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Pulse oximetry respiratory monitoring for assessment of acute childhood wheeze

David Wertheim[1] MA, PhD, Oana Anton[2] MRCPCH, MRes, Catherine Olden[3] RSCN, Sophie L.V. Le Maistre BM BS[2], Paul C. Seddon[3] BSc, MB ChB, PGCertMedEd.

[1]Faculty of Science, Engineering and Computing, Kingston University, Surrey, UK, [2]Brighton and Sussex Medical School, Brighton, UK and [3]Respiratory Care, Royal Alexandra Children's Hospital, University Hospitals Sussex, UK.

Address for Correspondence:

Professor Paul Seddon, Respiratory Care, Royal Alexandra Children's Hospital, Brighton BN2 5BE, United Kingdom.

Email: seddop@gmail.com

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What is already known on this topic

- Respiratory rate and pulsus paradoxus are key indicators to identify severe exacerbations associated with acute wheezy episodes in pre-school children.
- Both respiratory rate and pulsus paradoxus are problematic to monitor in clinical practice, and are therefore under-utilised.
- Analysis of the pulse oximeter plethysmogram trace enables accurate respiratory rate assessment in stable infants and children, and can identify features analogous to pulsus paradoxus.

What this study adds

- Recording accurate respiratory rate from the pulse oximeter plethysmogram is feasible in acutely wheezy young children in a busy emergency department
- In this setting, pulse oximeter plethysmogram analysis enables near-continuous monitoring of respiratory rate and of waveform features analogous to pulsus paradoxus.
- Pulse oximetry derived respiratory rate and pulsus paradoxus analogous features predict response to treatment and outcome of wheezy children in the emergency department.

How this study might affect research, practice or policy

- This technique could be developed to permit real-time readout of respiratory rate, in addition to oxygen saturation and heart rate, from a pulse oximeter.
- Analysis of pulsus paradoxus analogous features of the plethysmogram trace may provide a sensitive indicator of increased work of breathing.
- Monitoring of these key vital signs may permit earlier recognition of the child who is deteriorating or failing to respond to treatment.

Abstract:

Objective

There is a lack of objective measures to assess children with acute wheezing episodes. Increased respiratory rate (RR) and pulsus paradoxus (PP) are recognised markers, but poorly recorded in practice. We examined whether they can be reliably assessed from a pulse oximeter plethysmogram ("pleth") trace and predict clinical outcome.

Patients and Methods

We studied 44 children aged 1 to 7 years attending hospital with acute wheeze, following initial "burst" bronchodilator therapy (BT), and used custom software to measure RR and assess PP from oximeter pleth traces. Traces were examined for quality, and accuracy of RR measurement was validated against simultaneous respiratory inductive plethysmography. RR and PP at 1 hour after BT were compared with clinical outcomes.

Results

RR from pleth and RIP showed excellent agreement, with mean difference (RIP minus pleth) -0.5 breaths/minute (limits of agreement -3.4 to +2.3). 52% of one-minute epochs contained 10 seconds or more of pleth artefact.

At 1 hour after BT, children who subsequently required intravenous bronchodilators had significantly higher RR (median (IQR) 63 (62-66) vs 43 (37-51) breaths/minute) than those who did not, but heart rate and oxygen saturation were similar. Children with RR ≥55/min spent longer in hospital: median (IQR) 30 (22-45) vs 10 (7-21) hours. All children who subsequently required hospital admission had PP analogous pleth waveforms 1 hour after BT.

Conclusion

RR can be reliably measured, and PP detected, from the pulse oximeter pleth trace in children with acute wheeze, and both markers predict clinical outcome.

Abbreviations:

BT: “burst” therapy (10 puffs of Salbutamol inhaled every 20 minutes for 1 hour)

CAS: Clinical asthma score

ED: Emergency Department

HR: Heart rate

IQR: Inter-quartile range

PP: Pulsus paradoxus

Pleth: Pulse oximeter plethysmogram

RIP: Respiratory inductive plethysmography

RMP: Respiratory modulation of the pleth trace

RR: Respiratory rate

SpO_2: Arterial oxygen saturation as measured by pulse oximeter

RRp1: RR from pleth at 1 hour after completing “burst” therapy

Introduction

Acute wheeze is a common clinical problem in young children, whether as an isolated viral-induced episode or in the context of diagnosed asthma[1]. Assessing severity and response to treatment are particularly problematic in young children, with a lack of available objective measures[2]. Respiratory rate is recognised as a key clinical sign in assessing respiratory disease[3-6] but in clinical practice, using visual counting, it is often poorly performed and inaccurate[7 8]. Pulsus paradoxus (clinically detectable variation in pulse volume over the respiratory cycle), is a sign of increased work of breathing and a valuable marker of severe asthma exacerbations[6].

