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Early View

Research letter

End-tidal CO_2 partial pressure is a reliable surrogate of arterial CO_2 partial pressure across different O_2, CO_2, and barometric pressures

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End-tidal CO_2 partial pressure is a reliable surrogate of arterial CO_2 partial pressure across different O_2, CO_2, and barometric pressures

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Take home message: End-tidal CO_2 partial pressure provides an accurate estimation of $PaCO_2$ in healthy awake individuals over an extensive range of CO_2 pressures induced by 17 environmental conditions combining different O_2, CO_2 and barometric pressures.

To the Editor:

Accurate measurement of arterial carbon dioxide partial pressure ($PaCO_2$) is critical in emergency medicine as a marker of sufficient alveolar ventilation [1], and in human physiology to understand respiratory and cerebrovascular regulation [2]. The current gold standard technique to measure $PaCO_2$ is through arterial catheterization and analysis of blood gasses, although arterialized capillary blood (e.g. earlobe or fingertip) is often used to alleviate the invasiveness and risk associated with arterial sampling [3]. In either case, direct measurement of blood gasses does not allow for continuous data recording. Several pioneering works [4, 5] and recent studies [3, 6, 7] attempted to investigate non-invasive surrogates of $PaCO_2$ with greater temporal resolution. End-tidal carbon dioxide partial pressure ($P_{ET}CO_2$) represents a non-invasive measurement of alveolar ventilation, and is typically considered an adequate substitute for $PaCO_2$ in healthy adults [7]. However, $P_{ET}CO_2$ and $PaCO_2$ values may differ with discrepancies ranging between 1.8 and 4.9 mmHg in awake or anesthetized healthy individuals [8-10]. We aimed to investigate the $P_{ET}CO_2$-$PaCO_2$ relationship over a wide range of environmental conditions (combining different oxygen (O_2), carbon dioxide (CO_2), and barometric pressures (P_B)), to induce a large range of CO_2 pressure variations in resting healthy individuals.

Methods

Seventeen healthy males (mean±SD; age, 21 ± 2 years; body mass index, 22.8 ± 1.8 $kg \cdot m^{-2}$) volunteered and gave written informed consent to participate in this study. All participants were not taking any medication and were free from any cardiorespiratory and haematological diseases. Data on normal lung function and diffusion capacity to carbon monoxide of our participants are available elsewhere [11]. The experimental protocol was pre-registered at ClinicalTrials.gov (NCT04739904), approved from both the University of Ljubljana, Faculty

of Sport ethics committee (8/2020-316) and the Aosta Hospital Ethical Committee (06/05/2021.0038781.I), and performed according to the Declaration of Helsinki.

Participants were instructed to abstain from exercise (>12h), alcohol and caffeine (>24h), and avoid heavy meals (>4h), before testing. Participants were tested under the following seventeen environmental conditions while comfortably seated in a quiet and thermoneutral room: (1) normobaric normoxia (NNx), (2) normobaric hypercapnia (NNx+3%CO_2), (3) hypobaric hypoxia (HHx), (4) hypobaric normoxia (HNx), (5) hypobaric normoxic hypercapnia (HNx+3%CO_2), (6) hypobaric hypoxic isocapnia (with $P_{ET}CO_2$ clamped at NNx value (HHx+clamp)), (7) normobaric hypoxia (NHx), (8) normobaric hypoxic hypercapnia (NHx+3%CO_2), (9) normobaric hypoxic isocapnia, (10) normobaric hyperoxic (97%O_2) hypercapnia (3%CO_2; NHX+3%CO_2), (11) normobaric hyperoxic (94%O_2) hypercapnia (6%CO_2; NHX+6%CO_2), (12) hypobaric hyperoxic (97%O_2) hypercapnia (3%CO_2; HHX+3%CO_2), (13) hypobaric hyperoxic (94%O_2) hypercapnia (6%CO_2; HHX+6%CO_2), and (14-17) normobaric and hypobaric hypocapnia (i.e. voluntary hyperventilation, Hyp$\dot{V}_E$). Normobaric conditions were performed near sea-level (295 m; P_B = 737 ± 2 mmHg), while hypobaric measurements were carried out at high-altitude (3375 m; P_B = 503 ± 3 mmHg). NNx+CO_2 and NHx+CO_2 were induced by switching the inspired gas from ambient air to 3%CO_2 (in 20.93%O_2, balance N_2). In HNx and HNx+CO_2, participants breathed supplemental O_2 (FiO_2=32%, with 0.03%CO_2, balance N_2 and with 3%CO_2, balance N_2, respectively) to induce the same FiO_2 as in NNx. During conditions 6 and 9, end-tidal clamping was performed using a modified version of a breathing system detailed elsewhere [12]. Briefly, the system delivered high-flow, low-resistance inspired gas with a fixed FiO_2 and a varying $FiCO_2$. The inspiratory endpoint of this system included an open-ended reservoir where room air was mixed with 100% CO_2 compressed gas. The 8-L custom-made reservoir was connected, via a plastic flexible tube, to a two-way non rebreathing valve (2700

