Transcutaneous and End-Tidal CO_2 Measurements in Hypoxia and Hyperoxia

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BACKGROUND: Transcutaneous measurement of carbon dioxide (CO_2) has been proposed for physiological monitoring of tactical jet aircrew because in some clinical settings it mirrors arterial CO_2 partial pressure (P_aCO_2). End-tidal monitoring in laboratory settings is known to give high-fidelity estimates of P_aCO_2.

METHODS: The correspondence between end-tidal ($P_{ET}CO_2$) and transcutaneous PCO_2 ($tcPCO_2$) was examined in healthy volunteers under laboratory conditions of hyperoxia and hypoxia. Rest and exercise, skin heating and cooling, hyperventilation, and induced CO_2 retention were employed.

RESULTS: Neither measure followed all known changes in P_aCO_2 and $tcPCO_2$ changed when the skin temperature near the probe changed. Bland-Altman analysis showed significant nonzero slopes under most conditions. Regression analysis indicated that oxygen partial pressure (PO_2) in tissue 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, absorption atelectasis from breathing 100% O_2 may cause $P_{ET}CO_2$ to deviate from P_aCO_2.

DISCUSSION: Even as a trend indicator for P_aCO_2, $tcPCO_2$ is not useful under conditions that resemble those 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.

KEYWORDS: arterial gas, blood gas, pilot monitoring, physiological monitoring, hypocapnia, hypercapnia.

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Military aviators who regularly use oxygen masks may not always maintain normal carbon dioxide (CO_2) levels. The combination of complex respiratory loads with the usually elevated oxygen partial pressure (PO_2) and mild to moderate hypobaria has been postulated to cause hyper- or hypocapnia (under- or over-breathing). Because both alterations in CO_2 balance are associated with symptoms and signs, monitoring of aviator arterial CO_2 levels in the cockpit is of interest.

In the laboratory, measurement of end-tidal CO_2 partial pressure ($P_{ET}CO_2$) is the method of choice to study changes in arterial CO_2 partial pressure (P_aCO_2). Although the two variables are not identical, P_aCO_2 can be expressed as a linear function of $P_{ET}CO_2$ with a correction also for tidal volume.[9] However, the gas sample must be drawn at high flow from within the gas stream in a mask or mouthpiece, processed by a fast-response analyzer and digitized at an adequate rate, and signal quality must be confirmed by direct observation. Reliable measurement of end-tidal gas in a tactical aircraft, where space and power are restricted and where pilot head mobility must not be compromised, is a major technical challenge. Further, in an aviation environment, increased shunt fraction caused by atelectasis[5] may disturb the nominal relationship between $P_{ET}CO_2$ and P_aCO_2.

Transcutaneous PCO_2 ($tcPCO_2$) measurement is well-established for use in intensive care units and operating rooms. Although $tcPCO_2$ measures local tissue PCO_2, not P_aCO_2,[13,17] and is thus affected by tissue metabolism and local blood flow in addition to arterial values, it agrees well with P_aCO_2 in many clinical applications.[1,17] In some patients, for example those in respiratory failure,[11] $tcPCO_2$ provides a better indicator of P_aCO_2

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than does expired gas sampling. If the correspondence between $tcPCO_2$ and P_aCO_2 also applies in an aviation environment, the small electrode that detects CO_2 diffusing through the skin could be affixed to the chest surface, where it would not impede pilot mobility.

However, the hospital intensive care unit patients in whom the utility of $tcPCO_2$ has been established differ considerably from healthy aviators in the cockpit, such that the expected P_aCO_2 to $tcPCO_2$ relationship may not apply. In addition to dynamic changes in inspired PO_2, aviators may be exposed to widely varying cockpit temperatures and sudden changes in muscular activity. This study compared $tcPCO_2$ to $P_{ET}CO_2$ while inspired oxygen, skin temperature, metabolic rate, and CO_2 balance were manipulated. Practical extremes of inspired PO_2 were used; specifically, normobaric hyperoxia (100% oxygen) and normobaric hypoxia roughly equivalent to 16,000 ft (4880 m) above mean sea level (MSL) without supplemental oxygen (11.5% oxygen in nitrogen at a ground altitude of 900 ft (274 m) MSL. To determine whether either $tcPCO_2$ or $P_{ET}CO_2$ was a valid indicator of P_aCO_2 in the cockpit, we looked for appropriate changes in $tcPCO_2$ and $P_{ET}CO_2$ during maneuvers known to alter P_aCO_2 (voluntary hyperventilation at rest and resistance breathing during exercise) and appropriate stability in the face of manipulations that should not change it (local skin heating and cooling to alter local skin perfusion). Cycling exercise was used to increase metabolic CO_2 production. Method comparisons were made only between simultaneously collected $P_{ET}CO_2$ and $tcPCO_2$. We also considered association, agreement, and other explanatory variables in the relationship between transcutaneous and end-tidal CO_2 partial pressures. Agreement between the two would indicate that both approximate P_aCO_2, but divergence that further scrutiny of the physiological background of the measurements is needed.

METHODS

Subjects

The study was approved by the Institutional Review Board of the Naval Medical Research Unit - Dayton. All subjects gave written documentation of informed consent. Participating in the hyperoxic arm of the study were 14 volunteers (9 men and 5 women), 20 to 37 yr old. Of those, 12 (7 men and 4 women) also participated in the hypoxic arm.

