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Model-based Measurement of Gas Exchange in Healthy Subjects using ALPE Essential - Influence of Age, Posture and Gender*

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Abstract— **The ALPE Essential device for model-based measurement of pulmonary gas exchange status may be a useful alternative to current methods for diagnosing, monitoring and evaluating treatment related to pulmonary gas exchange. In this study, shunt and ventilation/perfusion mismatch were measured with ALPE Essential in 106 healthy subjects with the aim of investigating the influence of age, posture and gender on gas exchange parameters and evaluating the test-retest reliability of the measurements. Age and gender did not have statistically significant influence on gas exchange parameters, although there was a tendency for poorer matching of ventilation and perfusion with age. Posture was shown to be important when measuring gas exchange parameters. Absolute measurement reliability was acceptable with future studies in patients being necessary for accurate evaluation of relative reliability.**

I. Introduction

The primary function of the lungs is to allow efficient gas exchange securing that blood leaving the lungs are sufficiently oxygenated to supply organs and tissues of the body. The gas exchange status of the lungs is impaired either directly or indirectly in a number of patient groups such as heart failure patients, postoperative patients, and patients with respiratory disease. Measurement of pulmonary gas exchange status can in these patients be essential in diagnosing and monitoring disease and evaluating treatment.

Traditionally, oxygen gas exchange status is evaluated through surrogate measures such as pulse oximetry arterial oxygen saturation, venous and arterial blood gas samples, and indices such as the ratio of arterial partial pressure of oxygen to inspired oxygen (PaO_2/FiO_2). These measures have in common that they do not represent the underlying physiology and vary with extrapulmonary factors such as ventilation and changes in inspiratory oxygen levels [1,2].

The Automatic Lung Parameter Estimator (ALPE) is a model based technique for measurement of pulmonary gas exchange status [3]. A measurement with ALPE requires an examination of approximately 10-15 minutes duration where the subject sits or lies quietly and breathes through a mouth piece where inspired oxygen is modified in a number of steps and measurements are taken of inspired and expired gases, ventilation, and oxygen saturation. After the examination, two model parameters of a mathematical model of pulmonary gas exchange are identified constituting the output. These parameters describe gas exchange problems as separated into that occurring due to pulmonary shunt and that due to poor matching of ventilation and perfusion, the two primary factors causing impaired pulmonary gas exchange.

The gas exchange model used in ALPE has previously been successfully validated against the complex model of the reference technique for gas exchange measurement, the multiple inert gas elimination technique (MIGET) [4] demonstrating that the simple model of ALPE could accurately describe oxygen gas exchange in animal lung injury models [5-6]. In addition, ALPE has been used in several different patient groups for research [2, 7-8].

A commercial version of ALPE, ALPE Essential (Mermaid Care A/S, Nørresundby, Denmark) has been developed and approved for clinical use [9]. It is important that normal values are defined for ALPE Essential in diagnostic and monitoring purposes. These normal values should take into account factors that affect gas exchange in healthy subjects. Previous MIGET studies have shown that age and posture affect gas exchange in healthy subjects [10]. A recent study using ALPE have similarly seen an age effect [11]. It is also important that the reliability of measurements using ALPE Essential is investigated in the studied subjects.

The goals of this study were to investigate the dependency of ALPE Essential output parameters on posture, age and gender in healthy subjects; and the reliability of the ALPE Essential output parameters.

II. Methods

A. Gas exchange model parameters

The gas exchange model is a steady state model based on mass conservation and first principles (For a detailed description of the model see [3]). The model can be fitted to measurements by numerical identification of two model parameters. These parameters constitute the output of ALPE Essential and are a shunt percentage representing the percentage of pulmonary perfusion not reaching ventilated alveoli and oxygen normalization pressure (ONP), which is the extra oxygen pressure necessary to counter the oxygenation impairment due to ventilation-perfusion mismatch. ONP is calculated as the difference in partial pressure of oxygen between alveolar air and the mixed capillary blood leaving pulmonary capillaries prior to mixing with shunted venous blood. ONP has previously been reported as ΔPO_2 [3,7-8].

