Validation of a novel respiratory rate monitor based on exhaled humidity

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Editor's key points

- Current methods of monitoring postoperative respiratory rate (RR) are limited in their sensitivity and specificity for detecting respiratory depression.
- A novel RR monitor was evaluated using both bench and bedside tests with comparisons to capnometry, visual counting, and ECG monitoring.
- The respiR8™ monitor was accurate in measuring RR in both simulated and clinical conditions.

Background. Postoperative monitoring of ventilation is largely restricted to the measurement of haemoglobin-oxygen saturation ($\text{SpO}_2$) and respiratory rate (RR) derived from the ECG. $\text{SpO}_2$ measurement is inadequate when used with supplemental oxygen and ECG-derived RR is subject to artifacts. A new monitor measures RR by quantifying the humidity of exhaled air (respiR8™).

Methods. The accuracy of the system was tested using a breathing simulator. In healthy volunteers, the respiR8™ monitor was compared with two other methods of measuring RR: capnometry, visual counting, and ECG monitoring. The ability of the monitor to track changes in RR resulting from the infusion of 2.5 $\mu$g kg$^{-1}$ fentanyl was assessed and compared with RR measured from a validated flow measurement system. The RR in 50 postoperative patients measured with the respiR8™ was compared with that derived from the ECG. RR values were compared by population-based Bland–Altman analyses.

Results. The respiR8™ monitor was accurate in the range required in clinical practice. There was a close agreement between RR from respiR8™, capnometry, and manual counting of respiratory movements without bias (limits of agreement $\pm$ 1 bpm). The respiR8™ monitor was well able to accurately track RR changes from fentanyl. In postoperative patients, RR from respiR8™ and ECG had a bias of 1.7 (5.7) bpm due to greater RR values observed from the ECG due to artifacts.

Conclusions. The respiR8™ gives an accurate measurement of RR and is useful in postoperative care.

Keywords: complications; monitoring; postoperative care; recovery room; respiratory depression; respiratory rate

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Both after operation and during a variety of diagnostic or therapeutic procedures, spontaneously breathing non-intubated patients receive potent opioids to produce analgesia or sedation.1 Continuous monitoring of respiratory function in these patients is mandatory but is often less than optimal and is restricted to the measurement of haemoglobin-oxygen saturation derived from pulse oximetry ($\text{SpO}_2$), measurement of respiratory rate (RR) from the ECG, or both.2 On the ward, respiration is monitored by nursing staff who count thoracic movements as an index of RR at regular but infrequent intervals (e.g. every 2–4 or even 6 h). $\text{SpO}_2$ is not a measure of ventilation but gives an index of gas exchange in the lungs.3 Consequently, $\text{SpO}_2$ measurement is an inadequate method to assess ventilation, especially when the patient receives supplementary inspired oxygen.3–5 RR measurement derived from the ECG is not accurate as it is sensitive to various artifacts, such as that occur during coughing, shivering, retching, etc. Furthermore, methods of RR measurement that are not based on the measurement of flow at the mouth (directly or indirectly) always carry the possibility that apnoea related to the obstruction of the upper airways are missed as thoracic respiratory movements persist.6 These obstructed movements are often more vigorous than the movements with open airways. There are various non-invasive respiratory monitors on the market.7 Surprisingly, there is a lack of accepted standards for these devices. For example, there is no agreed convention regarding averaging time (or breaths) or accuracy. Recently, a new monitor has been introduced that measures RR based on the humidity of the exhaled air.
(respiR8® monitor). A humidity sensor placed on a facemask measures water vapour of the exhaled air. The derived humidity signal is electronically transmitted to a monitor that calculates RR on a breath-to-breath basis using a 3-breath averaging algorithm. The current study was designed to validate the respiR8 monitor. We did so by performing four separate studies. First, we assessed the accuracy of the system by using a breathing simulator that produced dry inspired and humid expired air at a range of in/expiration flows and RR. Next, in healthy volunteers, we compared the respiR8 monitor with two other monitors of RR: a capnometer and manual counting of thoracic breathing movements. We then assessed the ability of the monitor to track changes in RR caused by infusion of the potent opioid fentanyl in healthy volunteers and compared these changes with RR measured from the validated pneumotachograph/ResReg system, which is part of the ‘dynamic end-tidal forcing’ system in use in our laboratory to perform cardiorespiratory studies.³¹ Finally, we measured RR in postoperative patients and compared the values with that derived from the ECG.