Equipment

Transcutaneous data were collected using a TCM4/CombiM84 (Radiometer, Copenhagen, Denmark) with the probe temperature set to the standard 45°C and with the usual metabolic correction that subtracts 5 Torr from the raw $tcPCO_2$ value.[13] The probe, prepared and attached according to Radiometer instructions, was placed on the volar surface of the left forearm and a skin temperature probe (moorVMS-LDF laser Doppler, Moor Instruments, Wilmington, DE, USA) was affixed approximately 3 cm distant. At least 20 min were allowed for electrode stabilization before data collection began. End-tidal CO_2 was measured using a fast-response nondispersive infrared analyzer (GA-200, iWorx, Dover, NH, USA) using no filters, physical or electronic. The gas sampling pump was set to 400 mL · min^{-1}. The 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 (**Fig. 1A**). This placed the end of the sample line in the gas stream during both inspiration and expiration whether subjects breathed through nose or mouth. The sample line was continuous and without changes in diameter to prevent mixing in the line. A clean inspiratory measurement followed by a distinct expiratory pattern (**Fig. 1B**) was an indicator of sampling without excess mixing or signal smearing.

Subjects breathed gas delivered at atmospheric pressure through large-bore (35-mm diameter) respiratory tubing (VacuMed, Ventura, CA, USA) from a gas reservoir (60-L gas bag, Hans Rudolph, Shawnee, KS, USA) to a one-way nonrebreathing valve (Model 2700, Hans Rudolph) attached to a silicone oronasal mask (Series 7450, Hans Rudolph). The gas reservoirs were filled under manual control from cylinders of compressed gas and subjects breathed the test gas from the start to the end of the data collection.

Subjects in the hypoxic arm also wore a finger pulse oximeter (PalmSat 2500, Nonin Medical, Plymouth, MN, USA) on their right hands for safety monitoring; subjects were returned to room air breathing if peripheral hemoglobin saturation (S_pO_2) fell below 60% for more than a few seconds. All subjects wore a chest strap heart rate monitor (Polar Electro Inc., Bethpage, NY, USA), the output from which was used to control the cycle ergometer load (ExCalibur Sport, Lode B.V., Groningen, The Netherlands) during the study's exercise phase.

Subjects sat in an upholstered armchair until they transferred to the ergometer. They watched self-selected videos for distraction throughout their time in the laboratory. Because all comparisons were of simultaneous data, changes in breathing rate or volume, heart rate, blood pressure, or other aspects of sympathetic-parasympathetic activation in response to the material could only widen the range of the measurements. Data were collected under six sequential conditions: 1) 10 min of quiet seated rest; 2) 5 min of seated hyperventilation, when subjects breathed in time with a metronome at 30 breaths per minute; 3) up to 20 min of local skin cooling (cold); 4) up to 20 min of local skin heating (heat); 5) 10 min of cycle ergometer exercise; and 6) 5 min of resistive breathing during continued cycle exercise.

Cold was applied using a flexible gel freezer pack separated from the skin by a single layer of cloth towel. Heat was applied using a preheated household electric heating pad set to high. Both covered most of the volar surface of the forearm and were approximately centered over the TCM4 and temperature probes. Heating and cooling continued for a maximum of 20 min or until the skin temperature reading remained within 0.2°C for 2 min. During cooling and heating, a small spacer of closed-cell foam placed around the TCM4 and temperature sensors prevented excessive pressure on the probes. The TCM4 probe temperature was monitored to confirm that it remained steady during the temperature manipulations.

