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BASIC SCIENCE ARTICLE

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Effort and work-of-breathing parameters strongly correlate with increased resistance in an animal model

Rutger C. Flink[1]✉, Christopher J. L. Newth[2,3], Justin C. Hotz[2,3], Martin C. J. Kneyber[4], Patrick A. Ross[2], Frans H. de Jongh[1], Anton. H. van Kaam[1] and Robinder G. Khemani[2,3]

BACKGROUND: Effort of Breathing (EOB) calculations may be a reliable alternative to Work of Breathing (WOB) calculations in which Respiratory Inductance Plethysmography (RIP) replaces spirometry. We sought to compare EOB and WOB measurements in a nonhuman primate model of increasing extrathoracic inspiratory resistance simulating upper airway obstruction (UAO).
METHODS: RIP, spirometry, and esophageal manometry were measured in spontaneously breathing, intubated Rhesus monkeys utilizing 11 calibrated resistors randomly applied for 2-min. EOB was calculated breath-by-breath as Pressure Rate Product (PRP) and Pressure Time Product (PTP). WOB was calculated from the Pressure-Volume curve based on spirometry (WOB_{SPIR}) or RIP flow (WOB_{RIP}).
RESULTS: WOB, PRP and PTP showed similar linear increases when exposed to higher levels of resistive loads. When comparing WOB_{SPIR} to WOB_{RIP}, a similar strong correlation was seen for both signals as resistance increased and there were no statistically significant differences.
CONCLUSION: EOB and WOB parameters utilizing esophageal manometry and RIP, independent of spirometry, showed a strong correlation as a function of increasing inspiratory resistance in nonhuman primates. This allows several potential monitoring possibilities for non-invasively ventilated patients or situations where spirometry is not available.

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IMPACT:

- EOB and WOB parameters showed a strong correlation as a function of increasing inspiratory resistance in nonhuman primates.
- There was a strong correlation between spirometry-based WOB versus RIP-based WOB.
- To date, it has remained untested as to whether EOB is a reliable alternative for WOB and if RIP can replace spirometry in these measurements.
- Our results enable additional potential monitoring possibilities for non-invasively ventilated patients or situations where spirometry is not available.
- Where spirometry is not available, there is no need to apply a facemask post extubation to a spontaneously breathing, non-intubated infant to make objective EOB measurements.

INTRODUCTION

Lung disease in the neonatal and pediatric population is often accompanied by an increased airway resistance and/or reduced lung compliance. As a result, the work of breathing (WOB) or effort of breathing (EOB) of the patient will increase and this may lead to respiratory failure. Objective evaluation of WOB or EOB at the bedside is important to titrate respiratory support in both ventilated and nonventilated patients.

Calculating WOB requires information on the change in pleural pressure (most often measured by an esophageal balloon) and the accompanying displacement of air (i.e., volume, most often measured by spirometry). WOB measurements have been well studied and have had the assumed advantage of accuracy over esophageal manometry in that they capture pressure, flow and volume values rather than pressure alone with manometry.

However, calculating WOB also has practical disadvantages. It requires a measure of flow to calculate volume, which limits application in patients with large endotracheal tube leaks and those treated with non-invasive support. Secondly, WOB increases only when both volume and pressure change. Therefore, it may miss patient effort in isovolumetric situations, such as intrinsic PEEP, where initial changes in transpulmonary pressure do not result in an influx of volume into the lung, or when the change in

[1]Department of Neonatology, Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands. [2]Department of Anesthesiology & Critical Care Medicine, Children's Hospital Los Angeles, Los Angeles, CA, USA. [3]Keck School of Medicine, University of Southern California, Los Angeles, CA, USA. [4]Department of Paediatrics, Division of Paediatric Critical Care Medicine, Beatrix Children's Hospital Groningen, University Medical Center Groningen, The University of Groningen, Groningen, The Netherlands. ✉email: r.flink@medelink.nl

