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Comparison of Transcutaneous and End-tidal CO2 Measurements in Aerospace Environments

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STATEMENTS

Disclaimer

The views expressed in this technical report are those of the author and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, nor the U.S. Government.

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Human Research/Institutional Review Board (IRB) statement

The study protocol was approved by the Naval Medical Research Unit Dayton Institutional Review Board in compliance with all applicable federal regulations governing the protection of human subjects.

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ABSTRACT

Transcutaneous monitoring of carbon dioxide (CO_2) has been proposed for use in physiological monitoring of tactical jet aircrew because in some clinical settings it provides useful information about control of arterial CO_2 partial pressure. End tidal monitoring in a laboratory setting is known to give high-fidelity estimates of arterial CO_2 partial pressure (PCO_2). The correspondence between end-tidal ($P_{ET}CO_2$) and transcutaneous ($tcPCO_2$) measures of PCO_2 was examined under conditions of hyperoxia and hypoxia in healthy volunteers in a laboratory. Rest and exercise, skin heating and cooling, hyperventilation, and induced CO_2 retention were employed. Resting measurements at or near normoxia, and exercise measurements during breathing of 40% O_2 were also examined. Bland-Altman analysis of $tcPCO_2$ and $P_{ET}CO_2$ showed that the two were equivalent only during normoxic resting measurements. Regression analysis indicated that tissue PO_2 measured as transcutaneous PO_2 ($tcPO_2$) is an important explanatory variable for $tcPCO_2$ in addition to $P_{ET}CO_2$, and that local skin temperature also has an effect. Additionally, prolonged sitting while breathing 100% O_2 and hypoxic exercise caused $P_{ET}CO_2$ to deviate from P_aCO_2. Thus, $tcPCO_2$ is not useful as even a trend indicator for arterial PCO_2 in the highly dynamic tactical jet aircraft environment. $P_{ET}CO_2$ is also not a good indicator of CO_2 status in pilots who breathe nearly 100% O_2.

INTRODUCTION

Reliable estimation of arterial carbon dioxide partial pressure (P_aCO_2) of aircrew in the cockpit of a tactical aircraft is a major technical challenge. One option that has been considered is to measure transcutaneous PCO_2 ($tcPCO_2$). Just as end-tidal CO_2 ($P_{ET}CO_2$) monitoring can be relied on in the laboratory, transcutaneous measurement is well-established for use in the intensive care unit. Although $tcPCO_2$ measures local tissue PCO_2, not P_aCO_2 (Severinghaus, 1981; Radiometer, 2016), it tracks changes in P_aCO_2 in many clinical applications (e.g., Severinghaus, 1981; Aarrestad et al., 2016, Rodriguez et al., 2006. In some patients with very uneven distribution of ventilation in the lungs, $tcPCO_2$ provides a better indicator of P_aCO_2 than can be derived from expired gas sampling (Cox and Tobias, 2007; Lermuzeaux et al., 2016).

NAMRU-D was tasked to assess the utility of $tcPCO_2$ monitoring in the cockpit, because conditions common in aircraft could alter the P_aCO_2 to $tcPCO_2$ relationship. Factors affecting local tissue metabolism in pilots include inspired oxygen partial pressure (inspired PO_2), skin temperature, and whole body activity, all of which are easily manipulated in a laboratory setting where careful measurement of $P_{ET}CO_2$ reflects arterial PCO_2 (Jones et al, 1979). A study with the sole purpose of comparing the two methods was undertaken, supplemented by data from two other studies in which both end-tidal and transcutaneous PCO_2 were measured.

The $P_{ET}CO_2$ to $tcPCO_2$ comparison study examined the practical extremes of inspired PO_2, with testing during maximal normobaric hyperoxia (100% oxygen on the ground) and during hypoxia (11.5% oxygen in nitrogen at a ground altitude of 900 ft) roughly equivalent to 16,000 ft MSL without supplemental oxygen. (During the hypoxic exposure peripheral arterial hemoglobin saturation in a few participants dropped below 60%.) The two studies, which had other main goals, provided oxygen exposures between those extremes: normobaric normoxia -- 21% oxygen, and mild to moderate normobaric hyperoxia -- an average of approximately 28%, 35%, and 40% oxygen inhaled in the laboratory at approximately 900 ft altitude.

METHODS

All three studies were approved by the Institutional Review Board of Naval Medical Research Unit Dayton. All participants gave written documentation of informed consent.

One minute, steady-state averages of $P_{ET}CO_2$ and $tcPCO_2$ values were compared. IBM SPSS Statistics was used for statistical analysis. The association between $P_{ET}CO_2$ and $tcPCO_2$ was confirmed by correlation; agreement was assessed using a Bland-Altman plot and regression analysis of the difference vs. the mean (Altman and Bland, 1983; Bland and Altman, 1986); and further explanatory variables were considered by step-wise forward linear regression. Because the analysis was of the agreement between two measurements under each condition, measurements in the same individual under

different conditions were considered to be independent.

Transcutaneous data were collected using a TCM4/COMBI M84 (Radiometer, Copenhagen, DK) with the probe temperature at the standard 45°C and with a metabolic correction that subtracted 5 mmHg before displaying the value (Radiometer, 2012). Before the probe was attached, skin was cleaned with alcohol and let dry, and a single drop of Radiometer's standard electrolyte solution was used within the attachment ring to couple the probe to the skin. The probe was allowed to stabilize for at least 20 minutes before any data were collected.

End-tidal CO_2 was measured using a fast-response NDIR analyzer (GA-200, iWorx, Dover NH) with the sample line tip inserted into the gas stream, and with no filters, physical or electronic, in use. The target gas sampling flow rate was 400 to 500 mL/s.

Data set 1: Comparison experiment, 100% O_2 or 11.5% O_2 at ground level, rest and exercise

Fourteen volunteers participated in the hyperoxic, and twelve in the hypoxic, arm of the study. However, data from one participant in the hypoxic arm were lost because the probe was not properly coupled to the skin and the electrode read room air. Demographics are summarized in Table 1.

Instrumentation. Participants wore the transcutaneous probe on the volar surface of their left forearms. A skin temperature probe (moorVMS-LDF laser Doppler, Moore Instruments, Wilmington DE) was affixed approximately 3 cm away, with the distance established by letting the adhesive disks for each device touch without overlapping. Participants breathed either 100% oxygen (hyperoxic condition) or 11.5% oxygen in nitrogen (hypoxic condition) delivered at atmospheric pressure through large-bore (35 mm id) respiratory tubing (VacuMed, Ventura CA), from a gas reservoir (60 L gas bag, Hans Rudolph, Shawnee, KS), to a one-way (non-rebreathing) valve (Model 2700, Hans Rudolph), attached to a silicone oro-nasal mask (Series 7450, Hans Rudolph). The gas reservoirs were filled under manual control from cylinders of compressed gas. The gas analyzer sample line was inserted radially through a port on the connecting ring between the mask and the valve assembly until the end was approximately centered in the circular ring.

Participants in the hypoxic arm also wore a finger pulse oximeter (Nonin Medical, Plymouth MN) on their right hands for safety monitoring; participants were returned to air breathing if peripheral hemoglobin saturation (S_pO_2) was less than 60% for more than a few seconds. All participants wore a chest strap style heart rate monitor(Polar Electro Inc, Bethpage NY), the output from which was used to control the cycle ergometer (ExCalibur Sport, Lode B.V., Groningen, The Netherlands) during the exercise phase of the study.

Data were sampled at 100 Hz, displayed, and stored using a PowerLab, LabChart data acquisition suite (ADInstruments, Colorado Springs, CO). Participants watched videos for distraction throughout their time in the laboratory. They sat in a recliner chair until

they transferred to the ergometer, and they breathed test gas from the start to the end of data collection.

Data Collection. Data were collected under six sequential conditions (Fig. 1): 1) ten minutes of quiet seated rest; 2) five minutes of seated hyperventilation, when participants breathed in time with a metronome at 30 breaths per minute; 3) up to 20 minutes of local skin cooling ("cold"); 4) up to 20 minutes of local skin heating ("heat"); 5) ten minutes of cycle ergometer exercise; and 6) five minutes of resistive breathing ("RB"), with a resistive element in the inspiratory line during continued cycle exercise.

Figure 1. Timeline of the study

Cold was applied using a flexible gel freezer pack just removed from a nominally –18 °C freezer, separated from the skin by a single layer of cloth towel. The arm and cold pack were overwrapped with the rest of the towel to prevent the cold pack from sliding off. Heat was applied using a pre-heated household electric heating pad (000756-500-000U, Sunbeam Products Inc, Boca Raton FL), set to high and wrapped around the forearm over the probes. Heating and cooling continued for a maximum of 20 minutes or until the skin temperature reading remained within 0.2 °C for two minutes. During the cold and heat conditions, a small spacer of closed-cell foam placed around the TCM and temperature sensors prevented excessive pressure on the probes.

