CO\textsubscript{2} response curves), here the ventilatory response is the result of an increase in the mean P\textsubscript{CO\textsubscript{2}} value. The responses to mean P\textsubscript{CO\textsubscript{2}} rise, referred to as CO\textsubscript{2} response curves, and cannot, therefore, explain arterial P\textsubscript{CO\textsubscript{2}} homeostasis.

Increasing metabolic rate augments P\textsubscript{CO\textsubscript{2}} oscillations of respiratory frequency, both in the pulmonary alveolar compartment and later in the arterial blood. It was proposed by Band et al. in 1980 (6) that arterial P\textsubscript{CO\textsubscript{2}} oscillations constitute a respiratory control signal. In their study, a record of P\textsubscript{CO\textsubscript{2}} oscillations of respiratory frequency (indirectly recorded with a fast response pH electrode) was shown first with the subject at rest then during moderate exercise. The average rate of change of the rising limb of the P\textsubscript{CO\textsubscript{2}} oscillations increased from rest to exercise in the same proportion, as did the metabolic CO\textsubscript{2} production rate (V\textsubscript{\textsuperscript{\textsubscript{\text{\textsubscript{\textsuperscript{}}}}}CO\textsubscript{2}}). V\textsubscript{\textsuperscript{\textsubscript{\textsubscript{\textsuperscript{}}}}}CO\textsubscript{2} can change rapidly, and yet Forster et al. showed that there is little change in mean Pa\textsubscript{CO\textsubscript{2}} during exercise (22); there is, therefore, a respiratory control system in operation that utilizes a signal independent of mean Pa\textsubscript{CO\textsubscript{2}}. The hypothesis underlying the work of this paper is that something in the time course of naturally occurring respiratory arterial P\textsubscript{CO\textsubscript{2}} oscillations acts as a control signal influencing ventilation. This suggests that variations in the Pa\textsubscript{CO\textsubscript{2}} signal other than the mean value (dynamic component) can have an effect on mean ventilation. We have used the term “dynamic” to describe this putative signal.

If the P\textsubscript{CO\textsubscript{2}} oscillations that occur with each respiratory cycle normally have some effect on mean ventilation, it may be possible to affect mean ventilation by modifications in the oscillation time course or dynamic signal. The present study aims to test this hypothesis.

The normal alveolar P\textsubscript{CO\textsubscript{2}} oscillations result from alveolar P\textsubscript{CO\textsubscript{2}} dilution during inspiration (after clearance of the dead space) followed by increasing P\textsubscript{CO\textsubscript{2}} during expiration (continuing briefly during early inspiration during clearance of the respiratory dead space) (see Fig. 1, top). One way of altering the time course, or profile, of the respiratory oscillation is by tube breathing. An extended dead space (tube breathing) prolongs the end of the alveolar P\textsubscript{CO\textsubscript{2}} rising limb further than normal during early inspiration, thereby also shortening the following alveolar dilution phase (Fig. 1, middle). A different maneuver, using a tube with a loop and valves (tube plus loop), was employed by Cunningham et al. (15) to achieve a normal start to alveolar dilution but early onset of the rising limb. This profile is illustrated diagrammatically in Fig. 1, bottom. Cunningham et al. (15) found that ventilation was greater with tube breathing than with the tube plus loop maneuver. This effect on ventilation was presumed due to differences in the P\textsubscript{CO\textsubscript{2}} oscillation profiles rather than to mean P\textsubscript{CO\textsubscript{2}}. No other putative

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Fig. 1. Diagrammatic representation of PCO2 oscillations generated in the lung during the respiratory cycle. A: normal PCO2 oscillations. PCO2 rises during expiration and during inspiration of the initial dead space volume (up to x). B: early inspiratory CO2 pulse (simulated tube breathing), where the hollow rectangle shows the time taken for inspiration of the CO2 pulse. The last part of the pulse reaches the alveolar compartment after transit of the dead space (at time y). Dilution occurs after this, lasting until the end of inspiration. C: late inspiratory CO2 pulse (simulating the reverse maneuver where the normal dead space is cleared, followed by alveolar dilution then inspiration of gas of dead space composition, tube plus loop profile). The hollow rectangle again depicts the timing of the inspiratory CO2 pulse, which begins to reach the alveoli at z and finishes at the end of inspiration (y). PCO2 begins to rise at z, continues during expiration and, briefly, during inspiration of the dead space at the start of the following breath.

respiratory stimulus differed in the two runs apart from the different mechanical arrangements with the tube and the tube plus loop. In the same study, it was found possible to simulate the effect of tube and tube plus loop maneuvers by suitably timing early inspiratory or late inspiratory pulses of CO2-rich gas. Inspiration of early CO2 pulses (simulating tube breathing) again stimulated ventilation more than late inspiratory pulses. The ventilatory responses to the simulated tube and tube plus loop were less than with the real tube and tube plus loop. Nevertheless, the ventilatory differences were highly significant. These studies were undertaken in hypoxic resting subjects.

A similar result to that of Cunningham et al. (15) was obtained by Datta and Nickol (18), who also administered early and late inspiratory pulses of CO2-enriched gas. This, again, simulated tube breathing and the reverse maneuver (tube plus loop). The study of Datta and Nickol was, however, at normal oxygen tension (normoxia), and the subjects undertook moderate exercise (results of the maneuver in a pilot study at rest were negative). They obtained the same responses that Cunningham et al. (15) had obtained during resting hypoxia (namely, greater ventilation on early inspiratory CO2 pulses than on late inspiratory CO2 pulses). The ventilatory difference could not be explained by any difference in either mean end-tidal PCO2 or arterialized venous PCO2 on early pulses than on late ones. Datta and Nickol did not undertake ordinary CO2 response measurement (constant inspired CO2 concentration) as Cunningham et al. had done.

The present study was designed, first, to confirm the study of Datta and Nickol (18) by testing for different ventilatory effects of early inspiratory and late inspiratory CO2 pulse administration at sea level. We have extended them to examine acute hypoxia at sea level and subacute and chronic hypoxia at altitude (a little above 5,000 m, ~17,000 feet, at Everest and Kanchenjunga base camps). Six subjects were also tested after return to base camp from very high altitudes (above 7,000 m, ~23,000 ft.). Since responses to PCO2 oscillations are likely to be mediated at the peripheral arterial chemoreceptors, we attempted to block the peripheral arterial chemoreceptors (17, 30, 33). We studied the effects of acetazolamide and oxygen on the response in a limited number of subjects.

Our studies were all undertaken with the subjects working on an exercise cycle at 60 W in view of the finding of Datta and Nickol (18) of a significant effect during mild exercise but not at rest.