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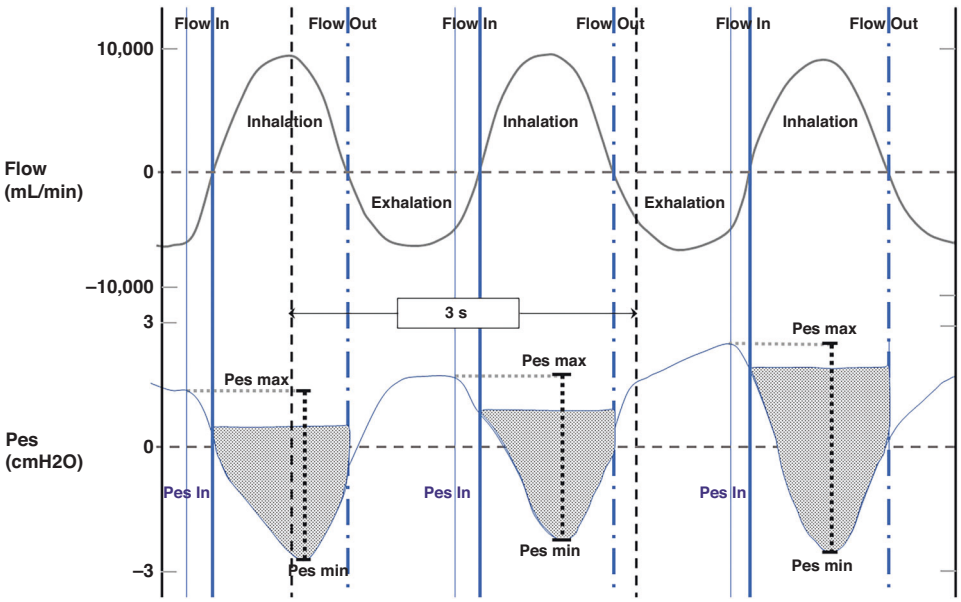

Fig. 1 Calculation of Pressure Rate Product (PRP) and Pressure Time Product (PTP). This figure shows the respiratory flow waveform in the upper panel in mL/min and the lower panel demonstrates the esophageal pressures in cmH_2O for the same breaths. The light solid vertical line is the esophageal inspiratory onset (Pes in); the heavy solid vertical line is the spirometry inspiratory onset (Flow in) and the interrupted vertical heavy line is the spirometry expiratory onset (Flow out). Inhalation depicts the changing inspiratory flow rate between the Flow In and Flow Out lines. Exhalation is depicted between Flow Out and Flow In lines. Delta Pressure [Pes(max) − Pes(min)]. Pes(max) is the maximum esophageal pressure determined from the esophageal inspiratory onset of the breath and Pes(min) is the lowest value between the breath's esophageal inspiratory onset and that of the next breath. The distance between the two interrupted heavy lines depicts a Time of 3 s. PRP is calculated by multiplying the respiratory rate of a breath by the delta pressure for that breath; PTP is calculated by the area under the curve (gray dotted area) between the inspiratory and expiratory onset of spirometry, multiplied by the respiratory rate. The respiratory rate is calculated on a breath-by-breath basis and defined as 60 over the time (in seconds) between two consecutive inspiratory esophageal onsets.

pressure is disproportionately higher than changes in volume (such as severe upper airway obstruction (UAO)).[1]

EOB measurements such as Pressure Rate Product (PRP) or Pressure Time Product (PTP) can theoretically be calculated from esophageal pressure only, although PTP still requires a flow measure to capture the inspiratory phase. They may be valid alternatives to WOB in many clinical scenarios and have been used in numerous research studies across the pediatric age spectrum,[2–4] with applications for upper and lower obstructed airways as well as pulmonary parenchymal disease.[5,6] An alternative, if the flow and volume components of work are deemed crucial, can be to substitute calibrated Respiratory Inductance Plethysmography (RIP) for spirometry, although this has not been previously validated. RIP uses non-invasive bands around the ribcage and abdomen, which provide immediate and non-invasive information on airflow and volume[7] and can be applied for patients who are not invasively ventilated or who have large endotracheal tube leaks.

