End-tidal carbon dioxide tension is a reliable surrogate of arterial carbon dioxide tension across different oxygen, carbon dioxide and barometric pressures

Received: 1 Oct 2022
Accepted: 4 Feb 2023

To the Editor:

Accurate measurement of arterial carbon dioxide partial pressure (P_{aCO_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 P_{aCO_2} is through arterial catheterisation and analysis of blood gases, although arterialised 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 gases does not allow for continuous data recording. Several pioneering works [4, 5] and recent studies [3, 6, 7] attempted to investigate noninvasive surrogates of P_{aCO_2} with greater temporal resolution. End-tidal carbon dioxide partial pressure (P_{ETCO_2}) represents a noninvasive measurement of alveolar ventilation, and is typically considered an adequate substitute for P_{aCO_2} in healthy adults [7]. However, P_{ETCO_2} and P_{aCO_2} values may differ with discrepancies ranging between 1.8 and 4.9 mmHg in awake or anaesthetised healthy individuals [8–10]. We aimed to investigate the P_{ETCO_2}–P_{aCO_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.

17 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 of the lung for carbon monoxide of our participants are available elsewhere [11]. The experimental protocol was pre-registered at ClinicalTrials.gov (NCT04739904), approved by 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 (>12 h), alcohol and caffeine (>24 h), and avoid heavy meals (>4 h) before testing. Participants were tested under the following 17 environmental conditions while comfortably seated in a quiet and thermoneutral room: 1) normobaric normoxia (NNx); 2) normobaric normoxic 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_{ETCO_2} clamped at NNx value (HHx+clamp)); 7) normobaric hypoxia (NHx); 8) normobaric hypoxic hypercapnia (NHx+3%CO_2); 9) normobaric hypoxic isocapnia (NHx+clamp); 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). 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 (inspiratory oxygen fraction (F_{IO_2}) 32%, with 0.03%CO_2, balance N_2 and with 3%CO_2, balance N_2, respectively) to induce the same F_{IO_2} as in NNx. During conditions 6 and 9, end-tidal clamping was performed using a modified version of a breathing system

Shareable abstract (@ERSpublications)
End-tidal CO_2 tension provides an accurate estimation of P_{aCO_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 https://bit.ly/3YuKPAY

Cite this article as: Manferdelli G, Narang BJ, Bourdillon N, *et al*. End-tidal carbon dioxide tension is a reliable surrogate of arterial carbon dioxide tension across different oxygen, carbon dioxide and barometric pressures. *ERJ Open Res* 2023; 9: 00507-2022 [DOI: 10.1183/23120541.00507-2022].

detailed elsewhere [12]. Briefly, the system delivered high-flow, low-resistance inspired gas with a fixed F_{IO_2} and a varying inspiratory carbon dioxide fraction. The inspiratory end-point 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 nonrebreathing 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_{ETCO_2} by the same magnitude as the increase observed during the corresponding hyperoxic hypercapnic condition. Each condition lasted 4 min. P_{ETCO_2} was continuously monitored by a calibrated metabolic cart (Ergocard Professional; Medisoft, Sorinnes, Belgium) and the 30-s average at the end of each stage was recorded. Arterialised capillary blood was collected from the earlobe during the last 30 s of each stage, and analysed for P_{aCO_2} using an arterial blood gas analyser (ABL-90 FLEX; Radiometer, Copenhagen, Denmark).

After having checked for normality by Shapiro–Wilk test, linear regression and correlation analyses between P_{ETCO_2} and P_{aCO_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 *versus* 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_{ETCO_2} and P_{aCO_2}; 95% confidence intervals were also calculated. All p-values were two-tailed, and statistical significance was defined *a priori* at p<0.05.

