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Influence of smoking and obesity on alveolar-arterial gas pressure differences and dead space ventilation at rest and peak exercise in healthy men and women

Sven Gläser [a,*,d], Till Ittermann [b,d], Beate Koch [a], Christoph Schäper [a], Stephan B. Felix [a], Henry Völzke [b], Raik Könemann [a], Ralf Ewert [a,d], James E. Hansen [c,d]

[a] *Department of Internal Medicine B — Cardiology, Intensive Care, Pulmonary Medicine and Infectious Diseases, University of Greifswald, Greifswald, Germany*
[b] *Institute for Community Medicine, SHIP/Clinical-Epidemiological Research, University of Greifswald, Walther-Rathenau-Str. 48, 17487 Greifswald, Germany*
[c] *Respiratory and Critical Care Physiology and Medicine, Harbor-UCLA Medical Center, Los Angeles Biomedical Research Institute at Harbor-UCLA, 1124 West Carson Street, RB2, Box 405, Torrance, CA 90502, USA*

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Summary
Background and aims: Besides exercise intolerance, the assessment of ventilatory and perfusion adequacy allows additional insights in the disease pathophysiology in many cardiovascular or pulmonary diseases. Valid measurements of dead space/tidal volume ratios (VD/VT), arterial (a′) — end-tidal (et) carbon dioxide (CO_2) and oxygen (O_2) pressure differences (p(a′-et)CO_2) and (p(et-a′)O_2), and alveolar (A)—a′ O_2 pressure differences (p(A-a′)O_2) require using blood samples in addition to gas exchange analyses on a breath-by-breath-basis. Smoking and nutritional status are also important factors in defining disorders. Using a large healthy population we considered the impact of these factors to develop useful prediction equations.

* Corresponding author. Medical Faculty of the Ernst-Moritz-Arndt University, Department of Internal Medicine B — Cardiology, Intensive Care, Pulmonary Medicine and Infectious Diseases, Sauerbruchstrasse, D-17475 Greifswald, Germany. Tel.: +49 38348622401; fax: +49 38348622422.

E-mail addresses: sven.glaeser@uni-greifswald.de, sven.glaeser@uni-greifswald.de (S. Gläser), till.ittermann@uni-greifswald.de (T. Ittermann), beate.koch@uni-greifswald.de (B. Koch), christoph.schaeper@gmail.com (C. Schäper), felix@uni-greifswald.de (S.B. Felix), voelzke@uni-greifswald.de (H. Völzke), raik.koenemann@uni-greifswald.de (R. Könemann), ewert@uni-greifswald.de (R. Ewert), jhansen@labiomed.org (J.E. Hansen).

[d] Those authors contributed equally to the work.

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Methods and results: Incremental cycle exercise protocols were applied to apparently healthy volunteer adults who did not have structural heart disease or echocardiographic or lung function pathologies. Age, height, weight, and smoking were analysed for their influence on the target parameters in each gender. Reference values were determined by regression analyses. The final study sample consisted of 476 volunteers (190 female), aged 25—85 years. Smoking significantly influences $p(A\text{-}a')O_2$ and $p(a'\text{-}et)CO_2$ at rest and peak exercise, and VD/VT during exercise. Obesity influences upper limits of VD/VT, $p(a'\text{-}et)CO_2$ and $p(et\text{-}a')O_2$ at rest as well as $p(A\text{-}a')O_2$ and $p(et\text{-}a')O_2$ at exercise. Reference equations for never-smokers as well as for apparently healthy smokers considering influencing factors are given.
Conclusion: Gender, age, height, weight, and smoking significantly influence gas exchange. Considering all of these factors this study provides a comprehensive set of reference equations derived from a large number of participants of a population-based study.

Introduction

Cardiopulmonary exercise testing (CPET) is widely used to assess cardiovascular, pulmonary, and musculoskeletal function in health and disease. Due to their prognostic and therapeutic implications, the primary parameters assessed include peak oxygen uptake ($peakVO_2$), anaerobic threshold (AT), and the efficiency of ventilation (VE) in removing carbon dioxide (VCO_2), the latter expressed as the ratio at the AT (VE/VCO_2@AT) or slope (VE vs. VCO_2). Ventilatory inefficiency can be primarily due to ventilation-perfusion-mismatching as well as impaired cardiac output and alveolar hyperventilation. Rather than sophisticated measures such as multiple inert gas elimination techniques, the clinical analyses of ventilatory and perfusion adequacy are usually based on interpretations of the above measurements plus measurements using arterial or well-perfused ear capillary (a′) blood. These measurements, all of which require blood samples, include physiological dead space/tidal volume ratio (VD/VT), arterial − end-tidal (et) carbon dioxide (CO_2) and oxygen (O_2) pressure differences ($p(a'\text{-}et)CO_2$) and ($p(et\text{-}a')O_2$), and alveolar (A)—a′ O_2 pressure differences ($p(A\text{-}a')O_2$),.[1] Furthermore, the efficiency of oxygen gas exchange is conventionally judged by the magnitude of alveolar-arterial difference in oxygen tensions ($p(et\text{-}a')O_2$ and $p(A\text{-}a')O_2$, respectively). Knowledge of these values during exercise is necessary to evaluate the severity of many pulmonary and cardiovascular diseases.[2]