Pulse oximetry is widely used to assess arterial oxygen saturation and also gives a pulse rate readout from the plethysmograph (pleth) waveform. Respiration modulates the pulsatile pleth trace resulting in baseline variation as well as pleth amplitude changes analogous to pulsus paradoxus[9]. We have previously shown that a respiratory waveform extracted from the pleth by an appropriate low-pass filtering algorithm gives a reliable measure of respiratory rate in healthy newborns[10], preterm infants with chronic lung disease[11] and young wheezy children[12]. We have also shown that respiratory rate can be derived from analysis of pleth amplitude variations analogous to pulsus paradoxus[10].

When respiratory status deteriorates, respiratory rate tends to increase before oxygen saturation decreases [13 14]. Thus continuous respiratory rate measurement could enable both earlier intervention and assessment of the response to treatment. However, both respiratory rate and pulsus paradoxus assessment are normally measured intermittently and are prone to observer error. The aim of this study was to determine the feasibility, accuracy and clinical value of applying pleth derived respiratory rate and pulsus paradoxus waveform assessment to young children attending a hospital emergency department (ED) with acute wheeze. We wished to determine whether a) the technique could accurately measure respiratory rate

compared to a gold-standard technique (respiratory inductive plethysmography) b) in a real-life acute clinical setting, a near-continuous measure of respiratory rate could be achieved, and c) measuring respiratory rate could assess response to treatment and predict clinical outcome. We also explored whether d) visible respiratory modulation of the pleth trace, analogous to clinical pulsus paradoxus, was associated with severity and outcome.

Patients and Methods

The study was carried out in the Emergency Department (ED) of the Royal Alexandra Children's Hospital, Brighton, United Kingdom. Ethical approval was given by the National Research Ethics Service London-Bloomsbury Committee (REC Reference 13/LO/1427). Children and parents were approached for informed consent as soon as practicable after arrival at the ED. Children were eligible if they were between 1 and 7 completed years of age, had a diagnosis of either acute asthma or viral induced wheeze, and required 'burst' inhaled bronchodilator therapy (BT) - 10 puffs of Salbutamol every 20 minutes for an hour. Children with life-threatening features requiring immediate critical care were excluded.

Demographic data and details of previous wheezing history and treatment were collected. Clinical data including heart rate (HR), RR by visual counting, arterial oxygen saturation measured by pulse oximeter (SpO_2) and Clinical Asthma Score (CAS)[15] were recorded 1 hour after completing BT. As soon as possible after consent, a Nonin 3150 pulse oximeter was attached to a finger or toe and connected by Bluetooth to a nearby laptop computer, to which the pleth trace from the oximeter was recorded continuously using Nonin OEM software. The signal was recorded as continuously as possible for up to 4 hours as tolerated.

Outcome data collected included: need for intravenous bronchodilator treatment, requirement for admission to inpatient ward and to high dependency unit, total duration of stay in hospital, and duration of requiring hourly (or more frequent) inhaled bronchodilator therapy.

In addition, in a subset of children, chest and abdomen respiratory traces using respiratory inductive plethysmography (RIP), and pulse oximeter pleth trace from Nonin device, were recorded simultaneously with a Nonin oximeter pleth trace onto a Somnoscreen Plus (SOMNOmedics GmbH, Germany) digital multichannel recorder for a 5 minute period, in order to validate the pleth measurement of respiratory rate.

HR, SpO_2 and the pleth signal were exported to a spreadsheet file. The HR, SpO_2, pleth and RIP thoracic and abdominal band data acquired on the Somnoscreen recorder were exported as edf files. Both sets of data were imported into custom software that we developed in MATLAB (The MathWorks, Inc., Natick, MA, USA). RIP RR was measured from the abdominal band trace.

RR from the oximeter pleth was derived as previously described[11 16]. In summary, the pleth signal was low-pass filtered (LPF) using a filter with a cut-off frequency at half the median HR calculated over one-minute epochs; this filters out the heart rate output but leaves the RR component[12]. The data were then visually analysed using a signal browser that displayed filtered pleth, raw pleth, SpO_2, HR, and RIP band data for the Somnoscreen recordings. In addition to measuring HR and RR from the pleth trace, we also calculated the HR/RR ratio, as our previous work suggested that this ratio is decreased during acute wheezy episodes – that is, RR increases disproportionately to HR[12].