The importance of the present studies is in the confirmation that the PCO2 time course (the dynamic component) may affect ventilation. The positive results reported here support the suggestion of Band et al. (6) that PCO2 oscillations may be a control signal in exercise.

The studies reported here have been presented in abstract form (11, 12, 28).

METHODS

The data presented here were obtained before and during two high-altitude expeditions. Both series included measurements at sea level and at just over 5,000 m high altitude (Himalayan base camps, Everest and Kanchenjunga; ~17,000 ft.) following a conservative ascent profile. The first expedition in 1994, The British Mount Everest Medical Expedition (BMEME), included a sea level study in hypoxia (inspired oxygen 12.5%) and measurements at Everest base camp (5,340 m, 17,520 ft) during the first 3 days (subacute hypoxia) and after 11–26 days (well acclimatized). Climbers to above 7,000 m (two had summited Everest) were also studied on their return to base camp (referred to as post-high). For the second expedition (Kanchenjunga 1998, K98, Medical Expeditions), sea-level studies included both acute hypoxia (inspired oxygen 14%) and normoxia. The high-altitude measurements at Kanchenjunga base camp (5,140 m, 16,860 ft) included both subacute (during the first 3 days) and well-acclimatized (4–32 days) measurements. All the studies presented here had been approved by East London and The City Research Ethics committee (1994) or Guys and St. Thomas Research Ethics committee (1998). All subjects gave written, informed consent under conditions conforming to ICH Good Clinical Practice.

The experiment required delivery of a pulse of CO2-enriched gas (PCO2 of ~40 Torr) at the correct oxygenation either during early inspiration for all breaths of an experimental run or during late inspiration for all breaths. Two 400-ml reservoirs were filled, when unused (during expiration), with either the CO2-enriched mixture or, for the BMEME expedition, a control, CO2-free gas. At sea level, these pulses were of either normoxic or hypoxic gas (12.5% O2, BMEME; or 14% K98). During inspiration, the gas reservoir was open at the distal end to the atmosphere (or for the CO2-free hypoxic gas, a 12.5% or 14% oxygen reservoir); the volume of the CO2 pulse was therefore limited to a maximum of 400 ml.

Subjects exercised on a cycle ergometer (Monark, Copenhagen, Denmark) and, wearing a nose clip, breathed through a low-resistance non-rebreathing valve (Hans Rudolph). One sampling port allowed measurement of airway PCO2 by infrared capnography (PK Morgan Capnograph, Chatham, UK) and mouth pressure via a second port.
The two reservoirs were alternatively connected to the inspiratory limb of the valve. Switching between test and control reservoirs was by means of a piston, driven by a solenoid actuated pneumatic cylinder (IMI Norgren Martonair, Lichfield, UK). The required switching worked from the swing of mouth pressure at the onset of inspiration, measured by a pressure transducer and pneumotachograph (Godart, Gould Instrumentation, Cleveland, OH). When a preset change in mouth pressure was reached, the resulting trigger was used to activate the pistons via a variable delay (Digitimer, Welwyn Garden City, UK). The pistons were triggered either immediately at the onset of inspiration (no delay, 0 ms), at the early pulse, or after a 300-ms delay (the late pulse). The late pulse was delivered at the mouth starting during midinspiration to reach the alveolar compartment in late inspiration. Pulse duration was normally 300 ms, occasionally shortened to 200 ms when the subject had a high respiratory rate. CO₂ (5%) was used for inspiratory pulses at sea level, and 10% at 5,000 m (to account for the lowered ambient barometric pressure).

The protocol for the first study (sea level and Everest base camp, BMEME 1994) is shown in Fig. 2. After settling comfortably at rest sitting on the saddle of the cycle ergometer, the subject cycled for 6 min before the onset of delivery of inspiratory pulses, initially of CO₂-free gas. The switching mechanism was turned on 1 min earlier to ensure correct functioning of the Digitimer and customize the subject to the switching. The idea was to bracket the test periods of inspiratory CO₂ pulses (each of 3-min duration) with CO₂-free pulses as a control. This was to find out whether the different timing of the switching (suitable for early or late pulses) was responsible for any differences in ventilation. The CO₂ pulses were given during the second and third 3-min periods, and CO₂-free pulses were given again in the fourth 3-min period. The sequences for both CO₂-free and CO₂ pulses were switched over from one subject to the next, i.e., early inspiratory pulses then late or late pulses then early. The arrangement was kept from the subject, although there was potential for them to know which was operative from audible differences in the timing of solenoid switching. Three-minute Douglas bag collections of expired gas were made during each of the four phases, and the volumes were measured by means of a dry-gas meter (Harvard Apparatus, Edenbridge, Kent, UK).

For the second set of experiments (Kanchenjunga base camp, 1998) preliminary experiments at sea level, using the 1994 protocol and with normoxic CO₂ pulses, were found to give rise to a marked order effect. This consisted of progressively increasing ventilation. Since the CO₂-free controls had been shown by the 1994 study not to cause the dynamic ventilatory effect, CO₂-free collections were omitted. The 1998 protocol adopted a second improvement, whereby an initial half minute on the particular CO₂ pulse regime (early or late) was introduced to allow some bodily adjustment to occur before the 2-min Douglas bag gas collection (see Fig. 3). The duration of the whole experiment was shortened (from 18 min) to 10 min, and the order effect was avoided. The volume of each Douglas bag collection was measured with a dry-gas meter (Harvard Apparatus, Edenbridge, Kent, UK).

Additional studies were undertaken to see the effects of 1) oxygen supplementation and 2) acetazolamide.

In four of the subjects who had been to very high altitude (BMEME 1994), the initial test on ambient air was repeated, and then, on the same day, a further test was undertaken with oxygen supplementation (via the inspiratory line). The flow of oxygen was adjusted to achieve an arterial oxygen saturation of >95%.

In three subjects with a large initial response (K98), the experiment was repeated, and then acetazolamide was given intravenously, and the experiment was undertaken again 30–60 min later. In two of the subjects, the dosage was 500 mg; in one subject, it was 250 mg.

**Statistical Methods**

For each experimental series, ventilations during runs on early and late pulses were compared by paired t-testing. Where end-tidal PCO₂ matching required assessment, end-tidal PCO₂ values on early pulses and late pulses were again compared by means of the paired t-test.

**RESULTS**

**Airway Pco₂ Profiles**

Figure 4 shows three short records of airway PCO₂: the effects of the inspiration of CO₂ free gas, inspiration of an early inspiratory pulse of CO₂-enriched gas, and inspiration of a late inspiratory pulse of CO₂-enriched gas.