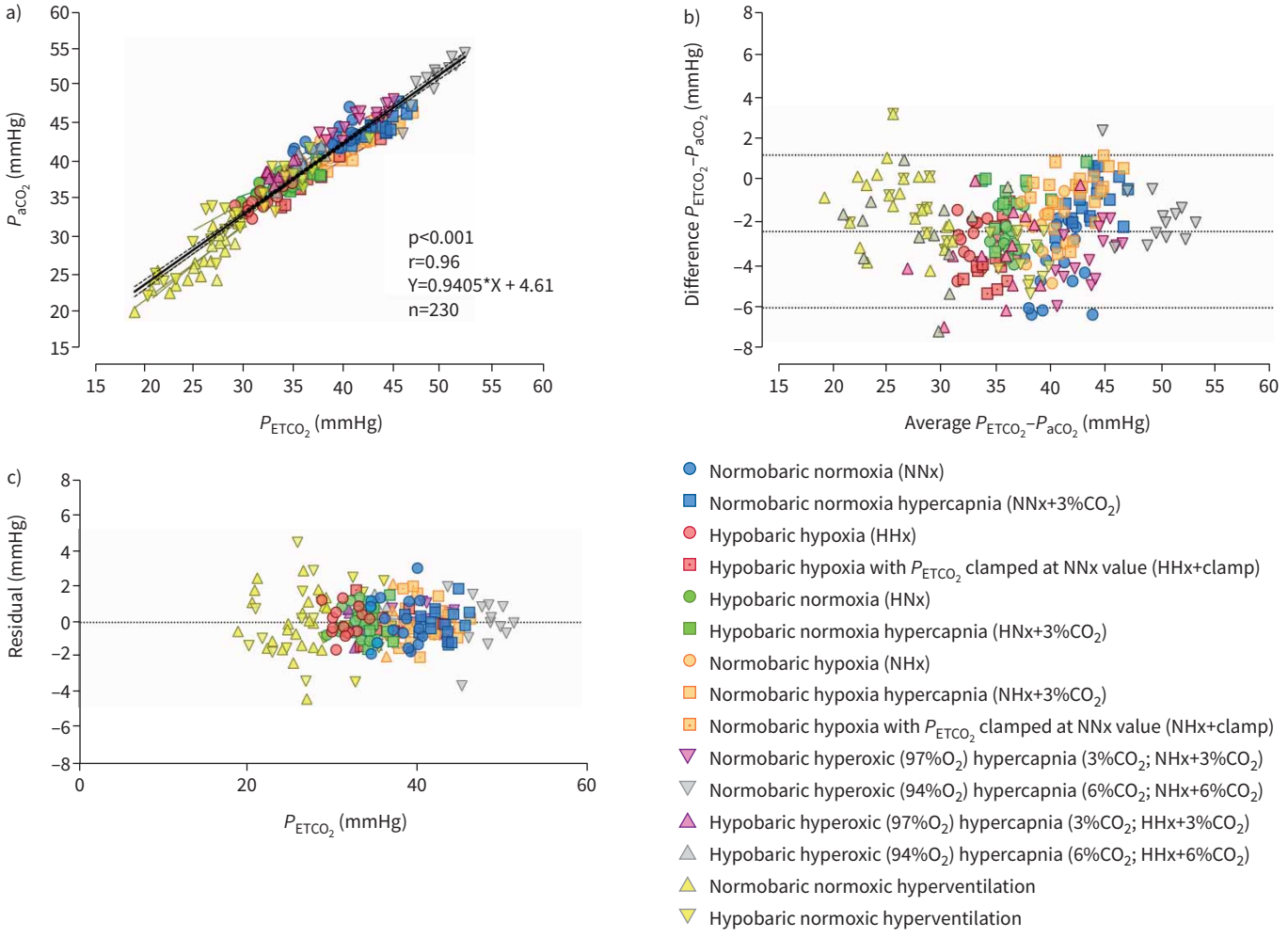

FIGURE 1 Pooled correlation and linear regression analyses of a) end-tidal carbon dioxide tension (P_{ETCO_2}) *versus* arterial carbon dioxide tension (P_{aCO_2}) measured during 17 experimental conditions and b) Bland–Altman plot of the actual difference *versus* the mean of P_{ETCO_2} and P_{aCO_2}; c) the residuals plot. In b) dotted lines represent the bias and the 95% confidence intervals. CO_2: carbon dioxide; O_2: oxygen.

P_{ETCO_2} and P_{aCO_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_{ETCO_2} was −2.43 mmHg (95% CI −6.08–1.23 mmHg; figure 1b). Taken separately, the bias ranged from −3.99 (95% CI −7.13– −0.85 mmHg) in NNx to −0.18 (95% CI −1.84–1.47 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).

P_{ETCO_2} represents an attractive, noninvasive alternative for P_{aCO_2} measurement. We observed a strong correlation between P_{ETCO_2} and P_{aCO_2} over a wide range of inspired CO_2 partial pressures in young healthy adults. Previous studies investigating the P_{ETCO_2}–P_{aCO_2} relationship in both healthy and mechanically ventilated individuals concluded that P_{ETCO_2} may [8, 9] or may not [13, 14] represent a surrogate of P_{aCO_2} in different population and/or experimental settings. There are several conditions where P_{ETCO_2} does not accurately reflect P_{aCO_2}, such as exercise, ageing and body position, as well as in patients with lung diseases [7]. Moreover, respiration and dead space undoubtedly influence both P_{ETCO_2} and P_{aCO_2}, although recent work reported a moderate-to-strong correlation between P_{ETCO_2} and P_{aCO_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 *versus* normobaric, normocapnic *versus* hypercapnic, normoxia *versus* hypoxia) on the P_{ETCO_2}–P_{aCO_2} relationship in healthy individuals, and demonstrated that the P_{ETCO_2}–P_{aCO_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_{ETCO_2} measurement provides an accurate estimation of P_{aCO_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. Therefore, our results support the use of P_{ETCO_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_{ETCO_2}–P_{aCO_2} relationship does not persist in patients with alveolar ventilation/perfusion abnormalities [7], leading to a significant underestimation of P_{aCO_2} [6]. Nonetheless, in healthy individuals, P_{ETCO_2} can be easily measured breath-by-breath or continuously, which is particularly useful in a variety of experimental and applied contexts.

