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Non-invasive monitoring of pulmonary blood flow, functional residual capacity, and shunt index in a porcine model

Maximilian Edlinger-Stanger[1], Caroline Fritz[2], Hanna C. McGregor[3], Spencer L. Bustin[3], Nathan Ayoubi[3], Harpreet K. Bath[3], Johannes Müller[4], Sebastian Kühnl-Brady[1], Thomas Schweiger[5], Julia Jedamzik[5], Marita Windpassinger[4], Michael Hiesmayr[1], Bernard P. Cholley[2,6] and Neal W. Fleming[7*]

Abstract

Background Management of mechanically ventilated patients can be improved with monitoring of key pulmonary function parameters that facilitate individualization and optimization. The VQm Pulmonary Health Monitor™ (PHM) (Rostrum Medical Innovations Inc., Vancouver, Canada) is a new monitor that continuously measures pulmonary blood flow (PBF), functional residual capacity (FRC) and a novel parameter: shunt index (Q_{si}). The goal of this study was to provide an initial assessment of the performance of the VQm PHM™ when compared with reference measures of PBF, FRC and intra-pulmonary shunt.

Methods This was a prospective, experimental, large animal (porcine) study. After baseline measurements, three interventions were performed: increased cardiac output (CO) using dobutamine infusion, increased PEEP (from 4 to 12 cmH_2O), and experimental shunt induced by an extracorporeal circuit. PBF, FRC and shunt were measured by the VQm Pulmonary Health Monitor™ (PHM) before and after each intervention. The PHM™ uses sequential gas delivery to deliver targeted alveolar concentrations of CO_2 or N_2O. PBF and FRC were calculated using CO_2 bolus delivery and the modified differential Fick equation. Shunt was estimated from the number of breaths required to eliminate N_2O after a 25-breath N_2O bolus and expressed as Q_{si}. PHM™-derived PBF and Q_{si} were compared to thermodilution CO and calculated Berggren shunt, respectively.

Results Studies were completed in 19 animals. Measurements of PBF, FRC and Q_{si} obtained from the PHM™ trended as expected following each intervention. The mean difference between paired values of PBF was -0.2 ± 0.9 L/min and the 95% limits of agreement were 1.5 and -1.9 L/min. Concordance was 94.1%. The mean baseline FRC was 1.7 ± 0.4 L and increased to 2.0 ± 0.6 L, following the increase in PEEP ($p = 0.0078$). For shunt (Q_{si}), the mean values during low (1 L/min) and high (50% of baseline CO) shunt value were 40 ± 4 and 27 ± 5, respectively, $p = 0.002$.

Conclusions PBF obtained through the modified differential Fick equation and Q_{si} obtained through N_2O uptake and decay dynamics by the VQm PHM™ provide comparable results to reference standards. FRC measurements trended as expected following interventions.

*Correspondence:
Neal W. Fleming
nwfleming@ucdavis.edu

Full list of author information is available at the end of the article

Keywords Pulmonary physiology, Pulmonary blood flow, Functional residual capacity, Intrapulmonary shunt, sequential gas delivery

Introduction

Management of mechanically ventilated patients can be improved with monitoring of key pulmonary function parameters [1]. The measurement of pulmonary blood flow (PBF), functional residual capacity (FRC) and shunt fraction could be used to individualize and optimize mechanical ventilation and improve outcomes. The VQm Pulmonary Health Monitor™ (PHM) (Rostrum Medical Innovations Inc., Vancouver, Canada) is a new monitor that uses a sequential gas delivery method to continuously measure PBF, FRC and a novel parameter: shunt index (Q_{si}).

