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Howe, Connor ; MacLeod, David ; Wainman, Liisa; Oliver, Sam; Ainslie, Philip

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Validation of a Non-invasive Assessment of Pulmonary Gas Exchange During Exercise in Hypoxia

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Abbreviations

$A\text{-}aDO_2$: Alveolar-to-arterial oxygen difference

ABG: Arterial blood gas

AGM100: MediPines Gas Exchange Monitor

F_IO_2: Fraction of inspired oxygen

$gPaO_2$: Calculated partial pressure of arterial oxygen via non-invasive methods

P_{50}: Partial pressure of oxygen associated with 50% oxygen saturation

P_AO_2: Alveolar partial pressure of oxygen

P_{Atm}: Atmospheric pressure

PaO_2: Partial pressure of arterial oxygen

PCO_2: Partial pressure of carbon dioxide

$P_{ET}O_2$: Partial pressure of end-tidal oxygen

PH_2O: Partial pressure of water

PO_2: Partial pressure of oxygen

RER: Respiratory exchange ratio

SaO_2: Oxygen saturation of arterial haemoglobin

SpO_2: Oxygen saturation of peripheral capillary

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Running Head: Non-invasive pulmonary gas exchange in hypoxic exercise

Authors: Connor A. Howe[1], David B MacLeod[2], Liisa Wainman[3], Samuel J. Oliver[4], Philip N. Ainslie[1]

[1]Centre for Heart, Lung, and Vascular Health, University of British Columbia- Okanagan, Kelowna, Canada.

[2]Department of Anesthesiology, Duke University Medical Center, Durham, United States.

[3]Department of Medicine, University of British Columbia, Vancouver, Canada

[4]Extremes Research Group, School of Sport, Health and Exercise Sciences, Bangor University, Bangor, UK.

Corresponding author: Connor A Howe, Centre for Heart, Lung and Vascular Health, School of Health and Exercise Sciences, University of British Columbia – Okanagan, 3333 University Way, Kelowna, British Columbia, Canada, V1V 1V7 Email address: connorahowe@gmail,com

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Abstract:

Background: Pulmonary gas exchange efficiency, determined by the alveolar-to-arterial PO_2 difference ($A\text{-}aDO_2$), progressively worsens during exercise at sea-level; this response is further elevated during exercise in hypoxia. Traditionally, pulmonary gas exchange efficiency is assessed through measurements of ventilation and end-tidal gases paired with direct arterial blood gas (ABG) sampling. Since these measures have a number of caveats, particularly invasive blood sampling, the development of new approaches for the non-invasive assessment of pulmonary gas exchange is needed.

Research Question: Is a non-invasive method of assessing pulmonary gas exchange valid during rest and exercise in acute hypoxia?

Study Design and Methods: Twenty-five healthy participants (10 female) completed a staged maximal exercise test on a cycle ergometer in a hypoxic chamber (F_IO_2=0.11). Simultaneous ABGs via a radial arterial catheter and non-invasive gas-exchange measurements (AGM100) were obtained in two-minute intervals. Non-invasive gas exchange, termed the O_2 deficit, was calculated from the difference between the end-tidal and the calculated PaO_2 (via pulse oximetry and corrected for the Bohr effect by using the end-tidal PCO_2). Non-invasive O_2 deficit was compared to the traditional alveolar to arterial oxygen difference ($A\text{-}aDO_2$) using the traditional Riley analysis.

Results: Under conditions of rest at room air, hypoxic rest and hypoxic exercise, strong correlations between the calculated gPaO2 and directly measured PaO2 (R^2=0.97; $p<0.001$; mean bias =1.70 mmHg) were observed. At hypoxic rest and exercise, strong relationships between the estimated and directly measured PaO_2 (R^2=0.68; $p<0.001$; mean bias =1.01mmHg) and O_2 deficit with the traditional $A\text{-}aDO_2$ (R^2=0.70; $p<0.001$; mean bias =5.24mmHg) remained.

Interpretations: Our findings support the use of a non-invasive measure of gas exchange during acute hypoxic exercise in heathy humans. Further studies are required to determine if this approach can be used clinically as a tool during normoxic exercise in patients with pre-existing impairments in gas exchange efficiency.