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B. Study protocol

The study was approved by the Ethical Committee of Region North Jutland, Denmark. The study population was a convenience sample of healthy Caucasian subjects from North Jutland, Denmark, encompassing family members, colleagues and acquaintances at the study site (Department of Anaesthesia and Intensive Care, Aalborg University Hospital, Aalborg, Denmark) from Sep 2008 to Jan 2009. Subjects were included in the study after giving informed written and oral consent according to the national Danish regulations. Subjects were included if they were healthy without anamnesis signs of disease, had resting blood pressure below 130/85 mmHg, had pulse oximetry arterial oxygen saturation ≥ 95 %. Exclusion criteria were dyspnea or current use of relevant medication. Subjects were included to equally represent both genders and predefined age groupings of 18-40, 41-50, 61-60, 61-70 and 71-80 years.

Subjects' age, gender, height, weight ans smoker/non-smoker were recorded. Two measurements were performed with an ALPE Essential device, one in semi recumbent posture with the headboard of the bed elevated with 15 degrees (ONP_{semi} and $Shunt_{semi}$), and one in sitting posture (ONP_{sit} and $Shunt_{sit}$). Half of the subjects in each age group were selected at random for a third measurement, in semi recumbent posture to evaluate test-retest reliability.

Each measurement was carried out by completing the built-in automated examination of ALPE Essential. Subjects were instructed to be relaxed and breathe normally through a mouth piece. Inspired oxygen was modified in a number of steps to characterize the end-tidal oxygen fraction to arterial oxygen saturation curve as previously described [3]. At each step, oxygen transport was monitored, and when steady state oxygen transport was detected, inspired and expired gas, ventilation, and pulse oximetry were recorded. After all steps were completed the ALPE Essential device identified shunt and ONP. Default blood gas values were used in the parameter identification as previously described [12].

C. Statistics

SPSS was used for statistical analysis (SPSS 19.0, SPSS Inc.). $P < 0.05$ was considered statistically significant. Distributions are reported as mean ± SD or as median, interquartile range (IQR), 5^{th} -95^{th} percentiles (weighted average method) and range if not appearing normally distributed on Q-Q plots [13]. Reliability distributions are reported as median (CI), IQR, and 5^{th} (CI) and 95^{th} (CI) percentiles with 95 % score confidence intervals (CI) [14].

Shunt and ONP for the genders were compared with Mann-Whitney U tests. Influence of age on shunt and ONP, and differences among age groups were analyzed with Spearman's rank correlation coefficient (ρ) and Kruskal-Wallis test, respectively. Within-subject changes in ONP and shunt with posture changes were assessed with Wilcoxon's matched pairs test. Test-retest relative reliability was assessed with Spearman's rank correlation coefficient. Absolute reliability was reported as bias and random error using median and variation of differences, respectively. Wilcoxon's matched pairs test was used to assess bias.

III. Results

A. Subjects

Data from 106 subjects were available for analysis, of which 105 subjects had measurements in both semi recumbent and sitting posture. 56 subjects had two measurements performed in semi recumbent posture for evaluation of test-retest reliability. These 56 subjects were evenly distributed across the two genders and had 10-13 subjects from each of the five age groups. Data for 13 subjects had been excluded prior to data analysis due to the following reasons: it was not possible for the subject to complete the required number of examinations (6 subjects), there was a technical malfunction (6 subjects), or the subject had respiratory disease (1 subject). Table I summarizes demographic data for subjects with measurements in both semi recumbent and sitting posture.

B. Shunt, ONP and gender

Table II summarizes distributions of shunt and ONP for the two genders in semi recumbent posture across all age groups. Both shunt and ONP distributions were not significantly different between male and female samples.

C. Shunt, ONP and age in semi recumbent posture

Fig. 1 illustrates ONP measurements in semi recumbent posture. There was a tendency for higher ONP values in older subjects, but majority of measurements were 0 kPa. Male and female subjects showed similar patterns. This was also illustrated by the low calculated Spearman's rank correlation coefficients which were 0.06 ($P = 0.70$) and 0.03 ($P = 0.81$), for male and female subjects, respectively. ONP measurements were not significantly different among the five age groups in male ($P = 0.77$) or female ($P = 0.22$) subjects.