Invasive techniques to measure cardiac output (CO) include bolus or continuous thermodilution using a Swan-Ganz catheter. Although this technique is considered to be a gold standard, it is known to be limited in precision and accuracy [2]. Further, use of Swan-Ganz catheters have inherent risks for the patient including increased incidence of infection, pulmonary emboli, chance of catheter misplacement and controversial data with respect to its' impact on clinical outcomes [3]. During mechanical ventilation, functional residual capacity (FRC) is the volume remaining in the lungs after exhalation. Measurements of FRC can be accomplished through nitrogen washout methods now available on some ventilators. Though a nitrogen washout is considered non-invasive, the measurement is lengthy and requires a step-change in FiO_2, which poses a risk for some patients. Shunt fraction is the percentage of the cardiac output that perfuses alveoli that are not oxygenated. It can be measured indirectly through analysis of arterial and mixed venous blood gas values, but this is invasive, intermittent and requires computations. We introduce a novel device the VQm PHM™ - to measure PBF, FRC and shunt fraction (Q_{si}) non-invasively and semi-continuously in mechanically ventilated patients. The goal of this study was to provide an initial assessment of the performance of the VQm PHM™ when compared with reference measures of PBF, FRC and shunt fraction during baseline and clinical interventions in animals.

Methods

Ethics

This was an animal experimental study performed at the Medical University of Vienna (MUV), Austria and Hôpital Européen Georges-Pompidou (HEGP) of Paris, France. All experiments done at the Medical University of Vienna (MUV) described in this article were reviewed and approved by the Austrian Federal Ministry of Education, Science and Research (BMBWF-66.009/0177-V/3b/2019) and experiments were carried out according to national animal research regulations (Directive 2010/63/EU, Tierversuchsverordnung 2012). All experiments done at HEGP described in this article were reviewed and approved by the Paris University Ethics Committee for Animal Experimentation (APAFIS #23,056). Care and handling of the animals were in accordance with the European Community Standards on the Care and Use of Laboratory Animals.

Animal preparation

For the experiments at MUV, animals were premedicated with ketamine (0.25 mg/kg) and midazolam (0.15 mg/kg). For administration of anesthetic induction agents, a peripheral ear vein was cannulated. General anesthesia was induced and maintained with propofol (15 mg/kg/h) and fentanyl (6 µg/kg/h) infusions. Endotracheal intubation was facilitated with rocuronium-bromide (0.6 mg/kg). Mechanical ventilation at baseline was initiated and maintained with a tidal volume of 10 ml/kg, respiratory rate of 12/min, PEEP of 4 cmH_2O and 21% oxygen (pressure-controlled mode). Arterial and central venous catheters were placed for monitoring blood pressure and drug administration, respectively, and a Swan-Ganz catheter was placed for monitoring CO. MUV experiments utilized central cannulation for the pump-driven extracorporeal circulation circuit and shunt fraction measurements, with right atrial (RA) and left atrial (LA) cannulas placed following a sternotomy. For the subsequent series of studies conducted at HEGP, anesthetic induction and maintenance were similar, but these experiments utilized peripheral cannulations of the inferior vena cava and descending aorta for shunt fraction measurements. Details regarding the preparation for these animals have been previously summarized [4].

The VQm PHM™ monitor

Measurement of PBF and FRC

The VQm PHM™ uses the technology of sequential gas delivery (SGD) and the modified differential Fick equation to measure PBF and FRC [5, 6]. The differential Fick equation estimates pulmonary capillary blood flow using the difference in volume of exhaled CO_2 (VCO_2) and end-tidal CO_2 during different breathing states [7]. To create the breathing states needed for the calculation, the VQm PHM™ uses SGD to divide the inhaled gas into two portions of known gas concentrations. This allows for the precise control of alveolar ventilation [5]. In this study, SGD also facilitated a precise and measurable change in VCO_2, by transiently increasing F_iCO_2 to 30%. Ordinarily,

the differential Fick equation requires two steady states to measure the CO_2 and does not provide an estimate of FRC. However, the modified differential Fick equation allows the VQm PHM™ to eliminate the requirement of two steady states and estimates FRC by adding an extra equation to the linear system [6]. The PBF value obtained by the VQm PHM™ was compared to PBF calculated using the following equation:

PBF_{calc} = Thermodilution Cardiac Output (TDCO) – Berggren shunt. [8], where Berggren shut was calculated according to the following equation [8]:

$$\frac{Q_s}{Q_t} = \frac{C_{CO2} - C_{aO2}}{C_{CO2} - C_{VO2}}$$

FRC values obtained by the VQm PHM™ were evaluated with respect to a qualitative change in FRC at different levels of PEEP.