Esophageal manometry has been used in pediatric research for many years. Measuring pleural or transpulmonary pressure in the assessment of grunting in hyaline membrane disease and more general pathologies in neonates was reported over 5 decades ago.[8–10] Esophageal pressure measurements, thus far, are infrequently incorporated into ventilators, implying that flow and esophageal pressure are measured by separate systems which then requires accurate synchronization of both signals in order to calculate WOB. The calculation of WOB is dependent on the inspiratory and expiratory onsets of spirometry and is therefore influenced in situations where there is asynchrony of thoracic (intercostal muscles) and abdominal (diaphragm) contributions.

To date, it has remained untested as to whether EOB is a reliable alternative for WOB and if RIP can replace spirometry in these measurements. Therefore, we sought to compare EOB and WOB measurements, based on calculations with and without spirometry, in a spontaneously breathing (intubated but not mechanically assisted), nonhuman primate model of increasing extrathoracic inspiratory resistance. Our hypothesis was that EOB and WOB parameters based on calculations with or without spirometry, would show similar changes in response to increased resistance.

MATERIALS AND METHODS

We performed an interventional study in adult Rhesus monkeys (*Macaca mulatta*) of similar weight and pulmonary development to human infants, performed at the Novartis Animal Care Facility in Basel, Switzerland. We used a total of 10 Rhesus monkeys with a mean age of 9.0 ± 4.1 years and a mean weight of 8.7 ± 2.5 kg. All monkeys tolerated the experiment, with no complications.

The study was approved by the Cantonal Animal Protection Committee and the Institutional Animal Care and Use Committee (IACUC) at Children's Hospital Los Angeles.

Anesthesia protocol

The monkeys were initially sedated with intramuscular ketamine 100 mg. We placed a 20 gauge peripheral intravenous catheter in the saphenous vein, and kept the animals anesthetized with a continuous propofol infusion at 10 mg/kg/h initially. The infusion rate was then calibrated to achieve spontaneous breathing with minimal movement or response to noxious stimuli. All monkeys were endotracheally intubated with a 4.5 mm ID cuffed endotracheal tube (Rüsch, Teleflex Medical, Bad Liebenzell, Germany), with the cuff inflated to occlude any audible air leak during spontaneous respiration. We placed a calibrated pneumotachometer (Viasys Variflex 51000-40094) at the end of the endotracheal tube to measure flow and volume. After stabilization following induction of anesthesia, baseline recordings were made of heart rate, respiratory rate, SpO_2, and temperature. Subsequently, each monkey also received continuous monitoring of electrocardiogram, pulse oximetry, end-tidal CO_2, and temperature. We monitored blood pressure non-invasively every 5 min.

Hardware and software

An esophageal balloon catheter (Avea SmartCath 8Fr, CareFusion, Houten, The Netherlands) was placed into the lower third of the esophagus, RIP bands (Viasys Healthcare, Hoechberg, Germany) around chest and abdomen at the level of the nipples and umbilicus, respectively, and a calibrated pneumotachometer (Variflex 51000-40094, Viasys, CA) was attached to the endotracheal tube.

We calculated the depth of esophageal balloon catheter tip placement from the oropharynx through directly measuring the distance from the mouth to the ear and to the sternal notch. The catheter position was confirmed through a series of complete and partial endotracheal tube occlusions, as previously described.[10] Signals were acquired at a sample rate of 200 Hz by the Bicore II (CareFusion, Houten, The Netherlands) and post-processed using a custom-made module in Polybench (Applied Biosignals GmbH, Weener, Germany).

The RIP signal was calibrated based on the isovolume maneuver, as previously reported.[7] A low pass filter of 5 Hz was applied to all signals.