The effect on the airway CO₂ time profile is to distort the downslope in Fig. 4B with early inspiratory pulses and show a later peak in Fig. 4C with late inspiratory CO₂-enriched pulses. These airway CO₂ profiles correspond with the different alveolar (and arterial) Pco₂ oscillation profiles shown in diagrammatic form in Fig. 1 and seen experimentally, indirectly, by means of arterial pH recording (27).

**BMEME Experimental Series**

In this series, in addition to ventilation being studied during administration of CO₂-enriched pulses early and late in inspiration (the main result), a control was included for the potential effect on breathing of audible differences in the timing of solenoid switching. The control sequences included solenoid switching but employed CO₂-free pulses (of ambient air or of a hypoxic gas mixture). The different timing of audible solenoid switching appeared to be the only potential confounding respiratory signal differing between runs on early and late inspiratory CO₂ pulses.

**Ventilatory difference between breathing in CO₂-enriched pulses in early inspiration and in late inspiration (BMEME94)**. Figure 5 shows individual and mean differences in ventilation between runs with early and with late inspiratory CO₂ pulses (dV) at sea level in acute hypoxia, soon after arrival at Everest base camp (1–3 days, Arrival BC, 5,340 m), and after a longer period at base camp (Well Accl, 11–26 days). The augmented
responses are shown for the subjects who had returned to 5,340 m after sojourn at very high altitudes (Post High, from 7,100 m, 23,300 ft., Pumori, to 8,848 m, 29,030 ft., Everest). In the figure, both individual and mean values (±SE) are shown. There is a trend with duration of hypoxia and with altitude.

The ventilatory differences, \( dV \), were significant for acute hypoxia (SL, hypoxia in Fig. 5, inspire 12.5% oxygen) despite the mean difference being small (just over 1 l/min). Mean ventilation with early \( \text{CO}_2 \) pulses was 38.4 l/min and with late \( \text{CO}_2 \) pulses 37.0 l/min, mean \( dV \) 1.39 l/min (\( n = 30, t = 2.72, P = 0.011 \)).

Soon after arrival at base camp (1–3 days, 5,340 m), ventilatory differences \( (dV) \) were nonsignificant (mean ventilation with early \( \text{CO}_2 \) pulses, 46.8 l/min, with late \( \text{CO}_2 \) pulses 45.8 l/min; mean \( dV \) 1.0 l/min; \( n = 31, t = 1.2, P = 0.24 \)). A subgroup in whom complete pairs of end-tidal \( \text{PCO}_2 \) values had been recorded also showed no significant difference in ventilation (mean ventilation was 45.5 l/min with early pulses and 46.4 l/min with late \( \text{CO}_2 \) pulses; mean \( dV \) was -0.86 l/min; \( n = 5, t = -0.406, P = 0.7, \) not significant).

After a longer period at base camp (11–26 days, referred to as well acclimatized in Fig. 5, the mean difference was large and highly significant (27 subjects, mean ventilation with early \( \text{CO}_2 \) pulses, 58.5 l/min, with late \( \text{CO}_2 \) pulses 52.7 l/min; mean \( dV \) 5.87 l/min; \( n = 27, t = 4.4, P = 0.00016 \)) and was also highly significant with the subgroup of those in whom matched end-tidal \( \text{PCO}_2 \) values were available (mean ventilation with early \( \text{CO}_2 \) pulses, 62.8 l/min, with late \( \text{CO}_2 \) pulses 55.3 l/min; \( dV \) 7.5 l/min; \( n = 18, t = 5.5, P = 3.89E-05 \)). Furthermore, in this subgroup, the end-tidal \( \text{PCO}_2 \) values were well matched (mean \( \text{PCO}_2 \) with early pulses 29.9 ± 0.6 Torr, with late pulses 29.4 ± 0.5 Torr; mean difference between \( \text{PCO}_2 \) mean values, 0.48 Torr, \( t = 1.72, P = 0.104 \)).

In subjects who had ascended to very high altitude (>7,100 m, 23,300 ft.), mean ventilations were 64.4 l/min on early inspiratory pulses, 50.9 l/min on late inspiratory pulses. Mean \( dV \) was therefore 13.5 ± 2.8 l/min (\( n = 6, t = 4.85, P = 0.0047 \)). It was necessary in one subject to give the late pulses first, since ventilation on early pulses was so great at the initial attempt that the experimental run could not be completed.
The effect of early inspiratory CO$_2$ pulses on ventilation was therefore greater than that of late inspiratory CO$_2$ pulses in well acclimatized subjects and in those who had been to very high altitude. This is the case despite there being no significant difference between end-tidal PCO$_2$ values during the two maneuvers. End-tidal PCO$_2$ values were also matched for hypoxia at sea level, and ventilatory differences were highly significant, although much smaller, than those that followed acclimatization at high altitude.

Control: pulses of CO$_2$-free gas early and late in inspiration. On early and late pulses of CO$_2$-free gas, there was no significant difference in ventilation for any of the experimental sets for the four situations described above.

For sea-level hypoxia, mean ventilation with early CO$_2$-free pulses was 34.2 l/min and with late CO$_2$-free pulses 33.1 l/min (mean difference in ventilation on early and late pulses, dV = 1.05 l/min; n = 30, t = 1.34, P = 0.19, not significant). For measurements made during the first 3 days at base camp, mean ventilations were 46.9 and 45.8 l/min on early and late pulses, respectively (mean difference in ventilation, dV = 1.1 l/min; n = 32, t = 0.17, P = 0.43, not significant). For well-acclimatized subjects, mean ventilations were 42.9 l/min on early air pulses and 41.5 l/min on late air pulses (mean dV = 1.4 l/min; n = 27, t = 1.7, P = 0.10, not significant). For the six subjects who had been to very high altitudes (Pumori, 7,100 m; Everest, 8,848 m), mean ventilations at base camp (again on early and late pulses of air) were 41.1 and 42.1 l/min. Mean dV was 1.0 l/min (n = 6, t = −1.52, P = 0.19, not significant).

Clearly, the different timing of the sound and/or vibration that accompanied switching for delivery of early and late pulses did not, per se, cause differences in ventilation.

**K98 Experimental Series**

In this series, end-tidal PCO$_2$ and ventilation differences were studied during inspiration of early and late CO$_2$-enriched inspiratory pulses. The CO$_2$-free pulse sequences were omitted. Assessment of PCO$_2$ matching has been done in all cases.

Ventilatory difference between breathing in CO$_2$-enriched pulses early and late in inspiration (K98). For sea-level normoxia, mean ventilation on early inspiratory (CO$_2$-enriched) pulses was 33.7 ± 0.98 l/min and with late inspiratory pulses mean ventilation was 31.6 ± 1.03 l/min. The mean difference between ventilation with early and late pulses, dV, was 2.12 l/min (n = 19, t = 3.04, P = 0.007, highly significant).