Methods

The respiR8® sensor and monitor

The respiR8 monitor is a novel RR monitor that uses exhaled humidity to monitor breathing frequency in postoperative patients and patients undergoing procedural sedation, analgesia, or both. The sensor, placed on a mask over the mouth and the nose, is made up of two electrodes on a polymer surface. The moisture of the exhaled air condenses over the sensor (provided that the ambient temperature is below body or exhaled air temperature). Owing to the moisture, an electrical signal over the electrodes is generated that corresponds with the amount of moisture. As the patient breathes in, the surface of the sensor is dried by a flow of ambient air passing over the surface and the signal returns to baseline. This analogue signal is converted to a digital signal (at a sample frequency of 60 Hz) at the cable connector and is then transmitted to a monitor. One algorithm in the monitor detects the peaks in the signal and converts this into RR; a second algorithm is applied to eliminate background noise. The number presented on the screen is the moving average of three breaths (Fig. 1). In our current studies, the lower and upper alarm limits of the monitor were set at 5 and 35 bpm and 5 and 25 bpm in volunteer and patient studies, respectively.

Bench tests

Initially, a series of experiments was performed to assess the accuracy of the respiR8 monitor over a range of air flow rates and inspiration:expiration (I:E) ratios. The 'Breath Sensor Test Rig' (Anaxsys, London, UK) or BSTR designed to test the performance of the respiR8® sensor was used. The BSTR simulates breathing with two controlled air streams. The moisture content of the two air streams is controlled using two dewpoint controllers. One air stream is of high relative humidity to simulate breath during exhalation. The dewpoint for this air stream is 35°C (i.e. the air is saturated with water at 35°C). This value is chosen as it is known that breath is saturated with water and while body temperature is ~37°C the air will be cooler when exiting the mouth. The second air stream has a low relative humidity to simulate ambient air during inhalation and the condensation point for this air stream is 5°C.

The two air streams are alternatively switched to allow only one air stream to flow over a sensor at any time. The air streams have flow rates controlled by two mass flow controllers and can be switched at a number of different rates with switching times as short as 0.6 s and as long as 6 s. The flow rates can be between 1.5 and 5 litre min⁻¹. Hence, a number of combinations of simulated tidal volumes, breathing rates, and I:E ratios are possible.

To test the monitor, a number of combinations of the variables (tidal volume, breathing rate, and I:E ratios) were used to determine the limits of these variables within which the respiR8 monitor performance was accurate. For example, a breathing rate of 50 bpm with a tidal volume of 50 ml was tested by using an inspiratory and expiratory flow of 5 litre min⁻¹, inspiratory time (Ti) of 0.6 s, and expiratory time (Te) of 0.6 s; a breathing rate of 5 bpm with a tidal volume of 600 ml was obtained by setting the flows at 5 litre min⁻¹, Ti=6 s, and Te=6s; a breathing rate of 9 bpm with tidal volume of 15 ml was tested by setting the flows at 1.5 litre min⁻¹, Ti=6 s, and Te=0.6 s. See also Table 1.

Human studies

Subjects

Twenty-eight healthy male (n=18) and female volunteers (n=10), aged 18–28 yr and BMI <30, and 50 postoperative patients were enrolled in the study after approval of the protocol by the local Human Ethics Committee of the LUMC. All subjects gave informed consent before the measurements. The study was registered at the Netherlands Trial Register (www.trialregister.nl) under number NTR3163.