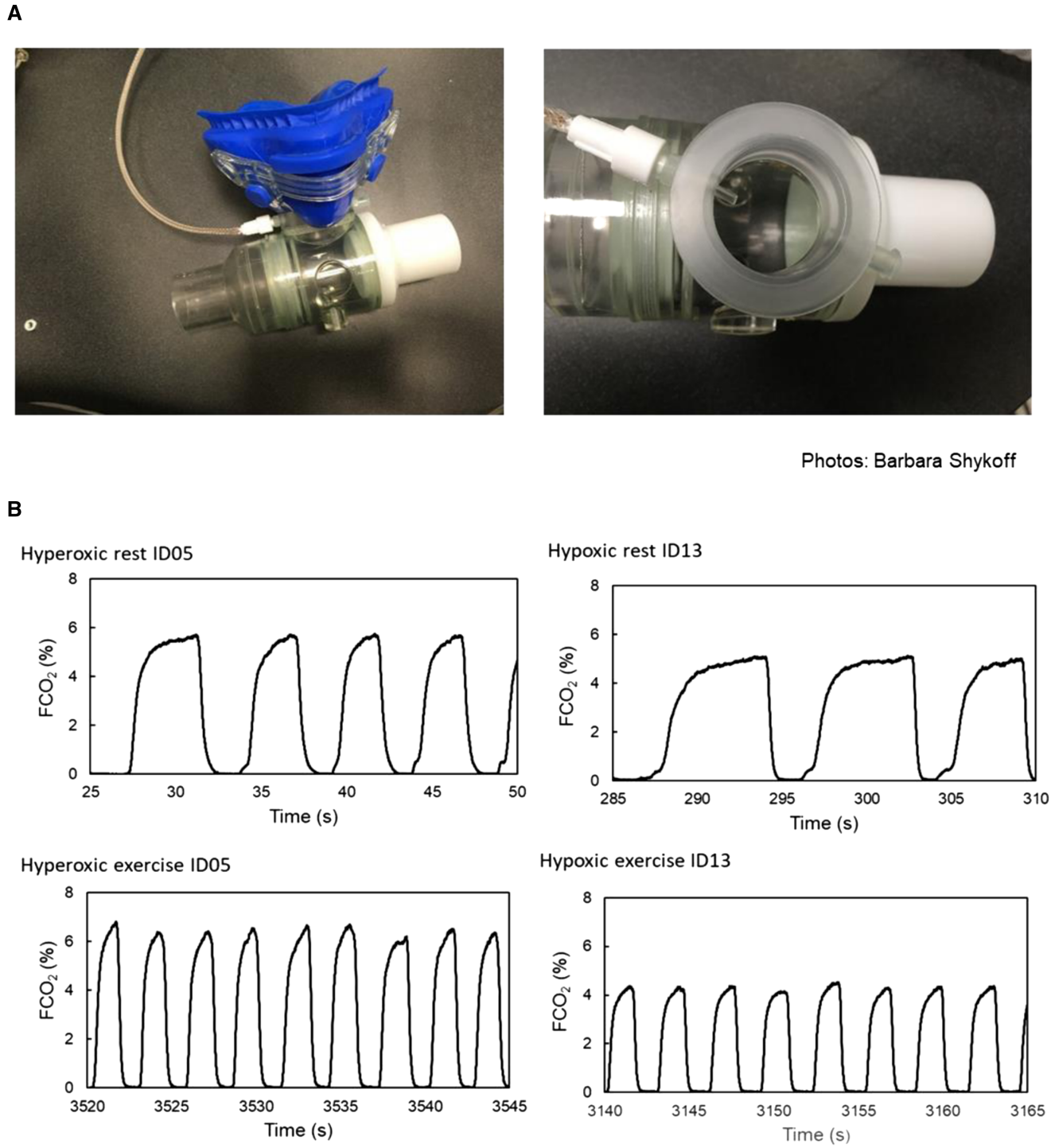

Fig. 1. Measurement of $P_{ET}CO_2$. A) Photograph of the sampling configuration. B) Sample tracings (25 s each) of percent CO_2 as a function of time (seconds from the start of data acquisition). Different subjects are shown for hyperoxia and hypoxia. Note the distinct plateau of inspired gas and the clean transitions between inspiration and expiration.

Procedure

The target heart rates for exercise during hyperoxia and hypoxia, respectively, were 80% and 60% of heart rate reserve. The ergometer load was increased incrementally until the target heart rate was reached and was adjusted to maintain it; the 10 min of exercise included the period of increasing load. For resistive breathing, a plug approximately 3 cm (1.25 inches) long with a 6-mm (0.25-inch) diameter hole was inserted into the inspiratory port of the nonrebreathing valve before another 5 min of exercise at the controlled heart rate.

Data were sampled at 100 Hz, displayed, and stored using a PowerLab LabChart data acquisition suite (ADInstruments,

Colorado Springs, CO, USA). Data from the last minute of each condition, when steady state could be assumed, were extracted and averaged using LabChart software. Breath-by-breath maxima of CO_2 and minima of O_2 from the mask, considered to be end-tidal values representative of alveolar gas, were extracted and averaged. The averages of $tcPCO_2$, $tcPO_2$, and skin temperature over the same time periods were computed. The known lag time of the TCM4 in response to changes in gas partial pressures[13] was ignored because the measurement periods were at steady state, that is, at least 4 min after any manipulation that might have altered P_aCO_2.

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:

$$P_AO_2 = F_IO_2(P_b - P_{water}) - P_{ET}CO_2 \quad \text{Eq. 1}$$

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 Torr, 6.3 kPa), $P_{ET}CO_2$ is considered to be a measure of alveolar PCO_2, 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 F_IO_2 is less than 1 and the respiratory exchange ratio is not equal to 1, some other minor terms enter the equation. However, the form given here still yields a close approximation to the correct value.)

The O_2 and CO_2 sensors in the gas analyzer unit are independent. However, the presence of high O_2 spreads the absorption spectrum of CO_2 (the value from which the partial pressure is derived), thereby reducing the measured value of CO_2. The manufacturer's correction factor for CO_2 measured in the presence of 95% O_2, 1.06, was applied to the end-tidal values during hyperoxia. (The correction factor for 100% O_2 is 1.067.)

Table I. Summary by Condition, Means (Standard Deviation), Partial Pressures in Torr.

	$tcPO_2$	$tcPCO_2$	$P_{ET}O_2$*	$P_{ET}CO_2$	T_{skin} (°C)
A. Hyperoxia					
Rest	374 (87)	33 (6)	661 (4)	32 (4)	28 (1)†
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)§
B. Hypoxia					
Rest	35 (8)	39 (3)	49 (5)	35 (3)	28 (2)**
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)¶

$tcPO_2$: trancutaneous PO_2; $tcPCO_2$: transcutaneous PCO_2; $P_{ET}O_2$: end-tidal partial pressure of O_2; $P_{ET}CO_2$: end-tidal partial pressure of CO_2; T_{skin}: skin temperature; RB: resistive breathing during exercise.

*Calculated values. For Part A, $N = 14$ unless marked: †$N = 12$: T_{skin} not measured in 3 subjects; ‡$N = 13$, §$N = 11$. One subject could not exercise because of a problem with the set-up. In Part B, $N = 11$ unless marked: **$N = 9$: T_{skin} not measured in 2 subjects. ††$N = 10$, ‡‡$N = 8$: 1 subject reached the low S_pO_2 safety limit during "heat". ‡‡$N = 8$, §§$N = 7$: two other subjects reached it before exercise. ¶$N = 6$: two who exercised reached the safety limit before resistance breathing.