Measurement of shunt

The VQm PHM™ estimates shunt using SGD to deliver a bolus of nitrous oxide (N_2O). N_2O has a low blood solubility and diffuses rapidly across the alveolo-capillary membrane. The blood-gas partition coefficient of N_2O is 0.47 leading to almost complete retention (ratio of $P_{arterial}/P_{mixed\ venous}$ ~1.0) of N_2O across lung areas of low ventilation/perfusion ratio (V/Q) and shunt, whereas dead space ventilation and high V/Q areas do not influence elimination to a significant degree [9]. Thus, the number of breaths necessary to eliminate N_2O after an N_2O bolus reflects the amount of shunt. We hypothesize that in the presence of shunt, the decay in exhaled N2O will be accelerated initially, whereas terminal elimination will be prolonged. Thus, the number of breaths required to reach 2.5% of the end-tidal N_2O concentration after an N_2O bolus should *decrease* in the presence of shunt.

To assess shunt fraction, a N_2O bolus consisting of 25 consecutive breaths at an F_iN_2O of 30% is delivered and the decay of N_2O is studied to estimate shunt. The characterization of the recirculation of the N_2O bolus, as well as the 25-breath step change, is used to estimate the shunted fraction of blood. The number of breaths required to achieve an end-tidal N_2O fraction that is 2.5% of the end-tidal N_2O at the end of delivery of a 25-breath bolus is defined as the Q_{si}. The Q_{si} measurement obtained by the VQm PHM™ was compared to the shunt fraction calculated using the Berggren equation.

Study design and protocol

After surgical preparation, when the animals were hemodynamically stable, F_iO_2 was set to 100% for at least five minutes to calculate the baseline Berggren shunt fraction. F_iO_2 was then set to 21% and a recruitment maneuver was performed to reverse any acquired atelectasis. A baseline CO measurement was obtained using bolus thermodilution (TDCO) [3, 10] and the corresponding baseline measurements were obtained using the PHM™. Each PHM™ measurement series consisted of two 3-breath CO_2 boluses at an F_iCO_2 of 30% (for measurement of PBF and FRC) and one 25-breath N_2O bolus at an F_iN_2O of 30% (for measurement of Q_{si}). Values of VQm PHM™ PBF and FRC measurement were calculated as the average of two measurements with each requiring a CO_2 bolus. Once baseline measurements were obtained for both the VQm PHM™ and the reference standards, the following interventions were applied to the animals:

Increased pulmonary blood flow

PBF was measured during baseline conditions and during increased CO induced by an intravenous infusion of dobutamine (5–10 $\mu g.kg^{-1}.min^{-1}$). Dobutamine infusions were titrated to achieve an increase in heart rate to 130% of baseline. When the animals were hemodynamically stable, PBF measurements were acquired using the VQm PHM™ and the reference measurements (TDCO – Berggren shunt). For the the VQm PHM™ monitor, two averaged measurements, 10 min apart, were analyzed [6]. TDCO values were calculated as the average of three sequential measurements.

Increased functional residual capacity

To test the FRC measurement, values obtained using the VQm PHM™ were compared during baseline conditions and following an increase in PEEP (from 4 to 12 cmH_2O). In lieu of a reference, the PEEP intervention was designed to show trend changes in the FRC measurement. Following each gas bolus, the RMI algorithm calculated the FRC, and the two averaged measurements, 10 min apart, were subsequently analyzed [6].

Increased shunt fraction

The Q_{si} measurement was obtained from the VQm PHM™ and compared to the reference standard (Berggren equation) during baseline, low shunt, and high shunt conditions. These measurements were completed only in the animals that underwent central cannulation (RA-LA shunt) because the peripheral cannulation precluded collection of accurate mixed venous and arterial blood samples required for the Berggren shunt calculations. For comparison among challenges for each animal, the end-tidal measurement was normalized to the end-tidal value of the last breath of the challenge. The initial flow through the extracorporeal circuit was set at 1 L/minute (Low Shunt). The extracorporeal flow was then increased to a target of 50% of the baseline CO (High Shunt).