series, Hans Rudolph, Kansas City, MO, USA) attached to a low dead-space face mask (Hans Rudolph mask, 7400 oronasal series; dead space, 73 mL). In the normobaric and hypobaric hyperventilation stages, participants were instructed to increase their frequency and/or depth of breathing to reduce their $P_{ET}CO_2$ by the same magnitude as the increase observed during the corresponding hyperoxic hypercapnic condition. Each condition lasted 4 min. $P_{ET}CO_2$ was continuously monitored by a calibrated metabolic cart (Ergocard Professional, Medisoft, Sorinnes, Belgium) and the 30-sec average at the end of each stage was recorded. Arterialized capillary blood was collected from the earlobe during the last 30 s of each stage, and analyzed for $PaCO_2$ using an arterial blood gas analyzer (ABL-90 FLEX, Radiometer, Copenhagen, Denmark).

After having checked for normality by Shapiro-Wilk test, linear regression and correlation analyses between $P_{ET}CO_2$ and $PaCO_2$ were performed by the least-squares residual method (Prism v.6.0, GraphPad Software, La Jolla, CA, USA). Residual plot analysis was used to determine the linear fitting of our data. Moreover, a linear regression of all the individual residuals vs. the average CO_2 response was tested to determine that there was not a systematic difference throughout the range of values. Bland–Altman analysis calculating the difference versus the mean was used to compare paired readings of $P_{ET}CO_2$ and $PaCO_2$; 95% confidence interval (95% CI) were also calculated. All *P*-values were two-tailed and statistical significance was defined *a priori* at $P < 0.05$.

Results

$P_{ET}CO_2$ and $PaCO_2$ showed a strong to very strong correlation for each of the 17 environmental conditions, separately ($r > 0.60$, $P < 0.044$) as well as when all conditions were pooled (**Figure 1a**). Bland–Altman analysis indicated that, when all conditions were pooled, the bias of the $P_{ET}CO_2$ was -2.43 mmHg (95% CI, -6.08 to 1.23 mmHg; **Figure 1b**). Taken separately, the bias ranged from -3.99 (95% CI, -7.13 to -0.85 mmHg) in NNx to -0.18

(95% CI, -1.84 to 1.47 mmHg) in NHx+3%CO_2. The linear regression analysis of the residuals showed that there was not a systematic difference throughout the range of values (Slope = -0.331, *P* = 0.798; **Figure 1c**).