In acute hypoxia (inspire 14% oxygen), mean ventilation on early pulses was 35.5 ± 2.0 Torr and on late pulses was 35.6 ± 2.1 l/min. Mean dV was −0.04 l/min (n = 9, t = −0.05, P = 0.96, not significant).

At altitude soon after arrival at base camp (1–3 days), mean ventilation on early pulses was 72.5 ± 4.26 l/min and on late pulses was 69.2 ± 3.68 l/min. Mean dV was 3.34 l/min (n = 16, t = 1.53, P = 0.148, not significant).

After a longer period (4–32 days), mean ventilation on early pulses was 67.4 ± 5.1 l/min and on late pulses was 61.0 ± 4.4 l/min. Mean dV was 6.38 l/min (n = 11, t = 3.39, P = 0.007, highly significant).

All values for dV from this series (K98) are shown in Fig. 6. In these experiments, a highly significant effect has been found at sea level in normoxia (although mean dV is small) and after subjects had become well acclimatized to the hypoxia of high altitude (resident more than 4 days). CO$_2$ pulses given at different times during inspiration are accompanied by greater ventilation when the pulse is given early than when it is given late. This was found even where it has been shown that end-tidal PCO$_2$ values were matched (see Matching of end-tidal PCO$_2$ with early and late CO$_2$-enriched inspiratory pulses). The magnitude of the response is small but significant in normoxia but is nonsignificant here in acute hypoxia. The ventilatory response is also small during the early phase of sojourn at high altitude (but nonsignificant), whereas the effect is large after sojourn for 2–3 wk.

Matching of end-tidal PCO$_2$ with early and late CO$_2$-enriched inspiratory pulses. The difference between end-tidal PCO$_2$ recorded during inspiration of early CO$_2$ pulses and late CO$_2$ pulses was always small and was not significant in any of the recorded states: sea level normoxia, acute hypoxia at sea level, soon after arrival at high altitude (base camp, Kanchenjunga, 5,140 m, 1–3 days), and after a longer period at base camp (4–32 days).

For sea level normoxia, mean PCO$_2$ on early inspiratory (CO$_2$-enriched) pulses was 48.1 ± 0.82 Torr, and on late inspiratory pulses mean PCO$_2$ was 48.2 ± 0.79 Torr. The mean difference between end-tidal PCO$_2$ with early and late pulses, dPCO$_2$, was −0.1 Torr (n = 19, t = −0.52, P = 0.612, not significant). For acute hypoxia, mean PCO$_2$ on early pulses was 45.5 ± 1.4 Torr and on late pulses was 44.8 ± 1.5 Torr. The mean difference, dPCO$_2$, was 0.71 Torr (n = 9, t = 1.69, P = 0.13, not significant).

At altitude soon (1–3 days) after arrival at base camp, mean PCO$_2$ on early pulses was 32.8 ± 0.67 Torr and on late pulses was 32.6 ± 0.65 Torr. dPCO$_2$ was 0.19 Torr (n = 16, t = 0.92, P = 0.37, not significant).

After a longer period at base camp (4–32 days, well acclimatized), mean PCO$_2$ on early inspiratory pulses was 32.7 ± 0.9 Torr and on late pulses was 33.0 ± 1.0 Torr. Mean dPCO$_2$ was −0.29 Torr (n = 11, t = −0.74, P = 0.47, not significant).
Summary of Ventilatory Responses: Both Studies

At sea level in normoxia ventilation was greater on early inspiratory CO$_2$ pulses than late inspiratory pulses; in acute hypoxia the same was true on one occasion (BMEME, 30 subjects, arterial oxygen saturation (SaO$_2$) mean 92%, SE 2.0%) but not on the other (K98, 10 subjects, SaO$_2$ mean 70.5%, SE 1.0%). SaO$_2$ values were not complete on all subjects.

At altitude, there was no response in the early phase (1–3 days after arrival at base camp; just over 5,000 m, ~17,000 ft.) in either study. Mean SaO$_2$ was 76.6 SE 1.3 BMEME94; 76.0 SE 1.2 K98. There was a highly significant response in well acclimatized subjects (>4 days at base camp) in both studies (SaO$_2$: 81.8 SE 1.1 BMEME94; 78.9 SE 1.9 K98). Ascent to extreme altitude potentiated the response on return to base camp. The study has therefore discounted an effect of mean end-tidal P$_{CO_2}$ on the extra ventilation during inspiration of early inspiratory pulses since end-tidal P$_{CO_2}$ values were well matched. The BMEME control study (with CO$_2$-free pulses) shows that the difference in timing of the sounds of the solenoid switching for early and late inspiratory pulses was not responsible for the ventilatory effect seen with CO$_2$ pulses.

CO$_2$ Response Curves: Average Steady-State Responses to Early and Late Inspiratory CO$_2$ Pulses

Figure 7 shows mean ventilation for early inspiratory pulses and late inspiratory pulses and ventilation on air. This allows us to see the mean values displayed as they would be for steady-state CO$_2$ response curves for both early CO$_2$ pulses and late CO$_2$ pulses. The four panels show the early and late pulse steady-state CO$_2$ responses; soon after arrival at altitude (Fig. 7A, 1–3 days, K98), after longer sojourn (4 days or longer) both for the BMEME94 (Fig. 7B) and K98 trip (Fig. 7C), and for the subjects who had returned to base camp (~5,000 m; 16,400 ft.) after climbing to very high altitude (Fig. 7D, 7,100–8,848 m, 23,300–29,030 ft.). The error bars (standard error of the mean) on ventilation are of value in showing the scatter of the means but do not address the differences between ventilations on early and late CO$_2$ pulses within subject (paired data). For the paired data, Fig. 7A was nonsignificant, and Fig. 7, B–D, were highly significant. However, inclusion of the mean points for air breathing allows a CO$_2$ response curve type of presentation given here. There is a larger steady-state ventilatory response overall to mean end-tidal P$_{CO_2}$ with early inspiratory pulses than with late ones.