Statistical Analysis

Steady-state 1-min 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[3] and further explanatory variables were considered with 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.

RESULTS

Data from one subject in the hypoxic arm were lost because the TCM4 probe was not properly coupled to the skin. This left seven men and four women in the hypoxic arm. At rest, the average end tidal percentages of oxygen were 95% during hyperoxia and 7% during hypoxia.

Either subjects hyperventilated spontaneously at rest for both hyperoxic and hypoxic exposures (mean $P_{ET}CO_2$ of 32 and 35 Torr, respectively, **Table I**, **Fig. 2**) or $P_{ET}CO_2$ diverged from P_aCO_2; during normoxia, normal P_aCO_2 lies between 38 and 42 Torr. Hyperventilation at rest and resistive breathing during exercise caused divergent responses in $tcPCO_2$ and $P_{ET}CO_2$ (Fig. 2), as did skin heating and cooling at rest (**Fig. 3**). Note that the TCM4 probe temperature was held at 45°C throughout the experiment; only the temperature of the skin surrounding the probe changed.

During hyperventilation, $P_{ET}CO_2$ decreased with both hyperoxia and hypoxia (hyperoxia: $\Delta = -5.4$ Torr, $t = 6.9$, df = 13, $P < 0.0001$; hypoxia: $\Delta = -4.5$ Torr, $t = 4.9$, df = 10,

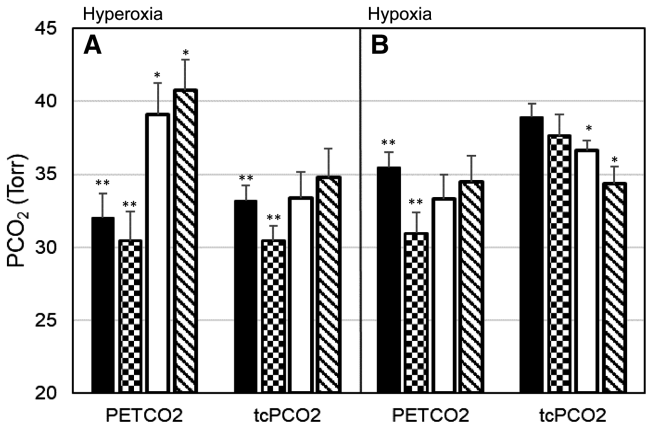

Fig. 2. End-tidal and transcutaneous PCO_2 after ventilatory interventions and exercise: A) hyperoxia, B) hypoxia. Error bars indicate standard error; *, ** $P < 0.05$, $P < 0.001$ for pairs indicated by matching symbols within the condition. Solid bars: rest, spontaneous breathing; checkerboard: rest, imposed hyperventilation; white: exercise, spontaneous breathing; diagonal stripe: exercise with resistive breathing.

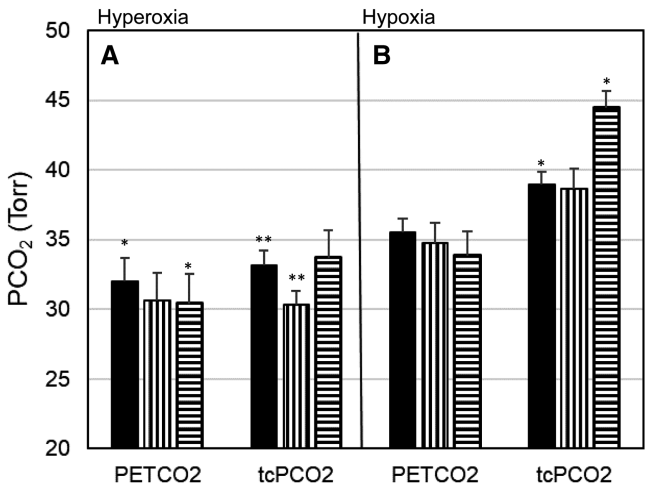

Fig. 3. End-tidal and transcutaneous P_{CO_2} after forearm heating and cooling: A) hyperoxia, B) hypoxia. Error bars indicate standard error; *, ** $P < 0.05$, $P < 0.001$ for pairs indicated by matching symbols within the condition. Solid bars: rest, ambient temperature; vertical stripes: cold; horizontal lines: heat.

$P < 0.001$) while $tcPCO_2$ decreased only during hyperoxia (hyperoxia: $\Delta = -2.8$ Torr, $t = 3.8$, df = 13, $P < 0.003$; hypoxia: $\Delta = -1.3$ Torr, $t = 1.37$, df = 10, $P = 0.2$).

During resistive breathing, $P_{ET}CO_2$ increased only during hyperoxia (hyperoxia: $\Delta = 1.7$ Torr, $t = 2.89$, df = 13, $P < 0.014$; hypoxia: $\Delta = 0.9$ Torr, $t = 1.05$, df = 5, $P = 0.3$) while $tcPCO_2$ did not change with hyperoxia ($\Delta = 1.4$ Torr, $t = 1.04$, df = 12, $P = 0.3$), but decreased with hypoxia ($\Delta = -0.8$ Torr, $t = 3.25$, df = 5, $P < 0.03$).