For exercise, the participant moved from the chair to an adjacent cycle ergometer. The target exercise heart rates during hyperoxia and hypoxia, respectively, were 80% or 60% of heart rate reserve, calculated by the Karvonen method (ACSM, 2000). Lode Ergometry Manager software was pre-programmed to increase the ergometer load incrementally until the target heart rate was reached and then to adjust the load to maintain it; the 10 minutes of exercise included the period of increasing load. For resistive breathing, a plug 1.25 inches long with a 0.25-inch diameter hole was inserted into the inspiratory port of the non-rebreathing valve before another five minutes of exercise at the controlled heart rate.

Data reduction Data from the last minute of each condition were extracted and averaged using LabChart software. Breath-by-breath maxima of the CO_2 from the mask (end tidal values) and the simultaneous end-tidal O_2, both representative of alveolar gas, were extracted and averaged, and the averages of $tcPCO_2$ and $tcPO_2$ and skin temperature were computed. The known lag time of the TCM in response to changes in gas partial pressures (Radiometer, 2012) was ignored because the measurement periods were presumed to represent steady-state.

The O_2 analyzer was calibrated for accuracy in the hypoxic range, and therefore was out of range for $P_{ET}O_2$ during hyperoxia. Instead, alveolar oxygen partial pressure (P_AO_2) during hyperoxia was calculated from the alveolar gas equation, as

$$P_AO_2 = F_IO_2 (P_b - P_{water}) - P_ACO_2 \quad [1]$$

where P_b is barometric pressure, P_{water} is the saturation partial pressure of water vapor at the normal body temperature of 37 °C (P_{water} = 47 mmHg, 6.3 kPa), and F_IO_2 is inhaled oxygen fraction (F_IO_2 = 1). When 100% oxygen is inhaled, P_AO_2 does not depend explicitly on the respiratory exchange ratio between rates of carbon dioxide elimination and oxygen extraction. (Note that if the fraction of inhaled oxygen is less than one and the respiratory exchange ratio is not equal to one there are some other minor terms that enter the equation. However, the form given here still yields a close approximation of the correct value.)

The O_2 and CO_2 analyzers in the gas analyzer unit are independent. However, the presence of high O_2 has a physical effect on the absorption spectrum of CO_2, the value from which the partial pressure is derived. The correction factor provided by the manufacturer for this analyzer for CO_2 measured in the presence of 95% O_2, the approximate concentration in end-tidal gas, 1.06, was applied to the end-tidal values during hyperoxia. (The correction factor for 100% O_2 is 1.067.)

Data set 2: Inspired 40% oxygen at ground level, mild to moderate exercise

The main purpose of the study from which these data were extracted was to examine physiological effects of marginal or inadequate regulator supply pressures. Participants attended three measurement sessions where they breathed 40% oxygen in nitrogen, delivered through an aviation demand regulator to an aviation mask. The mask used to deliver gas was tapped for insertion of the gas analyzer sample line, the end of which was inside the mask cavity, between the nose and mouth. For each session, five minutes with a good regulator inlet pressure was followed by five minutes at one of three lower supply pressures. Seventeen volunteers participated. CO_2 measurements from the final minute of each regulator supply pressure condition are presented here.

Participants exercised at 50 W on a cycle ergometer (Ergomedic 828E, Monark, Vansbro, Sweden). The exercise level was chosen to generate minute ventilations of approximately 25 L/min, at the upper end of the range previously measured in pilots during various stages of ground operations and flight (Gordge, 1993).

The transcutaneous probe was affixed to the skin of the participant's chest, approximately half-way between the shoulder and the suprasternal notch on the left side, below the clavicle and between ribs. Transcutaneous PCO_2 and PO_2 were recorded continuously within the TCM for later download. The gas signal from the mask was sampled at 100 Hz and recorded using LabView (National Instruments, Austin TX) hardware and software written for the purpose. End-tidal values were extracted in post–processing with Microsoft Excel. Event markers were used to synchronize the TCM and end-tidal signals.

Data Set 3: Inspired air or 35% O_2 at ground level, seated rest

The main purpose of the study was to explore physiological effects of regular fluctuations of oxygen partial pressure from normoxic to slightly hyperoxic gas. Participants attended four measurements sessions, each with four phases. During seated rest they breathed gas at ambient pressure from 60 L gas bags (Hans Rudolph, Shawnee KS), through large-bore (35 mm id) respiratory tubing (VacuMed, Ventura CA), to a one-way (non-rebreathing) valve (Model 2700, Hans Rudolph) attached to a silicone oro-nasal mask (Series 7450, Hans Rudolph). At each experimental session the breathing gases were 5 minutes of air, 20 minutes of either air or 35% oxygen, 30 minutes of either the same gas as in the previous period or of fluctuations between the two gases, and 30 minutes of air.

The TCM probe was affixed to the chest. The gas analyzer sample line was inserted radially through a port on the connecting ring between the mask and the valve assembly until the end was approximately centered in the circular ring. The signals from both the gas analyzer and the TCM were digitized and stored at 500 Hz using a PowerLab, LabChart data acquisition suite. DataPad software of that suite was used to extract and average end-tidal values and average TCM signals for the final minutes of each gas condition. Data are presented from 5 participants.

RESULTS

Table 1. Participant demographics, Data Set 1

Hyperoxia	9 men, 5 women			
	Age (years)	Height (cm)	Weight (kg)	BMI
Median	25	179	76	25
Range	20 to 37	154 to 196	54 to 118	20 to 31

Hypoxia	7 men, 4 women			
	Age (years)	Height (cm)	Weight (kg)	BMI
Median	26.5	177	79	25
Range	20 to 36	154 to 196	60 to 118	21 to 31

Table 2: Summary of Data Set 1 by experimental segment, means (standard deviation)

Hyperoxia n=14	**$tcPO_2$** mmHg	**$tcPCO_2$** mmHg	**$P_{ET}O_2$***	**$P_{ET}CO_2$**	**T_{skin}** °C
Rest	374 (87)	33 (6)	661 (4)	32 (4)	28 (1) ‡
			$F_{ET}O_2$ = 95%		
Hyperventilation	401 (93)	30 (8)	666 (5)	27 (5)	28 (1) ‡
Cold	389 (90)	30 (7)	662 (4)	31 (4)	22 (3) ‡
Heat	412 (89)	33 (8)	663 (4)	30 (4)	44 (1) ‡
Exercise	430 (95)†	33 (8) †	654 (6) †	39 (6) †	27 (1) ‡‡
RB	422 (89) †	35 (8) †	652 (7) †	41 (7) †	27 (1) ‡‡

RB: resistive breathing during exercise. T_{skin}: Skin temperature. * calculated values. ‡ n=12: T_{skin} was not measured in three participants. †n=13 ; ‡‡n=11. One participant could not exercise because of a problem with the set-up.

Hypoxia n=11	**$tcPO_2$** mmHg	**$tcPCO_2$** mmHg	**$P_{ET}O_2$**	**$P_{ET}CO_2$**	**T_{skin}** °C
Rest	35 (8)	39 (3)	49 (5)	35 (3)	28 (2) †
			$F_{ET}O_2$ = 7%		
Hyperventilation	31 (7)	38 (5)	52 (6)	32 (5)	28 (2) †
Cold	19 (5)	39 (4)	42 (2)	35 (3)	22 (2) †
Heat	21 (8) ‡	44 (8) ‡	45 (6) ‡	35 (5) ‡	43 (2) ‡‡
Exercise	23 (6) ‡‡	37 (5) ‡‡	49 (3) ‡‡	33 (2) ‡‡	28 (2) #
RB	19 (7) ##	35 (6) ##	45 (4) ##	34 (3) ##	28 (3)##

RB: resistive breathing during exercise. T_{skin}: Skin temperature. †n=9: T_{skin} was not measured in two participants. ‡ n=10, ‡‡n=8: One participant returned to air breathing during “heat”. ‡‡n=8; #n=7: Two other participants reached the S_pO_2 safety cut-off before exercise. ## n=6: Two who exercised reached the safety cut-off before resistance breathing.

Data Set 1: Effects of the interventions

Voluntary hyperventilation during rest and resistive breathing during exercise were used to manipulate P_aCO_2 (Table 2, Fig. 2). While hyperventilation caused significant ($p<0.001$ by 2-sided paired t-test,) decreases in $P_{ET}CO_2$ during both hyperoxia (n=14) and hypoxia (n=11), $tcPCO_2$ decreased only during hyperoxia ($p<0.003$). Resistive breathing during exercise caused a significant increase ($p<0.02$, n = 14) in $P_{ET}CO_2$ only during hyperoxia, and a significant ($p<0.03$, n = 6) decrease ($p<0.03$, n=6) in $tcPCO_2$ during hypoxia.