Volunteer studies

Volunteers participated in two studies. Study 1 (10 men/10 women), in which RR derived from three different methods (respiR8, capnometer, and manual counting of thoracic movement) was collected during breathing at three different preset frequencies. Study 2 (8 men), in which the effect of fentanyl infusion on RR was assessed on one occasion with the respiR8 and on another occasion using a pneumotachograph.

Study 1

A mask over the nose and the mouth was fitted to which the respiR8 sensor and a sample tube from a capnometer (Capnomac, Datex, Helsinki, Finland) were connected. The subject was asked to breathe according to a preset frequency. The subject was allowed to set the frequency on a metronome that he or she (but not the investigator) could see during breathing. The subject was asked to set the metronome...
at a low frequency (slow breathing at 5–10 bpm), a normal frequency (normal breathing at 10–20 bpm), or a high frequency (fast breathing at > 20 bpm). Each subject performed five breathing exercises at each of the three frequencies with each exercise lasting 1 and 10–15 min between exercises. The order of the frequencies was randomly chosen. The 1 min mean RR derived from the respiR8 and capnometer was collected. Furthermore, the investigator counted the number of breaths during that same minute.

Study 2
In eight male subjects, the effect of an i.v. infusion of 2.5 µg kg⁻¹ fentanyl (0.5 µg kg⁻¹ min⁻¹ for 5 min) on respiratory frequency was assessed. On one occasion, the RR was measured using the respiR8 system. On another occasion, the subjects breathed a normoxic gas mixture (FIO₂ = 0.21) through a pneumotachograph (#4813, Hans Rudolph, Shawnee, KS, USA) attached to a tight-fitted facemask through which the subject breathed. The inspiratory and expiratory times were determined from the flow pattern and respiratory frequency was calculated on a breath-to-breath basis [bpm = 60/(Ti + Te)] using the custom-made software ResReg (LUMC). The system was calibrated using a piston pump generating a 1 litre tidal volume at various stroke rates (0–20 strokes min⁻¹). There were at least 2 weeks between occasions; the sequence of the studies was randomized.

Measurement in patients
In the recovery room, the respiR8 facemask was fitted to 50 patients after surgery. All patients were extubated in the operating theatre and transported without oxygen to the recovery room. The facemask was connected to a tube through which the patients received 6–10 litre min⁻¹ of oxygen. All subjects were connected to an ECG (three-lead ECG
monitor, Philips, Eindhoven, The Netherlands) and ECG-derived RR was collected. To this end, a small constant current is applied to two of the electrodes (leads RA and Apex) of the ECG and the resultant voltage is measured. Inspiration increases the length in the current path increasing the impedance and changing the voltage. So, the voltage measured over the two electrodes is used as a marker for inspiration. For each patient, on five occasions spread over 10–15 min, the displayed rate of the respiR8 and the ECG-derived rate were simultaneously noted.

**Statistical analysis**

A population-based Bland–Altman analysis was performed on the data obtained in the patient study and in volunteer study.\(^1\)\(^1\)\(^2\)\(^1\) The statistical package NONMEM was used to analyse the differences between the measurements (respiR8 vs manual counting; respiR8 vs capnometry-derived RR; respiR8 vs ECG-derived RR).\(^1\)\(^3\) This analysis allows for the estimation of within-subject, between-subject, and inter-occasion (in the volunteer study: inter-frequency) variability in bias and variance of the differences. Bias or variability terms were fixed to zero when this did not increase the objective function more than 2 points (as determined by the Akaike information criterion). The variability of bias and variance were assumed to be normally and log-normally distributed, respectively. For the volunteer study, analyses were performed for each of the three breathing frequencies and additional analyses were performed where bias and variance

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<th>Recorded breath rate (bpm)</th>
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Variations in inspiration and expiration volumes and flows

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of the differences were constrained to be equal for three arms, to create an ‘overall’ Bland–Altman plot. In NONMEM, the likelihood of the observations as discrete differences was maximized under the assumption that the unrounded values are normally distributed, using its Laplacian conditional estimation method. See Appendix 1 for the NONMEM code.

