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O₂ AND CO₂ END-TIDAL TO ARTERIAL PARTIAL PRESSURE GRADIENTS
DURING PROGRESSIVE HYPOXIA

by

Richard B. Weiskopf and Ronald A. Gabel
US Army Research Institute of Environmental Medicine
Natick, MA 01760

and

Departments of Anesthesia, Peter Bent Brigham Hospital
and Harvard Medical School
Boston, MA 02115

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Please address all correspondence to:

Richard B. Weiskopf, M.D.
Major, MC
USA Research Institute of Environmental Medicine
Natick, MA 01760

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This human research study, in protocol form, was reviewed and approved by the Office of the Surgeon General for the Department of the Army in accordance with Army Regulation 70-25.

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Abstract. We measured end-tidal to arterial partial pressure differences for oxygen (ETaD₀₂) and carbon dioxide (ETaDCO₂) while examining the ventilatory response to rapidly progressive hypoxia in four men. Respiratory gases were measured continuously at the mouth by mass spectrometry. Arterial blood gases were measured 2-4 times during each study. At P_{O2} 40 torr, mean ETaD₀₂ was -0.7 ± 0.4 torr (S.E.) and mean ETaDCO₂ was -0.06 ± 0.04 torr (S.E.). Correction for lung-to-arm circulation time resulted in mean calculated ETaD₀₂ of 0.2 ± 0.3 torr. These gradients are sufficiently small that for most purposes, in normal, young, non-obese individuals, sitting at rest, end-tidal P_{O2} and P_{CO2} may be used as estimates of Pa_{O2} and Pa_{CO2} during determination of the ventilatory response to isocapnic progressive hypoxia.

AaD₀₂
hypoxia

AaDCO₂
mass spectrometry

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Introduction

Because of the variability in alveolar-to-arterial partial pressure gradients during steady-state normoxia and hypoxia (Kronenberg et al., 1971; Haab et al., 1969; Reeves et al., 1969; Weiskopf and Severinghaus, 1972), we have hesitated to depend upon expired gas values in our evaluations of the ventilatory response to hypoxia. Instead, we have routinely measured arterial blood gases to estimate the stimulus presented to the peripheral chemoreceptors.

In the hope of eliminating the potential risk of sampling arterial blood, we examined end-tidal to arterial partial pressure gradients for oxygen (ETaD_{O₂}) and carbon dioxide (ETaDCO₂) during the isocapnic progressive hypoxia test. We sought to sample and measure O₂ and CO₂ in blood and gas samples as accurately as current technology would allow. The results indicate that end-tidal to arterial oxygen and carbon dioxide gradients in normal man, as measured in the described manner during rapidly progressive hypoxia, are sufficiently small as to be relatively unimportant in assessing the hypoxic ventilatory drive of normal men.

Methods

a. Subjects

Four healthy male volunteers were studied. Their physical characteristics are given in Table 1.

b. Respiratory apparatus

Each subject, sitting upright, with a soft clip occluding his nostrils, breathed through a mouthpiece into a "Triple- J" valve (Collins) placed within a closed circle system containing a CO₂ absorber and a Wedge Spirometer (Med-Science, Model 570). By adjusting a valve within the circle, one of the investigators varied the amount of CO₂ absorption so as to maintain end-tidal PCO₂ as constant as possible throughout each test. Following several minutes at PETO₂ 110 torr, nitrogen was added to the system through a calibrated flow meter, and gas was evacuated from the circle system through a vacuum flow meter so that the net inflow and outflow matched changes in gas volume due to differences between gas release and gas uptake by pulmonary capillary blood, as well as O₂ consumption, CO₂ production, and CO₂ absorption. Each test, which was terminated at an end-tidal PO₂ of approximately 40 torr, took 3-5 minutes.

c. Analytic apparatus

1. Respiratory gases: CO₂ and O₂ were continuously measured at the mouth by mass spectrometry (Perkin-Elmer MGA 1100A). The

spectrometer has a lag time of approximately 250 milliseconds, a response time (to 1/e) of 30-35 ms, and a sampling rate of approximately 30 ml/minute. Water vapor was not measured but was assumed to be 47 torr in expired gas. Zero values for oxygen and carbon dioxide were set with research grade nitrogen (Matheson; certified minimum purity 99.9995% N₂). The oxygen channel was calibrated with outside air and research grade oxygen (Matheson; certified minimum purity 99.99% O₂); the carbon dioxide channel was calibrated with gas mixtures analyzed by the method of Scholander (1947). Output voltages of the mass spectrometer were set utilizing a digital voltmeter (Data Precision, Model 245) calibrated with standard voltages traceable to NBS standards. The accuracy of the mass spectrometer compared with Scholander analysis in our laboratory, is delineated by the following least-squares linear regression equations:

$$\text{CO}_2: M = 1.000 S - 0.04 \text{ Vol}\% \text{CO}_2 \quad (r = 1.0000; N = 20; \text{range } 0\text{-}16\% \text{CO}_2)$$

$$\text{O}_2: M = 0.999 S - 0.007 \text{ Vol}\% \text{O}_2 \quad (r = 1.0000; N = 14; \text{range } 0\text{-}100\% \text{O}_2)$$

where

M = volume % determined by mass spectrometry and

S = volume % determined by Scholander analysis.