Participants apparently hyperventilated at rest for both hyperoxic and hypoxic exposures (Fig. 2); during normoxia, normal P_aCO_2 lies between 38 and 42 mmHg. This

was probably true hyperventilation during hypoxia, but may have been a response to intrapulmonary shunt during hyperoxia (see Discussion). Tissue PO_2 also showed variability in response to the breathing interventions (Fig. 2).

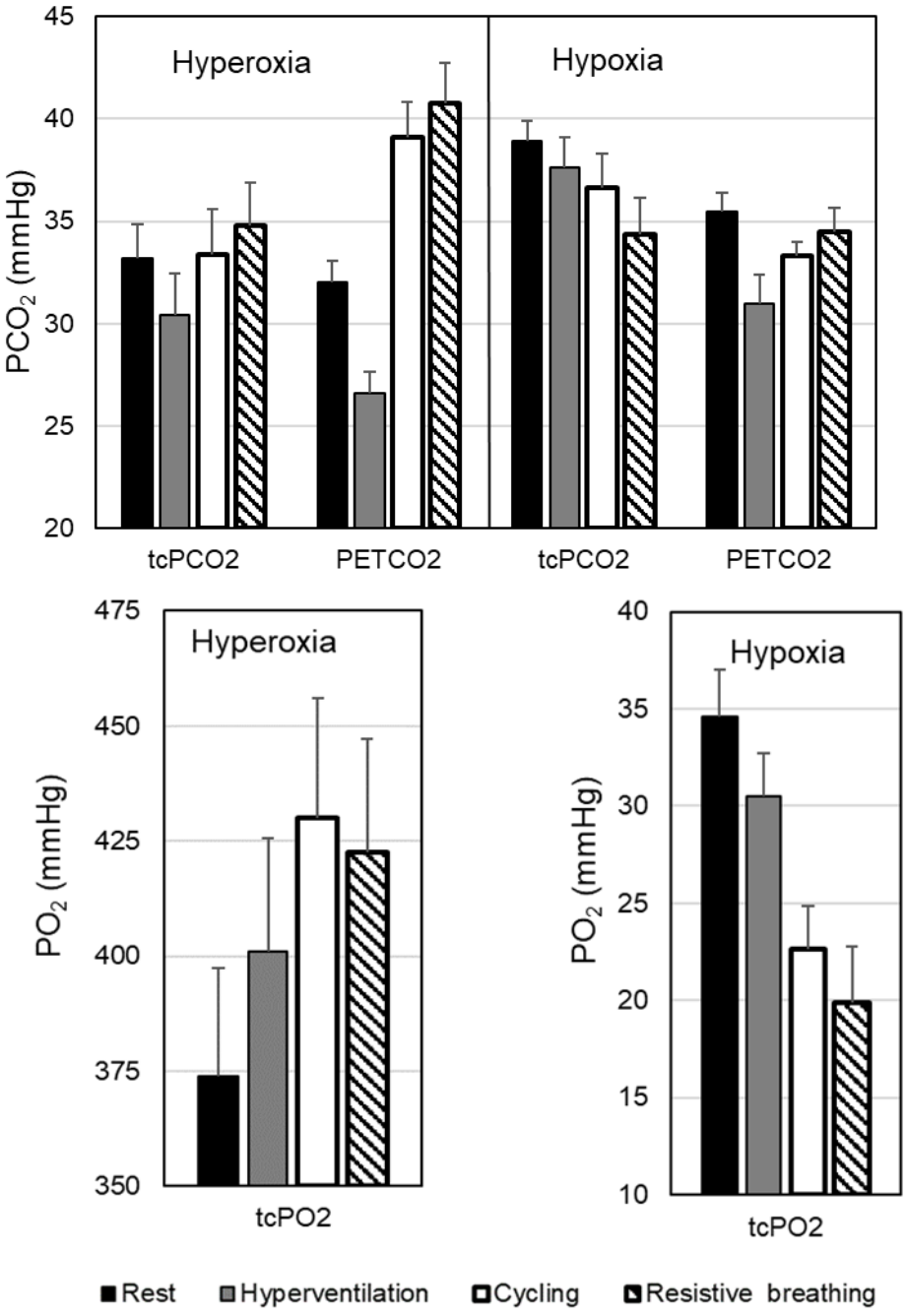

Figure 2. Measurements of PCO_2 and of transcutaneous PO_2 after interventions to change arterial PCO_2, Data Set 1. Bars indicate one standard error. Scales differ among plots. Solid bars: rest; open and

cross-hatched bars: exercise.

Skin cooling and heating were used in an attempt to alter skin perfusion without changing P_aCO_2. Skin temperature beside the TCM probe is shown in Figure 3; the temperature of the TCM probe as reported by the instrument remained at 44.9 °C throughout.

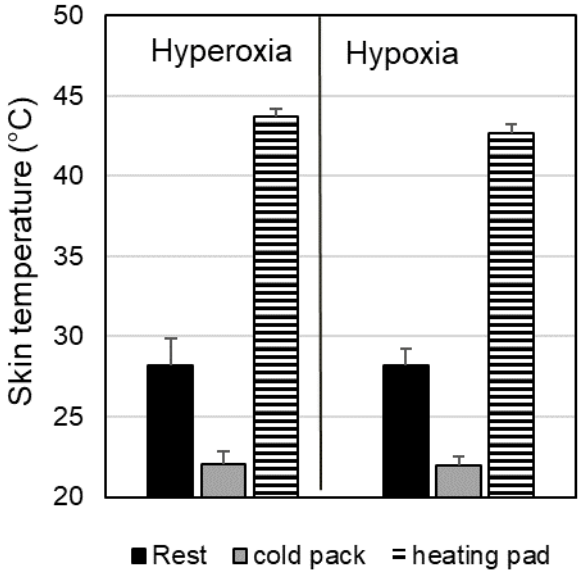

Figure 3. Skin temperature beside the TCM probe during temperature interventions, Data Set 1. Bars indicate one standard error.

The associated PCO_2 measurements are shown in Figure 4. During hyperoxia, forearm cooling was associated with a significant decrease in $tcPCO_2$ ($p<0.0005$ by paired t-test) with no statistically significant change in $P_{ET}CO_2$. Conversely, during hyperoxia forearm heating was not associated with change in $tcPCO_2$, but was associated with a significant ($p<0.005$) decrease in $P_{ET}CO_2$ relative to the rest period 45 minutes prior, but no change relative to the cold exposure 20 minutes earlier. During hypoxia, no significant change in either measure of CO_2 was observed during forearm chilling, while forearm warming was associated with significant increase ($p< 0.015$ by paired t-test, $n = 10$) in $tcPCO_2$ without significant change ($p>0.1$) in $P_{ET}CO_2$. The pairwise changes in transcutaneous PO_2 during changes in forearm skin temperature were marginally to highly significant (hyperoxia with cooling, $p <0.05$; hypoxia with heating, $p<0.02$; hypoxia with cooling, $p<0.008$; hyperoxia with heating, $p<0.001$).