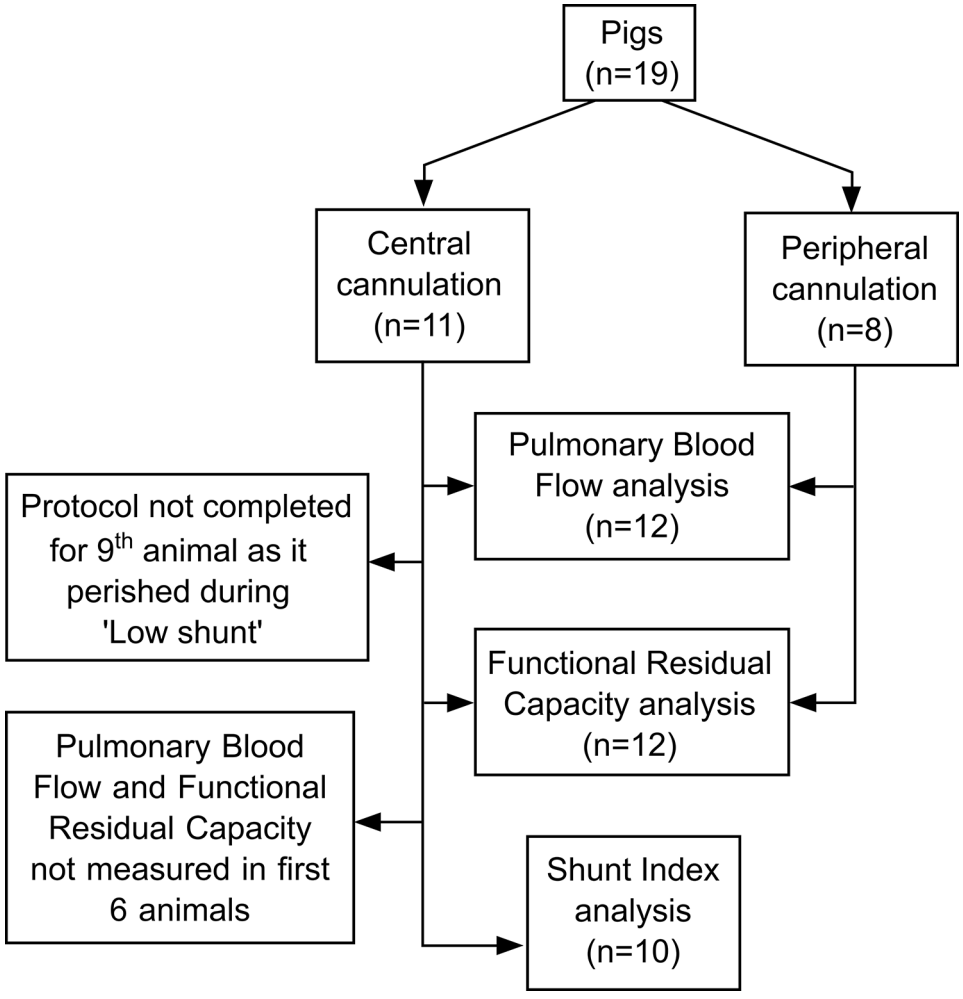

Fig. 1 Experimental design. A flow diagram of the parameters analyzed, n = number of animals in which measurements were analyzed

Statistical analysis

Bland-Altman representation was used to describe the agreement between PBF values obtained by the two methods [11]. Precision was defined as the standard deviation (SD) of the differences between the VQm PHM and reference (TDCO – Shunt). Bias was defined as the mean value of the differences. Limits of agreement were defined as bias ± 2 SD. The percentage of error was calculated as 2*SD/average CO [12]. A concordance analysis was conducted to assess the direction of change between the VQm PHM PBF measurement and the reference measure. An exclusion zone of 10% of the mean (8.1 L/min) was chosen [13]. Wilcoxon's signed rank test was used to compare paired shunt fraction values and Q_{si} values at low and high shunt flow, and to compare FRC

Table 1 VQm Pulmonary Health Monitor™ and reference measurements during clinical interventions*

