"Validation of indirect calorimetry for measurement of energy expenditure in healthy volunteers undergoing pressure controlled non-invasive ventilation support"

Waltteri Siirala[1] Tommi Noponen[2] Klaus T Olkkola[1] Arno Vuori[1] Mari Koivisto[3] Saija Hurme[3] Riku Aantaa[1]

[1]Department of Anaesthesiology, Intensive Care, Emergency Care and Pain Medicine, Turku University Hospital and University of Turku, Kiinamyllynkatu 4-8

FI-20521 Turku, Finland

[2]Turku PET Centre, Turku University Hospital, Kiinamyllynkatu 4-8

FI-20521 Turku, Finland

[3]Department of Biostatistics, University of Turku, Lemminkäisenkatu 1,

FI-20014 Turku, Finland

Running title

Indirect calorimetry during non-invasive ventilation

Email addresses

Waltteri Siirala – tuwasi@utu.fi

Tommi Noponen – tommi.noponen@tyks.fi

Klaus T Olkkola – klaus.olkkola@utu.fi

Arno Vuori – arno.vuori@tyks.fi

Mari Koivisto - markoiv@utu.fi

Saija Hurme – saija.hurme@utu.fi

Riku Aantaa – riku.aantaa@tyks.fi

Corresponding author

Dr Waltteri Siirala, MD

Tel: +358-2-3130000

ABSTRACT

Objective. The aim of this study was to assess the reliability of gas exchange measurement with indirect calorimetry among subjects who undergo non-invasive ventilation (NIV).

Methods. Oxygen consumption (VO_2) and carbon dioxide production (VCO_2) were measured in twelve healthy volunteers. Respiratory quotient (RQ) and resting energy expenditure (REE) were then calculated from the measured VO_2 and VCO_2 values. During the measurement period the subjects were breathing spontaneously and ventilated using NIV. Two different sampling air flow values 40 and 80 L/min were used. The gas leakage from the measurement setup was assessed with a separate capnograph.

Results. The mean weight of the subjects was 93 kg. There was no statistically significant difference in the measured values for VO2, VCO2, RQ and REE during NIV-supported breathing and spontaneous breathing. The change of sampling air flow had no statistically significant effect on any of the above parameters.

Conclusion. We found that REE can be accurately measured with an indirect calorimeter also during NIV-supported breathing and the change of sampling airflow does not distort the gas exchange measurement. However, using a higher sampling air flow in indirect calorimetry decreases the possibility for air leakages in the measurement system and increases the reliability of REE measurement.

Key words. indirect calorimetry, non-invasive ventilation, resting energy expenditure

INTRODUCTION

Indirect calorimetry is a method for energy expenditure estimation. It is based on gas exchange (oxygen consumption (VO_2) and carbon dioxide production (VCO_2)) measurements. Resting energy expenditure (REE), respiratory quotient ($RQ = VCO_2/VO_2$) and also the rate of fat and carbohydrate utilization can be assessed from the measured VO_2 and VCO_2 values [1].

Invasive ventilation has been the gold standard for treatment of hypoventilation for already 60 years [2]. However, a growing number of studies has proven that non-invasive ventilation (NIV) instead of invasive ventilation should often be considered even as the first line ventilation treatment both in acute as well in chronic hypoventilation [3, 4, 5, 6]. The benefit of NIV-supported breathing can be seen in shortened intensive care unit (ICU) stay [7] as well as in better quality of life indices especially among chronic hypoventilation patients [5].

Although many of the patients receiving NIV are given artificial nutrition we found no previous study in which indirect calorimetry would have been used for assessment of energy requirements among these patients. Indeed, the use of NIV makes the measurement of REE challenging, because NIV-ventilators are most often open system ventilators and therefore cannot be connected to the indirect calorimetry directly. Therefore we aimed to assess the accuracy of one commonly used indirect calorimeter (Deltatrac II metabolic monitor, Datex, Helsinki, Finland) during NIV-supported breathing with focus on air leakage during the measurements both in normal weight and in obese volunteers. The main hypothesis in our study was that the use of NIV would not distort the assessment of REE.

MATERIALS AND METHODS

Subjects

The study protocol was approved by the local ethics committee. Twelve non-smoking male subjects (the mean age was 33 years (range 19 – 62)) in good general health were recruited and they all provided a written informed consent before participation. Subjects with diseases potentially affecting REE such as thyroid dysfunction, high blood pressure requiring medication, asthma, COPD or heart disease were not considered for the study.