2. Blood gases: Radial arterial blood was drawn during a 1-3 breath period through an indwelling 18-gauge, Teflon cannula into syringes in which the dead space had been filled with heparin solution

(1000 units/ml). Samples were immediately placed in ice, and were analyzed within 90 minutes for PaCO_2 and PaO_2 by appropriate electrodes (Radiometer E5036 and E5046) at 37°C in thermostated glass and steel cuvetts (Radiometer, D616). pH was measured using a Severinghaus-UC electrode (Severinghaus, 1965). A calibrating gas or buffer was read before and after each blood reading. To minimize errors due to alinearity of the oxygen electrode, calibrating gases were carefully selected so that a gas value close to the blood value (as estimated from end-tidal values) was used for each calibration. Each sample was analyzed in duplicate. Values were corrected for electrode drift and to the subject's temperature (Severinghaus, 1966). PO_2 was also corrected for the gas/blood factor, ϕ_b , by a modification (Weiskopf, Nishimura and Severinghaus, 1971) of the method of Hulands et al. (1970).

d. Recording apparatus

Analog signals from the spirometer and mass spectrometer were recorded graphically on a Hewlett-Packard Model 7708 recorder and magnetically on a Tandberg Model 100 FM tape recorder (with flutter compensation) utilizing Scotch 801 instrumentation grade magnetic tape. For more critical analysis, the recorded tapes were replayed and graphic recordings reproduced on a Hewlett-Packard Model 7045A X-Y recorder calibrated at 4 torr/cm.

Results

The data are presented in Table 2. Each blood value is the mean of duplicate analyses. The mean differences (calculated without regard to sign) between two readings of the same blood sample were 0.43 ± 0.076 (S.E.) torr P_{aO_2} and 0.23 ± 0.046 (S.E.) torr P_{aCO_2} . The end-tidal values reported are the mean PET_{O_2} and mean PET_{CO_2} for breath(s) which occurred during sampling of arterial blood. In most instances the arterial blood was sampled during a single breath.

All tests of progressive hypoxia were performed with the subject maintained isocapnic, as determined by end-tidal PCO_2 . Despite the relative steady state with respect to CO_2 , $ETaDCO_2$ varied from -1.5 to 2.2 torr. During most tests the $ETaDCO_2$ progressively narrowed as P_{O_2} decreased. In all instances the $ETAD_{CO_2}$ virtually disappeared at P_{O_2} 40 torr (mean \pm S.E., -0.06 ± 0.04 torr; range, -0.2 torr to 0.0 torr). Measured $ETaDO_2$ at P_{O_2} 40 torr ranged from -2.9 to 0.6 torr, with a mean of -0.7 ± 0.4 (S.E.) torr.

Discussion

We attribute the lack of any large $ETaDO_2$ (range: -4.5 to 2.5 torr) throughout the rapid progression of hypoxia to two factors. The first, and probably more important, is that P_{aO_2} was falling at a rate such that the true end-tidal to arterial oxygen gradient was obscured by the time required for blood to circulate from the pulmonary capillaries to the radial artery. There have been many different

estimates for circulation time from lung to radial artery (Altman and Dittmer, 1971). We did not measure the pulmonary capillary to radial artery circulation time in these subjects, and it is likely to have varied during the course of each experiment as cardiac output and vascular resistance varied with rapid changes in P_{aO_2} . If we assume an average circulation time, however, we can estimate a value for $P_{ET}O_2$ at the time when the blood which was sampled was in alveolar capillaries. At each sampling of blood we know the rate at which $P_{ET}O_2$ was falling (Table 2). Assuming a pulmonary capillary to radial artery circulation time of 6 seconds (Altman and Dittmer, 1971), the range for calculated $ETaD_{O_2}$ (that is, gradients when $P_{ET}O_2$ values are corrected for time lag) becomes -1.4 to 6.0 torr (Table 2). An assumed shorter circulation time of 4 seconds would make this range of calculated $ETaD_{O_2}$ -1.8 to 4.9 torr, and an assumed longer circulation time of 10 seconds would make the range -0.4 to 8.4 torr.