Traces from the subset of children who had simultaneous pulse oximeter and SOMNOscreen Plus recording were analysed for visible respiratory modulation of the pleth trace (RMP) – analogous to clinical pulsus paradoxus, and defined as the presence of variations synchronous

with respiration in *both* the pleth baseline *and* beat-to-beat pulse amplitude. Sections of pleth trace with at least 20 seconds of regular respiratory pattern and little or no artefact were assessed for RMP by comparing with simultaneous RIP band traces, using software we developed with MATLAB (The MathWorks Inc., USA) to quantify and visualise pleth variability.

We compared markers derived from oximeter pleth analysis (RR, HR/RR ratio, and RMP) as well as HR and SpO_2, all from pulse oximetry at 1 hour after BT, to the following clinical outcomes:

- Subsequent need for hospital admission (and for admission to high dependency unit)
- Subsequent need for intravenous bronchodilator therapy
- Duration of hospital admission
- Duration of requiring at least hourly inhaled bronchodilators

We defined children as significantly tachypnoeic if RR was 55/min or above, equivalent to the 99th centile of RR in hospitalised children in this age group[17].

This was an exploratory study, but we carried out a prior power estimation based on our previous data on children attending with acute wheeze[12], indicating that mean (SD) respiratory rate at presentation to the hospital was 49 (13), and therefore that 54 children would be required to have 80% chance of demonstrating a mean difference of 10 breaths/minute between two clinical outcome groups.Data were analysed using Excel (Microsoft Corporation, USA) and Minitab v19 (Minitab LLC., USA). The Ryan-Joiner test in Minitab was applied to assess data distribution normality and parametric or non-parametric tests used as appropriate.

Results

60 children were screened for the study: seven had mild acute wheeze and did not require BT; the remaining 53 were recruited after parental consent. Of these, 4 would not tolerate the pulse oximeter probe to remain in place, and in 5 recording could not be started (because parental consent had not been received) until more than 1 hour after completing BT.

Results are presented on the remaining 44 children (14 girls), of median (range) age 41 (12 to 82) months. 40 children had suffered previous wheezing episodes, and 17 were on regular therapy to prevent wheezing (inhaled corticosteroids or montelukast).

Validation of respiratory rate recording

These data are on a subset of 35 children, median (range) age 42 (12-82) months in whom we were able to obtain a satisfactory 5-minute simultaneous recording of pleth and RIP. Figure 1 shows a sample segment of recording.

The mean (SD) RR from the abdominal RIP band traces was 44 (10), range 31 to 67 breaths/minute, and from the pleth was mean (SD) 44 (10), range 31 to 66 breaths/minute. The mean (SD) difference (RIP minus pleth) was -0.5 (1.4) breaths/minute; limits of agreement (RIP minus pleth) were -3.4 to +2.3 breaths/minute. Figure 2 shows a Bland-Altman plot of individual respiratory rate values from RIP and pleth.

Quality of pleth recordings

As shown in Figure 1, when a good quality pleth trace was available, the filtered pleth trace was almost identical in pattern and frequency to the RIP band traces. We have previously shown that this remains the case when respiration is irregular, with apnoeas[16]. Artefact in more than a small proportion of the pleth trace (as with the RIP trace) can reduce the confidence in measuring respiratory rate. The presence of artefact in 20 pleth recordings from 43 to 125 minutes in length was assessed by visual inspection, dividing the traces into 1-minute epochs. The mean (SD) proportion of 1-minute epochs affected by 10 seconds or more of artefact was 52.3 (19.4)%. We also looked at the maximum length of artefact-affected pleth recordings in the 11 children with 50% or more of epochs containing artefact. The median (range) figure for the longest artefact-affected segment was 17 (7-31) minutes.

Prediction of clinical outcome

All 44 children were treated initially with BT; 4 children subsequently required intravenous bronchodilator therapy (Salbutamol, Aminophylline or Magnesium sulphate) due to a poor response to inhaled therapy and all 4 were admitted to a high dependency unit (HDU). 35 children deemed improved and stable were allowed home directly from the emergency department, while 9 children were admitted to an inpatient ward (including the 4 admitted to HDU). Table 1 shows mean (SD) clinical parameters 1 hour after the end of BT.