Clinical interpretation requires knowledge of these values in healthy individuals.[3] So far, available reference datasets differ considerably and are limited by their sample size, method of patient recruitment, distributions of patients age and nutritional status, as well as the negation of the patients smoking habits or current medications.[4—10] Most of these data have been obtained using mouthpieces and arterial blood; their applicability to more widely used masks and well-perfused ear capillary blood has not been investigated and remains unclear.[9] A reduced exercise capacity due to smoking has been reported in healthy, non-obese volunteers,[11,12] but the effects on VD/VT and $p(A\text{-}a')O_2$ have not been described. Little is known on how to apply current reference values on patients with high body mass indices and smoking.

The aim of this study was to acquire a comprehensive set of CPET reference values on dead space ventilation and alveolar-arterial CO_2 and O_2 pressure differences in a reliable, large, healthy population of men and women over a wide range of body sizes and ages. The impact of smoking and obesity will also be assessed.

Methods

Study population

Study volunteers consisted of participants of the Study of Health in West Pomerania (SHIP). SHIP is a population-based project in northeast Germany.[13,14] From March 2003 until July 2006, a follow-up examination was performed (SHIP-1). From the sample of 3300 subjects, aged 25—85 years, 1708 individuals (834 males, 874 females) volunteered for cycle ergometer CPET with gas exchange measurements, 1640 in the additional investigation in blood gas analysis. Reference equations for key gas exchange parameters derived from this population and population characteristics have been published previously.[11,12] All participants gave written informed consent. The study conformed to the principles of the Declaration of Helsinki as reflected by an a priori approval of the Ethics Committee of the University of Greifswald.

Pre-exercise diagnostics and exclusion criteria

Socio-demographic, behavioural characteristics, smoking and medical histories were assessed using computer-assisted personal interviews administered by trained and certified staff. Previous disease histories, smoking habits and medication (anatomic-therapeutic-chemical [ATC] code)[15] were self-reported. Participants were classified as smokers if a regular behavioural consumption of cigarettes was reported. Pack years (PY) were calculated on the reported periods and consumption rates. Participants were advised to continue their usual medications. Shoeless height and weight were measured for the calculation of the body mass index (BMI = body weight (kg)/height^2 (m^2)). Spirometry and body plethysmography were assessed, defining normal lung function according to recommendations of the ECSC and previously published own reference values.[16—18] A 12-lead electrocardiogram was taken of each participant. All clinical tests were performed by experienced, trained and

Table 1 Descriptive statistics of the study sample.

Age (years)		*N*	Height (cm)	Weight (kg)	BMI (kg/m^2)	Smokers (%)	peakVO_2 (ml/min)
25–44	*f*	71	168 (163; 170)	69 (62; 80)	24.3 (22.0; 28; 3)	64.8%	1695 (1464; 2019)
	m	119	180 (175; 184)	84 (78; 93)	26.6 (24.6; 28.6)	66.4%	2526 (2095; 2914)
45–64	*f*	96	164 (160; 168)	72 (64; 83)	26.1 (24.1; 31.2)	40.6%	1593 (1359; 1787)
	m	124	177 (172; 180)	87 (76; 98)	27.6 (25.5; 30.6)	75.0%	2265 (1911; 2503)
≥65	*f*	23	160 (158; 165)	67 (61; 73)	25.7 (24.0; 29.0)	26.1%	1338 (1194; 1530)
	m	43	171 (168; 176)	76 (70; 93)	25.8 (24.2; 29.7)	69.8%	1849 (1590; 2135)
Total	*f*	190	165 (160; 168)	70 (63; 80)	25.6 (23.3; 29.4)	47.9%	1584 (1357; 1839)
	m	286	177 (172; 181)	84 (75; 95)	26.9 (24.8; 29.7)	70.6%	2296 (1901; 2647)

Quantitative data are presented as median, 25th, and 75th percentiles, qualitative data as absolute numbers and percentages. Smokers are defined as current smokers. *N* — absolute number of included participants; BMI — body mass index (kg/m^2); *f*: female; *m*: male. peakVO_2: peak oxygen uptake.

certified physicians and technicians, annually monitored by observers from an external Data Safety and Monitoring Committee.