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INTRODUCTION:

It is well established that pulmonary gas exchange efficiency, determined by the alveolar-to-arterial PO_2 difference ($A\text{-}aDO_2$) progressively worsens (i.e., the $A\text{-}aDO_2$ increases) in a workload-dependent manner during exercise in normoxia due to both pulmonary factors (a combination of alveolar ventilation-to-perfusion inequalities, diffusion limitation, and intrapulmonary right-to-left shunt) and non-pulmonary factors (i.e., extrapulmonary right-to-left shunt) [reviewed in: [1]]. This impairment in pulmonary gas exchange efficiency during exercise is further exacerbated in acute hypoxia, such that for any given oxygen consumption, the $A\text{-}aDO_2$ is greater when compared to exercise in normoxic conditions resulting in further hypoxemia [2].

The current gold-standard for assessing changes in gas exchange during exercise and/or in pathological conditions is via invasive sampling of arterial blood gases (ABG). However, there are several technical and logistical limitations that make the acquisition of these samples difficult; time to complete sampling & processing procedure; repeated blood sampling that may increase risk of infection and/or anemia; variability in the measure; requirement of a technically skilled operator; confinement to a laboratory or hospital; damage to the endothelium during catheter insertion [3]; possible anxiety during cannulation; and limitations of the traditional ideal $A\text{-}aDO_2$ calculations relating to the traditional Riley method of measuring alveolar O_2 [reviewed in: [4]]. For these reasons, there has been recent progress in a noninvasive method utilizing the MediPines Gas Exchange Monitor (AGM100)[1] for assessing impaired pulmonary gas exchange [5-8]. This method employs measuring end-tidal PO_2 and PCO_2 from the expired gas during steady-state breathing and then deriving the arterial PO_2 via pulse oximetry. Allowing for the Bohr effect by use of the end-tidal PCO_2, the difference between the end-tidal, which is assumed to equal alveolar PO_2, and the calculated PO_2 is defined as the oxygen deficit (O_2 deficit). Collectively, these studies have confirmed that this non-invasive procedure is a highly sensitive indicator of impaired pulmonary gas exchange in lung disease [5]. Additionally, in resting conditions in elderly healthy volunteers and in patients with lung disease, the estimated oxygen deficit correlates well with the directly measured $A\text{-}aDO_2$ [5,7,8]. Despite the promising developments in this non-invasive procedure, it has not been established if the AGM100 can

[1] The MediPines Gas Exchange Monitor was cleared by the US FDA

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accurately detect changes in pulmonary gas exchange efficiency during exercise, particularly under hypoxic conditions where substantial increases in the A-aDO_2 occur resulting in further arterial hypoxemia.

The aim of this study was to compare the predicted arterial PO_2 and oxygen deficit from the non-invasive method with directly measured arterial blood gases at rest and during graded exercise in acute hypoxia. We examined the related hypotheses that the non-invasive measures would be strongly related to the direct arterial blood gas assessments of pulmonary gas exchange efficiency.

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METHODS

Ethical approval

All participants gave written informed consent prior to participating. This study was approved by the University of British Columbia Clinical Research Ethics Board (H17-02687-A008) and conformed to the standards set by the *Declaration of Helsinki* (except registry in a database) and the Canadian Government Tri-council Policy Statement (TCPS2) for integrity in research.

Participants:

Fifteen male (28.1±6.2 years; body mass 77.2±9.4 kg; height 178.6±5.2 cm; BMI 24.2±2.5 kg/m^2) and ten female (24.9±3.6 years; body mass 63.1±3.9 kg; height 170.0±5.0 cm; BMI 21.9±1.7 kg/m^2) participants were recruited from the University of British Columbia Okanagan (344 m elevation). All participants were healthy and free from respiratory or cardiovascular disease, did not smoke, and self-reported engaging in 3-5hrs of moderate/vigorous physical activity per week. Participants were instructed to refrain from caffeine and alcohol for 12 hrs and strenuous exercise for 24 hrs before testing.