Inspiratory obstruction was achieved by placing eleven fixed calibrated resistors (range: 5 to 1000 cm H_2O/L/s, Hans Rudolph, Kansas City, MO) at the inspiratory limb of a Y shaped (nonrebreathing) valve (Hans Rudolph, Kansas City, MO) attached to the endotracheal tube. We have previously demonstrated that the endotracheal tube does not add any further resistance at these flows.[11] The order of resistors was random for each monkey, and each resistor was in place for 2 min. Monkeys were given 3 min of recovery with unobstructed breathing between resistors, with a longer time if vital signs had not returned to baseline. Recovery measurements were made 10 min following the removal of all inspiratory loading under room air conditions. Each monkey acted as its own control and all returned to their initial baseline of vital signs and PRP at the conclusion of the experiment.

Parameters

EOB was calculated as Pressure Rate Product (Delta Pes * Respiratory Rate) and Pressure Time Product (area under the esophageal pressure-time curve during inspiration * Respiratory Rate) (Fig. 1). PRP did not require the exact moment of expiration, as capturing the minimum esophageal pressure during a breath was sufficient to acquire delta pressure. However, PTP and WOB required integration during inspiration, terminated at the moment of expiration. For flow, the transition was defined by the points where the signal crossed zero and became either positive for inspiration or negative for expiration.

WOB was calculated from the Pressure-Volume curve (Campbell diagram, light gray area of Supplementary Fig. 1), using inspiratory and expiratory onsets based on spirometry or RIP flow. WOB is the area under the P-V curve during positive flow (i.e., inspiration on spirometry or RIP), normalized to V_T, resulting in an output expressed as Joules per Liter (J/L).[12] Since these monkeys were not receiving positive pressure ventilation, all WOB was related to the animal alone.

Each parameter was calculated instantaneously on a breath-by-breath basis during a 2-min exposure to the resistors. The individual values were ranked and the 90th percentile was used for the primary analysis. The response to introduced resistors differed for each monkey; effort could ramp up and stabilize very quickly (exhaustion), or effort could continue to increase until the end of the measurement (stamina). Therefore, the 90th percentile was chosen as more representative of the maximum achieved effort or work. Additionally, false (inspiratory) onsets, resulting in outliers, were filtered out using this method.

Statistics

Data is expressed as the median with IQR. Statistical analyses were performed using Graphpad Prism version 5.01 (Graphpad Software Inc, La Jolla, CA). PRP and PTP values were superimposed on the WOB_{SPIR} values, by applying the best-fit slope values of a linear regression of PRP and PTP versus WOB_{SPIR} to the y-axis value. A linear regression analysis was performed and R^2 values were calculated. A p value less than 0.05 was considered statistically significant.

RESULTS

From a total of ten Rhesus monkeys, one was excluded from analysis due to severe agitation and clinical exhaustion, making the signal analysis of the data not possible. WOB, PRP and PTP showed a similar increasing trend when exposed to higher levels of resistive loads. PRP deviated slightly from the WOB_{SPIR} and PTP when resistance exceeded 300 cmH_2O/L/s (Fig. 2).

When comparing Work of Breathing calculated by spirometry (WOB_{SPIR}) to Respiratory Inductance Plethysmography (WOB_{RIP}), a similar upgoing incline was seen for both signals as resistance increased. When resistance exceeded 300 cmH_2O/L/s, WOB based on RIP increased to a lesser extent than WOB based on spirometry, although these differences did not reach statistical significance overall and per level of resistance (Fig. 3).

The linear regression analysis over the whole range (0 to 1000 cmH_2O/L/s) identified that WOB_{SPIR} was almost perfectly correlated with PTP ($R^2 = 0.9805$), and very highly predicted by PRP ($R^2 = 0.9094$) and WOB_{RIP} (0.9075) (Table 1). The linear regression analysis from 0 to 300 cmH_2O/L/s identified that WOB_{SPIR} remained almost perfectly correlated from PTP ($R^2 = 0.9753$), and very highly predicted by WOB_{RIP} (0. 8921), and by PRP ($R^2 = 0.8835$).