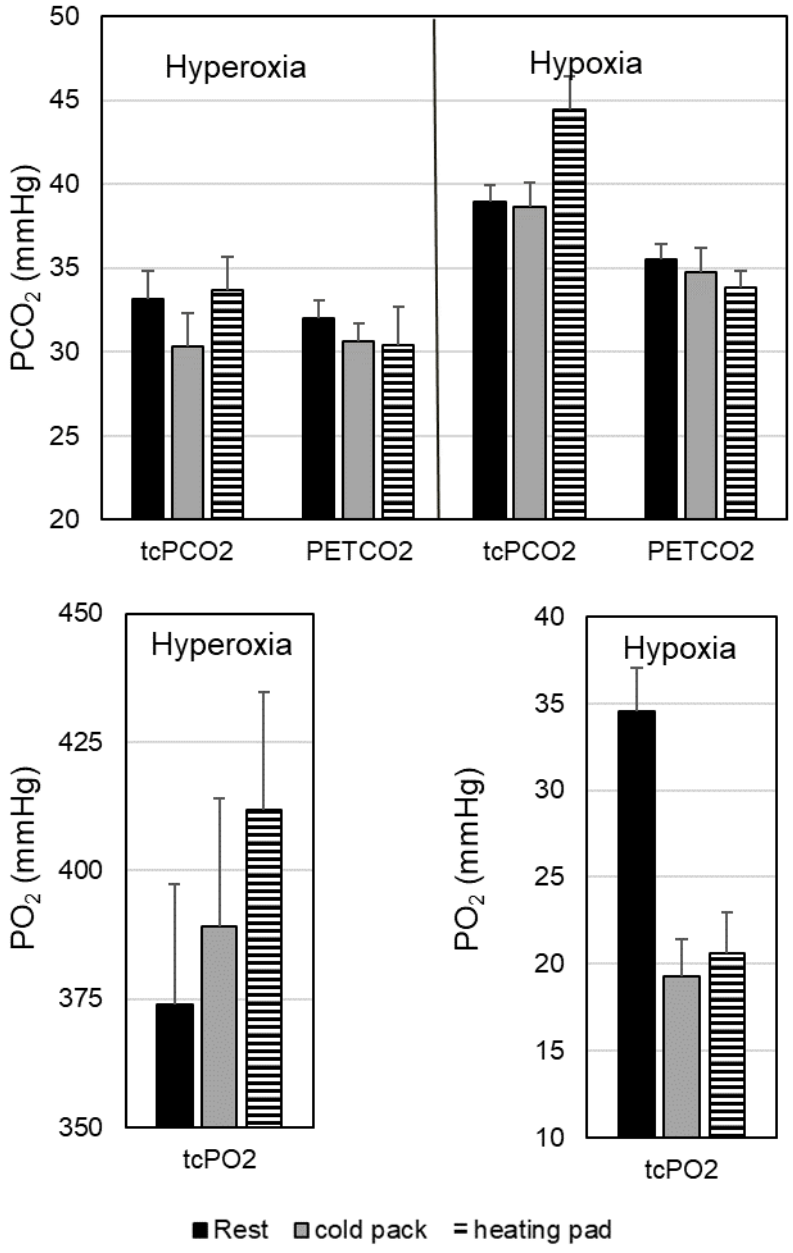

Figure 4. Measurements of PCO_2 and of $tcPO_2$ during temperature interventions, Data Set 1. Bars indicate one standard error.

Association of measures of carbon dioxide partial pressure

The correlations between $tcPCO_2$ and $P_{ET}CO_2$ (Fig. 5) are significant for all data sets except for Data Set 1 hypoxia during exercise (Table 3). However, scatter is large; for example, for Data Set 1, a "normocapnic" $P_{ET}CO_2$ of approximately 40 mmHg corresponds to $tcPCO_2$ readings from 30 to 50 mmHg, and a "normocapnic" $tcPCO_2$ reading of approximately 40 mmHg matches $P_{ET}CO_2$ from 30 to 53 mmHg. Further, the best linear regression equation to predict $tcPCO_2$ from $P_{ET}CO_2$ across Data Set 1,

$$tcPCO_2 = 0.70 \cdot P_{ET}CO_2 + 12 \qquad [2]$$

explains less than 34% of the variance in the $tcPCO_2$ data set (r^2=0.338).

Table 3. Pearson correlation coefficients r, $tcPCO_2$ to $P_{ET}CO_2$

Data Set	Rest R or Exercise E	r	n	p
1: 100% O_2	R	0.79	56	< 0.001
1: 100% O_2	E	0.76	27	< 0.001
1: 11.5% O_2	R	0.51	43	< 0.004
1: 11.5% O_2	E	0.23	16	**>0.35**
2: 40% O_2	E	0.65	62	< 0.001
3: 21% O_2	R	0.61	51	< 0.001
3: 35% O_2	R	0.62	12	0.031
3: Fluctuations	R	0.67	10	0.034

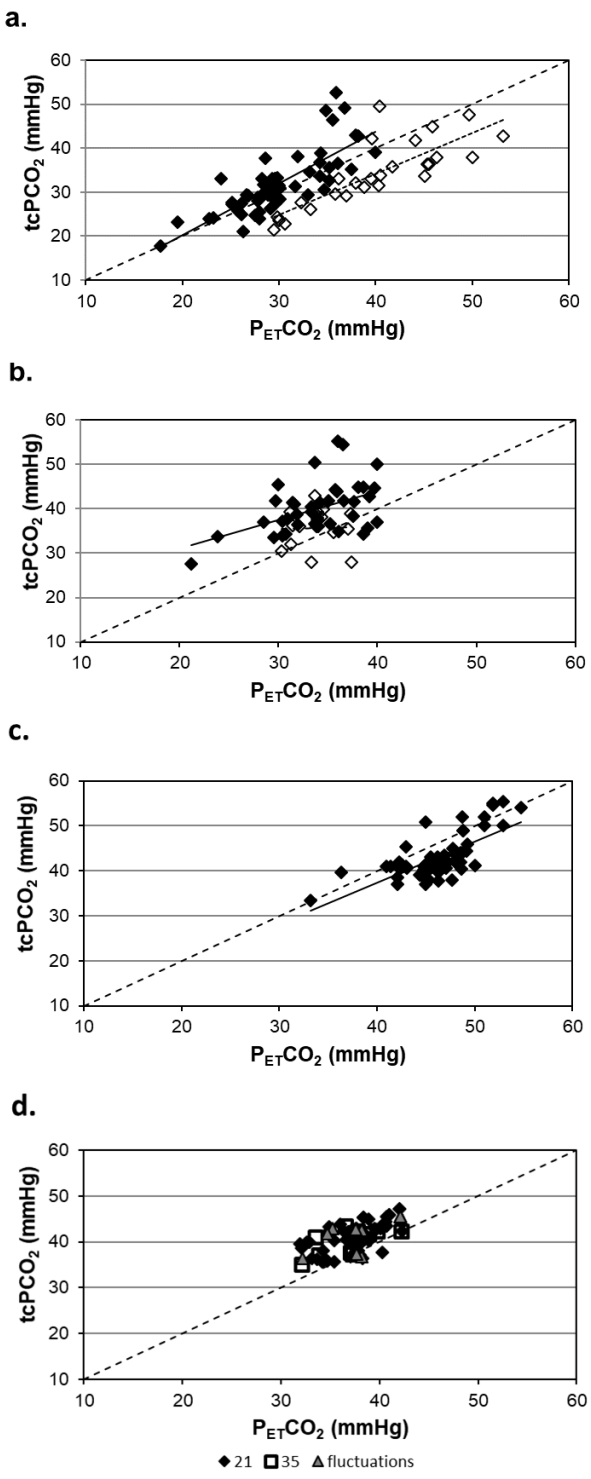

Figure 5. Correlation plots for measured CO_2, transcutaneous vs. end tidal. Solid and dotted lines: linear regressions. Dashed lines: lines of identity. a.100% O_2, rest (closed symbols) and exercise (open symbols); b. 11.5% O_2, rest (closed symbols) and exercise (open symbols); c. 40% O_2, exercise; d. 21% O_2, 35% O_2, or fluctuations between them, rest.

Association of measures of oxygen partial pressure

There is no expectation that $tcPO_2$ should represent P_aO_2. However, $P_{ET}O_2$ and $tcPO_2$ were correlated at rest with 100% O_2 inspired and with 11.5% O_2 inspired. They were also marginally correlated during exercise with hypoxia (Table 4; Fig. 6).

Table 4. Correlations of $P_{ET}O_2$ and $tcPO_2$ by data set.

Data Set	Rest R or Exercise E	r	n	p
1: 100% O_2	R	0.33	56	**<0.02**
1: 100% O_2	E	–0.22	27	>0.25
1: 11.5% O_2	R	0.63	43	**<0.001**
1: 11.5% O_2	E	0.46	16	**0.056**
2: 40% O_2	E	0.15	62	>0.23
3: 21% O_2	R	0.06	52	>0.38
3: 35% O_2	R	0.62	14	0.10
3: Fluctuations	R	0.67	11	0.28

One datum during hypoxia appears to be an outlier, as the only value above the line of identity on the correlation plot between $tcPO_2$ and $P_{ET}O_2$ (Fig. 6b). The values from that participant were not included in the later regression equations.

Under the hyperoxic condition of Data Set 1, $tcPO_2$ was highly variable, ranging from 159 to 591 mmHg, with mean (standard deviation) of 405 (89) mmHg. Analysis of variance indicated no effect of experimental period (rest, hyperventilation, cold pack, etc.), but found significant differences ($p < 0.0005$, $F = 3.39$, $df = 13$) of $tcPO_2$ among individuals. However, variability within individuals across the experimental conditions was sometimes as high as that among participants; the highest within-individual range in $tcPO_2$ was 173 mmHg.

For all measurements after more than 15 minutes of hypoxia (i.e., all interventions starting with the cold pack), $tcPO_2$ was lower than during initial rest (Table 2). Values of $tcPO_2$ during hypoxia ranged from 8 to 52 mmHg, with mean (standard deviation) of 24.7 (9.2) mmHg. The range in the first 15 minutes was 23 to 52 mmHg, and that in the latter period was from 8 to 35 mmHg. Inter-individual differences were also significant ($F = 2.54$, $df = 9$, $p<0.02$), and the range of values within individuals also was sometimes high; the maximum within-individual range of $tcPO_2$ was 25 mmHg.