During evaluation of ventilatory sensitivity to hypoxia, the most crucial need for accuracy in the measurement of P_{O_2} is where ventilation is most sensitive to a change in blood gas composition: at the lowest P_{O_2} achieved during the test (P_{O_2} approximately 40 torr). Measured $ETaD_{O_2}$ in our subjects at P_{O_2} 40 ranged from -2.9 to 0.6 torr, mean -0.7 ± 0.4 torr. Weil et al. (1970) reported end-tidal values as well as arterial blood values for P_{O_2} and P_{CO_2} during slowly (14-17 minutes)

progressive hypoxia. Each of their blood samples was drawn over about 20 seconds and thus included many breaths while PET_{O_2} was changing. There was no information regarding the details of blood gas analyses, and Pa_{O_2} and Pa_{CO_2} were reported only to the nearest one-half torr. With these limitations, Weil *et al.* (1970) found that $ETaD_{O_2}$ below PO_2 43 torr ranged from -5.9 to 2.8 torr.

Our calculated $ETaD_{O_2}$ s at PO_2 40 are relatively insensitive to incorrect estimates of circulation times because of the relatively slow rate of change of PO_2 at that level of oxygenation (-0.14 ± 0.04 torr/sec). Using an estimate of lung to radial artery circulation time of 6 seconds, calculated $ETaD_{O_2}$ at PO_2 40 ranged from -1.3 to 1.1 torr, mean 0.2 ± 0.3 (S.E.) torr. Calculated PET_{O_2} at PO_2 40 was not significantly different from Pa_{O_2} over the range of estimated lung to radial artery circulation times of 4 to 10 seconds.

We attribute these lower than expected calculated values, including the few negative values, to characteristics of the instrumentation used for gas analyses. The mass spectrometer measures so rapidly (response time to $1/e = 30-35$ ms) and utilizes such a small gas sample (30 ml/minute) that a measured end-tidal value must be very close to the lowest expired PO_2 , which is lower than the end-tidal values to which we are generally accustomed. Because the true PET_{O_2} is lower than the mean alveolar PO_2 , one would expect minimal or even negative values for $ETaD_{O_2}$ when a rapidly-responding oxygen analyzer is used.

The progressive narrowing of the $ETaD_{CO_2}$ during progressive hypoxia appears to have been related to PO_2 and not to \dot{V}_E , because at normoxic and mildly hypoxic levels the $ETaD_{CO_2}$ persisted during hypercapnic studies despite the greatly increased ventilation at each PO_2 . The narrowing of $ETaD_{CO_2}$ with decreasing PO_2 might be a result of the improvement of ventilation-perfusion matching known to occur with acute hypoxia (Dawson, 1969) although other factors, such as rate of change of PO_2 or alterations in respiratory frequency, might have been contributory.

Mean $ETaD_{CO_2}$ at PO_2 40 was -0.06 ± 0.04 torr (range -0.2 to 0.0 torr), which is within the error of measurement of $PaCO_2$. Use of end-tidal PCO_2 should not produce error in determination of ventilatory sensitivity to rapidly progressive hypoxia.

We conclude that PET_{O_2} and PET_{CO_2} may be substituted for PaO_2 and $PaCO_2$ during determination of normal man's ventilatory sensitivity to acute hypoxia, as measured by the rapid isocapnic progressive hypoxia test.

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TABLE 1

Physical Characteristics of Subjects

Subject	Age (yrs)	Ht (cm)	Wt (Kg)	S.A. (m ²)
C.J.	20	184.2	72.2	1.94
K.H.	23	181.6	72.6	1.93
V.F.	30	157.9	77.2	1.80
M.A.	18	180.3	74.9	1.94