Effect of Oxygen and Acetazolamide on the Dynamic Ventilatory Response

Effect of oxygen inhalation on response of four subjects who had been to very high altitude. The four subjects here were tested at ambient oxygen and with supplementary oxygen in both the CO$_2$-free inspire and the early and late inspiratory CO$_2$ pulses. SaO$_2$ on oxygen was >95%. For subjects 72, 73, 78, and 79, respectively, at ambient oxygen, ventilation was 65.5, 59, 55, and 80 l/min, respectively, on early CO$_2$ pulses and 52, 53, 44, and 62 l/min, respectively, on late CO$_2$ pulses. Mean ventilation was 64.9 ± 5.5 l/min on early CO$_2$ pulses and 52.8 ± 3.6 l/min on late CO$_2$ pulses (mean difference 12.1 ± 2.5 l/min, $t = 4.8$, $P < 0.02$). On supplementary oxygen, ventilations were 35, 16.5, 35.5, and 25 l/min for early pulses (mean 28 ± 4.5 l/min) and 38, 20, 45, and 23.5 l/min (mean 31.6 ± 5.9 l/min) for late pulses. On supplementary oxygen, the mean difference was 1.6 ± 2.7 l/min ($t = 0.59$, $P = 0.6$, not significant). In three of the four subjects, oxygen breathing abolished the dynamic ventilatory response, and it was halved in the fourth subject. Values for $dV$ are shown in Fig. 8. Supplementary oxygen abolishes or reduces the response.

Effect of acetazolamide on ventilatory response of three subjects at base camp. Three (K98) subjects (subjects A, B, and C) were tested before and after a single intravenous dose of acetazolamide, with two subjects on 500 mg and one on 250 mg (Fig. 9). The control tests of dynamic ventilatory response for each subject were undertaken at 15, 15, and 9 days (subjects A, B, and C, respectively) and were large (9.1, 17.2, and 10.6 l/min). On acetazolamide, ventilatory responses were −0.3 and −2.3 l/min for subjects A and B following 500 mg acetazolamide and 5.4 l/min in subject C on 250 mg acetazolamide. P$_{CO_2}$ values were well matched for early and late pulses (mean 30.4 and 30.5 Torr, dP$_{CO_2}$ −0.08 Torr; $P = 0.7$, not significant).
Acetazolamide appears to eliminate or reduce the ventilatory response to dynamic Pco2 changes, with an apparent dose response effect suggested by the complete suppression with 500 mg in two subjects and only a 50% reduction in the third subject given 250 mg.

A further finding was of lower mean end-tidal Pco2 values during runs on acetazolamide than was found during the runs preceding dosage. Unpaired Student's t-testing gave mean Pco2 values of 31.0 Torr before and 28.4 Torr following acetazolamide dosage (t statistic = 2.69, P = 0.0228).

**Overview of Ventilatory Responses (dV) and Their Significance**

Table 1 shows the number of subjects tested in each experimental series, the difference in ventilation between breathing early inspiratory CO2-enriched pulses and late inspiratory pulses (dV), and the probability that the result occurred by chance (p) in the fourth column. The mean differences between end-tidal Pco2 values on early and late pulses (dPco2) are shown, in the fifth column, for five of the situations studied. They are all <1 Torr, and none of them was significant. A significant ventilatory response (dV) occurred at sea level with normoxia and with one of the two occasions on which hypoxia was tested. The ventilatory response was nonsignificant for the period soon after arrival at base camp (just above 5,000 m) for both high-altitude expeditions. With further sojourn, the response emerged, becoming large and highly significant (both expedi-
tions); following ascent to very high altitude, responses were very large. Supplementary oxygen eliminated responses in three of these subjects and halved it in the fourth. Acetazo-
lamide was only tested on three subjects, but the results were consistent with elimination of the response on 500 mg and a reduction of the response on 250 mg, hinting at a dose-dependent effect.

**DISCUSSION**

The present study shows that there is greater ventilation with early inspiratory CO2-enriched pulses than with late ones (in several of the situations studied) despite equality of the end-
tidal Pco2. It was concluded in the study of Datta and Nickol (18) that the dynamic ventilatory response in normoxia was absent at rest but present with mild exercise. They therefore reported the exercise result: ventilation with early inspiratory pulses exceeded ventilation with late inspiratory pulses by an average value of 5.5 l/min. In our normoxic study, also in mild exercise, the ventilatory difference was rather less (2.1 l/min). The larger response of Datta and Nickol could have resulted from a higher mean Pco2 for the early pulses (1.2 Torr higher, against 0.1 Torr lower in our study). The improved Pco2 matching in the present study helps to exclude a mean Pco2 response as a confounder for the dynamic response. The likelihood that mean Pco2 did not contribute to the ventilatory difference between runs with early and with late inspiratory pulses is supported by the differences in end-tidal Pco2 varying a little and in opposite directions in different series with significant responses. For example, the late altitude results from the two expeditions show opposite Pco2 differences (see Table 1). Figure 7 illustrates an average steady-state response for early inspiratory pulses separately from late inspiratory pulses. The early pulse responses are greater than the late ones.

One might expect the greater ventilation with early inspiratory pulses to draw in more CO2-rich gas than for ventilation on late pulses. This concentrating effect was presumably offset by extra dilution from the excess ventilation. The possibility that arterial (as distinct from end-tidal) Pco2 may have been higher with early than with late pulses suggests a potential confounder. However, the large responses in subjects following return from very high altitude were eliminated by supplemental oxygen despite early and late inspiratory CO2 pulse administration. There is therefore no obvious link between the ventilatory differences and mean Pco2 values. Because of these factors, the good matching of end-tidal Pco2 was arrived at to some extent empirically, although the chambers holding a standard (400 ml) meant that this was a limit to CO2 pulse magnitude.

The dynamic ventilatory response in normoxia was small at sea level yet highly significant. For acute hypoxia at sea level, we have presented two studies, with the earlier one showing a significant dynamic ventilatory response (BMEME94, inspire 12%, number of subjects 30, SaO2 70.5%), and with the later one (K98, inspire 14%, number of subjects 9, SaO2 92%) being not significant. The difference in significance may have been due to either the difference in hypoxic severity and/or the number of subjects. Responses were nonsignificant soon after arrival at 5,000 m (Table 1) for both expeditions but were large and highly significant when measured after sojourn for more
than 4 days (well acclimatized). The largest differences in ventilation occurred in subjects who had returned to 5,000 m after exposure to very high altitude. Possible reasons for these variations in response will be considered shortly.

We need to consider justification for use of the term dynamic to describe the ventilatory response in the present study. The hypothesis underlying the study is that changes in P\textsubscript{CO\textsubscript{2}} during the respiratory cycle, which occur repeatedly in the steady state, carry extra information over and above that due to the mean P\textsubscript{CO\textsubscript{2}} value. The term dynamic has been utilized here to signify this variation. If the difference in ventilation between runs with early inspiratory CO\textsubscript{2} pulses and late CO\textsubscript{2} pulses is due to within-breath P\textsubscript{CO\textsubscript{2}} variation, then it is deemed sense to use a specific term, in this case dynamic, to describe the ventilatory response to CO\textsubscript{2}. This distinguishes it from the steady-state CO\textsubscript{2} response (response to the mean P\textsubscript{CO\textsubscript{2}}). Steady-state ventilatory responses to inhalation of CO\textsubscript{2} have been studied comprehensively for over a century, an early landmark being the study of Haldane and Priestley in 1905 (23). They have been well reviewed by Cunningham, a major contributor to the field (14, 16, 17).