The RR data obtained in study 2 were averaged and the mean data (95% confidence interval) obtained from the methods were visually compared.

Results

Bench tests

The results of the respiR8 monitor during breathing simulations are given in Table 1. The respiR8 performance was accurate for breathing rates up to 40 bpm, when tidal volumes varied between 50 and 500 ml with IE ratios between 1:10 and 10:1. The respiR8 performance was accurate at low exhalation flow rates so long as the tidal volume remains at values >16 ml: performance of the respiR8 sensor was affected at low tidal volumes under conditions that allow buildup of humidity in the mask, that is, the combination of low inhalation and exhalation flow rates and IE ratios >3. This occurs, for example, when tidal volume = 15 ml and Ti = 6 s and Te = 0.6 s (IE ratio = 10). An example of the humidity tracing sampled at 60 Hz obtained in a volunteer is given in Figure 1A. In Figure 1B, a 68 min tracing of RR of a volunteer watching TV is given. The monitor remained operative for more than 24 h. Local regulations demand replacement of the mask and sensor after 24 h use.

These data indicate a high accuracy of the respiR8 monitor with respect to RR. Note that it is not a monitor of respiratory adequacy and shallow breaths are detected as breaths provided sufficient volume passes across the sensor.

Volunteer studies

Study 1

The RR ranged from 5 to 35 bpm (Fig. 2). The NONMEM population Bland–Altman analysis of the overall data set (combining data on the three test frequencies: slow, normal, and rapid breathing) comparing respiR8 with manual counting of thoracic movements and respiR8 with RR from capnometry are given in Figure 3A and B. Parameter estimates are given in Table 2. For the comparison of respiR8 and manual counting, the overall analysis yielded a bias of 0.105 (0.039) bpm [population value (SE)] and variance of 0.363 (0.040) (SD = 0.602, limits of agreement −1.08 and 1.29 bpm). Significant inter-frequency variability was observed on variance: 0.280 (0.134) but not on bias. Significant between-subject variability on bias or variance was not detected. For the comparison between respiR8 and capnometry-derived RR measurements, the overall analysis yielded a bias of −0.104 (0.037) bpm and variance 0.130 (0.031) (SD = 0.361, limits of agreement −0.81 and 0.60 bpm). Significant inter-individual variability [0.431 (0.301)] and inter-frequency variability [0.559 (0.336)] on variance was detected but none on bias.

The bias estimated for each of the three breathing frequencies was 0 (0) bpm for respiR8 against manual counting at the normal breathing rate, 0.172 (0.052) bpm at the slow breathing rate, and 0.117 (0.060) bpm at a fast breathing rate, and for respiR8 against capnometry-derived RR

Fig 2 CONSORT flow chart of the studies in volunteers (A) and patients (B).
Study 2
The RR measurements after fentanyl administration are shown in Figure 4. The overall pattern is similar and the peak respiratory depression was detected at 5 min (respiR8) and 6 min (pneumotachograph) (Fig. 2). There are some differences visible: the RR values measured with the pneumotachograph are somewhat greater than the values measured with the respiR8 and the variability in the pneumotachograph RR data is greater than that observed with the respiR8.

Patient study
The RR of 50 patients (23 men, 27 women), with median age 52.5 yr, range 18–84 yr, and median BMI 25.6 kg m\(^{-2}\), range 19.0–41.5 kg m\(^{-2}\) (13 had a BMI >30), was measured in the recovery room after major abdominal surgery (Fig. 2). The measurements was \(-0.159 (0.039)\) bpm at the normal breathing rate, \(0 (0)\) bpm at the slow breathing rate, and \(-0.098 (0.059)\) bpm at a fast breathing rate.