Experimental overview

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While resting in the supine position a radial artery catheter (20-gauge; Arrow, Markham, ON, Canada) was inserted into the left radial artery under local anesthesia (Lidocaine, 1.0%) and ultrasound guidance. The arterial catheter was attached to an inline waste-less sampling system (Edwards Lifesciences, TruWave VAMP, CA, USA). Following cannulation, participants entered a normobaric hypoxia chamber (F_IO_2 = 0.11) for 30-minutes. Following a 30-minute period of seated rest (in hypoxia), participants completed an incremental cycling test to exhaustion on an up-right cycle ergometer (Excalibur Sport, Lode, London, UK). To match relative exercise time between sexes, male participants began cycling at 20 watts, increasing by 30 watts every 2 minutes, while females began cycling at 15 watts, increasing by 20 watts every 2 minutes. All participants were instructed to cycle at a comfortable cadence (between 50 and 80 RPM) on an individual basis and to exercise until maximal volitional exhaustion. Subjects were asked to breathe through a small mouthpiece connected to a galvanic O_2 and infrared CO_2 analyzer, and were fitted with a pulse oximeter (Unimed U405S-06 Reusable Soft Finger Sensor, Unimed, Shenzhen, China) for AGM100 (MediPines Corporation, Yorba Linda, USA) measurements both at rest and throughout the exercise test. Simultaneous AGM100 measurements and arterial ABG samples were obtained during normoxic rest prior to entering the hypoxia chamber, during hypoxic rest, and in the last 30 seconds of each exercise stage. From each blood gas sample, any air bubbles were immediately evacuated from the syringe, and blood analysis was performed within 10-minutes of sampling with a commercially available gas analyzer (ABL90 FLEX, Radiometer, Copenhagen, Denmark). The blood gas analyzer was calibrated at a minimum of every 8 hours using manufacturer's standard internal quality checks. Reported variables that were calibrated and analyzed included PaO_2, $PaCO_2$, pH and oxygen saturation of arterial oxyhaemoglobin (SaO_2). For the present study, the within day coefficient of variation of measurement for PaO_2 was 1.5% and 2.1% for $PaCO_2$, respectively. The between-day coefficient of variation of the main variables (end-tidal gases, SpO_2 and O_2 deficit) of the AGM100 following exposure to normobaric hypoxia (F_IO_2 = 0.12) was <5%.

Non-invasive gas exchange monitoring

Non-invasive gas-based assessment of arterial PaO_2 ($gPaO_2$) was obtained by converting SpO_2 obtained from the finger pulse-oximeter using the Hill equation as shown below:

$$PaO_2\text{^}n = (P_{50}\text{^}n) \times [SpO_2/(1 - SpO_2)] \qquad \text{Eq 3.}$$

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Whereby P_{50} represents the PO_2 associated with 50% oxygen saturation (27mmHg), and n represents a constant of 2.7. The P_{50} was adjusted by the measured end-tidal PCO_2 [9,10]. Simultaneous assessment of end-tidal gases allows for PCO_2 associated changes in the oxygen affinity of hemoglobin to be accounted for using the Kelman subroutine. However, it is not possible to allow for changes in pH caused by alterations in base excess, as discussed previously [5-8]. Although the AGM100 software, by default, averages breath data over the previous eight breaths to get steady normalized sampling, for this study, gas exchange data were averaged over 20-seconds at the end of each stage to limit the influence of ventilatory artifacts on influencing the measure. It has been previously stated that it is important to capture "steady state" values during each non-invasive session [4]. During steady-state respiration, a dynamic equilibrium exists between oxygen and carbon dioxide and averaged values are highly reproducible as they are derived from the lung at functional residual capacity.

Alveolar PO_2 (P_AO_2) was calculated via the alveolar gas equation [11] and coupled with direct arterial PaO_2 measurements for the standard assessment of A-aDO_2 gradient to compare against the non-invasive O_2 deficit measure:

$$P_AO_2 = (P_{Atm} - PH_2O) \times F_IO_2 - P_ACO_2 \times [F_IO_2 + ((1-F_IO_2)/RER)] \quad \text{Eq 4.}$$

Where P_{Atm} and PH_2O are the barometric pressure and water vapor pressure, respectively; P_AO_2 and P_ACO_2 are the alveolar partial pressures of oxygen and carbon dioxide, respectively; F_IO_2 is the fraction of inspired oxygen; RER is the respiratory exchange ratio. RER was estimated using linear regression whereby RER was assumed to equal 0.80 at rest and 1.10 during the final stage of exercise.

The traditional A-aDO_2 was calculated from $P_AO_2 - PaO_2$ obtained from equation 4 above and from the ABG. O_2 deficit assessed by the AGM100 was determined to be the difference from $P_AO_2 - gPaO_2$ whereby P_AO_2 is assumed to equal end-tidal O_2 and $gPaO_2$ is calculated as described earlier. A third method of assessing pulmonary gas exchange efficiency was also employed to account for variability in the traditional Riley method of assessing P_AO_2. Termed the "modified method", A-aDO_2 was calculated as $P_AO_2 - PaO_2$ whereby P_AO_2 is assumed to equal end-tidal PO_2 as is the case with the non-invasive method, while PaO_2 is obtained from the direct arterial sample.