Consideration of Mechanisms

The fact that there is variation in the magnitude and significance of the ventilatory response raises the question of how such ventilatory differences are mediated. Responses are not stimulated directly at the lung by alveolar CO\textsubscript{2} oscillations; transmission via the intervening circulation to a receptor (the carotid body) is required. Once detected, the information must be carried from the carotid body via the sinus nerve chemoreceptor fibers to reach the respiratory center, presumably undergoing some processing either along the way or specifically in the brain.

Starting at the alveolar compartment, where the respiratory oscillations are generated, are their properties such that P\textsubscript{CO\textsubscript{2}} oscillations are a good candidate for ventilatory control, in particular in exercise? Yamamoto modeled the time profile of the alveolar P\textsubscript{CO\textsubscript{2}} oscillation within the respiratory cycle (36) and also suggested (37) that, if alveolar P\textsubscript{CO\textsubscript{2}} oscillations were conveyed from the lung to become arterial P\textsubscript{CO\textsubscript{2}} oscillations, these would include information needed for rapid control of ventilation in response to changes in metabolic rate. Yamamoto and Edwards (38) increased the apparent metabolic rate of rats by venous infusion of CO\textsubscript{2}-rich blood; the rats sustained P\textsubscript{CO\textsubscript{2}} homeostasis. Furthermore, P\textsubscript{CO\textsubscript{2}} oscillations of respiratory frequency have been demonstrated indirectly in the arterial blood of man and animals by Band and Semple by means of a fast-response pH electrode (4). There is little, if any, attenuation of the oscillations during transit in the arterial blood. The lack of smoothing is compatible with the horizontal velocity profile found in major arteries and illustrated in Caro et al. (10). In a study by Band et al. in 1978 (3), it was shown that recorded pH oscillations were a good surrogate for P\textsubscript{CO\textsubscript{2}} oscillations. Arterial pH oscillations have also been recorded at rest and in exercise by Band et al. in 1980 (6). The recording of Band et al. (6) showed augmentation of the (calculated P\textsubscript{CO\textsubscript{2}}) rate of change of the oscillation upslope and amplitude in proportion to the increase in metabolic rate.

Rapid changes in P\textsubscript{CO\textsubscript{2}} (within-breath) have been shown to have positive and negative ventilatory effects, where ventilation was affected alternately or single breaths were stimulated by brief arterial CO\textsubscript{2} pulses. These studies did not address the possibility considered in the present paper: the idea that P\textsubscript{CO\textsubscript{2}} oscillations might stimulate additional ventilation over and above that expected from the mean P\textsubscript{CO\textsubscript{2}} value. The alternate breath effects were mediated by having alternate breath differences in alveolar and, consequently, arterial P\textsubscript{CO\textsubscript{2}}. One type involved alternate inspirates of CO\textsubscript{2}-enriched gas (close to the alveolar concentration) both in humans and in cats. The response was alternate differences in breath-by-breath ventilation. These studies are reviewed by Wolff (35). The early inspiratory and late inspiratory CO\textsubscript{2} pulses were also given alternately by breath, generating the expected alternate breath arterial pH profiles, reproduced in Metias et al. (27). They also stimulated alternation of ventilation breath by breath.

There is a high-gain differential plus proportional neural response to arterial P\textsubscript{CO\textsubscript{2}} oscillations at the carotid body, with large oscillations in carotid chemoreceptor nerve fiber discharge frequency. These oscillations in firing occur indepen-

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**Table 1. Dynamic ventilatory responses**

<table>
<thead>
<tr>
<th>Ventilatory Responses</th>
<th>n</th>
<th>dV (E – L), l/min</th>
<th>P Value</th>
<th>dPCO\textsubscript{2} (E – L), Torr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normoxia, 1998</td>
<td>19</td>
<td>2.12</td>
<td>0.007</td>
<td>−0.10</td>
</tr>
<tr>
<td>Acute hypoxia, 1994</td>
<td>30</td>
<td>1.39</td>
<td>0.011</td>
<td></td>
</tr>
<tr>
<td>Acute hypoxia, 1998</td>
<td>9</td>
<td>−0.04</td>
<td>0.96</td>
<td>+0.71</td>
</tr>
<tr>
<td>Arrival at base camp, 1994</td>
<td>31</td>
<td>1.01</td>
<td>ns (0.24)</td>
<td></td>
</tr>
<tr>
<td>Arrival at base camp, 1998</td>
<td>16</td>
<td>3.34</td>
<td>ns (0.15)</td>
<td>+0.19</td>
</tr>
<tr>
<td>Well acclimatized, 1994</td>
<td>27</td>
<td>5.9</td>
<td>0.00016</td>
<td></td>
</tr>
<tr>
<td>PET\textsubscript{CO\textsubscript{2}} matched</td>
<td>18</td>
<td>7.5</td>
<td>0.00004</td>
<td>+0.48</td>
</tr>
<tr>
<td>Well acclimatized, 1998</td>
<td>11</td>
<td>6.38</td>
<td>0.007</td>
<td>−0.29</td>
</tr>
<tr>
<td>Post very high, 1994</td>
<td>6</td>
<td>13.5</td>
<td>0.0047</td>
<td></td>
</tr>
<tr>
<td>Effect of oxygen, 1994</td>
<td>4</td>
<td>12.1 to 1.6</td>
<td>0.016 to ns (0.6)</td>
<td></td>
</tr>
<tr>
<td>Acetazolamide, 500 mg (K98)</td>
<td>2</td>
<td>A. 9.1 to −0.3</td>
<td>ns (0.6)</td>
<td></td>
</tr>
<tr>
<td>Acetazolamide, 250 mg (K98)</td>
<td>1</td>
<td>B. 17.2 to −2.3</td>
<td>ns (0.6)</td>
<td></td>
</tr>
</tbody>
</table>

The table shows the number of subjects in each individual situation, with the mean difference in ventilation (dV) between inspiration of early CO\textsubscript{2}-enriched pulses of gas (E) and late inspiratory pulses (L). Values are expressed as early minus late magnitudes (E – L). The number of subjects studied (n) is shown, and the P value is shown. PET\textsubscript{CO\textsubscript{2}}, end-tidal P\textsubscript{CO\textsubscript{2}}; ns, not significant.
dently of the phase relation between the respiratory cycle and the $PCO_2$ oscillation at the carotid body (3). Hence, chemoreceptor firing shows a continuous, large amplitude oscillation in response to arterial $PCO_2$ oscillations. Afferent chemoreceptor firing responses can be elicited at any part of the respiratory cycle. Afferent arterial chemoreceptor firing appears to oscillate smoothly and continuously in response to arterial $PCO_2$ oscillations in the local blood supply.