Discussion

$P_{ET}CO_2$ represents an attractive, non-invasive alternative for $PaCO_2$ measurement. We observed a strong correlation between $P_{ET}CO_2$ and $PaCO_2$ over a wide range of inspired CO_2 partial pressures in young healthy adults. Previous studies investigating the $P_{ET}CO_2$-$PaCO_2$ relationship in both healthy and mechanically-ventilated individuals concluded that $P_{ET}CO_2$ may [8, 9] or may not [13, 14] represent a surrogate of $PaCO_2$ in different population and/or experimental settings. There are several conditions where $P_{ET}CO_2$ does not accurately reflect $PaCO_2$ such as exercise, aging, body position, as well as in patients with lung diseases [7]. Moreover, respiration and dead space undoubtedly influences both $P_{ET}CO_2$ and $PaCO_2$ though a recent work reported a moderate-to-strong correlation between $P_{ET}CO_2$ and $PaCO_2$ across a wide range of dead space to tidal volume ratios [15]. However, in this study we only focused on understanding the influence of different environmental conditions (i.e., hypobaric vs. normobaric, normocapnic vs. hypercapnic, normoxia vs. hypoxia) on the $P_{ET}CO_2$-$PaCO_2$ relationship in healthy individuals, and demonstrated that the $P_{ET}CO_2$-$PaCO_2$ relationship remains valid across numerous environmental conditions combining different levels of O_2, CO_2, and barometric pressures.

In conclusion, these novel findings suggest that $P_{ET}CO_2$ measurement provides an accurate estimation of $PaCO_2$ in healthy awake individuals over an extensive range of CO_2 pressures induced by various environmental conditions combining different O_2, CO_2 and barometric pressures. Our results therefore support the use of $P_{ET}CO_2$ as an alternative to invasive monitoring and/or repeated arterial blood gas analyses in applied environmental physiology research. However, the present findings can be only used to draw conclusions in healthy

adults, since the $P_{ET}CO_2$-$PaCO_2$ relationship does not persist in patients with alveolar ventilation-perfusion abnormalities [7], leading to a significant underestimation of $PaCO_2$ [6]. Nonetheless, in healthy individuals, $P_{ET}CO_2$ can be easily measured breath-by-breath or continuously, which is particularly useful in a variety of experimental and applied contexts.

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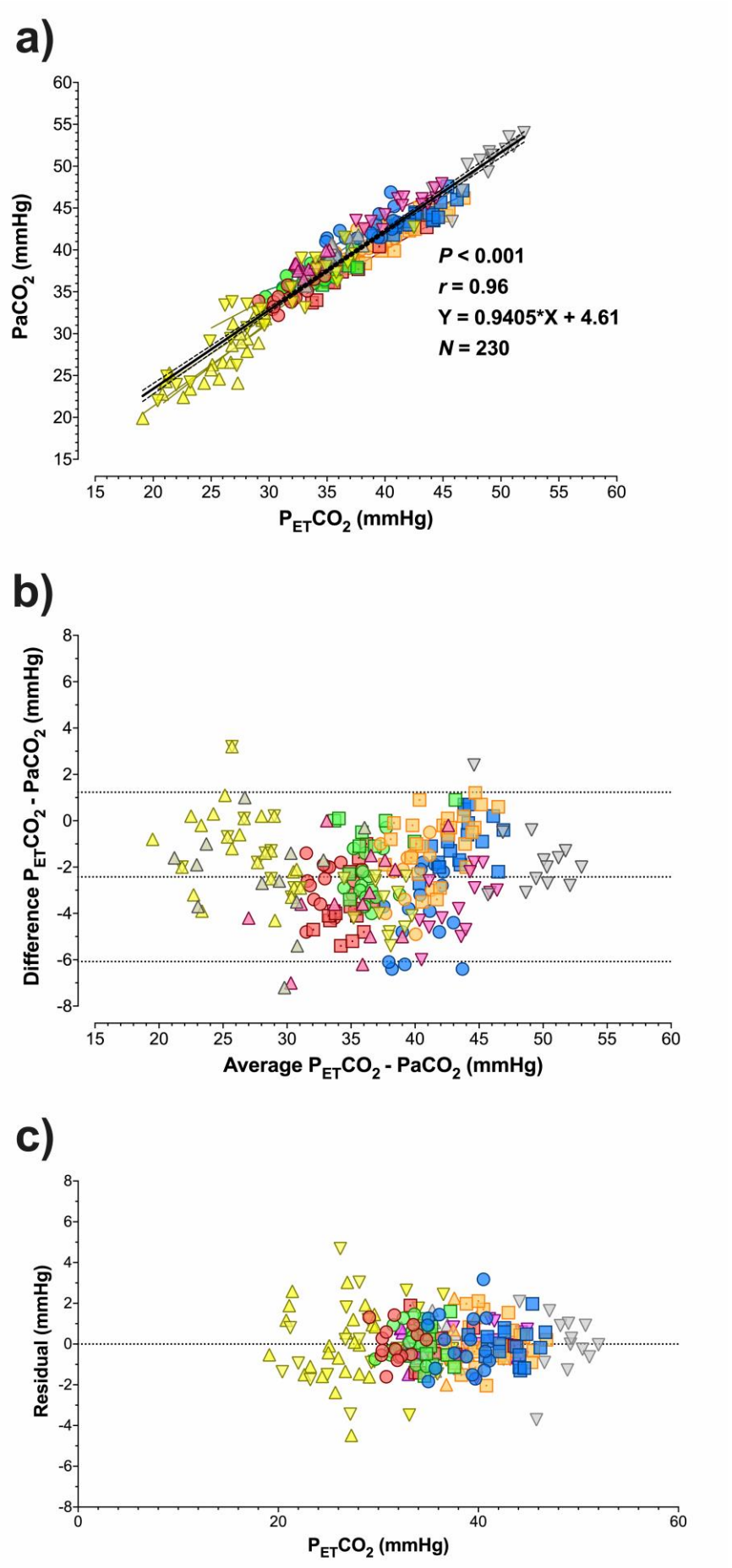
Figure Captions