Giorgio Manferdelli [1,4], Benjamin J. Narang[2,3,4], Nicolas Bourdillon[1], Tadej Debevec [2,3,5] and Grégoire P. Millet [1,5]

[1]Institute of Sport Sciences, University of Lausanne, Lausanne, Switzerland. [2]Department of Automation, Biocybernetics and Robotics, Jožef Stefan Institute, Ljubljana, Slovenia. [3]Faculty of Sport, University of Ljubljana, Ljubljana, Slovenia. [4]Joint first authors. [5]Joint senior authors.

Corresponding author: Giorgio Manferdelli (giorgio.manferdelli@unil.ch)

Provenance: Submitted article, peer reviewed.

The experimental protocol for this study was pre-registered at ClinicalTrials.gov with identifier number NCT04739904.

Acknowledgements: The authors thank all the volunteers who enthusiastically participated in this research project, the team at Torino Hut (Italy) where the high-altitude data collection was carried out, and SkyWay Mont Blanc (Entrèves, Italy) who supported the transport of the equipment and the participants to Torino Hut.

Conflict of interest: No conflicts of interest, financial or otherwise, are declared by the authors.

Support statement: This work was funded by the Swiss National Science Foundation (SNSF grant number 320030L_192073) and the Slovenian Research Agency (ARRS grant number N5-0152).

References

1 Petersson J, Glenny RW. Gas exchange and ventilation–perfusion relationships in the lung. *Eur Respir J* 2014; 44: 1023–1041.

2 Ogoh S. Interaction between the respiratory system and cerebral blood flow regulation. *J Appl Physiol* 2019; 127: 1197–1205.

3 Huttmann SE, Windisch W, Storre JH. Techniques for the measurement and monitoring of carbon dioxide in the blood. *Ann Am Thorac Soc* 2014; 11: 645–652.
4 Haldane JS, Priestley JG. The regulation of the lung-ventilation. *J Physiol* 1905; 32: 225–266.
5 Nunn JF, Hill DW. Respiratory dead space and arterial to end-tidal carbon dioxide tension difference in anesthetized man. *J Appl Physiol* 1960; 15: 383–389.
6 Lermuzeaux M, Meric H, Sauneuf B, *et al.* Superiority of transcutaneous CO_2 over end-tidal CO_2 measurement for monitoring respiratory failure in nonintubated patients: a pilot study. *J Crit Care* 2016; 31: 150–156.
7 Nassar BS, Schmidt GA. Estimating arterial partial pressure of carbon dioxide in ventilated patients: how valid are surrogate measures? *Ann Am Thorac Soc* 2017; 14: 1005–1014.
8 Yosefy C, Hay E, Nasri Y, *et al.* End tidal carbon dioxide as a predictor of the arterial P_{CO2} in the emergency department setting. *Emerg Med J* 2004; 21: 557–559.
9 Razi E, Moosavi GA, Omidi K, *et al.* Correlation of end-tidal carbon dioxide with arterial carbon dioxide in mechanically ventilated patients. *Arch Trauma Res* 2012; 1: 58–62.
10 Sullivan KJ, Kissoon N, Goodwin SR. End-tidal carbon dioxide monitoring in pediatric emergencies. *Pediatr Emerg Care* 2005; 21: 327–332.
11 Manferdelli G, Narang BJ, Bourdillon N, *et al.* Physiological responses to exercise in hypoxia in preterm adults: convective and diffusive limitations in the O_2 transport. *Med Sci Sports Exerc* 2023; 55: 482–496.
12 Olin JT, Dimmen AC, Subudhi AW, *et al.* A simple method to clamp end-tidal carbon dioxide during rest and exercise. *Eur J Appl Physiol* 2012; 112: 3439–3444.
13 Doppmann P, Meuli L, Sollid SJM, *et al.* End-tidal to arterial carbon dioxide gradient is associated with increased mortality in patients with traumatic brain injury: a retrospective observational study. *Sci Rep* 2021; 11: 10391.
14 Tymko MM, Ainslie PN, MacLeod DB, *et al.* End tidal-to-arterial CO_2 and O_2 gas gradients at low- and high-altitude during dynamic end-tidal forcing. *Am J Physiol Regul Integr Comp Physiol* 2015; 308: R895–R906.
15 McSwain SD, Hamel DS, Smith PB, *et al.* End-tidal and arterial carbon dioxide measurements correlate across all levels of physiologic dead space. *Respir Care* 2010; 55: 288–293.