It has become clear from the various studies above that stimuli around the frequency of respiratory oscillations in $PCO_2$ are transmitted from lungs to respiratory center (via the circulation and carotid body) and affect breathing.

The “Gating” Effect

Very brief arterial pulses of $CO_2$-enriched saline, upstream of the carotid body, have been found to stimulate the ongoing inspiratory tidal volume in the anesthetized cat but only when the arterial pulse arrives at the carotid body during the latter half of inspiration. This contrasts with the nerve firing response to arterial $PCO_2$ oscillations, which shows a continuous oscillatory response in firing frequency, the firing response to carotid body stimulation occurs at all phases of respiration. Maximum stimulation of the ongoing tidal volume by arterial $CO_2$ pulses occurs toward the end of inspiration. This phenomenon has been consistently demonstrated by Band et al., Black et al., and Eldridge among others (2, 8, 21). There is therefore a timing window or gate late in inspiration during which the stimulus is effective. A similar timing gate occurs with brief, direct electrical stimulation of the sinus nerve, despite a burst of firing in response to the stimulus at any part of the respiratory cycle, as shown by Black and Torrance and Eldridge (9, 20). Since carotid chemoreceptor neutral responses to arterial stimuli are independent of timing in the respiratory cycle, the gate phenomenon is centrally mediated. The way in which the central brain stem gating of the sinus nerve chemoreceptor neural input occurs has been studied in some detail by Young et al. (39). The study of Young et al. shows a very definite difference in the effect of brief stimulation from either arterial or neuronal (chemoreceptor) stimuli during the critical late inspiratory phase. This suggests that it will be the part of the arterial $PCO_2$ oscillation occurring at the carotid body (and in the afferent chemoreceptor firing) during mid to late inspiration, which will have an effect on breathing. Hence, carotid body detection of the arterial $PCO_2$ oscillation is essential to the gating phenomenon, but gating occurs where the arterial chemoreceptor firing is processed. Although there are many different ventilatory stimuli, which are potential candidates for the unexplained ventilatory response seen in exercise, in our experiments only the $CO_2$ pulse timing differed between the early pulse and late pulse runs. The potential confounder, the different timing of the clicks of the solenoid switching mechanism, has been examined and found not to cause a differential ventilatory response.

Physiological phenomena that may underlie responses to the arterial $PCO_2$ and carotid arterial chemoreceptor oscillations. Attempting to explain the differences found here between dynamic ventilatory responses at sea level and the early and late responses at altitude requires consideration of the route taken by the information from alveoli to ventilatory response, in particular the intervening circulation. The timing of arrival of the $PCO_2$ oscillations at the carotid body will be affected by the cardiac output and carotid arterial blood flow and, as regards the phase relation to the respiratory cycle, also by the respiratory period. Coulter et al. (13) found that in normal subjects the time delay in circulatory transport from lung to ear (close to the carotid body) remained at twice the respiratory period as both shortened with progressive exercise. Their study result has been reviewed in Cunningham et al. (17). With a two respiratory period $CO_2$ oscillation transport lag in the circulatory path between lung and carotid body, the arterial oscillations, as they arrive at the carotid body, will be in phase with breathing. Hence, the inspiratory part of the carotid arterial $PCO_2$ oscillation will occur during inspiration, the expiratory part during expiration. Any factor altering the circulatory transport time from lung to carotid body or altering the respiratory period will change the phase relationship between the $PCO_2$ oscillation at the receptor and the respiratory cycle.

Figure 10 shows, diagrammatically, $PCO_2$ oscillations at the carotid body that will result from early inspiratory pulses in the left panels and those derived from late inspiratory pulses in the right panels. The in-phase $PCO_2$ oscillations are shown in the top panels (circulatory lag equals a whole number of respiratory cycles, two in humans). The part of the oscillation occurring at the critical, late inspiratory timing is marked with an o. The short black bar indicates the critical timing (during which there is ventilatory sensitivity to rapid changes). In the middle panel, oscillations delayed by more than two respiratory cycles result in a so-called phase lead, and in the bottom panels the circulation is faster, giving a time delay shorter than two

![Fig. 10. The figure shows diagrammatically $PCO_2$ oscillations at the detector (carotid body) after circulation from the lung. In A, the modified oscillations are from early inspiratory $CO_2$ pulses, whereas in B they result from late inspiratory pulses. Arrival at the carotid body may follow a whole number of respiratory cycles (normally 2, in humans), in which case they are in phase (the same timing as at the lung top 2 panels). The middle 2 panels show a phase-advanced version, where the circulatory transport time is a little prolonged. The bottom 2 panels show a phase-retarded version from slightly accelerated circulation. The black rectangles represent the timing of respiratory sensitivity to the afferent chemoreceptor signal also shown on each oscillation (as a small circle (o). For the top and middle panels the $PCO_2$ values show very little difference at the sensitive timing; but, for the bottom panel (accelerated circulation), the early pulse profile (A) is higher with a positive rate of change at the sensitive timing, whereas the late-pulse profile shows a lower value with a negative rate of change.](image-url)
respiratory cycles (resulting in a phase lag of the arterial oscillation relative to the respiratory cycle). The top two panels show little difference in the oscillation $P_{CO_2}$ value at the critical late inspiratory timing, whereas for the bottom panel, with an accelerated circulation, the difference is near maximal. The responsiveness of the carotid body chemoreceptors to rate of change may exaggerate the difference in the neural stimulus since it is positive for the early pulse oscillation and negative for the late pulse oscillation.

The timing effects illustrated here will also be affected by changes in respiratory period. It is possible that the phase relation shown in Fig. 10, bottom, occurs when there is a positive response but does not occur when responses are nonsignificant. However, the lack of response soon after arrival at altitude, at the time of the accelerated circulation discussed by Reeves (29), does not immediately fit this scenario. One might expect an improved coupling of circulation and respiratory period once more time has been allowed for acclimatization. Again this does not fit with the significant responses in well-acclimatized subjects. The reasons for the differences in responses at sea level and the early and later altitude responses are therefore not at all clear. The dynamic responses, in general, appear to require either hypoxia and/or exercise. The possibility that the altitude studies would work at rest has not been examined. However, Cunningham showed that the phenomenon could be demonstrated at rest in hypoxia (15) but, as mentioned earlier, Datta and Nickol (18) were unable to demonstrate a significant dynamic response in normoxic subjects at rest. In view of some of the large responses seen at high altitude, it would be worth repeating the studies in resting subjects.