Figure 1. Pooled correlation and linear regression analyses of $P_{ET}CO_2$ vs. $PaCO_2$ measured during 17 experimental conditions (**Panel a**) and Bland-Altman plot of the actual difference versus the mean of $P_{ET}CO_2$ and $PaCO_2$ (**Panel b)**. **Panel c** shows the residuals plot. In panel B, dotted lines represent the bias and the 95% confidence intervals. ***Blue circles***, normobaric normoxia (NNx); ***blue squares***, normobaric normoxia hypercapnia (NNx+3%CO_2); ***red circles***, hypobaric hypoxia (HHx); ***red dot-in-squares***, hypobaric hypoxia with $P_{ET}CO_2$ clamped at NNx value (HHx+clamp); ***green circles***, hypobaric normoxia (HNx); ***green squares***, hypobaric normoxia hypercapnia (HNx+3%CO_2); ***orange circles***, normobaric hypoxia (NHx); ***orange squares***, normobaric hypoxia hypercapnia (NHx+3%CO_2); ***orange dot-in-squares***, normobaric hypoxia with $P_{ET}CO_2$ clamped at NNx value (NHx+clamp); ***purple upside down triangles***, normobaric hyperoxic (97%O_2) hypercapnia (3%CO_2; NHX+3%CO_2); ***grey upside down triangles***, normobaric hyperoxic (94%O_2) hypercapnia (6%CO_2; NHX+6%CO_2) ; ***purple triangles***, hypobaric hyperoxic (97%O_2) hypercapnia (3%CO_2; HHX+3%CO_2); ***grey triangles***, hypobaric hyperoxic (94%O_2) hypercapnia (6%CO_2; HHX+6%CO_2); ***yellow triangles and yellow upside down triangles***, normobaric and hypobaric normoxic hyperventilation (Hyp$\dot{V}_E$), respectively.


a)
PaCO2 (mmHg)
PETCO2 (mmHg)
P < 0.001
r = 0.96
Y = 0.9405*X + 4.61
N = 230
b)
Difference PETCO2 - PaCO2 (mmHg)
Average PETCO2 - PaCO2 (mmHg)
c)
Residual (mmHg)
PETCO2 (mmHg)