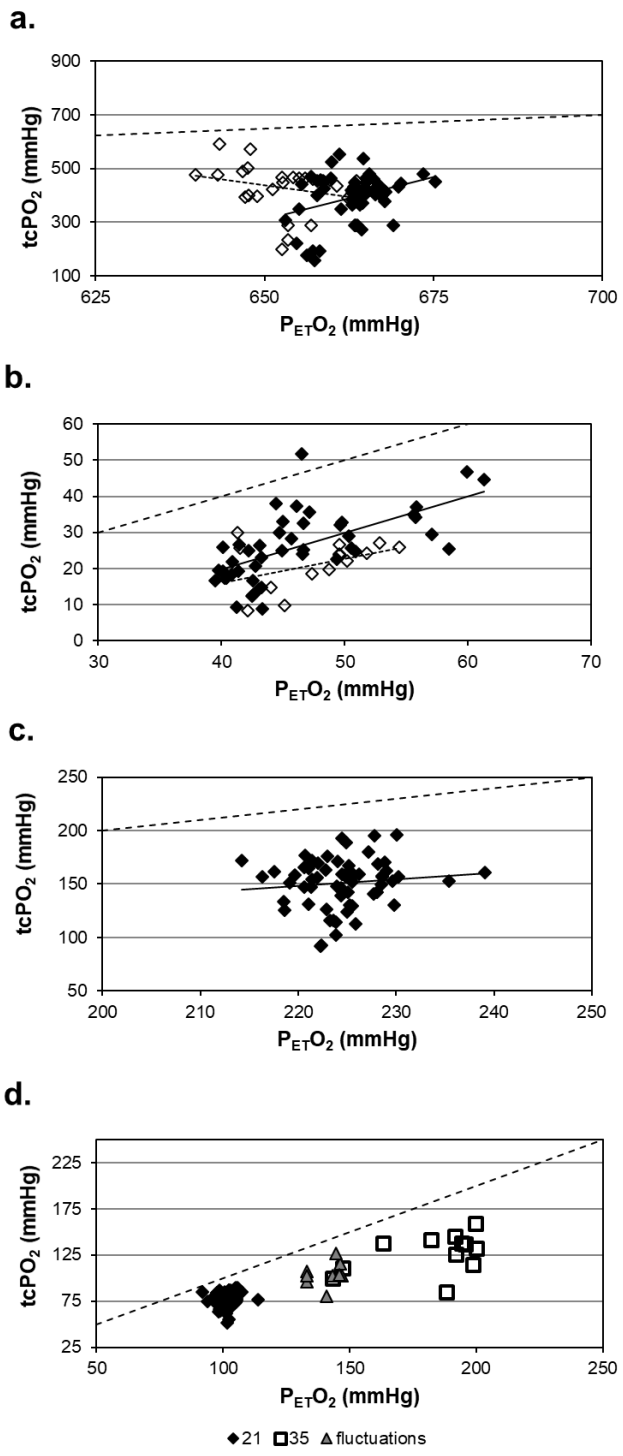

Figure 6. Correlation plots for measured oxygen, transcutaneous vs. end tidal. The axes are scaled differently across plots. Solid and dotted lines: linear regressions. Dashed lines: lines of identity. a.100% O_2, rest (filled symbols) and exercise (open symbols); b. 11.5% O_2, rest (filled symbols) and exercise (open symbols); c. 40% O_2, exercise; d. 21% O_2, 35% O_2, or fluctuations between them, rest.

Agreement of measures of CO_2

A Bland Altman (BA) plot, also known as Tukey Mean difference plot, shows the difference between two assessments of ostensibly the same quantity against their mean. The slopes of the BA plots to assess the agreement between end-tidal and transcutaneous measures of PCO_2 are given in Table 5. The slopes were significantly greater than zero when participants breathed 11.5% or 40% O_2 (Fig. 7 b and c), the scatter increased with increasing PCO_2 when participants breathed 100% O_2 (Data Set 1; Fig. 7a), and the mean difference was greater than zero for all data from Data Set 3 (Fig. 7, Table 6).

Table 5. Slopes of BA plots for CO_2, by data set.

Data Set	Rest R or exercise E	slope	SE slope	n	p
1: 100% O_2	R	0.44	0.09	56	**<0.01**
1: 100% O_2	E	0.01	0.1	27	>0.9
1: 11.5% O_2	R	0.4	0.2	43	**<0.05**
1: 11.5% O_2	E	1.0	0.3	16	**<0.01**
2: 40% O_2	E	0.3	0.1	62	**<0.01**
3: 21% O_2	R	0.2	0.1	52	0.19
3: 35% O_2	R	–0.04	0.3	14	>0.9
3: Fluctuations	R	–0.07	0.3	11	>0.7

"SE" means standard error, "p" means probability that slope equals 0.

Table 6. Mean differences, (transcutaneous – end tidal) PCO_2, for data sets where BA slopes do not differ from zero

Data Set with slope = 0	Mean difference mmHg	SD mmHg	Range mmHg
1: 100% O_2 E	-5.31	5.2	–12 to 9
3: 21% O_2	3.95	2.7	–2.5 to 8.4
3: 35% O_2	3.31	2.4	0.1 to 7.7
3: Fluctuations	3.8	2.8	–1.4 to 7.7

For the small subset of the data where the BA slopes for $tcPCO_2$ and $P_{ET}CO_2$ were not different from zero, the variability in the difference was large.

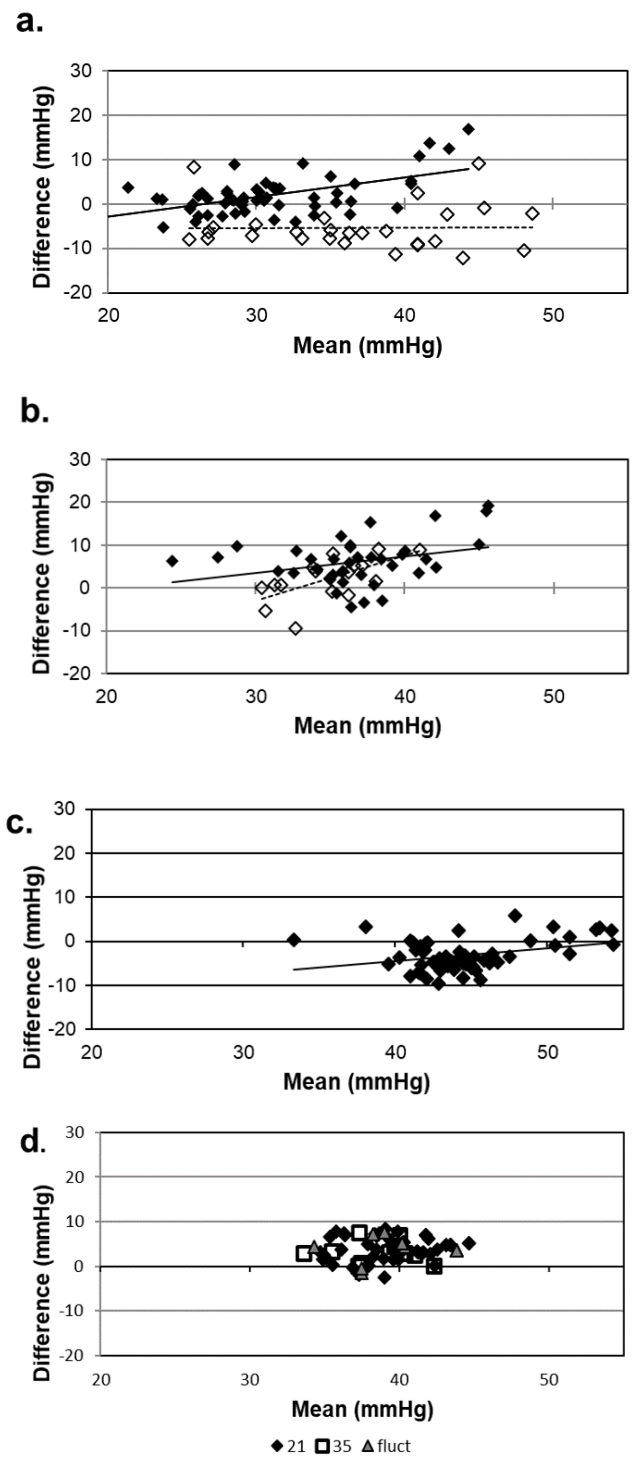

Figure 7. Bland Altman plot, (transcutaneous – end tidal) PCO_2 plotted against the mean of the two measurements. a.100% O_2, rest (filled symbols) and exercise (open symbols); b. 11.5% O_2, rest (filled symbols) and exercise (open symbols); c. 40% O_2, exercise; d. 21% O_2, 35% O_2, or fluctuations between them, rest.