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Data Statistical Analyses

Statistical analyses were performed using Prism Graphpad 8, IBM SPSS Statistics Version 24, and R statistical software. Linear regression and Bland–Altman analysis was performed [11] using Prism Graphpad to evaluate the agreement between the estimated arterial PO_2 and oxygen deficit from the non-invasive method with directly measured ABGs at rest and during graduated exercise in acute hypoxia. Further, repeated measures correlation analysis [13] were performed using R (rmcorr package Version 0.3.0; https://cran.r-project.org/web/packages/rmcorr/) to account for inter-individual variability. Mean bias and precision (±1 SD) are reported using the Bland-Altman plots whereby the difference between the non-invasive measure and "gold standard" (Y-axis) are plotted against the "gold standard" (X-axis). Potential sex differences between males and females during exercise were evaluated using a linear mixed model in SPSS with sex and exercise stage assigned as fixed effects and participants as random effects. Reported p-values are two tailed with significance set at $P \leq 0.05$ for all statistical tests.

RESULTS

Twenty-five volunteers were included in this study, yielding N=206 data points for comparison between AGM100 and ABG. Oxygen deficit during rest and exercise in males and females are presented in Figure 1A & 1B. Linear regression data comparing non-invasive and directly measured PO_2 in males and females during rest and all exercise time points in hypoxia are presented in Figure 2A. Under combined conditions of normoxic rest, hypoxic rest and hypoxic exercise, the results revealed strong correlations between the calculated $gPaO_2$ and directly measured PaO_2 (R^2=0.97; p<0.001; mean bias =1.70 mmHg). During rest in normoxic conditions, a moderate correlation was observed across all participants (R^2=0.29; p=0.013) with low mean bias and relatively large variability (mean bias= -0.95±9.33 mmHg). At hypoxic rest and exercise, the strong correlations between $gPaO_2$ and ABG PaO_2 (R^2=0.68; p<0.001) remained with no statistical differences between sexes (P=0.99) (males: R^2=0.69, females R^2=0.62; both p<0.001). This relationship remained present when analyzed using repeated

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measures correlation (R^2=0.59; p<0.001). When compared against rest conditions in hypoxia, the correlation was also very strong (R^2=0.85; p<0.001). However, if resting data is excluded, the strength of correlation was reduced (males: R^2=0.53, females: R^2=0.46; both p<0.001). Although the O_2 deficit was not different at maximal exercise, females exhibited greater arterial hypoxemia (both ABG PaO_2 and $gPaO_2$ were lower) than males across exercise trials (p<0.001). Bland-Altman analysis are presented in Figure 2B in the corresponding right-hand panel. There was low mean bias between $gPaO_2$ and PaO_2 (0.96±2.75 mmHg) during rest and all exercise stages in hypoxia with minimal differences between sexes (males=0.80 mmHg, females=1.17 mmHg).

The A-aDO_2 and oxygen deficit data are compared in Figure 2C and 2D. Although the conventional A-aDO_2 gradient measure and O_2 deficit show both a strong correlation (R^2=0.71; P<0.001) and repeated measures correlation (R^2=0.74), O_2 deficit was reflected in a positive mean bias (5.24±4.96 mmHg). Part of the positive mean bias was evident in the lower A-aDO_2 values at each exercise stage, including negative values during rest and light exercise. Finally, as displayed in Figure 3, the mixed method utilizing $P_{ET}O_2$ rather than the Riley estimated alveolar O_2 (via Eq 4.) to calculate A-aDO_2 presents similar values compared to O_2 deficit (R^2=0.87; mean bias=1.72±2.69 mmHg).

DISCUSSION

The purpose of this study was to test the validity and reliability of a non-invasive method for assessing pulmonary gas exchange at rest and during exercise in acute hypoxia. The main findings of this investigation were the following: Despite the modest results in resting room air conditions, strong relationships and low mean bias were observed during hypoxic rest and exercise between the calculated $gPaO_2$ and directly measured PaO_2 (R^2=0.68; p<0.001; mean bias =1.01 mmHg) and O_2 deficit with A-aDO_2 (R^2=0.71; p<0.001; mean bias =5.24 mmHg). Moreover, a small yet significant difference in exercise-induced hypoxemia was also revealed whereby females presented with greater degree of arterial hypoxemia across rest and exercise that was detected in both directly measured and calculated PaO_2. The following discussion

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considers the evidence, experimental limitations and the relevance underlying the findings of this study.