Subjects with the following criteria were excluded from the present study: past myocardial infarction, signs of ischaemia/infarction, right or left bundle branch block, a cardiac pacemaker, stenosis or insufficiency of the cardiac valves, ventricular dysfunction found by echocardiography, abnormal lung function,[16–18] self-reported pulmonary diseases neuromuscular or musculoskeletal disorders based on neurological examination, anaemiaand/or the use of drugs which might influence on cardiovascular, pulmonary, anti-allergic or anti-inflammatory function. For never-smoking reference equations, all smokers were excluded, leaving a subpopulation of 325 (124 female) subjects. The final study population to quantify the influence of obesity and smoking consisted of 476 apparently healthy smokers and never-smokers.

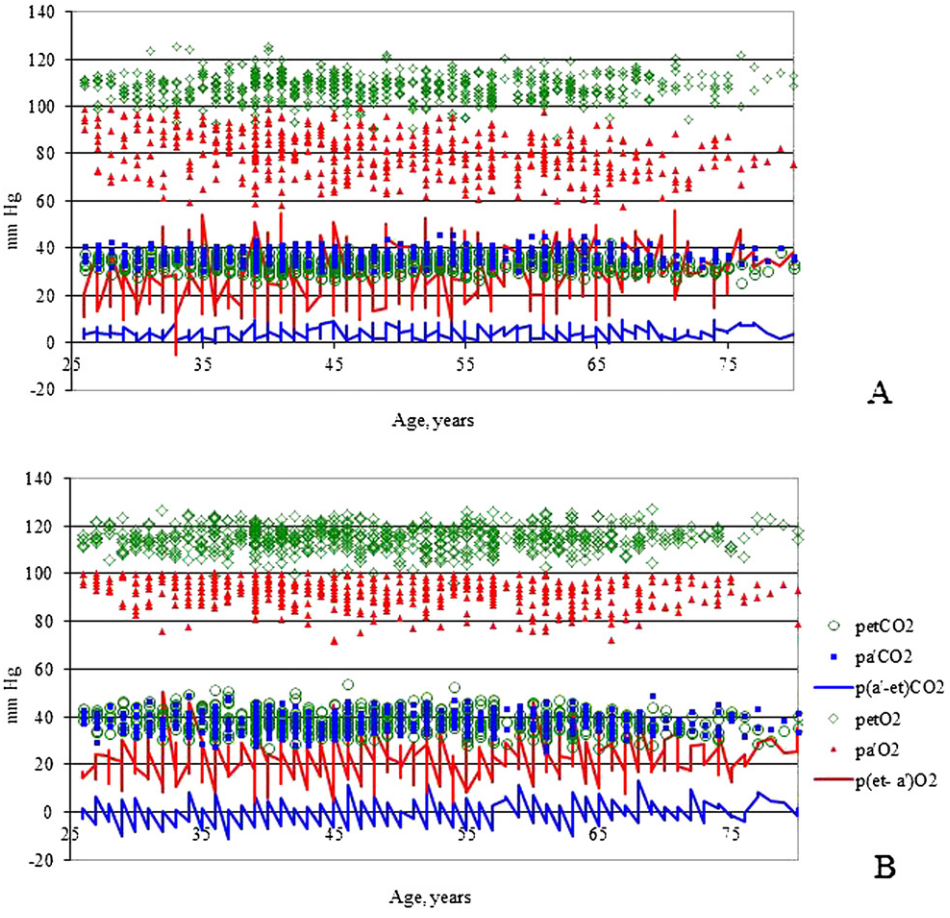

Figure 1 Individual results for blood gases (pa′O_2 and pa′CO_2), end-tidal expiratory partial pressures (petO_2 and petCO_2) and differences (p(a′-et)CO_2 and p(et-a′)O_2) of all subjects at rest (part A) and under peak exercise (part B).

Table 2 Influence of smoking on gas exchange variables.

Variable	Percentile	β coefficient (95% confidence intervall)	*p*
Resting variables			
$p(et\text{-}a')O_2$ (mmHg)	90th	2.56 (4.91; 0.21)	0.033
$p(A\text{-}a')O_2$ (mmHg)	50th	2.26 (0.13; 4.40)	0.038
Peak exercise variables			
VD/VT ratio	50th	0.04 (0.02; 0.06)	<0.001
VD/VT ratio	90th	0.03 (0.01; 0.06)	0.025
$P(a'\text{-}et)CO_2$ (mmHg)	50th	1.27 (0.43; 2.10)	0.003
$p(et\text{-}a')O_2$ (mmHg)	90th	2.12 (4.02; 0.22)	0.029
$p(et\text{-}a')O_2$ (mmHg)	95th	2.95 (5.83; 0.08)	0.044
$p(A\text{-}a')O_2$ (mmHg)	95th	3.19 (0.33; 6.05)	0.029

Variables with statistical significant influence of smoking, non-significant variables are not shown.
All models adjusted for age, sex, height, and weight.