Study Design and Methods

The VO_2, VCO_2, respiratory quotient ($RQ = VCO_2/VO_2$) and REE were determined with indirect calorimetry (Deltatrac II metabolic monitor, Datex, Finland). Deltatrac II metabolic monitor is an open-system indirect calorimeter, which is designed to measure VO_2 and VCO_2 from ventilation gases both in spontaneous breathing as well in invasively ventilated subjects. All measurements were performed in the morning after 10 hours fasting. In the study morning, the subjects were asked to avoid caffeine and nicotine products and excess physical activity. All subjects rested 20 – 30 min in supine position before the measurements. The measurements were carried out in a quiet room with a temperature of approximately 20 - 22 °C. The weight and the height of the subjects were measured. Their fat content was assessed with a body fat scale (BF 400 Body Fat Monitor and Scale, Omron, Germany). Vital signs which included heart rate, continuous ECG, minute ventilation, respiratory rate, and arterial oxygen saturation with pulse oximeter were all non-invasively recorded (Datex-Ohmeda S/5, Oregon, USA) simultaneously with the gas exchange measurements.

Non-invasive ventilation (NIV)

Non-invasive ventilation was carried out with an open system ventilator (Breas PV 403, Mölnlycke, Sweden). The subjects were ventilated via a face mask using pressure-controlled ventilation (PCV) mode. In this open system ventilation technique all inspiration gases are conducted from the ventilator via a single tube to the face mask, but instead of an expiration tube, the expiratory gases are delivered to the room air via small apertures in the face mask.

Measurement of gas exchange with Deltatrac II

Deltatrac II has two measuring modes: canopy mode and respirator mode. The canopy mode is intended for measurements in spontaneously breathing patients. In that mode the inspiratory and expiratory gases are mixed under a half ellipsoidal see-through plastic canopy of approximately 25 L in volume [8]. The respirator mode in turn is intended for measurements in mechanically ventilated patients. In that mode, the expired gases are usually collected through a mixing chamber to which the expiratory tubing of the ventilator is connected [8]. As the respirator mode cannot be employed during open system ventilation, we assessed whether the canopy mode would yield in a reliable gas exchange measurement in this situation.

During the measurement the canopy was placed around the subject's head in airtight fashion with a flexible sleeve (Figure 1). All ventilation gases are mixed in the canopy and a constant air flow is drawn from the canopy into the monitoring device. The device has two different sampling air flow settings (40 and 80 L/min) for adults. The sampling air flow value is related to the ventilation capacity of the studied subject: at weight range 20-120 kg a flow value of 40 L/min is recommended and when the subject weight is over 120 kg a value of 80 L/min should be used [8]. We measured each subject using both the 40 and 80 L/min sampling air flow values with and without NIV as we wanted to exclude the possibility of air leakage. With the 80 L/min air flow value a plausible leakage should be minimized. The VO_2 and VCO_2 from mixed ventilation gases were measured in six occasions for each subject as shown in Figure 2. Each measurement took approximately 20 min. The first seven minutes of all the calorimetry data were discarded to allow the subjects to stabilize under the canopy [9]. Single VCO_2, VO_2, RQ and REE values differing more than 1.5 x standard deviation (SD) of the mean of the raw signal were considered being related to irregular breathing and were filtered out. After filtering the remaining signal values were averaged.

The REE is calculated from the measured VCO_2 and VO_2 values using the manufacturer's equation [8] which is derived from the original de Weir's equation [10]:

$$\text{REE (kcal/day)} = 5.50 \times VO_2\ \text{(mL/min)} + 1.76 \times VCO_2\ \text{(mL/min)} - 1.99 \times \text{UN (g/day)},$$

where UN is the amount of nitrogen excreted in urine during 24 hours. The error in measured REE is less than 2% if urine nitrogen is not measured [1]. In our study we used a constant UN value of 13 g/d.

Assessment of the gas leakage from the measurement circuit

Possible gas leakage was assessed by measuring the CO_2 and O_2 from the inlet aperture of the canopy throughout the measurements with an extra capnograph (Datex Ohmeda S/5, Oregon, USA) (Figure 1). The capnogram signal was smoothed with a 10-point sliding average and all CO_2 values above 0.06 % were classified as a leakage. The area under the CO_2 concentration-time curve (AUC) of the leakage peaks was calculated using the trapezoidal rule. The leakage peaks in the O_2 signal coincided with the CO_2 leakage peaks. The O_2 signal was processed in a similar way as CO_2 signal after it was inverted and the signal baseline was set to zero. The AUC values of CO_2 and O_2 leakage measurements were averaged and the measurements having AUC values 10 % above these mean values were classified to be significant. The 10 % cut-off value for CO_2 and O_2 leakages was based on visual screening. At 10 % level the minor leakages remained below the cut-off and only clear leakages were detected.