Validation during exercise

During exercise in acute hypoxia, albeit with a positive mean bias of ~5 mmHg, the non-invasive AGM100 was strongly correlated with that of the classic A-aDO_2 measure. Exercise intensity dependent increases in O_2 deficit in both male and female participants occurred following a similar pattern of pulmonary gas exchange impairment compared to previous hypoxic exercise studies using invasive techniques [e.g., [2,14,15]]. Moreover, during rest and exercise in acute hypoxia the AGM100 estimated gPaO_2 was strongly correlated with PaO_2 and exhibited low mean bias (<3 mmHg). This finding is consistent with previous reports at rest in healthy participants in acute hypoxia [6] and in patients with chronic obstructive pulmonary disease [5]. Improvements in pulse oximeter design and related signal detection algorithms may explain our improved results compared to previous reports during exercise [16]. A further important observation was that the AGM100 detected a significant difference in gPaO_2 during exercise whereby female participants exhibited a greater degree of hypoxaemia during exercise. This is not a novel finding in itself and is likely due to differences in lung volume and airway diameter [reviewed in; [17]], work of breathing [18], and mechanical ventilatory constraint between sexes [19,20] however, this finding and the high reproducibility of measures (i.e., between-day coefficient of variation of O_2 deficit in hypoxia of <5%), highlights the sensitivity of the non-invasive AGM100 to detect subtle differences in pulmonary gas exchange between even healthy volunteers.

Although the classic A-aDO_2 method is considered the current "gold standard" and is used extensively in research for assessing pulmonary gas exchange both at rest and during exercise, it is not without its caveats. Indeed, it is not uncommon to observe negative A-aDO_2 values at rest or during light exercise [reviewed in: [1]], a physiologically improbable finding. This was also the case in our study whereby utilizing the classic A-aDO_2 equation exhibited a mean negative gradient at rest and low intensity exercise in acute hypoxia in 59 out of 203 sample points. Linear regression analysis between the classic A-aDO_2 equation and the non-invasive O_2 deficit measure

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revealed a strong correlation between the two measures (see Fig 2C and 2D); however, O_2 deficit exhibited a relatively higher mean bias, eliminating the physiologically improbable negative gradient, though presenting with greater levels of impaired gas exchange during strenuous exercise. Utilization of a "modified method" A-aDO_2 equation whereby $P_{ET}O_2$ was assumed to equal alveolar O_2 - as is the case with the AGM100 - eliminated the occurrence of negative pulmonary gradient values. Thus, the possible sources of error in the traditional method are likely resultant of issues with the calculation of P_AO_2 utilizing Riley analysis and can be divided into two possible areas of concern that should be considered. 1) variability in the values for alveolar PCO_2 acquired from the arterial sample and 2) the ventilatory parameters which are acquired non-invasively and are not physiologically produced or rely on certain assumptions including F_IO_2 and respiratory quotient. Utilizing single timepoint arterial sampling to assess pulmonary gas exchange during an exercise stage is likely highly susceptible to ventilatory artifacts and sampling time discrepancies between the arterial and ventilatory variables required for the classic A-aDO_2 equation whereby brief episodes of altered ventilation may result in transient fluctuations in $PaCO_2$ [5]. Indeed, lack of steady state conditions through anxiety induced hyperventilation at rest while seated on a cycle ergometer have previously been suggested to cause negative A-aDO_2 values [1]. This observation indicates that this lack of steady-state may be exacerbated under acute hypoxic conditions whereby marked hyperventilation and related arterial hypocapnia are elicited [20]. As the non-invasive AGM100 measurement utilized a 20s average of each exercise stage for the assessment of $gPaO_2$ and O_2 deficit, it is likely less influenced by acute ventilatory artifacts which may occur during exercise or in hypoxia whereby a "steady-state" is difficult to obtain unless averaged over a period of time. Further, as discussed previously [5], the traditional A-aDO_2 equation is heavily favoured towards regions of the lung with abnormally low ventilation-perfused ratios whereas end-tidal PO_2 values represent a more uniform distribution of ventilation-perfused areas of the lung.