Exercise testing

The CPET, using a calibrated electromagnetically braked cycle ergometer (Ergoselect 100, Ergoline, Germany) was performed with a physician in attendance according to a modified Jones protocol: 3 min of rest, 1 min of unloaded cycling at 60 rpm, stepwise increases in work load of 16 W/min until symptom-limited or terminated by the physician due to chest pain or ECG abnormalities, and 5 min of recovery.[19] Gas exchange and ventilatory variables were analysed breath by breath using a VIASYS HEALTHCARE system (Oxycon Pro, Combitox mask), which had been recalibrated just prior to each test. Twelve-lead ECG's were recorded during rest and every minute thereafter; pulse oximetry was monitored continuously; and blood pressure was obtained by cuff sphygmomanometer every two minutes. Prior to the test, patients were encouraged to reach maximal exhaustion; during exercise no further motivation was utilised. If the participant agreed, one ear lobe was accurately prepared with Nonivamid/Nicoboxil (Finalgon Creme®, Boehringer Ingelheim, Germany) at least 10 min prior to drawing blood to ensure free capillary blood flow independent of local manipulations. An incision was done using a sterile lancet immediately prior to drawing blood. Only subjects with adequate (that means free and unforced) blood flow were included. The capillary blood was collected in a 55 μl capillary (Clinitubes®, Radiometer, Copenhagen, Denmark) and immediately transferred to the blood gas analyzer (time delay between drawing blood and analyses <30 s).

Table 3 Influence of obesity on gas exchange variables.

Variable	Percentile	β coefficient (95% confidence intervall)	*p*
Resting variables			
VD/VT ratio	95th	−0.05 (−0.09; −0.01)	0.033
$P(a'\text{-}et)CO_2$ (mmHg)	90th	−1.14 (−2.15; −0.12)	0.028
$p(et\text{-}a')O_2$ (mmHg)	90th	4.91 (8.14; 1.69)	0.003
$p(et\text{-}a')O_2$ (mmHg)	95th	6.05 (7.87; 4.22)	<0.001
Peak exercise variables			
$p(et\text{-}a')O_2$ (mmHg)	50th	2.00 (3.89; 0.10)	0.039
$p(A\text{-}a')O_2$ (mmHg)	50th	2.93 (1.32; 4.54)	<0.001
$p(A\text{-}a')O_2$ (mmHg)	95th	3.98 (0.48; 7.48)	0.026

Variables with statistical significant influence of obesity (BMI >30 kg/m^2), non-significant variables are not shown.
All models adjusted for age, sex, and ever smoking.

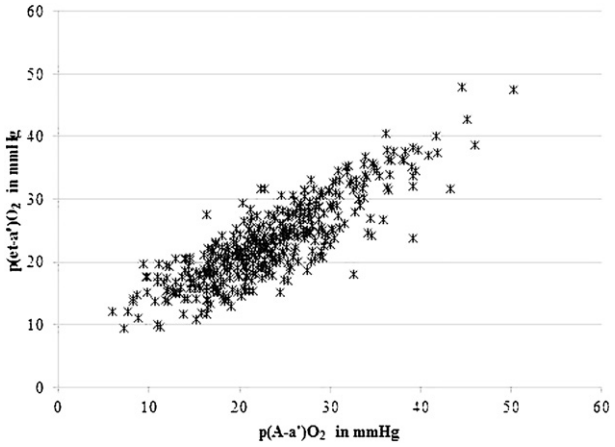

Figure 2 Correlation of endtidal to arterial oxygen partial pressure ($p(et\text{-}a')O_2$) to alveolar arterial oxygen difference ($p(A\text{-}a')O_2$) during peak exercise. Correlation coefficient (R^2) is 0.72 ($p < 0.005$).

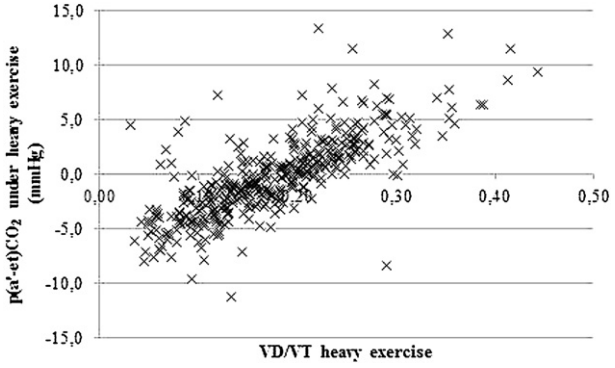

Figure 3 Correlation of arterial to endtidal carbon dioxide partial pressure ($p(a'\text{-}et)CO_2$) to dead space ventilation (VD/VT) during peak exercise. Correlation coefficient (R^2) is 0.59 ($p < 0.005$).