DISCUSSION

Our animal model of extrathoracic UAO showed a strong correlation between EOB and WOB parameters as a function of increasing inspiratory resistance. Additionally, there was a strong correlation between spirometry-based WOB versus Respiratory Inductance Plethysmography-based WOB, and they resulted in nearly identical values at low to moderate levels of WOB.

All parameters showed an upgoing trend with increasing resistance (see Figs. 2, 3). In addition, the results showed high correlations between WOB_{SPIR} and all measured parameters, with slightly higher R^2 values for PTP (see Fig. 4a, b, c). This could be expected as the onset of inspiration and expiration for PTP was based on spirometry, rendering the time intervals utilized for the integrations equal.

Up to a resistance of 300 cmH_2O/L/s, both the spirometry-based and non-spirometry-based parameters showed a high degree of similarity. However, increasing the resistance further resulted in an increasing dispersion of these parameters. This finding might be explained by the increasing physiological phase angles (phase lags) between esophageal pressure, RIP and spirometry due to the

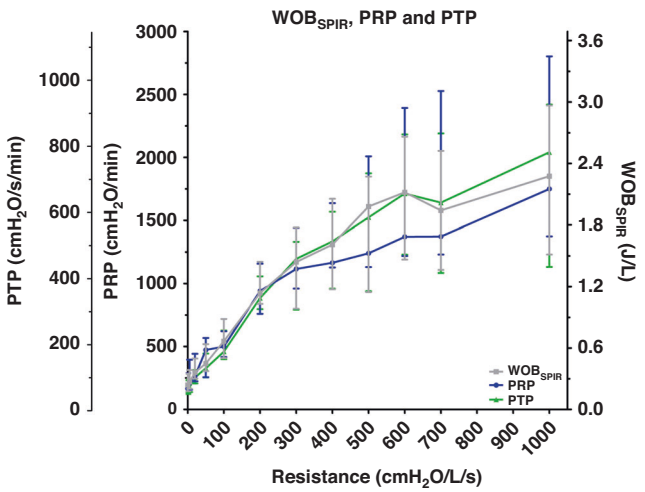

Fig. 2 Superimposed Work-of-breathing based on spirometry (WOB_{SPIR}), Pressure Rate Product (PRP) and Pressure Time Product (PTP) against a range of resistors (0–1000 cmH_2O/L/s). Results are depicted as median ± IQR. PRP and PTP were superimposed based on applying a ratio acquired by the calculated slope values of the best-fit regression line versus WOB_{SPIR}. Note the similar upgoing trend in the lower resistance range (0–300 cm H_2O/L/s), with a flattening curve for PRP in the higher resistance range (400–1000 cm H_2O/L/s).