TABLE I. Subject demographics

	Age group (yrs)				
	18-40	***41-50***	***51-60***	***61-70***	***71-80***
n	22	22	21	21	20
Male (%)	50	45	48	52	50
Age (yrs)	31 ± 7	45 ± 3	56 ± 4	65 ± 3	74 ± 2
Smokers (n)	3	2	4	6	5
BMI (kg/m^2)	24 ± 3	25 ± 4	25 ± 4	25 ± 3	24 ± 2

TABLE II. Gender Differences

	Shunt (%)				
	Median	*IQR*	*5^{th} – 95^{th} perc*	*Range*	*P*[a]
Male	0	0 - 0	0 - 6	0 - 11	0.52
Female	0	0 - 0	0 - 9	0 - 9	
	ONP (kPa)				
Male	0.0	0.0 - 0.6	0.0 - 2.4	0.0 - 3.3	0.97
Female	0.0	0.0 - 1.3	0.0 - 3.0	0.0 - 4.0	

a. Mann-Whitney U test

Only 7 male subjects and 5 female subjects had shunt measurements higher than 0 %. These were larger for older subjects (not shown). For shunt, correlation coefficients were 0.13 (P = 0.37) and 0.23 (P = 0.09), for male and female subjects, respectively. Shunt measurements were not significantly different among the five age groups in male (P = 0.17) or female (P = 0.28) subjects.

D. Shunt, ONP and posture

Table III summarizes within-subject changes in shunt and ONP with changing posture from semi recumbent to sitting. The majority of shunt changes were < 5 % and statistically insignificant. Results show a worsening in ONP with changing from semi recumbent to sitting posture, these changes being statistically significant.

Fig. 2 illustrates the distribution of ONP measurements across age groups for measurements in sitting posture. In comparison to ONP distributions in semi recumbent posture illustrated in Fig. 1, it can be seen that a greater number of subjects showed values of ONP greater than 0 kPa, and again that larger values were seen in older subjects. This tendency of a larger change in older subjects, in particular for the oldest age group, was also seen in shunt, but in fewer subjects compared to ONP (not shown).

E. Reliability of Shunt and ONP measurement

Table IV summarizes within-subject differences from repeated measurement of shunt and ONP. There were not statistically significant systematic biases between measurements. Correlation coefficients were statistically significant but weak for shunt and moderate for ONP.

TABLE III. CHANGES WITH POSTURE

	Shunt$_{sit}$ – Shunt$_{semi}$ (%)				
	Median	***IQR***	***5th – 95th perc***	***Range***	***P^a***
Male	0	0 - 0	-3 - 5	-6 - 9	0.53
Female	0	0 - 0	-4 - 3	-9 - 6	0.61
	ONP$_{sit}$ – ONP$_{semi}$ (kPa)				
Male	0.0	0.0 - 0.4	-0.7 - 1.5	-1.4 - 2.6	0.02
Female	0.0	0.0 - 0.6	-1.1 - 1.9	-1.9 - 2.4	0.03

a. Wilcoxon's matched pairs test

TABLE IV. TEST-RETEST RELIABILITY

	Test2 - Test1					
	Median (95 % CI)	***IQR***	***5th perc (95 % CI)***	***95th perc (95% CI)***	***ρ^a***	***P^b***
ΔShunt (%)	0 (0 - 0)	0 - 0	-6 (-9 – 0)	8 (0 - 13)	0.43	0.61
ΔONP (kPa)	0.0 (0.0 - 0.0)	-0.1 - 0.0	-1.1 (-1.7 - -0.4)	0.8 (0.2 - 1.2)	0.70	0.70

a. Spearman's rank correlation coefficients were statistically significant (P < 0.01)

b. Wilcoxon's matched pairs test

IV. DISCUSSION

A. Factors influencing shunt and ONP

Overall, shunt and ONP levels were zero or low in the majority of subjects resulting in narrow ranges. This was also shown by Moesgaard et al. who studied 60 healthy subjects with ALPE [11].