Table 4 Reference equations for gas pressure differences and dead space to tidal volume ratio.

Variable		Percentile	Equation
VD/VT	Resting value	50th	−0.432 + 0.0019*A + 0.0034*H + 0.0001*W − 0.020*G
		90th	−0.124 + 0.0016*A + 0.0026*H − 0.0004*W − 0.044*G
		95th	−0.287 + 0.0022*A + 0.0030*H + 0.0007*W − 0.031*G
	Peak exercise	50th	−0.251 + 0.0026*A + 0.0013*H + 0.0001*W + 0.029*G
		90th	−0.032 + 0.0023*A + 0.0008*H + 0.0003*W − 0.003*G
		95th	0.414 + 0.0025*A − 0.0013*H + 0.0002*W − 0.030*G
$P(a'\text{-}et)CO_2$ (mmHg)	Resting value	50th	−9.3 + 0.03*A + 0.06*H + 0.003*W + 1.0*G
		90th	−9.9 + 0.07*A + 0.08*H − 0.019*W + 1.0*G
		95th	+6.6 + 0.03*A − 0.01*H + 0.013*W + 0.3*G
	Peak exercise	50th	−16.0 + 0.11*A + 0.04*H − 0.010*W + 2.3*G
		90th	−12.9 + 0.12*A + 0.05*H − 0.011*W + 2.2*G
		95th	7.5 + 0.11*A − 0.03*H − 0.019*W − 0.5*G
$p(A\text{-}a')O_2$ (mmHg)	Resting value	50th	−5.3 + 0.26*A − 0.01*H + 0.18*W + 1.9*G
		90th	−41.7 + 0.23*A + 0.36*H − 0.01*W + 3.9*G
		95th	3.7 + 0.18*A + 0.09*H + 0.05*W + 5.2*G
	Peak exercise	50th	−1.0 + 0.05*A + 0.07*H + 0.14*W − 1.2*G
		90th	−0.5 + 0.06*A + 0.10*H + 0.18*W − 1.7*G
		95th	21.9 + 0.09*A − 0.01*H + 0.16*W − 2.5*G
$P(et\text{-}a')O_2$ (mmHg)	Resting value	50th	−1.80 + 0.31*A + 0.02*H + 0.10*W + 0.7*G
		90th	−21.40 + 0.36*A + 0.20*H + 0.07*W + 1.7*G
		95th	−8.00 + 0.32*A + 0.11*H + 0.10*W + 3.9*G
	Peak exercise	50th	−24.95 + 0.17*A + 0.17*H + 0.10*W + 1.5*G
		90th	0.94 + 0.20*A + 0.04*H + 0.22*W − 2.2*G
		95th	12.16 + 0.16*A − 0.01*H + 0.22*W − 1.8*G

Prediction equations for gas pressure and tidal volume to dead space ventilation at rest and peak exercise derived from age (A) in years, height (H) in cm, weight (W) in kg and gender (G). Men are encoded by "1", women by "2".

Table 5 Reference equations for gas pressure differences and dead space to tidal volume ratio considering smoking status.

Variable		Percentile	Equation
VD/VT	Peak exercise	50th	−0.185 + 0.039*S + 0.0024*A + 0.0011*H − 0.0002*W + 0.022*G
		90th	0.111 + 0.033*S + 0.0019*A + 0.0003*H − 0.0001*W − 0.009*G
		95th	0.447 + 0.027*S + 0.0013*A − 0.0012*H + 0.0002*W − 0.035*G
$P(a'\text{-}et)CO_2$ (mmHg)	Peak exercise	50th	−15.1 + 1.3*S + 0.09*A + 0.04*H − 0.012*W + 2.0*G
		90th	−4.0 + 1.4*S + 0.09*A + 0.01*H − 0.010*W + 1.5*G
		95th	9.8 + 1.2*S + 0.06*A − 0.01*H − 0.055*W − 1.3*G
$p(A\text{-}a')O_2$ (mmHg)	Resting value	50th	6.1 + 2.3*S + 0.22*A − 0.06*H + 0.1729*W + 2.0*G
		90th	15.2 + 2.0*S + 0.13*A + 0.08*H + 0.0093*W − 0.2*G
		95th	23.3 − 0.1*S + 0.17*A + 0.08*H − 0.0631*W − 0.6*G
	Peak exercise	50th	13.2 + 0.4*S + 0.05*A − 0.01*H + 0.1178*W − 1.4*G
		90th	33.5 + 1.8*S + 0.03*A − 0.05*H + 0.1177*W − 4.7*G
		95th	38.3 + 3.2*S + 0.02*A − 0.09*H + 0.1432*W − 2.3*G
$P(et\text{-}a')O_2$ (mmHg)	Resting value	50th	25.0 + 0.7*S + 0.24*A − 0.09*H + 0.0893*W − 1.6*G
		90th	6.1 + 2.5*S + 0.24*A + 0.09*H + 0.0361*W + 2.5*G
		95th	43.6 + 2.2*S + 0.17*A − 0.10*H + 0.1216*W − 0.9*G
	Peak exercise	50th	6.0 + 1.0*S + 0.10*A + 0.03*H + 0.0837*W − 0.5*G
		90th	22.4 + 3.5*S + 0.15*A + 0.04*H + 0.1105*W − 1.9*G
		95th	47.7 + 4.9*S + 0.06*A − 0.15*H + 0.1447*W − 2.8*G