Another area to consider regarding different responses is the augmented carotid chemoreceptor mean firing rate, higher on arrival at altitude than after acclimatization. The higher mean firing rate would reduce the ratio of the amplitude of the oscillation in firing frequency to the mean value. Whether this is relevant will depend on the way in which oscillating afferent chemoreceptor discharge is processed as regards ventilation. Furthermore, lower ratio of the amplitude to mean firing frequency is a feature of acute hypoxia, as shown by Band and Wolff (5), yet responses occur in acute hypoxia, as shown in the present study and earlier by Cunningham et al. (15). Further work is therefore required to clarify the underlying mechanisms.

**Blockade of peripheral arterial chemoreceptors.** The effect of the carbonic anhydrase inhibitor acetazolamide in abolishing or reducing the dynamic ventilatory response (Fig. 9) may seem paradoxical in that improved oxygenation on acetazolamide (diamox, invaluable in the prophylaxis and treatment of acute mountain sickness) rather suggests stimulation (7). This is the basis of the effectiveness of diamox in the prophylaxis and therapy of acute mountain sickness. Indeed, we have found ventilatory stimulation after giving intravenous acetazolamide (mean $P_{CO_2}$ lowering) while losing the dynamic response. The stimulation of ventilation on acetazolamide is thought to be mediated centrally and is compatible with a blockade of the peripheral arterial chemoreceptors. The central stimulation of steady-state ventilation by carbonic anhydrase inhibition is not directly mediated, since it can occur with carbonic anhydrase-blocking drugs with little blood-brain barrier penetration (e.g., benzolamide). Carbonic anhydrase inhibitors are known to act on local carbonic anhydrase at the blood-brain barrier (24, 30). Carbonic anhydrase inhibition probably results in cerebral endothelial blockade of $CO_2$ equilibration (30, 31). The stimulus to mean ventilation on acetazolamide seems therefore likely to result from higher central $P_{CO_2}$. The lowering of $P_{CO_2}$ we found in our subjects on acetazolamide, although small, is compatible with modest stimulation of ventilation.

Returning to the peripheral arterial chemoreceptors, carbonic anhydrase inhibition is also known to reduce the speed of response of the carotid body as shown, for ventilation, by Teppema et al. (32) and for afferent peripheral arterial chemoreceptor firing by Itturiaga et al. (25). Hence, the respiratory oscillations in peripheral chemoreceptor discharge frequency will be attenuated by acetazolamide. The drug therefore eliminates (or reduces) the dynamic stimulus (peripherally) yet still increases mean ventilatory drive (centrally).

Breathing supplementary oxygen to bring arterial oxygen saturation up to 95% reduced mean ventilation, and abolished (or reduced) the dynamic response to $CO_2$. The effect on mean ventilation is thought to be due to the loss (or reduction) of mean firing of the peripheral arterial chemoreceptors. This is presumed to explain the loss of the dynamic ventilatory response. The similar ventilatory inhibition for both early- and late-pulse runs can be assumed to be due to loss of hypoxic drive. Anecdotally, one of the authors found shallow oscillations in peripheral chemoreceptor firing in hyperoxia during the study of Band et al. (3), which would be phase shifted by slowing of the circulation in hyperoxia.

Acetazolamide and breathing supplementary oxygen confirm peripheral chemoreceptor mediation of the dynamic ventilatory response. Support for the carotid body-mediated control of ventilation in exercise comes from the study of Waserman et al. (34) comparing the ventilatory and $P_{CO_2}$ time courses in normal subjects and those in whom the carotid bodies had been resected. Isocapnia was sustained in the normal subjects during the early part of exercise, whereas $P_{CO_2}$ rose, peaking at ~5 min, in the carotid body-resected subjects. It is assumed that oxygen delivery to the exercising tissues kept pace with demand, and $CO_2$ production rose similarly. The increased $CO_2$ delivery to the lung was matched by the ventilatory changes in the normal subjects, whereas the ventilatory increase was considerably delayed in the carotid body-resected subjects. We propose that an adequate dynamic ventilatory response depends on the carotid body detection of arterial $P_{CO_2}$ oscillations of respiratory frequency.

A similar mechanism is known to operate via the carotid arterial baroreceptors, where reduction in pulsatility of the arterial blood pressure, with a constant mean value (as occurs with hemorrhage) results in a reduced mean baroreceptor firing (1) and an increase in peripheral resistance (19).

Discussion here emphasises the importance of arterial $P_{CO_2}$ oscillation transport, carotid body detection, and central (brain stem) processing in the dynamic ventilatory response. Further work is needed before an integrated account will be available. Such an account should explain the means by which the rapid $P_{CO_2}$ changes, present in the respiratory oscillations, can affect mean ventilation. It is intriguing that climbers returning from higher altitudes showed the greatest dynamic ventilatory drive, and yet supplementary oxygen could abolish it. Extensive studies in altitude athletic training using the “live high, train
low” methodologies of Levine and Stray-Gundersen among others (26) have shown that the precise altitude of sojourn during training is important, and we speculate that this would influence their dynamic ventilatory response. The superior athletic performance of Sherpa and Tibetan native peoples might be related more closely to dynamic than to conventional measures of ventilatory drive.

In summary, the present work has shown that ventilation may differ at a given $P_cO_2$ as a result of differences in the profile of $P_cO_2$ oscillations of respiratory frequency. Although the changes here are artificial, $P_cO_2$ oscillation changes have been shown to change the respiratory drive in their own right. $P_cO_2$ oscillations can therefore supply a ventilatory drive, independent of mean $P_cO_2$, as proposed in the introduction. The naturally occurring $P_cO_2$ oscillations, although different, change far more in moderate exercise (6) than our artificial changes. The naturally occurring $P_cO_2$ oscillations also appear to be phase locked to the respiratory cycle (13, 14), and changes in their magnitude and timing may well underlie the appropriate ventilatory increases that sustain isocapnia in moderate exercise. The subject remains a difficult challenge since changes in their magnitude and timing may well underlie the profile of $P_aCO_2$ (4).

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Data from patients during altitude training are (to some extent) unphysiologic.

The dynamic ventilatory response could well be an important drive to breathing during exercise, with the potential for scaling ventilation in relation to the metabolic rate.

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REFERENCES