Methodological Considerations

The AGM100 has emerged to be effective for the non-invasive quantification of abnormal pulmonary gas exchange [5–8]; however, this approach cannot differentiate between the contributing mechanisms of impaired gas exchange (e.g., diffusion limitation, hypoventilation,

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ventilation/perfusion heterogeneity and shunting). Although different approaches (e.g., multiple inert gas elimination techniques, etc.) may provide insight into these factors, it is important to note that no assessment is perfect, and the AGM100 assessment provides a simple, non-invasive method for assessing pulmonary gas exchange, via O_2 deficit, in a time conscious and easily repeatable manner [4]. Moreover, the method in which the O_2 deficit is calculated overcomes several limitations of the classic Riley analysis of the A-aDO_2, including: 1) lung units with high V/Q are included in the analysis rather than only units with abnormally low V/Q [5]; 2) it provides instantaneous calculations of gPaO_2; 3) the O_2 deficit is completely non-invasive; and, on the basis of the current study, 4) the calculation of gPaO_2 and O_2 deficit remain valid during exercise. Of note, some limitations of the AGM100 device have been elegantly reviewed [22]. The relevant points in the context of our experimental design are as follows. First, the PaO_2 calculations are based on the subroutines developed by Kelman to correct for the allosteric effect of changes in PCO_2 on the oxygen affinity of hemoglobin, known as the Bohr effect [9,10]. The Kelman's solutions assume that the change in PCO_2 shifts the arterial PO_2 along the normal buffer line. Second, given the shape of the oxyhemoglobin dissociation curve is flatter at the upper range of oxygen saturation, the variability of gPaO2 widens at the SpO2 >97% as indicated by the weaker relationship (R^2=0.3) observed in our study. Third, the same considerations of the effects of temperature on gPaO_2 also remain unknown. Our validation data during exercise support the absence of a major influence of temperature on gPaO_2 and O_2 deficit. Moreover, recent mathematical simulations suggest that the influence of both temperature and base excess on calculated gPaO_2 are modest (e.g., <3mmHg) [4]. Although we would not anticipant any compensatory alterations in acid-base balance in the current acute study, the changes in core (esophageal) temperature with acute exercise are also small (<0.5 ^oC).

CONCLUSION

This study found that pulmonary gas exchange efficiency measured using a non-invasive gas exchange monitor provided a valid and reliable measure against directly measured arterial blood gasses during hypoxic exercise. Further, the non-invasive oxygen deficit was strongly correlated with A-aDO_2 values obtained from the classic A-aDO_2 equation without presenting with negative O_2 gradient values. These results provide promising evidence to support the use of non-invasive

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gas exchange assessments during hypoxic exercise which may be applicable to both laboratory and clinical patient assessments. Further studies are now required to determine if this approach can be used clinically as a tool during normoxic exercise in patients with pre-existing impairments in gas exchange efficiency.

Author contributions

C.A.H., D.B.M., L.W., S.J.O., and P.N.A were involved in data collection. C.A.H. and P.N.A. were involved in data analyses and interpretation. C.A.H. and P.N.A. drafted the manuscript. All authors critically reviewed the manuscript. C.A.H. and P.N.A. conceived the study design. All authors approved the final version of this manuscript and agree to be accountable for all aspects of the work. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

Acknowledgments

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Figure Legends

Figure 1: Oxygen deficit (O_2 deficit) during rest and cycling exercise during stages 1-9 of an incremental maximal exercise test in normobaric hypoxia (F_IO_2=0.11). Figure 1A; Data are presented as individual data points normalized to percent of maximal workload with lines of best fit. Male participants are represented by blue open circles with a solid line and female participants are represented by red open circles with a dashed line. Figure 1B; Data are presented as group means ± SD for each absolute workload. Male participants (blue bars) began cycling at 20 watts, increasing by 30 watts every two minute while females (red bars) cycled at 15 watts, increasing by 20 watts every two minutes. The total number of exercise stages completed are as follows: six stages= 1 male, 1 female; seven stages= 5 males, 4 females; eight stages= 7 males, 4 females; nine stages= 2 males, 1 female.