Prediction equations for gas pressures and tidal volume to dead space ventilation at rest and peak exercise derived from age (A) in years, height (H) in cm, weight (W) in kg, gender (G) and smoking status (smoking − S). Smoking (S) is coded as "0" for no and "1" for yes. Men are encoded by "1", women by "2".

Gas exchange variables and blood gases

VE, tidal volume, VO_2 and VCO_2 were acquired on a breath-by-breath basis and averaged over 10-s intervals. PeakVO_2 was defined as the highest 10-s average of VO_2 in late exercise or early recovery; peak heart rate was averaged over that same period; peak O_2 pulse was calculated as peakVO_2 divided by peak heart rate. The AT was determined according to Wasserman et al.[3] At rest as well as on peak exercise end-tidal gas pressures for O_2 ($petO_2$) and CO_2 ($petCO_2$) were estimated using a 10-s average interval. At rest and again prior to the cessation of exercise, capillary blood was drawn from a hyperaemic ear lobe. Blood gases ($pa'O_2$, $pa'CO_2$), pH, O_2 saturation, and actual bicarbonate levels (HCO_3^-) were immediately measured using a Radiometer Kopenhagen System (ABL 510, Radiometer, Kopenhagen, Denmark). The system was calibrated daily according to the manufactures recommendations.

Dead space ventilation was calculated according to the Enghoff modification of the Bohr equation and correction for apparatus dead space:

$$VD/VT = (pa'CO_2 - peCO_2)/pa'CO_2 - VDM/(VT - VDM)$$

where $peCO_2$ is the mixed expired CO_2 tension and VDM the apparatus dead space.[3] The breathing apparatus dead space was calculated as 70 ml (mask and flow sensor) in accordance to manufacturers recommendation. Mixed expired CO_2 tension was calculated as follows:

$$peCO_2 = 863 \times VCO_{2(STPD)}/VE_{(BTPS)}$$

Alveolar-arterial O_2 differences were assessed both as end-tidal − capillary ($p(et\text{-}a')O_2$) and calculated alveolar-arterial differences ($p(A\text{-}a')O_2$)[20]:

$$p(A-a)O_2 = 150 - (paCO_2/RER) + (pa'CO_2 * 0.21 * (1 - RER)/RER) - pa'O_2,$$

where RER is the respiratory exchange ratio.

Statistical analysis

Reference formulae for the 50th, 90th, and 95th percentiles of $p(A\text{-}a')O_2$, $p(et\text{-}a')O_2$, $p(a'\text{-}et)CO_2$ and VD/VT at rest and peak exercise were calculated by quantile regression models,[21] adjusted for ever smoking, age, sex, height, and weight. The association between obesity and the above parameters at rest and peak exercise were assessed by quantile regression models adjusted for ever smoking, age, and sex. To account for possible non-linear associations of age, height, and weight with these parameters fractional polynomials were applied.[22] The dose—response relation was found using fractional polynomials up to degree 2 with all possible combinations of powers selected from the set (−2, −1, −0.5, 0, 0.5, 1, 2, 3) and compared to the model with the untransformed exposure variable using the log likelihood to determine the best-fitting model. If none of the fractional polynomial models fitted the data significantly better than the one using the untransformed exposure variable, no transformation was used. A $p < 0.05$ was considered as statistical significant. All analyses were performed using Stata 12.0 (Stata Corporation, College Station, TX, USA).

Results

The final study population consists of 476 apparently healthy participants (190 females) with a median age of 48 years (interquartile range 39—60). Of these, 113 (45 females) were obese and 293 (91 females) were current or former smokers (median consumption 13.7 PY; interquartile range 6.6—27.4). Further characteristics of the study population are given in Table 1. The main reasons for termination of exercise in the present study were fatigue (56.5%) or dyspnoea (10.8%), or both. The mean exercise duration gradually decreased with increasing age, averaging 12.0 min in those 25—34 years old and 7.3 min in those over 65 years.