Influence of $tcPO_2$

Forward regression analysis shows a significant effect of $tcPO_2$ on $tcPCO_2$ for most data sets (Table 7). Rest and exercise for hyperoxia and hypoxia were combined.

Table 7: Regression parameters. $tcPCO_2 = Constant + \Sigma(B_i \cdot Predictor_i)$.

100% O_2

Predictor	B	SE (B)	β	t	p	Δr^2
Constant	23	3		7.6	<0.0005	
$P_{ET}CO_2$	0.66	0.05	0.67	12.9	<0.0005	0.45
$tcPO_2$	–0.052	0.005	–0.59	–11.5	<0.0005	0.33
T_{skin}	0.23	0.05	0.22	4.2	<0.0005	0.05

Hypoxia (11.5% O_2)

Predictor	B	SE (B)	β	t	p	Δr^2
Constant	7.9	6.9		1.1	0.25	
$P_{ET}CO_2$	0.66	0.16	0.45	4.1	<0.0005	0.19
$tcPO_2$	–0.20	0.07	–0.33	–2.95	0.005	0.22
T_{skin}	0.46	0.11	0.48	4.3	<0.0005	0.11

40% O_2

Predictor	B	SE (B)	β	t	p	Δr^2
Constant	–4.77	6.87		–0.7	0.49	
$P_{ET}CO_2$	0.9	0.1	0.7	7.10	<0.0005	0.42
$tcPO_2$	0.04	0.02	0.22	2.26	<0.03	0.05

21% O_2 (Air)

Predictor	B	SE (B)	β	t	p	Δr^2
Constant	21	6		3.8	<0.0005	
$P_{ET}CO_2$	0.7	0.3	0.61	5.4	<0.0005	0.37
$tcPO_2$	-0.09	0.42	-0.23	-2.1	<0.04	0.05

35% O_2

Predictor	B	SE (B)	β	t	p	Δr^2
Constant	18	9		2.0	0.072	
$P_{ET}CO_2$	0.6	0.2	0.6	2.5	0.031	0.39

Fluctuations:

Predictor	B	SE (B)	β	t	p	Δr^2
Constant	14	11		1.3	0.22	
$P_{ET}CO_2$	0.7	0.3	0.7	2.6	0.034	0.45

r^2: regression coefficient, interpretable as fraction of variance explained by the regression equation; B: regression coefficient, the multiplier of the predictor variable; SE(B): standard error of B; β: standardized coefficient; t: t-statistic; p: probability that coefficient = 0; Δr^2: incremental change in r^2 caused by adding the predictor to the regression equation. Units of $P_{ET}O_2$, tcPO2: mmHg. T_{skin}: Skin temperature, °C, measured only for 100% and 11.5% O_2.

DISCUSSION

The question addressed here was whether, under conditions like those experienced in tactical jet aviation, changes in $tcPCO_2$ reliably correspond to changes in P_aCO_2. This study indicates that they do not. The difference between $P_{ET}CO_2$ and $tcPCO_2$ sometimes varied with the mean of the measurements and always showed large variability. However, both $tcPCO_2$ and $P_{ET}CO_2$ differ from P_aCO_2, the value we wish to assess.

Transcutaneous partial pressure is a direct measure of local tissue conditions; gas diffuses through the skin from capillaries directly beneath the probe (Radiometer, 2016; Severinghaus, 1981). Skin tissue PCO_2, that is, $tcPCO_2$, is higher than P_aCO_2 by the balance of the rate of CO_2 added by local metabolism to the rate of local CO_2 washout; the standard metabolic correction factor of –4 to –5 mmHg is intended to compensate for the difference (Radiometer, 2012). Local tissue perfusion (blood flow per mass of tissue) affects the difference of tissue gas partial pressures from those in arterial blood; higher perfusion brings the tissue values closer to arterial gas and vice versa. Thus, changes in $tcPCO_2$ reflect changes in P_aCO_2 only if local tissue perfusion and metabolism remain similarly matched for the period of interest.

$P_{ET}CO_2$ is a direct sample of the last alveolar gas to leave the lungs during expiration. Under most physiological conditions, blood leaving pulmonary capillaries is in equilibrium with the gas in the alveoli served by those capillaries. In other words, the local alveolar and end-capillary partial pressures are equal. However, local alveolar gas differs from end tidal gas because local alveolar gases vary within the lungs during a breath and because ventilation-to-perfusion ratios are non-uniform. Based on the “first in, last out” sequence of lung filling and emptying (Engel and Paiva, 1981), the end-tidal gas comes mostly from the dependent regions. Further, local capillary partial pressure is not the same as mean arterial partial pressure; arterial blood is a mixture from all pulmonary capillaries. Normal alveolar- to arterial oxygen partial pressure differences during normoxia range from about 8 to 10 mmHg for the ages of our participants (https://www.merckmanuals.com/professional/multimedia/clinical-calculator/a%20a%20gradient). The relation between P_aCO_2 and $P_{ET}CO_2$ under normoxic conditions was found by Jones, Robertson and Kane (1979):

$$P_aCO_2^J = 5.5 + 0.90 \cdot P_{ET}CO_2 - 0.0021 \cdot V_T \qquad [3]$$

where CO_2 partial pressures are in mmHg, V_T is tidal volume measured in mL_{BTPS}, and $P_aCO_2^J$ indicates the corrected value based on the Jones et al. model. For a normocapnic P_aCO_2 of 40 mmHg and a normal resting tidal volume of approximately 600 mL, $P_{ET}CO_2$ and $P_aCO_2^J$ values are nearly identical.

Good agreement between $P_{ET}CO_2$ and $tcPCO_2$ would indicate equal utility of the two measurements as indicators of P_aCO_2. However, in the data presented here,

lack of agreement was evident when CO_2 balance was deliberately manipulated in hyper- and hypoxia (Fig. 2) and when skin temperature was changed near the transcutaneous probe (Fig. 4). Bland Altman plots (Fig. 7) indicate the lack of correspondence of individual pairs of measurements. The regression equations for each condition (Table 7) indicate that $tcPO_2$ and, to a lesser extent, skin temperature around the transcutaneous probe relate to the divergence of the measurements.

All measurements here were made during prolonged steady measurements where response time of the analyzers is immaterial. However, measurements of $tcPCO_2$ cannot detect short-term perturbations to CO_2 control. The lag time from the initiation of a gas change in the lungs to the start of the $tcPCO_2$ response is 14 to 16 seconds (Radiometer, 2012), some of which is the time needed for blood to travel from the lungs to the tissue. Blood recirculation time at rest (time for a change in alveolar gas to be reflected in the venous blood entering the lungs) is approximately 25 seconds at rest, shorter at exercise (Morris et al., 2007), and the delay from lungs to brain, estimated using lung to ear-lobe transit time, 6 seconds at rest (Ryan and Bradley, 2005). However, $tcPCO_2$ reaches 90% of its final reading only after about 78 seconds (Radiometer, 2012); the electrode takes at least 60 s to stabilize at a new value. In contrast, the infrared CO_2 analyzer has a transit-plus-response time of 150 mL when sample flow is 150 mL/min, reading the new gas composition in the lungs before the change reaches the brain.

<u>$tcPO_2$, $tcPCO_2$, $P_{ET}O_2$, $P_{ET}CO_2$, and inhaled PO_2</u>

Normoxia and near-normoxia

Tissue normally regulates its perfusion to match its metabolic needs. Local relative hypoxia is met with nearly-immediate vasodilation, because removal of oxygen from hemoglobin molecules also releases nitric oxide (NO), a vasodilator (Allen and Piantadosi, 2006; Allen et al., 2009). Thus, an increase in local metabolic rate generates a matching increase in oxygen delivery, and, as a side effect, a matching wash-out of the locally-produced CO_2; $tcPCO_2$ trends with P_aCO_2 under conditions of normoxia or near-normoxia, and the fixed metabolic correction (Radiometer, 2012) brings the $tcPCO_2$ reading close to P_aCO_2. Similarly, at rest $P_{ET}CO_2$ represents P_aCO_2, as stated in relation to Equation 3, above.

Hyperoxia

Because hemoglobin-mediated vasodilation is directly proportional to the local concentration of deoxyhemoglobin (Allen et al., 2009), hyperoxia in skin capillaries blunts or abolishes the matching of perfusion to local metabolic rate. The absence of local control of perfusion during 100% O_2 breathing in this experiment is evident in the relation of $tcPO_2$ to P_aO_2 confirmed by the correlation at rest of $tcPO_2$ and $P_{ET}O_2$ (Table 4, Fig. 6a). Almost none of the hemoglobin is in the taut deoxygenated form if PO_2 is greater than 100 mmHg, and $tcPO_2$ readings for participants breathing 100% O_2 ranged from 159 to 591 mmHg (Fig. 6a). When the metabolic needs of skin can be satisfied by

oxygen dissolved in plasma, $tcPCO_2$ and $tcPO_2$ are related; $tcPO_2$ represents P_aO_2 reduced by local oxygen consumption, local CO_2 production is proportional to the oxygen consumed, and $tcPCO_2$ indicates P_aCO_2 plus locally-produced CO_2. However, the maintenance of the steady offset between $tcPCO_2$ and P_aCO_2 is lost in the absence of modulation of perfusion to regulate oxygen supply.