TABLE 2 Expired Gas and Blood Gas Values during Progressive Hypoxia

Subject	PETCO ₂ (torr)	Paco ₂ (torr)	ETaDCO ₂ (torr)	PETO ₂ (torr)	PaO ₂ (torr)	ETaDO ₂ (torr)	Rate of Change of PETO ₂ (torr/sec)	Calculated PETO ₂ * (torr)	Calculated ETaDO ₂ + (torr)	VE (L·min ⁻¹) (BTPS)
C.J.	39.9	38.8	1.1	104.4	95.7	8.7	0	92.5	2.7	
	38.6	39.6	-1.0	88.4	89.8	-1.4	-0.69	74.3	2.8	
	37.8	38.6	-0.8	70.9	71.5	-0.6	-0.56	36.2	-1.0	
	37.3			34.8	37.2	-2.4	-0.23	75.3	3.1	13.4
	38.7			71.1	72.2	-1.1	-0.70	56.3	0.4	17.0
40.5			54.6	55.9	-1.3	-0.28	38.7	-1.3	22.8	
38.5			37.1	40.0	-2.9	-0.27				
K.H.				110.0	97.6	12.4	0	83.5	6.0	22.5
	39.4			80.0	77.5	2.5	-0.59	59.5	2.0	25.0
	39.0			57.6	57.5	0.1	-0.32	41.5	0.9	36.9
	39.5			40.5	40.6	-0.1	-0.16	82.3	4.0	43.3
	44.9			80.4	78.3	2.1	-0.32	41.6	0.0	63.4
46.0			41.0	41.6	-0.6	-0.10				
V.F.				100.7	98.5	2.2	0	78.4	3.9	17.8
	40.0	41.2	-1.2	75.0	74.5	0.5	-0.57	54.5	1.3	26.2
	40.4	40.6	-0.2	52.7	53.2	-0.5	-0.30			50.6
	39.0	39.0	0	39.5	38.9	0.6	0	76.9	1.8	38.4
	44.8	42.6	2.2	74.3	75.1	-0.8	-0.43	60.1	-1.2	52.2
44.5	43.5	1.0	58.6	61.3	-2.7	-0.25	40.7	0.8	94.2	
45.9	46.0	-0.1	40.2	39.9	0.3	-0.09	77.2	1.2	16.4	
M.A.	41.6	41.0	0.6	73.2	76.0	-2.8	-0.66	60.2	1.0	20.9
	40.7	41.4	-0.7	57.5	59.2	-1.7	-0.45	43.5	1.1	53.6
	40.5	40.7	-0.2	41.4	42.4	-1.0	-0.35	77.6	0.0	25.9
	44.6	45.0	-0.4	74.7	77.6	-2.9	-0.48	59.5	-1.4	36.8
	43.8	44.4	-0.6	58.1	60.9	-2.8	-0.24	46.8	-0.1	62.7
44.0	44.0	0.0	46.3	46.9	-0.6	-0.08	58.9	-0.4	10.1	
40.0	41.5	-1.5	54.8	59.3	-4.5	-0.68			19.7	
39.6	40.6	-1.0	39.9	39.2	0.7	0			53.2	
42.0	42.0	0.0								

* Calculated PETO₂ = measured PETO₂ - (6 seconds) × (rate of change of PETO₂)

+ Calculated ETaDO₂ = calculated PETO₂ - PaO₂

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14 REPORT DOCUMENTATION PAGE		AD INSTRUCTIONS BEFORE COMPLETING FORM
1. REPORT NUMBER M 11/76	2. GOVT ACCESSION NO. FUSARTEM-M-11/76	3. RECIPIENT'S CATALOG NUMBER
4. TITLE (and Subtitle) O ₂ and CO ₂ End-Tidal to Arterial Partial Pressure Gradients during Progressive Hypoxia		5. TYPE OF REPORT & PERIOD COVERED
7. AUTHOR(s) Richard B. Weiskopf [redacted] Ronald A. Gabel		8. CONTRACT OR GRANT NUMBER(s) 12/17p
9. PERFORMING ORGANIZATION NAME AND ADDRESS US Army Research Institute of Environmental Medicine, Natick, MA 01760		10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS 16/ 3A161101A91C
11. CONTROLLING OFFICE NAME AND ADDRESS US Army Research Institute of Environmental Medicine, Natick, MA 01760		12. REPORT DATE 11/ Nov 75
14. MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office)		13. NUMBER OF PAGES 15
		15. SECURITY CLASS. (of this report) UNCLASSIFIED
		15a. DECLASSIFICATION/DOWNGRADING SCHEDULE
16. DISTRIBUTION STATEMENT (of this Report) Distribution of this report is unlimited.		
17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)		
18. SUPPLEMENTARY NOTES Submitted for publication to <u>Respiration Physiology</u> .		
19. KEY WORDS (Continue on reverse side if necessary and identify by block number) AaD _{O₂} AaD _{CO₂} hypoxia mass spectrometry sub O ₂ sub CO ₂ Breathing gases?		
20. ABSTRACT (Continue on reverse side if necessary and identify by block number) We measured end-tidal to arterial partial pressure differences for oxygen (ETaD _{O₂}) and carbon dioxide (ETaD _{CO₂}) while examining the ventilatory response to rapidly progressive hypoxia in four men. Respiratory gases were measured continuously at the mouth by mass spectrometry. Arterial blood gases were measured 2-4 times during each study. At P _{O₂} 40 torr, mean ETaD _{O₂} was -0.7 sub O ₂ sub CO ₂		

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± 0.4 torr (S.E.) and mean $ETaD_{CO_2}$ was -0.06 ± 0.04 torr (S.E.). Correction for lung-to-arm circulation time resulted in mean calculated $ETaD_{O_2}$ of 0.2 ± 0.3 torr. These gradients are sufficiently small that for purposes, in normal, young, non-obese individuals, sitting at rest, end-tidal P_{O_2} and P_{CO_2} may be used as estimates of PaO_2 and $PaCO_2$ during determination of the ventilatory response to isocapnic progressive hypoxia.

sub CO2

+ or -

+ or -

sub O2



sub O2

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