Fig. 1 gives an overview for data.

Influence of smoking and obesity on dead space ventilation and gradients

Significant associations between smoking and the median, 90th percentile, or 95th percentiles of arterial-alveolar gas tension differences and dead space ventilation at rest and peak exercise are given in Table 2.

Table 3 shows significant associations of obesity (>30 kg/m^2) and gas exchange. Applying BMI as a continuous variable, significant associations were also seen for $p(et\text{-}a')O_2$ at rest and during exercise (median), as well as $p(A\text{-}a')O_2$ during exercise (median and 95th percentile). Fig. 2 illustrates the influence of BMI on $p(A\text{-}a')O_2$ during peak exercise.

Age was associated with most of the variables at rest in the quantile regression models, but not significantly with the 95th percentile of $p(a'\text{-}et)CO_2$ and with the 90th and 95th percentiles of the $p(A\text{-}a')O_2$. During exercise, age was significantly associated with the median and the 90th percentile of the VD/VT, the median and 90th percentile of $p(a'\text{-}et)CO_2$, and the median and 90th percentile of $p(et\text{-}a')O_2$. Gender was only significantly associated with the median of $p(a'\text{-}et)CO_2$ at exercise, the 90th percentiles of VD/VT at rest, and the $p(A\text{-}a')O_2$ at exercise.

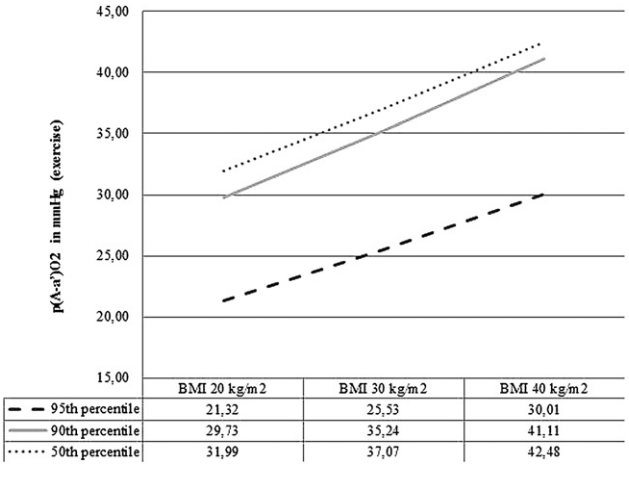

Figure 4 Influence of body mass index (BMI) on alveolar arterial oxygen difference ($(p(A\text{-}a')O_2)$ in mmHg) during peak exercise exemplarly for a 40 years old male never-smoker of 180 cm height.

End-tidal to arterial oxygen partial pressure differences were significantly correlated with $p(A\text{-}a')O_2$ at rest ($R^2 = 0.78$; $p < 0.005$) and during exercise (Fig. 2). Arterial to end-tidal carbon dioxide differences were significantly correlated to VD/VT during exercise (Fig. 3).

Reference equations for dead space ventilation and pressure differences

Reference equations for the 50th, the 90th, and the 95th percentiles of gas partial pressure differences and VD/VT ratios at rest and peak exercise for never-smokers are given in Table 4. Table 5 gives reference equations to ascertain the influence of smoking. All equations contain age, height, weight, and gender (Fig. 4).

Discussion

This study demonstrates in an apparently healthy adult population that VD/VT, $p(a'\text{-}et)CO_2$, $p(A\text{-}a')O_2$, and $p(et\text{-}a')O_2$ are influenced by age, height, weight, gender, and cigarette smoking. For example, smoking significantly widens $p(A\text{-}a')O_2$ and $p(a'\text{-}et)CO_2$ at rest and peak exercise, whereas VD/VT is significantly increased only during exercise. Our results provide at least two opportunities: first, to calculate reference values based on healthy never-smokers and second, to estimate the deleterious influence of smoking on gas exchange in apparently otherwise healthy men and women.