Forearm cooling was associated with no decreases in $P_{ET}CO_2$ (hyperoxia: $\Delta = -1.4$ Torr, $t = 2.0$, df = 13, $P = 0.067$; hypoxia $\Delta = -0.7$ Torr, $t = 2.2$, df = 10, $P = 0.054$), but a large decrease in $tcPCO_2$ during hyperoxia ($\Delta = -2.9$ Torr, $t = 7.1$, df = 13, $P < 0.0001$) and no change during hypoxia ($\Delta = -0.25$, $t = 0.54$, df = 6, $P = 0.6$).

Forearm heating during hyperoxia also was associated with $P_{ET}CO_2$ lower than during rest ($\Delta = -1.6$ Torr, $t = 3.43$, df = 13, $P < 0.005$), but not different from that during cold ($\Delta = -0.2$ Torr, $t = 0.44$. df = 13, $P = 0.6$). However, during heating with hypoxia, $P_{ET}CO_2$ was not different from that during rest ($\Delta = -1.8$ Torr, $t = 1.82$, df = 5, $P = 0.1$). In contrast, with forearm heating during hyperoxia, $tcPCO_2$ did not differ from that at rest ($\Delta = 0.5$, $t = 0.9$, df = 13, $P = 0.38$), while during heating with hypoxia, $tcPCO_2$ increased ($\Delta = 5.4$, $t = 3.0$, df = 9, $P < 0.02$).

Overall, $tcPCO_2$ and $P_{ET}CO_2$ were correlated ($r = 0.58$, $t = 8.5$, df = 140, $P < 0.001$), but scatter was large. For example, a "normocapnic" $P_{ET}CO_2$ of approximately 40 Torr corresponded to $tcPCO_2$ readings from 30 to 50 Torr, and a "normocapnic" $tcPCO_2$ reading of approximately 40 Torr matched $P_{ET}CO_2$ from 30 to 53 Torr. Further, the best linear regression equation to predict $tcPCO_2$ from $P_{ET}CO_2$ across all data,

$$tcPCO_2 = 0.70 \cdot P_{ET}CO_2 + 12 \qquad \text{Eq. 2}$$

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

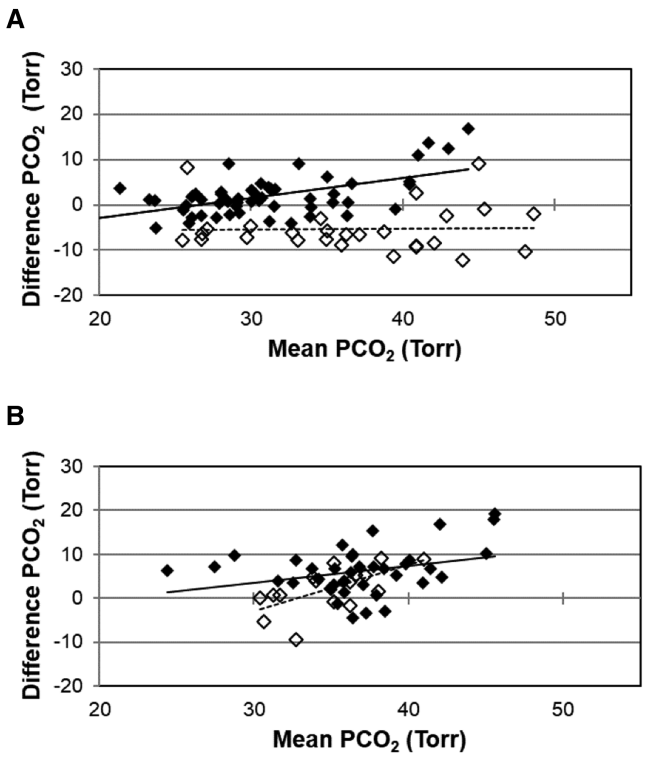

Fig. 4. Bland Altman plot, (transcutaneous and end-tidal) P_{CO_2} plotted against the mean of the two measurements: A) hyperoxia, B) hypoxia. Rest: black symbols, solid fitted lines. Exercise: white symbols, dashed fitted lines.

When hyperoxia and hypoxia, rest, and exercise were considered separately, correlations between $tcPCO_2$ and $P_{ET}CO_2$ were significant (hyperoxia rest: $r = 0.79$, $t = 9.4$, df = 54, $P < 0.001$; hyperoxia exercise: $r = 0.81$, $t = 6.76$, df = 24, $P < 0.001$; hypoxia rest: $r = 0.51$, $t = 3.78$, df = 41, $P < 0.001$) except during hypoxic exercise ($r = 0.03$, $t = 0.10$, df = 12, $P = 0.39$).

During hyperoxia (Table I, section A), the offset between oxygen partial pressure measured in tissue and in alveolar gas, that is, between $tcPO_2$ and $P_{ET}O_2$, was very large; $tcPO_2$ ranged from 159 to 591 Torr, with mean (SD) of 405 (89) Torr while $P_{ET}O_2$ exceeded 650 Torr. During hypoxia (Table I, section B), the offset between $P_{ET}O_2$ and $tcPO_2$ was approximately 20 Torr. However, $P_{ET}O_2$ and $tcPO_2$ were correlated at rest during both hyperoxia (r = 0.33, $N = 56$, $P < 0.02$) and hypoxia (r = 0.63, $N = 43$, $P < 0.001$).

For all measurements after more than approximately 15 min of hypoxia (i.e., all interventions starting with the cold pack), $tcPO_2$ was lower than it was during initial rest. Values of $tcPO_2$ during hypoxia ranged from 8 to 52 Torr, with mean (SD) of 24.7 (9.2) Torr. The range was 23 to 52 Torr in the first 15 min, and 8 to 35 Torr in the latter period. Interindividual 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 Torr.