Table 2 Parameter estimates of the population Bland–Altman analysis. \(\omega^2\), a measure of between-subject variability in the log-domain; \(\nu^2\), a measure of inter-frequency variability in the log-domain (only available in the volunteer study where three separate breathing frequencies were tested); NA, not available; *not present in the statistical model as adding this parameter did not yield an improvement in objective function

<table>
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<th>Estimate (SE)</th>
<th>(\omega^2) (SE)</th>
<th>(\nu^2) (SE)</th>
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<tr>
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<tr>
<td>Variance</td>
<td>0.36 (0.04)</td>
<td>*</td>
<td>0.28 (0.13)</td>
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<td>respiR8 vs capnography</td>
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<tr>
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<tr>
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<tr>
<td>Bias</td>
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<tr>
<td>Variance</td>
<td>8.59 (1.10)</td>
<td>0.43 (0.14)</td>
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Fig 3 RR measurements in healthy volunteers (n=20). Population Bland–Altman analysis of respiR8 vs (a) manual counting of thoracic respiratory movements and (a) capnometry-derived RR. In both graphs, the analysis of the combined data set is given (i.e. normal, fast, and slow breathing). The broken green lines are the limits of agreement (±1.96 so). The analyses indicate that the biases are close to zero for both respiR8 vs manual counting and respiR8 vs capnometry-derived RR.

Fig 4 Effect of 2.5 \(\mu\)g kg\(^{-1}\) i.v. fentanyl on RR measured in eight volunteers using the respiR8 on one occasion and a pneumotachograph on another. Values are mean (SEM).

Fig 5 Bland–Altman comparison of respiR8 and ECG-derived RR measurement is given in Figure 5. The estimated bias was 1.72 (0.248) bpm and
respiratory movements by the hand. Counting the derived RR measurements and counting the number of breaths seems intuitively to be the least accurate.

The per-sonance descriptions indicate that the respiR8 accurately measures RR under experimental non-human conditions.

Similar observations were made in experimental human studies. The population Bland–Altman analysis of respiR8 and manual counting RR measurement occurring 5–6 min after i.v. infusion.14 The current data using the inspiratory/expiratory flow signal to calculate RR are in close agreement with these previous data. Similarly, changes in RR as measured by the respiR8 monitor were as expected, with a peak effect at f = 5 min. On average, RR data from the pneumotachograph exceeded those obtained from the respiR8 monitor. We relate this to various factors. Apart from the possible between-occasion variability in pharmacokinetics and pharmacodynamics, the somewhat tighter facemask as is used in our ‘dynamic end-tidal forcing’ setup (to prevent air leakage between the face and the mask) might cause some respiratory stimulation. A somewhat higher dead space might also be of influence. These factors may also be responsible for the greater variability in the data observed with the pneumotachograph. Despite these small differences, both methods were able to detect the effect of fentanyl on RR accurately, and conclusions drawn from the two methods are similar. Whether this holds after performing a pharmacokinetic–pharmacodynamic analysis remains unknown for now.

The respiR8 monitor was well able to measure RR in postoperative patients. The population Bland–Altman analysis of the data showed the existence of a bias between the respiR8 and ECG-derived methods of almost 2 breaths (limits of agreement=6 breaths), with the ECG-derived method giving greater values over the entire RR range (from 5 to 25). No significant variabilities were detected within and between subjects or over-time. The value of the bias and limits of agreement reflects the inaccuracy of the ECG-derived method. The observed 2-breath bias was related predominantly to movement artifacts and shivering. No observations of upper airway obstructions were made in our subjects.