Our resting VD/VT values tend to be higher than in most other series[6,7,10,23] but these series do not consider the influence of smoking, gender and obesity. The most comprehensive interpretation of reference values by Hansen and colleagues gives a mean ± SD VD/VT range of 0.29 ± 0.06 <40 years and 0.30 ± 0.08 >40 years in men at rest, 0.17 ± 0.05 <40 years and 0.20 ± 0.07 >40 years at the AT, and 0.16 ± 0.04 <40 years and 0.19 ± 0.07 >40 years at peak exercise.[1] Although our median values for male never-smokers are generally lower at rest and the upper limit of normal values for obese male smokers are reasonably similar, our study much better describes the influence of age, gender, obesity, and cigarette smoking. The results of our study provide mean values of 0.23 (upper limit by the 90th percentile: 0.33) at rest and 0.12 (upper limit by the 90th percentile: 0.23) at peak exercise for a 40 year old man of 80 kg and 180 cm of height. The difference of our reference equations to those previously reported by others becomes obvious since the upper limits reported by us are just a little above the mean values reported by others (upper limits reported by Hansen: 0.45 at rest, 0.30 at peak exercise).[1] In the clinical setting, these upper limits of normality, applying the 90th and 95th percentiles, are of major importance. The addition of $p(a'\text{-}et)CO_2$ values is also of importance, since they correlate well with VD/VT measurements.

Potential reasons for the differences between studies may lay in methodology. Besides differences in exercise protocols, selection bias and study design, most of the datasets reported in the past used mouthpieces,[1,6,7,23] whereas this study used masks. Our study was not designed to assess methodological differences between masks and mouthpieces. However, our personal impression is that — at least in Europe — masks are the preferred tool in the clinical routine. Differences include the increase in apparatus dead space plus unknown influence of different breathing patterns. In our data set we did not find any influence of breathing frequency or tidal volume to frequency ratio on VD/VT calculations. However, the differences between masks and mouthpieces are not clear, and reference data for both methods are of potential importance.

This study also adds reference values for $p(et\text{-}a')O_2$ and $p(A\text{-}a')O_2$ to the literature. Mean $p(A\text{-}a')O_2$ reference limits of 8 ± 4 mmHg at rest with an increase to 11 ± 4 mmHg at peak exercise have been suggested for ages 20—39 years and 13 ± 7 at rest, and 19 ± 9 at peak exercise for ages 40—69 years.[1] The results of our study reveal higher mean values at rest (e.g. 180 cm, 40 years and 80 kg male: mean of 19 mmHg with an upper limit of 35 mmHg) but similar values at peak exercise (mean of 22 and upper limit of 31 mmHg). These values correspond to those reported by Asmussen and Jones.[7,24] In many current clinical situations as well as in large cross sectional studies, blood gases are measured using capillary rather than arterial blood. Compared to arterial blood, capillary blood may be diluted by mixed venous blood resulting in alterations of $pa'O_2$.[25] Applying $p(A\text{-}a')O_2$ rather than $p(et\text{-}a')O_2$ may reduce the potential influence of the methodological limitation by obtaining capillary blood. However, during optimised circumstances with high procedural standards and an apparently healthy population as in this study both parameters correlate very well (Fig. 1). We did not find sufficient previous publications to compare our data to those reported by others. Our findings of lower paO_2 at rest with increasing age and increasing $petO_2$ and $pa'O_2$ during exercise and confirms the findings of others. To the best of our knowledge, the magnitude of wider $p(et\text{-}a')O_2$ and $p(A\text{-}a')O_2$ during peak exercise with increasing age has not been specifically previously reported.

Finally, this study investigates the influence of obesity and smoking on gas exchange. Most importantly, obesity influences almost all gas tension variables at exercise. Thus, considering weight as well as height in reference equations appears to be reasonable. In addition, the presented reference equations demonstrate the influence of smoking in the assessment of patients.

This study has limitations. Some recruitment bias was present in our study population. For example, the extent of PY consumption of cigarettes may be lower in the participants compared to the general population. However, the percentage of smokers seems to be representative for the general population and is comparable to those reported for other cohorts.[26] We did not investigate the potential differences between arterial and capillary blood sampling. Obtaining direct arterial blood is impractical in large epidemiological cohort studies and uncommonly used in many clinical practices. These reference equations are applicable to investigations using capillary blood and should parallel the findings using direct arterial samples. Finally, blood gases were obtained at peak exercise only and it remains unclear, to what extent these measures may be transferable to values at anaerobic threshold as well. Previously published data by Sue and Wasserman clearly showed in very well investigated small groups of volunteers, that the main change in VD/VT and well as gas tension differences appears between rest and anaerobic threshold.[9,10] We finally assume that peak exercise measures are applicable to values at anaerobic threshold as well.

Conclusion

In conclusion, this study provides reference equations for dead space ventilation and alveolar-arterial gas tension differences in a large population based study and represents a reliable base to interpret these measures in diseased populations.

Disclosures

All authors state they have nothing to disclose.

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Author contribution

All authors' state to have significantly contributed to the conception and design as well as the analysis and interpretation of data, drafting of the manuscript and revising it critically for important intellectual content; and the final approval of the manuscript submitted. All authors state to have nothing to disclose.

Conflict of interest statement

None declared.

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