Bland Altman (BA) plots of $tcPCO_2 - P_{ET}CO_2$ vs. the mean of the two for the individual data groupings, hyperoxia or hypoxia, rest or exercise, showed a general lack of agreement of the two measures (**Fig. 4**). The slopes were significantly greater than

Table II. Regression Parameters: $tcPco_2$ = Constant + Σ(B_i • $Predictor_i$).

PREDICTOR	B	SE(B)	β	*t*	*P*	Δr^2
A. Hyperoxia (100% O_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
B. Hypoxia (11.5% O_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

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, where r^2 is the regression coefficient, interpretable as fraction of variance explained by the regression equation. Units of $P_{ET}O_2$, $tcPo_2$: Torr. T_{skin}: skin temperature in °C, not measured in all subjects.

zero except during hyperoxic exercise, when the scatter from −12 to 9 Torr appeared to increase with increasing Pco_2. The slopes were as follows: hyperoxic rest slope = 0.44, standard error (SE) = 0.09, $t = 4.96$, $P < 0.001$; hyperoxic exercise slope = 0.01, SE = 0.15, $t = 0.07$, $P = 0.94$; hypoxic rest slope = 0.37, SE = 0.17, $t = 2.10$, $P = 0.04$; hypoxic exercise slope = 1.04, SE = 0.35, $t = 3.02$, $P < 0.009$.

Forward regression analysis showed significant effects of $tcPo_2$ and skin temperature beside the TCM4 probe on $tcPco_2$ (**Table II**). Rest and exercise were combined. Data for one subject during hypoxia were omitted because $tcPo_2$ exceeded $P_{ET}o_2$, suggestive of a small air leak under the TCM4 probe.

DISCUSSION

The question addressed here was whether changes in $tcPco_2$ reliably correspond to changes in P_aCO_2 under conditions like those experienced in tactical jet aviation. This study indicates that they do not. Hyperventilation by definition lowers and resistance breathing during exercise elevates[6] P_aCO_2. However, hyperventilation and resistance breathing during hyperoxia and hypoxia did not cause the expected changes in $tcPco_2$. Further, local skin temperature, which should not affect P_aCO_2, sometimes altered $tcPco_2$.

This study also compared $P_{ET}CO_2$ and $tcPco_2$ and examined what is known about their relationships to P_aCO_2. Bland Altman plots (Fig. 4) indicated the lack of correspondence of individual pairs of $P_{ET}CO_2$ and $tcPco_2$ measurements. The regression equations for hyperoxia and hypoxia (Table II) indicate that $tcPo_2$ and, to a lesser extent, skin temperature around the transcutaneous probe relate to the divergence of the measurements. Both of those relate to local effects, and thus $tcPco_2$ values. However, either or both $tcPco_2$ and $P_{ET}CO_2$ may have differed from P_aCO_2 for some of the measurements. Although we do not have data for the factors that cause $P_{ET}CO_2$ to deviate from P_aCO_2, values from the literature provide some answers.

Transcutaneous partial pressure is a direct measure of local tissue conditions; gas diffuses through the skin from capillaries directly beneath the probe.[13,17] 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 is intended to compensate for the difference.[13] Local tissue perfusion (blood flow per mass of tissue) affects the difference of tissue gas partial pressures from those in arterial blood. 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, and thus $P_{ET}CO_2$ from any small region of the lung represents P_aCO_2 from the same region. Differences in ventilation and perfusion across regions and the overall averaging caused by gas and blood mixing causes the two values to differ slightly overall. However, the relation between P_aCO_2 and $P_{ET}CO_2$ under normoxic exercise conditions is linear, with a small dependence on tidal volume,[9] and for resting values the correction between them is very small and often ignored.

All measurements here were made during prolonged, steady conditions (4 or more minutes after the start of any intervention), where response time of the analyzers is immaterial, and more than 20 min after electrode placement; the difference between $tcPco_2$ and P_aCO_2 during normoxic rest becomes stable approximately 8 min after electrode fixation.[19] However, it is important to note that $tcPco_2$ measurements cannot detect short-term perturbations. The lag time from initiation of a gas change in the lungs to the start of the $tcPco_2$ response is 14–16 s,[13] some of which is the time needed for blood to travel from the lungs to the tissue. Blood recirculation time, the time for a change in alveolar gas to be reflected in venous blood entering the lungs, is approximately 25 s at rest, shorter during exercise,[14] and the delay from lungs to brain, estimated using lung to earlobe transit time, is 6 s at rest.[16] Transcutaneous Pco_2 reaches 90% of its final reading only after about 78 s;[13] the electrode takes at least 60 s to stabilize at a new value after a change in arterial blood. Therefore, rapid changes in P_aCO_2 cannot be detected with $tcPco_2$ measurements. In contrast, the infrared CO_2 analyzer used here has a transit-plus-response time of 150 ms when sample flow is 150 mL · min^{-1} (manufacturer's specification sheet), reading the new gas composition in the lungs almost as soon as it is exhaled.