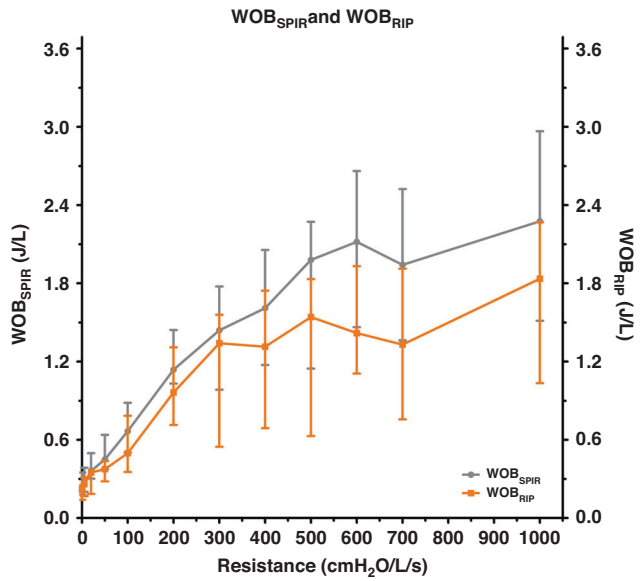

Fig. 3 Superimposed Work-of-breathing based on spirometry (WOB_{SPIR}) and Work of breathing based on Respiratory Inductance Plethysmography (WOBRIP) against a range of resistors (0–1000 cm H_2O/L/s). Results are depicted as median ± IQR. WOB_{RIP} was superimposed based on applying a ratio acquired by the calculated slope value of the best-fit regression line versus WOB_{SPIR}. Note the similar upgoing trend in the lower resistance range (0–300 cm H_2O/L/s), with a flattening curve for PRP in the higher resistance range (400– 1000 cm H_2O/L/s).

Table 1. Correlation coefficients (R^2) of WOB_{SPIR} versus PTP, PRP and WOB_{RIP} for different resistance ranges.

	Resistance (cmH_2O/L/s)		
WOB_{SPIR} versus	**0–1000**	**0–300**	**400–1000**
PTP	0.9805	0.9753	0.9615
PRP	0.9094	0.8835	0.7950
WOB_{RIP}	0.9075	0.8921	0.8850

high resistance. As resistance increases, the time between diaphragmatic contraction (abdominal component on RIP), negative intrathoracic pressure generation (esophageal pressure), and flow may increase relative to unobstructed breathing.

At first glance this finding suggests that in contrast to the trend of WOB changes, the absolute values may not be comparable over the full range of the resistance applied. However, airway resistance exceeding 200 cmH_2O/L/s is very uncommon in pediatric clinical practice,[13] and differentiating within the extremes of excessively high WOB may not be clinically relevant. Therefore, our results indicate that WOB measured with spirometry or RIP provides similar and accurate values in the clinical range of resistance changes.

Although there was a good correlation between WOB_{SPIR} and WOB_{RIP}, we would have expected a slope value of the linear regression close to one. There are several explanations as to why increased resistance resulted in lower WOB_{RIP} values compared to WOB_{SPIR}. When exposed to higher levels of resistance, both patients and monkeys become more agitated, which is reflected in the quality of recorded signals. Movements have limited effects on esophageal pressure signal quality, as the large negative deflections during high effort breaths mask agitation induced (movement) artifacts. Spirometry generally remains trustworthy, with limited to no effects of agitation on the signal, with the exception of events such as coughing. RIP, however, with the elastic bands placed around the chest wall and abdomen, is prone to movement artifacts and any agitation of the subject. This is also reflected by the reported increase of phase angles between the chest wall and abdominal compartment as breathing effort increased.[3,14] Both the impaired signal quality and increased breathing asynchrony at higher levels of resistance may compromise the agreement between WOB_{RIP} and other EOB and WOB parameters.

This study has several limitations. First, this was a model of extrathoracic upper airway resistance, therefore caution is needed when extrapolating these results to lower airway diseases. However, lower airway disease can be viewed simply as many smaller resistors in series which should have a similar impact on the effort or WOB as one major resistor in the upper airways, although this resistance is intrathoracic rather than extrathoracic. Second, in subglottic edema from both viral croup and post-extubation edema, there is an element of expiratory obstruction (albeit much less than the inspiratory obstruction,[1]) whereas our model had no expiratory obstruction.

Third, this model mainly addressed the resistive work, while tissue elastic work, which is increased in cases such as ARDS, might be underrepresented. Therefore, it is unknown if these parameters have the same response to increased elastic work as to increased resistive work.