We analysed the two comparative data sets in volunteers (study 1) and patients using a population-based Bland–Altman analysis in NONMEM (Appendix 1). We did so to take into account the repeated and often correlated measurements obtained in each subject.12 Our method yielded, apart from accurate estimates of bias and variance, indications for the location of the variability in the data ranging from within-subject variability, between-subject variability, to inter-occasion (inter-frequency) variability. Other methods to obtain between- and within-subject variability have been published before, for example, using a component of variance technique.12 15

Continuous monitoring of RR in spontaneously breathing patients who receive potent opioids for analgesia or sedation is important and is recommended by national anaesthesia
societies. It is therefore not surprising that various techniques, often quite different in underlying technology, are available. These include measurement of CO₂ (using a mask or nasal catheter), acoustic methods (assessing breath sounds on the throat of the patient), impedance systems (e.g. from ECG monitors), and measurement of thoracic and abdominal respiratory movement. The respiR8 is a novel breathing monitor that is distinct from the other devices, in that (i) it is small and mobile and may be used anywhere in or outside the hospital (such as during transport from or to and on the surgical ward where other devices are not available); (ii) it does not rely on thoracic and/or abdominal respiratory movements, and hence, it will detect hypopnoea/apnoea from both central and peripheral (e.g. upper airway obstruction) origins; and (iii) it is a continuous monitor of RR on a breath-to-breath basis. Our study did not encounter situations in which the monitor failed to assess RR. This can occur when the patient takes the mask off, or when air saturated with water vapour is inhaled. The current study was not designed to compare the respiR8 monitor with any of these mentioned devices or techniques. Therefore, a comparison with regard to accuracy or ability to detect specific respiratory events cannot be made here. Our study does provide ample evidence that the respiR8 accurately measures RR in volunteers and postoperative patients and is able to correctly track opioid-induced respiratory depression. Since it is a small and portable device using a novel and robust measurement technique, we believe that it might gain an important place in patient management, both perioperatively and in the acute care setting.

Declaration of interest
R.M. is the Editor-in-Chief of the BJA.

Funding
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Appendix 1: NONMEM code for population-based Bland–Altman analysis

$PROBLEM BLAND-ALTMAN
$DATA sheet1.d
; select DV
$INPUT ID MNUM SPD STOP CAPN RESP SMR
; select the THETAs and ETAas for the bias (BS) and variance (VAR)
; of the differences for the three speed groups
SPD1 = 0
SPD2 = 0
SPD3 = 0
IF (SPD.EQ.1) SPD1 = 1
IF (SPD.EQ.2) SPD2 = 1
IF (SPD.EQ.3) SPD3 = 1

; BS0 and VR0 are overall levels
; BS1 and VR1 include interindividual variability
; BS and VAR additionally include interoccasion variability
BS0 = THETA(1) * SPD1 + THETA(2) * SPD2 + THETA(3) * SPD3
BS1 = BS0 + ETA(1)
BS = BS1 + ETA(2) * SPD1 + ETA(3) * SPD2 + ETA(4) * SPD3
VR0 = THETA(4) * SPD1 + THETA(5) * SPD2 + THETA(6) * SPD3
VR1 = VR0 + ETA(5)
VR = VR1 * EXP(ETA(5))

; take into account of the fact that the DVs are integers
DDVU = DV - BS + 0.5
DDVL = DV - BS - 0.5
S = SQRT(VAR)

; PHI is NONMEM’s function for the cumulative normal distribution
DMA = DDVU / S
PRU = PHI (DMA)
DMA = DDVL / S
PRL = PHI (DMA)

; likelihood of observation
Y = PRU - PRL

; confidence interval
BSL = BS - S * 1.96
BSU = BS + S * 1.96

; averages for B-A plot
MSR = (STOP + RESP) / 2
MCR = (CAPN + RESP) / 2

$THETA
0.1
0.1
0.1
(0.01, 0.5, 25)
(0.01, 0.5, 25)
(0.01, 0.5, 25)

$OMEGA 0.1
$OMEGA BLOCK(1) 0.1
$OMEGA BLOCK(1) SAME
$OMEGA BLOCK(1) SAME

$EST MAXEVAL = 9999
$SIG = 3
$NOABORT MSFO = msfo METH = 1 LIKELIHOOD LAPLACE
$COVR PRINT = E
$TABLE FILE = stream NOPRINT NOAPPEND
ID MNUM SPD STOP CAPN RESP SMR CMR MSR MCR
BS BS1 BS BS1 VR0 VR1 VAR Y OBJI