Tissue normally regulates its perfusion to match its metabolic needs. Local relative hypoxia is met with near-immediate vasodilation because removal of oxygen from hemoglobin molecules also releases the vasodilator nitric oxide.[2] Thus, an increase in local metabolic rate generates a matching increase in oxygen delivery and, as a side effect, a matching washout of the locally produced CO_2. A large body of literature confirms that $tcPco_2$ trends with P_aCO_2 during normoxic rest. However, the even during normoxia, correspondence of tissue and arterial values is approximate. A recent large, clinical study

combining patients and healthy volunteers compared $tcPCO_2$ measured for 30 min with P_aCO_2 at the end of that period.[19] Overall limits of agreement showed that $tcPCO_2$ just before the arterial sample was taken ranged from approximately 12 Torr higher to 2 Torr lower than P_aCO_2 even in supine individuals. Further, the bias, that is, the mean difference, $tcPCO_2 - P_aCO_2$, was higher in those who were hypocapnic (P_aCO_2 < 31 Torr) than in those who were normocapnic (35 mmHg < P_aCO_2 < 45 Torr), and greater in that normocapnic group than in those who were mildly hypercapnic (45 Torr < P_aCO_2 ≤ 50 Torr). Although those values are between, not within, individuals, greater bias at low than at high P_aCO_2 casts some doubt on $tcPCO_2$ as a trend indicator of changes in CO_2 balance even during normoxia.

Some investigators[4] report success with transcutaneous monitoring during exercise tests, but the American Association for Respiratory Care guidelines[15] do not recommend the technique except at rest. The guidelines also recommend against the use of $tcPCO_2$ in those breathing hyperoxic gases. To our knowledge, effects on $tcPCO_2$ of local skin heating and cooling during normoxia have not been addressed elsewhere. Moderate vasoconstriction has not been found to perturb measurements, while profound vasoconstriction reduces the correlation between $tcPCO_2$ and P_aCO_2 (see studies cited in Melhedegaard Thomsen[13]).

The moderately steady offset between $tcPCO_2$ and P_aCO_2 is lost in the absence of modulation of perfusion to regulate oxygen supply. Hyperoxia in skin capillaries blunts or abolishes it because the regulatory vasodilation is proportional to the local concentration of deoxyhemoglobin.[2] Almost no hemoglobin is deoxygenated if PO_2 is greater than 100 Torr, and $tcPO_2$ readings for our subjects breathing 100% O_2 considerably exceeded that value.

$P_{ET}CO_2$ may not represent P_aCO_2 when people breathe 100% O_2 at rest; lack of inert gas in the lungs promotes atelectasis and development of intrapulmonary shunt in regions subject to airway closure.[5,20] If venous admixture caused by the shunt adds CO_2 to arterialized blood, arterial chemoreceptors up-regulate pulmonary ventilation to maintain normal mixed arterial PCO_2. The increased minute ventilation reduces alveolar PCO_2 until arterial blood, the mixture of shunt fraction (with venous PCO_2), and pulmonary capillary blood (with alveolar PCO_2) has normal P_aCO_2. Thus, in the presence of shunt, $P_{ET}CO_2$ is lower than P_aCO_2, with values that appear to indicate hyperventilation ($P_{ET}CO_2$ < 38 Torr), like those measured when our resting subjects breathed 100% O_2 (Table I, section A).

The decrease in $P_{ET}CO_2$ from the initial resting measurement to that during forearm heating (Fig. 3) is consistent with an increase in shunt fraction with time at rest. As is consistent with the presence of shunt, resting $P_{ET}CO_2$ measured here was lower than P_aCO_2 measured directly by others[10,20] in young men breathing 100% O_2 near sea level: P_aCO_2 of 37 Torr, N = 4,[20] and P_aCO_2 of 38 Torr, N = 8.[10] Exercise and the change in posture from seated upright in the chair to seated, legs down, on the cycle ergometer apparently eliminated the shunt; $P_{ET}CO_2$ in the 10th minute of hyperoxic exercise was close to the anticipated normal 38 to 42 Torr (Table I, section A; Figs. 2A and 4A).

Systemic hypoxia causes global skin vasodilation.[18] Further, the concentration of bound nitric oxide in arterial blood has been shown to be low in people breathing 12% oxygen at sea level.[12] Thus the hypoxic condition here probably eliminated the capacity for local vasodilation. Changes in local metabolic rate would then dominate any changes in $tcPCO_2$. Indeed, $tcPO_2$ explained more of the variance in $tcPCO_2$ than did $P_{ET}CO_2$ (Table II, section B) and, during exercise, $tcPCO_2$ was not correlated with $P_{ET}CO_2$. As in hyperoxia, but for different reasons, the maintenance of the steady offset between $tcPCO_2$ and P_aCO_2 was lost in the absence of local oxygen-regulated modulation of perfusion.

During hypoxia, hyperventilation is the normal response. The $P_{ET}CO_2$ values here (Table I, section B) are comparable to P_aCO_2 measured directly by others[8] under similar conditions, where P_aCO_2 of 34 (7) Torr [mean (SE)] was measured at rest and 32 (0.6) Torr during mild exercise in subjects breathing 11% O_2 at sea level. Thus, $P_{ET}CO_2$ during hypoxia can be considered to be a good representation of P_aCO_2 even though the dispersion of ventilation to perfusion ratios has been shown to increase at an equivalent altitude of 15,000 ft MSL,[7] impairing both O_2 and CO_2 transfer. $P_{ET}CO_2$ here did not increase with resistive breathing during hypoxic exercise; the hypoxic ventilatory drive apparently counteracted the effects of the resistance.