Fourth, the WOB and PTP calculations did not include the chest wall compliance components. Differentiating lung and chest wall components for WOB calculations requires that the subject allows passive inflation from positive pressure. These monkeys were not sedated sufficiently to allow passive inflation. Accordingly, we were not able to compartmentalize the chest wall from the resistive and elastic components of WOB and PTP. We chose this animal model because Rhesus monkeys have high chest wall compliance in relation to lung compliance, similar to neonatal and pediatric patients. For this reason, we do not anticipate that the WOB and PTP relationships we have described are significantly impacted by not separating chest wall components, as the contribution of the chest wall component to WOB and PTP is expected to be very low.[15,16]

Finally, as noted above, in clinical situations there will be some expiratory resistance, which was not included in our animal model.[17] Under these circumstances the expiratory muscles may increase the esophageal pressure signal at end-expiration and make computation of delta esophageal pressure slightly more complicated.

Despite these limitations, we believe this study is clinically relevant. If EOB or WOB can be utilized for the assessment of flow resistive work without the need for spirometry, this allows several additional monitoring tools for critically ill patients, especially during non-invasive ventilation. If inclusion of volume or flow is desired, but spirometry is not available, it could be substituted by RIP.

Thus, we believe these respiratory parameters have the potential to guide bedside adjustments of ventilator settings at an individual level, providing the clinician with better monitoring tools to reduce over- and under- treatment with ventilatory support and to wean the patient from the ventilator and following extubation.

CONCLUSION

EOB and WOB parameters, independent of spirometry, showed a strong correlation as a function of increasing inspiratory resistance in nonhuman primates. This allows several potential monitoring possibilities for non-invasively ventilated patients or situations where spirometry is not available. By using esophageal manometry, either with or without RIP, there is no need to apply a facemask post extubation or in a spontaneously breathing, non-intubated infant or young child in order to obtain a volume signal