The 4 children who later required intravenous bronchodilator therapy (and HDU admission) had significantly higher RR from pleth at 1 hour after BT (RRp1) than those who did not require IV therapy - median (IQR) 63 (62-66) vs 43 (37-51) breaths/minute (p=0.001, Mann-Whitney test). HR/RR ratio at 1 hour after BT was lower in the patients who required IV therapy compared with those who did not: median (IQR) 2.6 (2.6-2.7) vs 3.7 (3.2-4.2) (p=0.001, Mann-Whitney test). CAS was higher in those who required IV therapy: median

(IQR) 9 (8.25-11.25) vs 7 (6.0-8.75) . There was no significant difference in HR or SpO_2 at 1 hour after BT between the two groups (for HR p=0.19, for SpO_2 p=1.0, Mann-Whitney test). Figure 3 illustrates these markers graphically in relation to clinical outcome.

Children who had RRp1 of 55/min or above spent longer in hospital: median (IQR) 30 (22 to 45) vs 10 (7 to 21) hours (Mann-Whitney p=0.008). There was a non-significant trend for children with RRp1 55/min or above to have longer duration of needing inhaled bronchodilator hourly or more frequently: median (IQR) 70 (60 to 146) vs 15.9 (57 to 490) minutes (Mann-Whitney p=0.38).

Respiratory modulation of the pleth trace

Pleth traces and RIP band recordings from 40 children with 5-minute simultaneous pleth and RIP band recordings were evaluated. In 9 children there was insufficient regular artefact-free respiratory trace to assess for RMP, so results are presented for 31 children. Figure 4a illustrates a child showing clear variation with respiration both in pleth baseline and in beat-to-beat pleth amplitude variation. By contrast, there are no consistent baseline variations in pleth or beat-to-beat amplitude changes associated with respiratory rate in the child shown in figure 4b.

Nine children who had no clear RMP were all discharged from the emergency department with median (IQR) time to discharge 10.2 (6.9 to 16.0) hours. Twenty-two children with clear RMP had longer median time to discharge of 22.6 (8.9 to 30.0) hours (Mann-Whitney p=0.04), with 8 requiring inpatient admission (4 to HDU). RMP appeared most evident visually in periods of regular respiration.

Discussion

Clinical assessment of children with acute severe wheezing episodes is problematic, and objective measures are needed. We have developed a technique for extracting a respiratory waveform from the pleth trace of a standard pulse oximeter. We have demonstrated that this approach yields an accurate estimate of respiratory rate, and that a pleth trace of adequate quality can be obtained over long periods even in the challenging setting of unwell children in a busy emergency department. In this study we observed that the mean proportion of one-minute epochs affected by artefact (at least 10 seconds) was 52%. Previously, in stable, sleeping infants with chronic lung disease, we found that 20% of pleth epochs – but also 10% of RIP band epochs - were affected by artefact[11]. It is not surprising that artefact was more frequent in the older children in this study, who were awake, mobile, and acutely unwell. Nevertheless, the availability of almost 50% of 1-minute epochs artefact-free would allow near-continuous respiratory rate monitoring. Even in the most artefact-affected traces, the longest continuous affected period was 31 minutes.

Our results suggest that respiratory rate derived from the pleth trace can be used to assess response to treatment; specifically, that children with persisting rapid respiratory rate after initial high dose inhaled bronchodilator therapy are more likely to require admission to hospital, intravenous bronchodilator therapy and a longer hospital stay. Our results also

suggest that absence of visible respiratory modulation of the pleth is associated with better outcomes. Although the presence of RMP (likely a sign of increased work of breathing) was associated with need for intravenous bronchodilator therapy, there was a large standard deviation in the time to discharge; this suggests that RMP can also be seen in children who are not severely ill.

Tachypnoea is a recognised feature of acute severe asthma in adults, in whom respiratory rate correlates negatively with spirometric markers of airway obstruction[18]. In children there is a lack of empirical evidence, but national guidelines encourage recording of respiratory rate and quote thresholds (without supporting data) to distinguish severe from moderate acute asthma[5 19]. We are not aware of previous studies demonstrating an association between respiratory rate and outcomes in acute severe wheeze. This may be partly due to the difficulties and inaccuracies involved in clinical counting of respiratory rate[7].

A potential criticism is that we used an arbitrary cutoff RR to identify those children who were significantly tachypnoeic after initial treatment, and one which is different from the cutoffs described in clinical guidelines to define a severe attack[5]. However, we based the cutoff value on normative data from large numbers of observations; these data [17 20] have demonstrated that the normal RR values quoted in current guidelines are unrepresentative. The value of 55 breaths/minute is the mid-point of the 99th centiles for RR for the lower (60/minute) and upper (50/minute) ends of our participants' age range[17].