Intervention	Pulmonary blood flow, L/min		Functional residual capacity, L	Shunt	
	VQm PHM™	Reference	VQm PHM™	VQm PHM™, Shunt Index (breaths)	Reference, Berggren Shunt (%)
Baseline	6.7 ± 1.1	6.6 ± 1.0	1.7 ± 0.4	49 ± 5	8.0 ± 2.4
High cardiac output	9.1 ± 2.6†	9.7 ± 2.6†	-	-	-
High PEEP	-	-	2.0 ± 0.6†	-	-
Low shunt	-	-	-	40 ± 4†	20.2 ± 2.3†
High shunt	-	-	-	27 ± 5†	44.0 ± 5.5†

*Data are presented as mean ± SD; †Data with a *p* value of < 0.05 was considered statistically significant; PEEP, positive end expiratory pressure

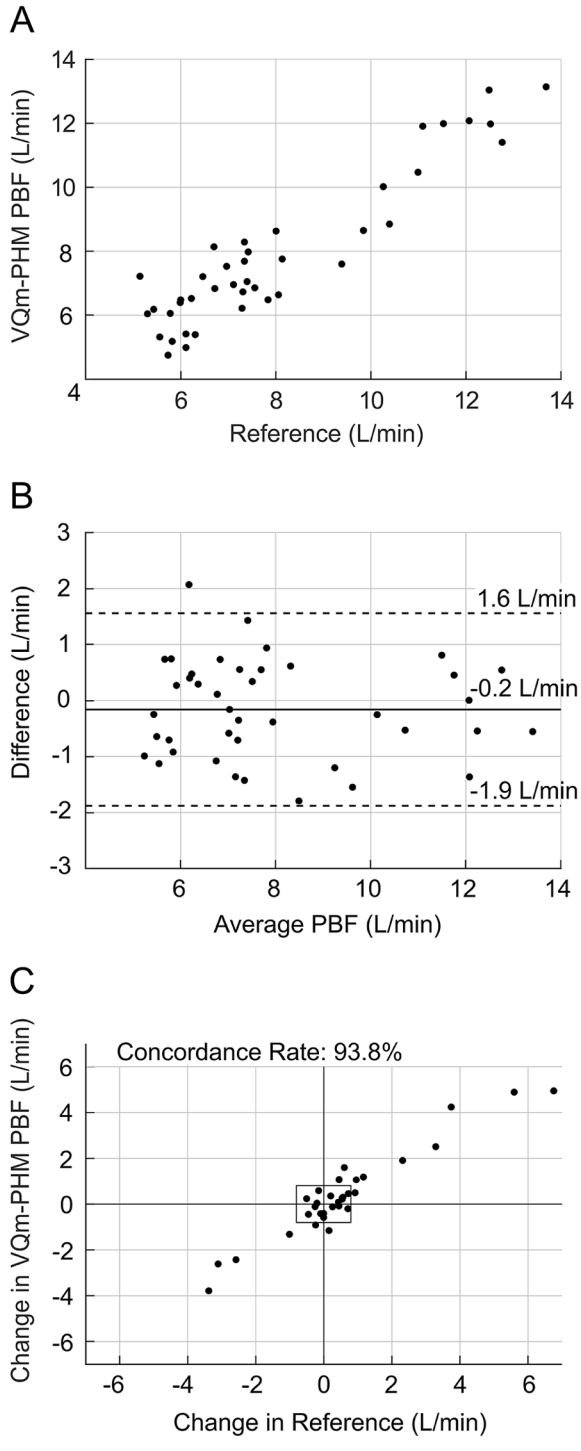

Fig. 2 Pulmonary Blood Flow. **A**) Paired Pulmonary Blood Flow (PBF) measures obtained from the VQm Pulmonary Health Monitor (PHM)™ and reference measure (Thermodilution cardiac output – Berggren shunt) during baseline and increased cardiac output, **B**) Bland-Altman representation of agreement between reference and values obtained using the VQm PHM™, **C**) Concordance analysis of the direction of change between VQm PHM™ PBF measurements and reference PBF (**C**)

values at baseline and high PEEP. A value of $p<0.05$ was considered to be significant.