$P_{ET}CO_2$ also may not represent P_aCO_2 when people breathe 100% O_2 at rest, because lack of inert gas in the lungs promotes atelectasis and intrapulmonary shunt in regions subject to airway closure (Wagner et al., 1974). Venous admixture from shunt causes P_aO_2 to be lower than mean alveolar PO_2; $P_{ET}O_2$ with 100% O_2 inhaled is higher than P_aO_2. The venous admixture also adds CO_2 to arterialized blood. Chemoreceptor control adjusts pulmonary ventilation to maintain normal mixed arterial PCO_2. Breathing thus increases to decrease alveolar PCO_2 until the arterial mixture of shunt fraction with venous PCO_2 and pulmonary capillary blood at alveolar PCO_2 is at normal P_aCO_2. Thus, in the presence of shunt, $P_{ET}CO_2$ is lower than P_aCO_2, with values that may suggest hyperventilation ($P_{ET}CO_2$ < 38 mmHg), like those when resting participants breathed 100% O_2 (Table 2, Fig. 5a). A probable increase in shunt fraction with time during seated rest is reflected in the decrease in $P_{ET}CO_2$ during seated rest from the initial measurement to that with the heating pad (Fig. 4). As is expected in the presence of shunt, $P_{ET}CO_2$ measured here during rest (Table 2, Fig. 4) was lower than P_aCO_2 measured by others in young men breathing 100% O_2 near sea level, P_aCO_2 of 37 mmHg, n =4 (Wagner et al., 1974) and P_aCO_2 of 38 mmHg, n = 8 (Lambertsen, 1953).

During exercise, the increased ventilation and the change in posture from recliner chair to cycle ergometer probably cleared the atelectasis causes by seated rest; $P_{ET}CO_2$ in the 10^{th} minute of hyperoxic exercise was close to the anticipated 38 to 42 mmHg (Table 2, Figs 2, 5a). Shunt can be ruled out during exercise with 40% O_2 in these experiments by the elevated $P_{ET}CO_2$ (Fig. 5c).

Hypoxia

Systemic hypoxia causes global skin vasodilation (Simmons et al., 2007). Further, the concentration of bound NO in arterial blood is low during breathing of 12% oxygen at sea level (McMahon et al., 2002). Thus, inhaling of 11.5% O_2 probably removed the capacity for local vasodilation. Changes in local metabolic rate likely controlled the changes in $tcPCO_2$, as suggested by the fact that $tcPO_2$ explained more of the variance in $tcPCO_2$ than did $P_{ET}CO_2$ (Table 7). Tissue PO_2 was governed primarily by the overall arterial oxygen supply, shown by the correlation at rest between $tcPO_2$ and $P_{ET}O_2$ (Table 4, Fig. 6b). As in hyperoxia, but for different reasons, the maintenance of the steady offset between $tcPCO_2$ and P_aCO_2 is lost in the absence of modulation of perfusion to regulate oxygen supply.

$P_{ET}CO_2$ during hypoxic rest, like that during normoxic rest, can be considered to be a good representation of P_aCO_2. Hypoxia reduces the driving force for O_2 transfer in the lungs but has little effect on carbon dioxide transfer in the lungs at rest; the gradient for CO_2 transfer is not disturbed and the changes in ventilation to perfusion ratios caused by hypoxia at rest are minor (Gale et al., 1985). However, with hypoxic exercise, the rate of oxygen transfer in the lungs becomes

limited by the rate of diffusion, meaning that the PO_2 in blood leaving pulmonary capillaries is lower than the PO_2 in the alveolar gas (Torre-Bueno, 1985; Hannon et al., 1968). Although alveolar PO_2 and PCO_2 remain linked through the alveolar gas equation, arterial PO_2 is less tightly linked to $P_{ET}O_2$ or $P_{ET}CO_2$ than it is during hypoxic rest. Increased hypoxemia will drive $P_{ET}CO_2$ down through the hypoxic ventilatory response. Further, at an equivalent altitude of 15,000 feet the dispersion of ventilation to perfusion ratios has been shown to increase (Gale et al., 1985), impairing both O_2 and CO_2 transfer. Based on the "first in, last out" sequence of lung filling and emptying (Engel and Paiva, 1981), the end-tidal gas comes mostly from the dependent regions independent of the perfusion distribution. However, the $P_{ET}CO_2$ values (Table 2, Figs. 2 and 4) are comparable to P_aCO_2 measured directly by others under similar conditions, where P_aCO_2 of 34 (7) mmHg [mean (SE)] has been measured at rest and 32 (0.6) mmHg at mild exercise in participants breathing 11% O_2 at sea level (Hammond et al, 1986).

Effects of interventions

The manipulations of P_aCO_2 and of local temperature caused $P_{ET}CO_2$ and $tcPCO_2$ to diverge. Hyperventilation lowers $P_{ET}CO_2$ and P_aCO_2. However, $tcPCO_2$ did not decrease during voluntary hyperventilation in hypoxia while $P_{ET}CO_2$ did (Fig. 2). Under normoxia and hyperoxia, resistive breathing during heavy exercise increases $P_{ET}CO_2$ (Shykoff and Warkander, 2012) and during mild to moderate exercise increases directly-measured P_aCO_2 (Forster et al., 1993). During hypoxia, resistive breathing reduces minute ventilation at rest, thus increasing P_aCO_2 (Rebuck and Juniper, 1975).

With resistive breathing and mild to moderate exercise reported here, the increase in $P_{ET}CO_2$ was significant only during hyperoxia. During hypoxic exercise a decrease in minute ventilation stimulated by the resistance breathing would have decreased arterial oxygen content further, particularly in the face of the diffusion-limited rate of oxygen transfer in the lungs. Lower hemoglobin oxygen saturation would have increased the hypoxic ventilatory drive, and thus the minute ventilation. The net effect was a non-significant increase in $P_{ET}CO_2$ relative to cycling exercise without resistive breathing. The concomitant changes in $tcPCO_2$ were a non-significant increase during hyperoxia and a significant decrease during hypoxia with resistive breathing and exercise relative to that with exercise alone.

Local heating and cooling should not alter P_aCO_2 or $P_{ET}CO_2$, but heating and cooling change skin perfusion and local metabolic rate. Although $P_{ET}CO_2$ in hyperoxia was significantly lower during heating than at the end of the initial ambient temperature condition (Table 2, Fig. 4), the effect may have been that of cumulative atelectasis and intrapulmonary shunt (Wagner et al., 1974) resulting from the elapsed time seated while hyperoxic. Local cooling caused a decrease in $tcPCO_2$ during hyperoxia but no change during hypoxia. Local heating caused no change in $tcPCO_2$ in hyperoxia but an increase during hypoxia.

Relationships between $tcPCO_2$ and $P_{ET}CO_2$

Significant correlations (Table 3, Fig. 5) between $tcPCO_2$ and $P_{ET}CO_2$ indicate the expected associations of the two variables in most cases; both are related to P_aCO_2. The notable exception is that the correlation between tissue- and end-tidal PCO_2 was not statistically significant during hypoxic exercise. As is discussed above, the amount of CO_2 produced in the skin is proportional to the amount of O_2 consumed in the same tissue. Local oxygen consumption is limited by arterial PO_2 during systemic hypoxia caused by breathing 11.5% O_2. Under resting, perfusion-limited conditions, arterial PO_2 is proportional to alveolar PO_2, and alveolar PO_2 is negatively proportional to alveolar PCO_2, measured here as $P_{ET}CO_2$. Even if the direct relation between $P_{ET}CO_2$ and $tcPCO_2$ becomes tenuous under these conditions, the indirect coupling of arterial PO_2 and $tcPCO_2$ remains through the alveolar gas equation relating $P_{ET}O_2$ and $P_{ET}CO_2$, Equation 2. Once oxygen transfer becomes diffusion limited during exercise, however, the secondary correlation of $tcPCO_2$ and $P_{ET}CO_2$ is broken.