Regression analysis of $tcPCO_2$ as a function of $P_{ET}CO_2$ and our small set of other measured variables (Table II) showed that $tcPO_2$ and skin temperature explained significant fractions of the variance in $tcPCO_2$ during hyperoxia and hypoxia. The coefficient on $tcPO_2$ was negative; an increase in $tcPO_2$ is a marker for increased perfusion relative to metabolic activity, leading to decreased $tcPCO_2$, and vice versa.

Skin temperature on the forearm (not the constant temperature under the TCM4 probe) entered the regression equations with positive coefficients. Skin warming increases local blood flow, and vice versa, which would imply a negative coefficient. However, in the regression equations, $tcPO_2$ entered the equation before skin temperature and increased $tcPO_2$ implies increased perfusion. The temperature effect is thus an adjustment to any temperature effects that already manifest in $tcPO_2$.

The goal of these experiments was to determine the utility of $tcPCO_2$ and, secondarily, of $P_{ET}CO_2$ as in-flight measures of CO_2 balance over a wide range of aviation-relevant situations. Conditions where changes in or stability of P_aCO_2 could be predicted were tested, but P_aCO_2 was not measured. Thus, the fidelity of the measurements to arterial values can only be inferred.

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. The perturbation of the balance between local perfusion and local metabolism probably scales with the magnitude of the disturbance from normoxia or from thermal equilibrium.

Even in the laboratory $P_{ET}CO_2$ is difficult to measure well, particularly in people who are permitted to breathe through either nose or mouth. Fidelity of measurements was made possible by extending the gas sample line into the gas stream rather than sampling from a port in the mask wall and by attention to sample line configuration and sample flow. Confidence in the measurements was gained by inspection of the resulting breath-by-breath traces and by observing faithful measurement of the known inspiratory gas, but mixing and dilution from the mask and valve dead space cannot be completely excluded.

In tactical aircraft, hypoxia is a rare event that requires immediate corrective action. Thus, the relevance to normal flying of CO_2 monitoring during hypoxia is low. Hyperoxia is the norm in tactical aircraft, particularly in the Navy where the breathing gas is either 100% oxygen or the maximum oxygen concentrator output except during mask-off ground operations. Because the aircraft cabin pressure in flight is lower than atmospheric pressure on the ground, the hyperoxia in the aircraft is at lower partial pressures than that measured here except during takeoff and landing. However, cabin altitude is maintained at 8000 ft (2438 m) MSL in many tactical jets for aircraft altitudes from 8000 to 24,000 ft (2438 to 7315 m) MSL. Because tissue Po_2 with greater than 90% oxygen at 8000 ft MSL is expected to exceed 100 Torr, the hyperoxic measurements here are directly relevant to most phases of flight. As discussed previously, hyperoxia at rest interferes with $tcPco_2$ as a measure of P_aCO_2, and close to 100% oxygen at any altitude also reduces the fidelity of $P_{ET}CO_2$ as a measure of P_aCO_2 because it induces intrapulmonary shunt.

Rest and exercise were included in this study since both occur depending on the phase of flight; the product of mean tidal volume and mean frequency measured during flight (Gordge D. In-flight measurement of aircrew breathing in Navy aircraft. Technical Memorandum #TM 93-59 SY, N62269/93/VX/0006. Naval Air Warfare Center Aircraft Division, Patuxent River, MD, 1993) yields 26 $L \cdot min^{-1}$ during routine flight and 42 $L \cdot min^{-1}$ during aerial combat maneuvers as estimates of average minute ventilation, much higher than the resting value of 6 to 10 $L \cdot min^{-1}$.

These experiments did not include any hypobaric exposures. However, measures that do not apply under normobaria are unlikely to be better suited to hypobaria. Neither $tcPco_2$ nor $P_{ET}CO_2$ may be useful measures in the cockpit if the aircrew breathes 100% O_2; the problem of atelectasis and shunt with 100% O_2 during seated rest is independent of the altitude at which 100% oxygen is delivered.

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 was measured only at exercise. No measurements were made during normoxia. Nevertheless, because the conditions chosen include those in tactical aircraft and demonstrate problems with $tcPco_2$ as a measure of P_aCO_2, they sufficed to answer the primary question of whether transcutaneous monitoring of carbon dioxide is suitable for physiological monitoring of tactical jet aircrew.

Several subjects 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 Po_2. There may have been a related change with time in P_aCO_2. However, because the drift occurred over 15 min or more, the response of the transcutaneous monitor was sufficient to follow it. Had the two measurements been equally valid surrogates for P_aCO_2, they would have been equally affected.

The TCM4 probe in this study was on the forearm, while many other studies have used chest placement, and chest placement has been proposed for aircraft use. Both chest and forearm are recommended by the manufacturer[13] and have been shown to give equivalent results during normoxic rest.[19] Both have homogenous capillary beds and large blood vessels and hair can be avoided. The forearm was chosen to facilitate the changes in local skin temperature. Since arterial blood gases are uniform throughout the body, the only difference related to probe location is in skin perfusion.

In summary, our data indicate that transcutaneous Pco_2 is an unreliable indicator of changes in P_aCO_2 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. Hyperoxia removes the coupling of skin perfusion to local metabolism, allowing the offset between P_aCO_2 and tissue Pco_2 to vary. Alterations in breathing gas or changes in whole-body work (exercise) can further alter the relationship. Even if they were feasible, end-tidal gas measurements in tactical aircraft, where pilots breathe hyperoxic gas, could incorrectly suggest hypocapnia in the presence of intrapulmonary shunt. Measurement of carbon dioxide in military aviators during flight remains an intractable problem.

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