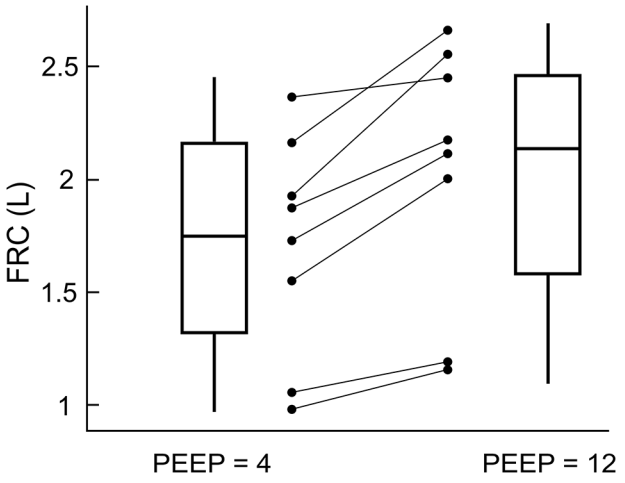

Fig. 3 Functional Residual Capacity. Functional Residual Capacity (FRC) values obtained from the VQm Pulmonary Health Monitor™ during baseline and increased positive end-expiratory pressure (PEEP). The error bars encompass the 95% confidence interval

Results

A total of 19 male swine weighing 80.3±5.1 kg were studied in Vienna (n=11) and in Paris (n=8) (Fig. 1). Measurements (mean±SD) obtained during clinical interventions are presented in Table 1.

Pulmonary blood flow

PBF analysis was completed in 12 animals (4 from MUV, 8 from HEGP) as shown in Fig. 1. The PBF data consisted of 42 paired measurements (Fig. 2A). Bland-Altman analysis indicated a standard deviation of the difference between VQm PHM™ and TDCO of 0.9 L/min with a mean difference of -0.2 L/min (Fig. 2B). The 95% limits of agreement were 1.5 and −1.9 L/min. The percentage error between the two methods was 21.0%. A concordance analysis was conducted using sequential values as available in each animal and a concordance rate of 94.1% was obtained using a 10% exclusion zone (Fig. 2C).

Functional residual capacity

FRC analysis was completed in the same 12 animals used for PBF analysis. 17 measurements were available at baseline (PEEP=4 cm H_2O) and 24 measurements were available at high PEEP (12 cm H_2 O). The mean FRC during baseline and high PEEP were 1.7 $\pm$ 0.4 L and 2.0 $\pm$ 0.6 L, respectively, $p = 0.0078$ (Table 1). Figure 3 shows that the FRC measurement trended with clinical intervention as expected when measured by the VQm PHM™.

Shunt index

Measurement of shunt fraction and shunt index (Q_{si}) was completed in 10 animals (all male, average weight

79.8 ± 5.8 kg). (Fig. 4A). The mean shunt fraction for these 10 paired measurements during low and high shunt flow was 0.20 ± 0.02 and 0.44 ± 0.05, respectively, $p = 0.002$. The mean Q_{si} for these 10 paired measurements during low and high shunt flow was 40 ± 4 and 27 ± 5, respectively, $p = 0.002$.

Discussion

Measurements of PBF, FRC and shunt fraction (Q_{si}) obtained from the PHM™ trended as expected following each intervention. PBF obtained through the modified differential Fick equation and Q_{si} obtained through N_2O uptake and decay dynamics by the VQm PHM™ provide comparable results to reference measures. Parameters that provide insight into the individual ventilation-perfusion (V/Q) relationships of a patient can help clinicians understand underlying pathophysiological processes and guide patient management to optimize therapy and improve outcomes. PBF provides the clinician with a measurement of the amount of blood effectively interacting with air in the alveoli. Optimization of FRC, the volume of air that remains within the lungs after exhalation, may improve lung compliance, airway resistance, right ventricular afterload, and pulmonary gas exchange [14]. The measurement of FRC has been advocated as a valuable tool for optimizing respiratory settings during mechanical ventilation [15]. Q_{si}, a novel parameter derived by the PHM™, provides a measurement reflecting shunt fraction which can be calculated in critically ill patients to monitor the effectiveness of pulmonary oxygenation [16]. Currently there are no bedside devices that non-invasively measure all three of these parameters. In the present study, we non-invasively measured PBF, FRC and Q_{si}, in pigs using the VQm PHM™. Measurements were compared to reference standards. The VQm PHM™ provided non-invasive, semi-continuous estimations of PBF, FRC and Shunt fraction.