Another potential criticism is that we may have included children with different pathophysiological conditions: younger children with viral induced wheeze and older children with asthma. We recruited children broadly across the preschool years (over 12 months to under 7 years), and the nature of wheezing illness undoubtedly changes over this period. However, acute wheezing episodes remain predominantly viral-triggered throughout childhood[21], while categories of wheezing illness remain fluid over the preschool years[22].

There have been previous attempts to use the pulse oximeter pleth trace to assess increased work of breathing in acute wheeze. Krishnan et al.[23] recently reported that "visually detected pulsus paradoxus" on the pleth trace at presentation to the emergency department had higher relative risks of adverse outcomes, although the authors' definition of "pulsus paradoxus" was unclear[24]. Previous studies examining pulsus paradoxus-related phenomena from the pleth trace in acute wheeze have shown some association with lung function[25 26], but no clear correlation with clinical outcome[27]. We observed that RMP was most evident in periods of regular respiration which suggests that respiratory pattern should be considered when making such assessments. Our results are in keeping with those of Krishnan et al.[23]; in this study we clearly defined the phenomenon of visible respiratory modulation of the pleth (RMP), analogous to clinical pulsus paradoxus. However, further work is needed to refine and validate a measure of the amount of respiratory modulation of the pleth trace, and to demonstrate that RMP can be reliably detected using the pleth trace alone.

The technique we have described has potential to improve the management of acutely wheezy children by providing near-continuous monitoring of a key physiological measurement (respiratory rate), which may become elevated before there is a fall in SpO_2, without the need for an additional measuring device on the child. Clearly further development work is needed to allow the respiratory rate calculation to be performed in real time, and to provide real-time quality control for artefact, but both these should be readily achievable with appropriate software. In addition to these technical considerations, caution is needed before advocating widespread introduction of continuous RR monitoring: in infants with bronchiolitis, continuous SpO_2 monitoring has not been shown to improve clinical outcomes compared to intermittent SpO_2 monitoring[28], and over-reliance on SpO_2 measurements in bronchiolitis may lead to increased hospital admissions[29]. Larger clinical studies are needed

to determine whether pleth-derived monitoring of RR and of PP equivalents are effective in guiding decision-making in the acutely wheezy child.

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Clinical Trial Registration

The study was registered on the NIHR Portfolio, UK CRN Number 15742

Competing interests

None

Author Contributions

Prof Wertheim and Prof Seddon conceptualized and designed the study, carried out analysis of the data, drafted the initial manuscript, and reviewed and revised the manuscript.
Sister Olden and Dr Banks designed the data collection instruments, collected data, and carried out the initial analyses. Dr Anton carried out further data analysis and contributed to writing the manuscript.
Sister Olden tragically died in 2019. All other authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Table 1 : Summary of clinical parameters recorded 1 hour after completing Burst Therapy (BT).

Parameter 1 hr after BT	mean (SD)
SpO_2	92.7 (2.3)
CAS	7.5 (1.9)
HR	160 (15.0) /min
RR	45.4 (10.3) /min
HR/RR ratio	3.66 (0.72)

Figure legends:

Figure 1: Example of 30 seconds duration section of recording with respiratory rate approximately 39/minute. The 'raw' pleth trace shows baseline undulations synchronous with respiration.

Figure 2: Bland Altman plot showing the difference between RIP band and filtered pleth derived measurements of respiratory rate against the mean value. The two points in red are outside the limits of agreement shown by the horizontal lines for the lower limit of agreement (LLA) and the upper limit of agreement (ULA).

Figure 3: Individual value plots of RR (A), HR/RR (B), HR (C) and SpO_2 (D) against whether discharged from the Emergency Department (ED), admitted to a general ward or a admitted to the High Dependency Unit (HDU). Each point is plotted as a blue circle with the yellow diamond symbols indicating the median value for each category.

Figure 4: Twenty second duration sections of recording of pleth (pink upper trace) and RIP band (blue lower trace). For each graph the centre trace (brown) shows the change in beat-to-beat amplitude of the pleth trace; each beat-to-beat amplitude point is shown with a circle marker. The upper graph (A) shows an example with clear baseline and pulse amplitude variation with respiratory rate. The lower graph (B) shows an example with no consistent baseline and pulse amplitude variation with respiratory rate from abdominal RIP band trace.