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Figure 2: Linear regression and Bland-Altman figures for gas exchange monitor assessed partial pressure of arterial oxygen (gPaO2) vs arterial blood gas assessed partial pressure of arterial oxygen (ABG PaO_2) [A,B] and oxygen deficit vs the traditional alveolar to arterial difference of oxygen (A-aDO_2) [C,D] presented as individual data points at hypoxic rest and at all stages of hypoxic exercise. Male data points are indicated by blue open circles and solid linear regression lines. Female data points are indicated by red open circles and dashed linear regression lines. R^2 and P-values presented in the figures represent both male and female data points combined. The single solid line and dotted lines in the Bland-Altman plots represent mean bias and ± SD respectively.

Figure 3. Pulmonary gas exchange efficiency displayed as the 1) Traditional A-aDO_2 (black line); calculated using estimated alveolar O_2 from Riley analysis and directly measured partial pressure of arterial oxygen (PaO_2) via arterial catheterization. 2) O_2 deficit (dark grey line); non-invasively assessed using estimated alveolar PO_2 from end-tidal PO_2 and calculated PaO_2. 3) A mixed method A-aDO_2 (light grey line); assessed using estimated alveolar O_2 from end-tidal O_2 and directly measured PaO2 via arterial catheterization. Data are presented as group means ± SD during rest and cycling exercise during an incremental maximal exercise test in normobaric hypoxia (F_IO_2=0.11).

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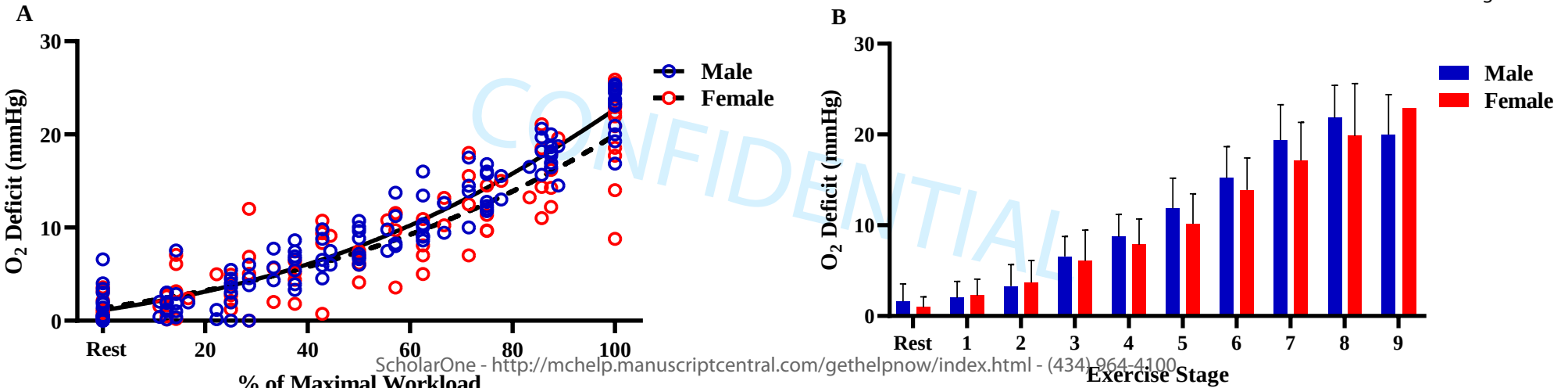