Pulmonary blood flow

The results from this animal study show good agreement and trending ability between the VQm PHM™ and TDCO (Fig. 2B/D). According to Critchley et al. [13], a 94.1% concordance rate between the VQm PHM™ and TDCO is consistent with an acceptable trending ability. The standard deviation of the differences in the two techniques (± 0.85 L/min) is comparable to other non-invasive CO technologies such as Bioimpedance or Doppler ultrasound [12]. Critchley and Critchley [12] have reported limits of agreement in studies evaluating Bioimpedance to be ± 37% and Doppler ultrasound to be ± 65%. The 21% percent error between VQm PHM™ and TDCO is within the clinically acceptable limit (± 30%) proposed to consider interchangeability between the reference and the new technique [12].

Functional residual capacity

Increased PEEP resulted in expected increase of the FRC measurement by the VQm PHM™. A reference FRC measurement was not performed during these studies. Additional studies are required to compare PHM™ FRC to FRC measurements determined using a N_2 washout method.

Shunt index

For this evaluation, a pump-driven extracorporeal circuit was used to create a titratable, quantifiable, controlled right to left atrial shunt. The shunt fraction was characterised by the shunt index, Q_{si}. The reference measure, Berggren shunt, estimates the shunt fraction using mixed venous and arterial blood analysis.

When compared to Berggren shunt, Q_{si} (the number of breaths required to reach 2.5% of the end-tidal N_2O concentration after an N_2O bolus) decreased as expected during high shunt values. Although Q_{si} does not provide the actual measurement of shunt, it is inversely related to

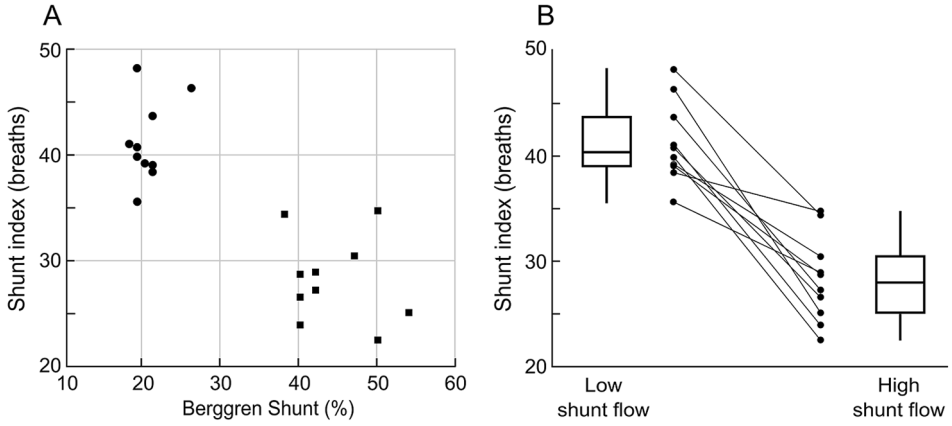

Fig. 4 Shunt Index. **A**) Paired shunt measures obtained from the VQm Pulmonary Health Monitor (PHM)™ and reference measure (Berggren Shunt). **B**) Shunt Index (Q_{si}) measurements obtained from the VQm PHM™ during low shunt and high shunt. The error bars encompass the 95% confidence interval

shunt fraction. This index could provide clinically useful information since an increase in shunt fraction will result in reduced arterial oxygen content.

This study has limitations. The bolus TDCO technique is considered as a gold standard, but it is known to be limited in both precision and accuracy [2]. The limited reproducibility of the TDCO measurements precludes tight agreements with measurements obtained using novel techniques measuring CO. We used triplicate measurements with 10 ml iced saline solution to minimize this variation and enhance the accuracy of CO measurements [17]. Given the complex experimental preparation and experimental design, we were not able to achieve all the planned measurements in each animal. PBF and FRC measurements in 6 animals from the MUV were not obtained. Q_{si} was only measured in animals that were centrally cannulated because the peripheral cannulation precluded collection of the accurate mixed venous and arterial blood samples required for the Berggren shunt calculations. Additionally, these experiments were designed as "proof of concept" rather than a definitive validation. A porcine animal model was developed because their anatomy and physiology are most similar to those of humans. We evaluated three specific interventions to assess the performance of this novel monitoring system. Further confirmatory studies need to be performed in mechanically ventilated patients to evaluate performance in more complex clinical scenarios. Additional studies will also be required to assess cost-benefit comparisons to currently available monitors as well as the safety and potential benefits of the VQM PHM™ on patient outcomes. Lastly, there was no gold standard employed for the FRC measurements.