Statistical analysis

Continuous variables were characterized using means and standard deviations (SD) or range of values. The measured VO_2, VCO_2, RQ and REE values were analyzed using general linear mixed models. NIV, weight and air flow were used as fixed effect and subject as random effect. The results of analyses were quantified using differences of least squares mean estimates with 95% confidence intervals (95% CI) and mean weight level. The normal distribution assumption of the residuals were assessed for justification of the analysis.

The leakages of O2 and CO2 during NIV-supported breathing were analyzed using logistic regression. NIV, weight and air flow were used as fixed effect and subject as random effect. P-values less than 0.05 were considered as statistically significant. Statistical analyses were carried out using SAS system for Windows, Version 9.2 (SAS Institute Inc, Cary, NC, USA).

RESULTS

The mean weight of the subjects was 93 (range 69 – 128) kg and the mean body fat percent was 25 (11.9 – 37.8) %. The vital signs (such as heart rate, peripheral arterial oxygen saturation and ECG) among each subject were all stable and within respective normal ranges at the time of the measurements (data not shown). The mean values for measured VO_2, VCO_2, RQ and REE from the 72 measurements were 272 (SD 36) mL/d, 219 (SD 39) mL/d, 0.8 (SD 0.1) and 1856 (SD 254) kcal/d, respectively. The mean pressure used in NIV was 11 (SD 1) cmH_2O.

The individual values for the measured VO_2, VCO_2, RQ and REE from all measurements are presented in Figure 3. The weight-adjusted mean estimates and the difference in the mean for the measured VO_2, VCO_2, RQ and REE with 95% confidence limits from each subject during spontaneous and NIV-supported breathing, and during 40 and 80 L/min sampling air flow are presented in Table 1. There was no statistically significant difference in the measured values for VO2, VCO2, RQ and REE during NIV-supported breathing and spontaneous breathing. The level of the sampling air flow had no statistically significant effect on any of the above parameters.

The use of NIV exposed the measurement circuit for gas leakage. With 10 % as the cut-off for gas leakage, gas leakages for VO_2 and VCO_2 were detected 13 and 14 times during NIV-supported breathing, respectively. During spontaneous breathing gas leakage for VO_2 and VCO_2 was detected only once. Compared to the lower air flow of 40 L/min, the higher air flow of 80 L/min decreased the number of calculated leakage periods for VO_2 from 8 to 5 ($P = 0.046$) and that for VCO_2 from 8 to 6 ($P = 0.1$). The weight of the subject had no impact on the likelihood of gas leakage (data not shown).

DISCUSSION

We designed this study to assess whether indirect calorimetry would yield reliable energy expenditure measurement during NIV-supported breathing. Our main finding was that the use of the NIV subjected the system to minor leakages but did not distort the measurements markedly. Neither ventilation mode, sampling air flow or subject weight had an effect on VO_2 VCO_2, RQ and REE.

Deltatrac II metabolic monitor is an indirect calorimeter designed almost three decades ago [8]. The device has been used in various studies and it has been shown to have a good overall accuracy both in intubated patients as well in spontaneously breathing subjects [11, 12, 13, 14]. Takala et al measured the effect of positive end-expiratory pressure (PEEP) and peak inspiratory pressure (PIP) during invasive ventilation and found no statistical difference in the measured values for VCO_2 and VO_2 when PEEP varied between 0 – 10 cmH_2O and PIP between 13 – 63 cmH_2O. When they compared the measured VO_2 and VCO_2 values with the reference values from laboratory simulations, the mean error for VO_2 was 4 ± 4 % and for VCO_2 2 ± 2 % [11].