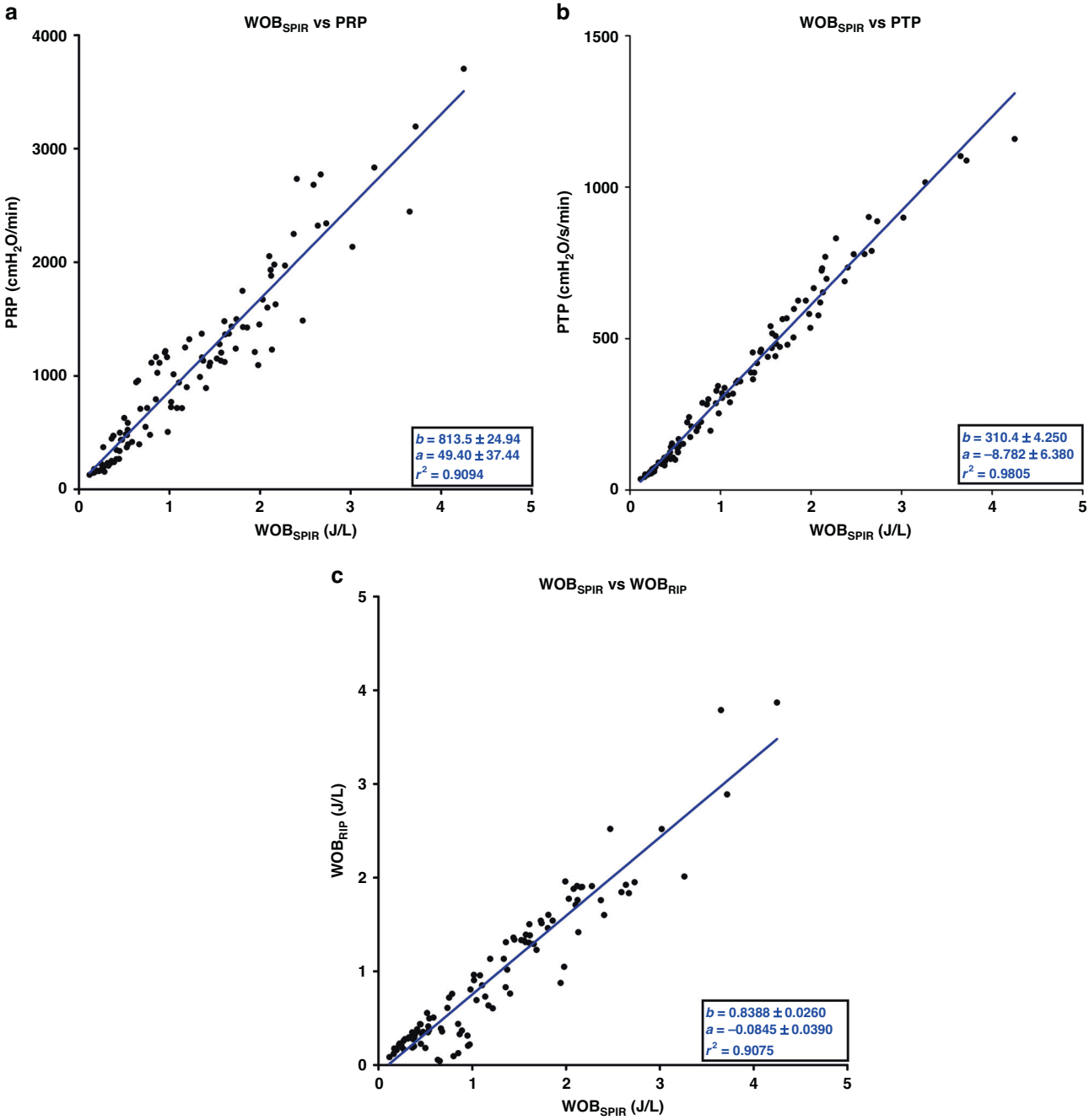

Fig. 4 Scatter plots of Work of Breathing based on Spirometry (WOB_{SPIR}) versus Pressure Rate Product (PRP), Pressure Time Product (PRP) and Work of Breathing based on RIP (WOB_{RIP}) of all data. a Scatter plot of Work of Breathing based on Spirometry (WOB_{SPIR}) versus Pressure Rate Product (PRP) of all data. The linear regression line is superimposed on the graph. All data points ($n = 108$) from 9 monkeys at a resistor range of 0–1000 cm H_2O/L/s are included within this graph. Some scattering is present, which might have been caused by the variability within the esophageal manometry signal alone, versus WOB_{SPIR} which is dependent and triggered on spirometry. **b** Scatter plot of Work of Breathing based on Spirometry (WOB_{SPIR}) versus Pressure Time Product (PTP) of all data. The linear regression line is superimposed on the graph. All data points ($n = 108$) from 9 monkeys at a resistor range of 0–1000 cm H_2O/L/s are included within this graph. A good fit is shown over the complete range of resistors, which is to be expected as both parameters are dependent on esophagral pressure and spirometry. **c** Scatter plot of Work of Breathing based on Spirometry (WOB_{SPIR}) versus Work of Breathing based on Respiratory Inductance Plethysmography (WOB_{RIP}) of all data. The linear regression line is superimposed on the graph. All data points ($n = 108$) from 9 monkeys at a resistor range of 0–1000 cm H_2O/L/s are included within this graph. Note that WOB_{RIP} underestimates WOB_{SPIR} at some data points in the lower range (<1.0 J/L). This could have been an effect of the quality of the measurements obtained by the RIP bands (e.g., placement or interference).

which may require sedation and change the flow dynamics.[1,6] Additionally, with only one incoming signal required, calculations of PRP are not compromised by signal asynchronies recorded by different measurement tools.

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

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AUTHOR CONTRIBUTIONS

Conception and design: R.F., R.K., C.N. Analysis and interpretation: R.F., J.H., M.K., F.d.J., C.N., A.v.K., R.K. Drafting the paper for important intellectual content: R.F., A.v.K., F.d.J., M.K., C.N., R.K.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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Correspondence and requests for materials should be addressed to Rutger C. Flink.

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