Conclusions

We describe the performance of a novel pulmonary assessment monitor, the VQm PHM™ designed to measure PBF, FRC and shunt fraction. In this experimental setting, we found good agreement between the VQm PHM™ and reference values of PBF. The changes in Q_{si} and FRC measurements trended as expected following the various maneuvers applied to the model. Further confirmatory studies need to be performed in mechanically ventilated patients.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s41231-023-00146-8.

Supplementary Material 1

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Authors' contributions

Maximilian Edlinger-Stanger: Conceptualization, Data curation, Investigation, Methodology, Formal Analysis, Project administration, Resources, Writing – review & editing. Caroline Fritz: Conceptualization, Investigation, Data Curation, Methodology, Project Administration, Resources, Writing – review & editing. Hanna C. McGregor: Conceptualization, Data Curation, Investigation, Methodology, Writing – review & editing. Spencer L. Bustin: Data Curation, Investigation, Formal Analysis, Writing – review & editing. Nathan Ayoubi: Conceptualization, Project Administration, Supervision, Writing – review & editing. Harpreet K. Bath: Writing – original draft, Writing – review & editing. Johannes Müller: Investigation, Writing – review & editing. Sebastian Kühnl-Brady: Investigation, Data Curation, Writing – review & editing. Thomas Schweiger: Investigation, Writing – review & editing. Julia Jedamzik: Investigation, Writing – review & editing. Marita Windpassinger: Investigation, Writing – review & editing. Michael Hiesmayr: Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Resources. Bernard P. Cholley: Conceptualization, Funding acquisition, Investigation, Methodology, Project Administration, Resources, Formal Analysis, Supervision, Writing – review & editing. Neal W. Fleming: Conceptualization, Investigation, Methodology, Project Administration, Supervision, Formal Analysis, Writing – review & editing. All authors read and approved the final manuscript.

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Data availability

The datasets during and/or analysed during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This was an animal experimental study performed at the Medical University of Vienna (MUV), Austria and Hôpital Européen Georges-Pompidou (HEGP) of Paris, France. All experiments done at the Medical University of Vienna (MUV) described in this article were reviewed and approved by the Austrian Federal Ministry of Education, Science and Research (BMBWF-66.009/0177-V/3b/2019) and experiments were carried out according to national animal research regulations (Directive 2010/63/EU, Tierversuchsverordnung 2012). All experiments done at HEGP described in this article were reviewed and approved by the Paris University Ethics Committee for Animal Experimentation (APAFIS #23056). Care and handling of the animals were in accordance with the European Community Standards on the Care and Use of Laboratory Animals.

Consent for publication

Not applicable.

Competing interests

Hanna C. McGregor, Spencer L. Bustin, Nathan Ayoubi, and Harpreet K. Bath were employed at Rostrum Medical Innovations at the time of conduction of this study.

Author details

[1]Department of Anaesthesia, Intensive Care Medicine and Pain Medicine, Division of Cardiac Thoracic Vascular Anaesthesia and Intensive Care Medicine, Medical University of Vienna, Vienna, Austria
[2]Department of Anesthesia and Intensive Care Medicine, Hôpital Européen Georges-Pompidou, AP-HP, Paris F-75015, France
[3]Department of Clinical Research, Rostrum Medical Innovations Inc, Vancouver, Canada
[4]Department of Anaesthesia, Intensive Care Medicine and Pain Medicine, Medical University of Vienna, Vienna, Austria

[5]Department of Surgery, Medical University of Vienna, Vienna, Austria
[6]Université Paris Cité, INSERM S_1140, Innovations thérapeutiques en hémostase, Paris F-75006, France
[7]Department of Anesthesiology and Pain Medicine, UC Davis School of Medicine, Sacramento, USA

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