Bland Altman plots

Without a significant correlation between two quantities the two are not interchangeable. However, correlation alone is not sufficient to indicate agreement. A Bland Altman plot of difference against average is a standard visual and statistical approach to determining agreement between two measurements (Altman and Bland, 1983; Bland and Altman 1986). The pairwise difference between the two variables used as the y-axis in the BA plot is an obvious metric for agreement. The average of the two measurements used as the x-axis is the best available estimate of the true value if both variables contain error, and the difference is not an arithmetical function of the average as it is of each of the components. If both $tcPCO_2$ and $P_{ET}CO_2$ represent P_aCO_2, the difference between them will be constant as the mean of the two changes.

During rest with 100% O_2 inhaled, during hypoxia, and during exercise with 40% O_2 inhaled, the differences between $tcPCO_2$ and $P_{ET}CO_2$ was a significant linear function of their means (Table 5, Figure 7). However, in participants at rest in these experiments who breathed 21%, 35% O_2, or fluctuations between them, neither the BA slopes (Table 5, Fig. 7d) nor BA offsets ($tcPCO_2 - P_{ET}CO_2$) were statistically different from zero (Table 6, Fig 7d), consistent with the discussion above. [Note that $tcPCO_2$ has been corrected for metabolic and probe temperature components, that is, for a predetermined offset from P_aCO_2 (Radiometer, 2012).] Even for those data sets where the BA slope was not different from zero, the differences between the two measures ranged widely; a 5 mmHg change in PCO_2 has large physiological significance, yet the range of the differences was larger than that for all data sets.

The factors that make $tcPCO_2$ differ from P_aCO_2 with 100% O_2 inhaled and during hypoxia have been discussed. Lack of correspondence of $P_{ET}CO_2$ to P_aCO_2 corroborates the discussion of why of $tcPCO_2$ is an unreliable measure of P_aCO_2 under those extreme physiological conditions. However, near normoxia,

$tcPCO_2$ is a valid measure of P_aCO_2. In the data presented here, near normoxia extends to 35% O_2 inhaled during rest (Data Set 3), but not, apparently, to 40% O_2 inhaled during exercise (Data Set 2). The difference for a small increment of inhaled O_2 fraction deserved a second look.

Application of Equation 3 to convert from $P_{ET}CO_2$ to $P_aCO_2^J$ reduced the BA slope to 0.18 (SE 0.04), but the slope remained significantly different from zero; at least one of $tcPCO_2$ and $P_aCO_2^J$ differed from P_aCO_2 by more than a constant offset. Exercise alone may be enough to disturb the relationship between $tcPCO_2$ and P_aCO_2; exercise duration and intensity affect the degree of vasodilation or vasoconstriction in the skin circulation (Taylor et al., 1988). Additionally $tcPCO_2$ might deviate from P_aCO_2 if even mild hyperoxia during exercise alters the match of perfusion to metabolism in skin capillaries. $P_aCO_2^J$ could differ if mild hyperoxia or the slight positive pressure (4 cm H_2O) in the aviation mask alters the distribution of ventilation to perfusion in the lungs enough into change the relation between $P_{ET}CO_2$ and P_aCO_2.

We did not measure $tcPCO_2$ and $P_{ET}CO_2$ together during normoxic exercise. Although some investigators (e.g., Carter and Banham, 2000) have had success with transcutaneous monitoring during exercise tests, American Association for Respiratory Care guidelines (Restrepo et al., 2012) do not recommend the technique except in people at rest.

Other explanatory variables

Regression analysis of $tcPCO_2$ as a function of $P_{ET}CO_2$ and other measured variables (Table 7) showed that $tcPO_2$ and skin temperature (measured only in Data Set 1) explained significant fractions of the variance in $tcPCO_2$ for several levels of inspired O_2.

Transcutaneous PO_2

The coefficient on $tcPO_2$ was negative for 100% O_2, hypoxia, and air breathing; an increase in $tcPO_2$ is a marker for increased perfusion relative to metabolic activity, leading to decreased $tcPCO_2$, and vice versa, whether the probe is on the forearm (100% O_2 and hypoxia, rest and exercise) or on the chest (21% O_2, rest). With 21% O_2 inhaled, the coefficient of $tcPO_2$ was small, and $tcPO_2$ for air breathing was not correlated with $P_{ET}O_2$ (Table 4), consistent with the idea that tissue PO_2 was controlled by the microcirculation under normoxic conditions. The positive coefficient of $tcPO_2$ in the regression with 40% O_2 (exercise, probe on the chest) is harder to explain, but may reflect the complexity of the control of skin circulation during exercise.

Skin temperature

Skin temperature on the forearm, available only for Data Set 1, entered the regression equations with positive coefficients, consistent with a reported

increase in skin metabolic rate with temperature (Restrepo et al. 2012).[1] Under normoxia, skin warming from 33 °C to 43°C is also known to increase local blood flow more than 15-fold and to increase tissue oxygen saturation as measured through the skin (Kuliga et al, 2017). Our measurements of effects of temperature on $tcPO_2$ under hyper- or hypoxic conditions were not entirely consistent with that result (Figure 3, Table 7). However, in the regression equations, $tcPO_2$, a marker of coupling of perfusion to metabolism, entered the equation before skin temperature; the temperature effect is thus an adjustment to any temperature effects that appear to be perfusion effects.

Limits of the experimental design

The goal of the experiments that produced Data Set 1 was to test the agreement between $tcPCO_2$ and $P_{ET}CO_2$ over a wide range of aviation-relevant situations. The environmental conditions applied were extreme hyperoxia and hypoxia plus local skin temperature extremes. These challenges were of greater magnitude than would be expected in an aircraft, and the perturbation of the balance between local perfusion and local metabolism probably scales with the magnitude of the disturbance from normoxia and thermal equilibrium. Rest and exercise were included, since both occur during various phases of flight. Finally, an attempt was made to have a wide range of $P_{ET}CO_2$ by including voluntary hyperventilation and resistive breathing. As has been discussed, hyperoxia at rest and extreme hypoxia with exercise reduce the fidelity of $P_{ET}CO_2$ as a measure of P_aCO_2. Although this makes it more difficult to determine that $tcPCO_2$ does not agree with P_aCO_2 the data can be corroborated by physiological explanations.

The experiments did not include any hypobaric exposures, but measures that do not apply under normobaria are unlikely to be better-suited to hypobaria. Hyperoxia as administered here was more extreme than that experienced in flight; at a cabin altitude of 8,000 feet, PO_2 with 100% oxygen is roughly equivalent to that with 75% oxygen at sea level. However, all phases of flight should be covered by physiological monitoring, to include ground operations, take-off and landing. Further, the condition of tissue PO_2 exceeding 100 mmHg would be satisfied with 100% O_2 at 8,000 ft (or 75% O_2 at ground level). On a related note, the problem of atelectasis and shunt with 100% O_2 during seated rest, that at altitude exists at altitude independent of the PO_2; $P_{ET}CO_2$ also may not be a useful measure in the cockpit.

Although all conditions were measured during both hyperoxia and hypoxia, local heat, local cold, and hyperventilation were measured only during rest and CO_2 retention only at exercise, and none of them, including exercise, was measured during normoxia. Nevertheless, because the interventions demonstrated problems with the methodology, the limited set of conditions sufficed to answer the primary question here.

Several participants had to stop the hypoxic exposure early because their peripheral hemoglobin saturation fell too low after varying exposure durations. This indicates a slow change over time in the relationship between inspired and arterial gas, a change

[1] This citation is a review which cites another review. The experimental basis of this statement has not been located.

that suggests a related change with time in P_aCO_2. Because the drift occurred over 15 minutes or more the response of the transcutaneous monitor was sufficient to follow it. If the two measurements had been equally valid surrogates for P_aCO_2 they would have been equally affected.

CONCLUSIONS and RECOMMENDATIONS

Transcutaneous measurement of CO_2 cannot be used in the environment of tactical aviation. The PCO_2 in the skin under the electrode is a function of P_aCO_2, but also of the skin PO_2 and local skin temperature, neither of which is easily held constant in the cockpit. Variations in breathing gas or changes in whole-body work (exercise) can alter the measurement without changes in P_aCO_2.

End-tidal gas measurements are also unlikely to be feasible in tactical aircraft. Further, even reliable end-tidal measurements can incorrectly suggest hypocapnia in the presence of even non-pathological atelectasis and intrapulmonary shunt, both of which are expected when aircrew breathe nearly 100% O_2.. End tidal measurements that indicate hypercapnia (CO_2 retention) can be interpreted directly, but those showing hypocapnia (hyperventilation) require corroborating data.

Measurement of carbon dioxide in military aviators during flight remains an intractable problem. The recommendations from this effort are:

1) Do not try to adapt transcutaneous monitoring for use in flight.
2) Do not try for direct measurement of end tidal PCO_2 from an aviator's mask.
3) Consider entirely different measurements to look for possible hyperventilation. For example, would an analysis of the minute ventilation associated with a PE in comparison with minute ventilations for similar activities without PE indicate over- or under-breathing?

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