Shunt and ONP were not significantly different between the two genders. This is in contrast to Crapo et al. who found gender as a significant predictor of arterial oxygen levels [15]. However, our findings are in agreement with Olfert et al., who reported no significant differences in MIGET indices of ventilation/perfusion mismatch between resting female and male subjects matched for age, height and aerobic fitness [16].

Shunt and ONP were not statistically significant between age groups, nor were age and shunt and ONP significantly correlated. However, the number of subjects presenting with shunt or ONP above zero and maximum measured ONP and shunt levels increased with age, in particular for ONP, as illustrated in Fig. 1 and 2.

Previous studies have reported similar trends [10-11,17], and that the reduction in arterial oxygenation with age is due

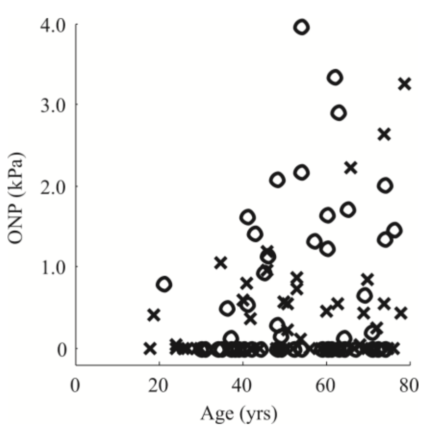

Figure 1. Subject ONP versus subject age for semi recumbent posture, with indication of male subjects (x) and female subjects (o).

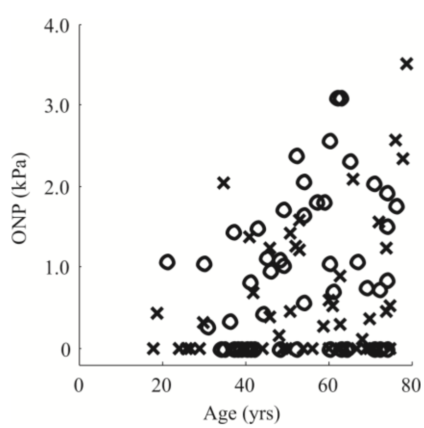

Figure 2. Subject ONP versus subject age for sitting posture, with indication of male subjects (x) and female subjects (o).

To ventilation/perfusion mismatch rather than shunt [17]. This ventilation/perfusion mismatch worsening with age may be due to an increase in closing volume with age [17-18].

Changing posture from semi recumbent to sitting significantly increased ONP. In contrast, previous studies showed that ventilation/perfusion was worse and closing volume larger in supine than sitting posture [10, 18]. This discrepancy may partly be explained by the results of Nunn and co-workers who showed functional residual capacity to increase from supine to semi recumbent to standing posture but then decrease from standing to sitting [19] indicating that both semi recumbent and sitting postures are suboptimal. There was a tendency for older subjects to show greater changes in ONP with changes in posture, as can be seen from comparison of Fig. 1 and 2. This is in agreement with closing volume changes with posture reported by Leblanc et al. [18].

B. *Reliability of measurements*

Repeated measurements of shunt and ONP were significantly but weakly or moderately correlated. This has likely been affected by limited shunt and ONP ranges in the study population, indicating need for future studies in patient populations. Shunt and ONP IQR were similar to or less than previously reported variation in healthy adult subjects [7]. The 5th -95th percentiles of within-subject differences for shunt and ONP were similar to or less than reported inaccuracy in using pulse oximetry for estimating shunt and ONP [7], and can thus be considered clinically insignificant.

C. *Study limitations*

The study did not control for smoking or body composition, which has previously been shown to affect gas exchange [e.g. 15]. However, distributions of smokers and BMI across age groups were similar and there were an overall small number of smokers in the study.

Default blood gas values were assumed for parameter identification potentially worsening accuracy. However, Smith et al. showed that use of default blood gas values was accurate when compared to arterial blood gas samples [12].

V. CONCLUSION

Results indicate that gender and age may be unimportant when determining shunt and ONP values with ALPE Essential, although inter subject variation increased with age. Posture was important when measuring shunt and ONP. Absolute measurement reliability was acceptable, but studies in patients are necessary for broader ranges of shunt and ONP allowing better assessment of relative reliability.

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