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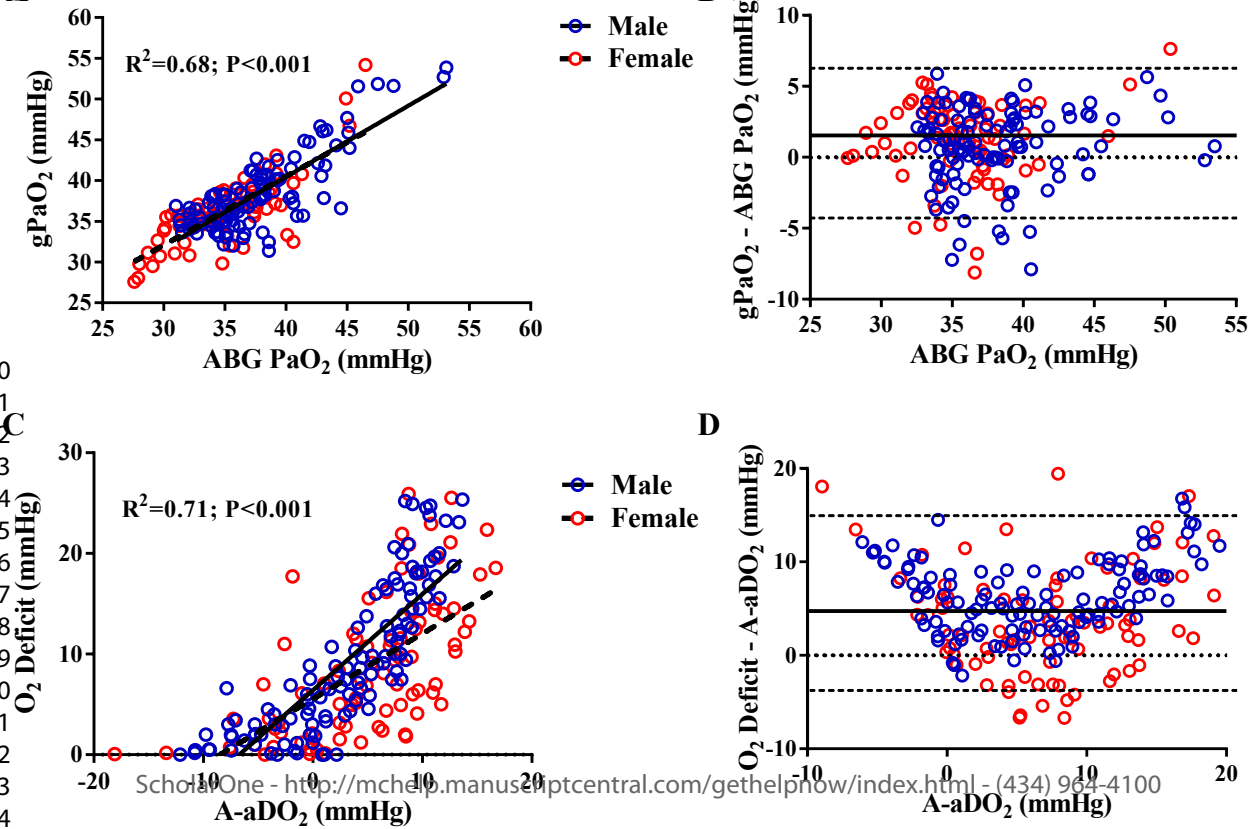

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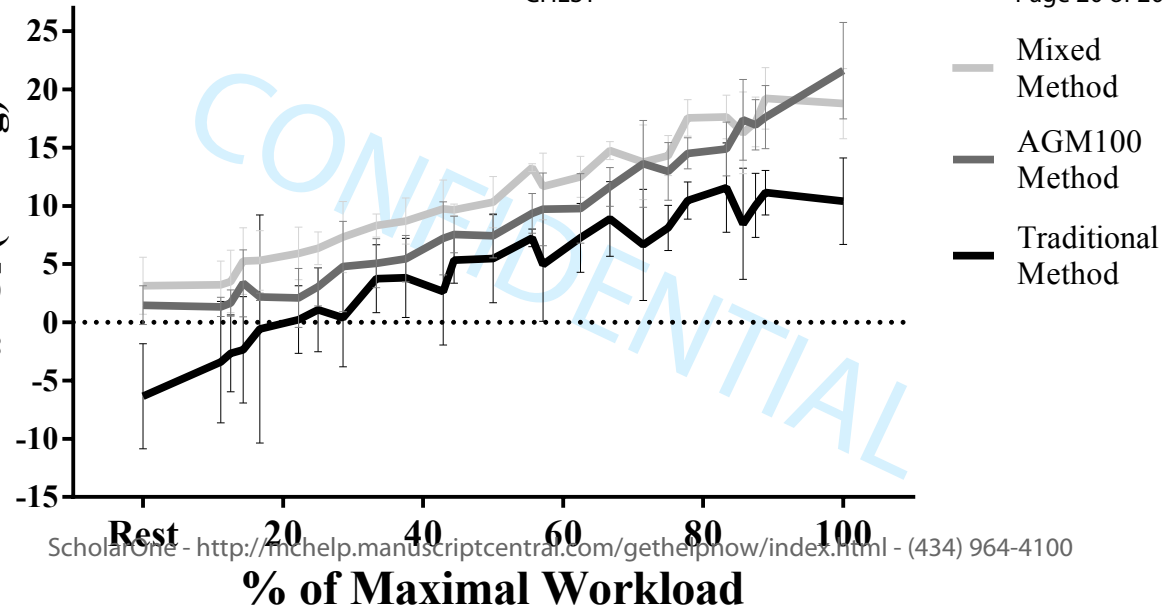

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