REE can be measured also in spontaneously breathing subjects. Then the gases are measured from a canopy where the inspired and expired gases mix. The use of the canopy mode has been criticized for being more vulnerable for gas leakages than the respirator mode in which all gases are in a closed loop and can reliably be collected from an outlet tube [8, 15]. However, if the leakages are carefully eliminated, the accuracy of the method should be similar to that in respirator mode. In the same study made by Takala et al [11] they compared the results from 25 healthy subjects using canopy mode to reference values, and found an error of 4 ± 2 % for VO_2 and 3 ± 2 % for $VCO_{2.}$ Compared to spontaneous breathing the likelihood of gas leakages was increased during NIV-supported breathing in the present study. This is understandable because the use of pressure support during inspiration may deliver extra air to the subject which in turn may increase the likelihood for gas leakage [11]. We quantified gas leakage with the use of capnography at the canopy's inlet aperture. Obviously, air leakage was more pronounced when the sampling air flow of 40 L/min was used. When the flow was increased to 80 L/min, the likelihood of leakage was decreased. We also observed that an increase in the sampling air flow from 40 to 80 L/min was not associated with clinically significant differences in any of the measured parameters (VO_2, VCO_2, RQ or REE). Thus, the reliability of indirect calorimetry during NIV-supported breathing can be increased by using higher sampling air flow.

The development of non-invasive ventilation techniques has increased the use of such techniques also in the treatment of hypoventilated patients instead of mechanical ventilation requiring endotracheal intubation [3, 4, 7]. It is obvious that estimation of energy requirements of these patients using predictive equations, such as the Harris-Benedict equation, may result in incorrect, usually too high REE estimates [16, 17, 18, 19]. Thus, it would be advantageous to establish their nutrition therapy on individually measured REE. Nevertheless, non-invasive ventilators do not have expiratory gas tubings which could be used for the collection of gas samples for calorimetry. Therefore, the only way to measure the gas exchange during NIV-supported breathing is the canopy mode. To eliminate the gas leakages, it is important to carefully wrap the subject with a plastic sleeve. In addition, it is important to place the expiration valve of the ventilation mask near to the canopy's aperture from which the mixed gases are suctioned to the indirect calorimetry (Figure 2). Our study demonstrates that VO_2, VCO_2, RQ and REE measurements during NIV-supported breathing can be accomplished with Deltatrac II in the canopy mode.

The main weakness of our study was the small number of study subjects. The study design allowed us to examine the differences in VO_2, VCO_2, RQ and REE measurements between the NIV-supported breathing and spontaneous breathing as well between two different sampling air flows. Unfortunately, we were not able to make equivalence analyses. The second reservation is related to the use of normal room air with NIV during the whole measurement period. The measurement of VO_2 with indirect calorimetry may be distorted if supplemental O_2 is used in the inspiratory gas mixture. The higher the FiO_2, the higher the error will be for VO_2 measurement [15]. This should be taken into consideration if additional oxygen is used during indirect calorimetry, particularly as ICU the patients are rarely ventilated without oxygen supply.

CONCLUSION

In conclusion, the present study demonstrates that indirect calorimetry is reliable in healthy adult subjects both during spontaneous breathing and during NIV-supported breathing. Using higher sample air flow decreases the possibility of air leakages in the measurement system and increases the reliability of REE assessment.

LEGENDS TO THE ILLUSTRATIONS

Figure 1 Flowchart of the study: NIV = non-invasive ventilation. The first measurement was carried out during spontaneous ventilation using 40 L/min flow value in Deltatrac II (Datex, Helsinki, Finland). The second, third and fourth measurement were carried out during spontaneous breathing with NIV support by using 80, 40, and 80 L/min flow values, respectively. The fifth and sixth measurements were carried out during spontaneous ventilation using 40 and 80 L/min flow values. Each measurement took approximately 20 min.

Figure 2 Measurement setup: The head of the subject was covered with a plastic half ellipsoidal canopy. A plastic sleeve of the canopy was wrapped carefully under the pillow and around the inspiration tubing to minimize any leakages in the measurement circuit. The subject was ventilated with ambient air via the facemask with non-invasive ventilator (Breas PV 403, Mölnlycke, Sweden). Expiratory gases exit from the valve next to the facemask. The possible gas leakage (dashed arrow) from canopy's inlet aperture was measured with Datex CO_2 analyzer (Datex Ohmeda S/5, Oregon, USA).

Figure 3 Scattergram of the individual values for the measured VO_2, VCO_2, RQ and REE: VO_2 = oxygen consumption (mL/min), VCO_2 = carbon dioxide production (mL/min), RQ = respiratory quotient (VCO_2/VO_2), REE = resting energy expenditure (kcal/d), NIV = non-invasive ventilation. Open circles denote measurements during 40 and closed circles during 80 L/min sampling air flow. The solid line represents the linear regression line for the measurements during 40 and the dashed line during 80 L/min sampling air flow.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTION

All authors have participated in conception and design of the study, analysis and interpretation of the data, drafting of the article and critical revision of the article for important intellectual content, and approved the final version of the article.

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