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Respiratory effort from the photoplethysmogram

Paul S. Addison

Minimally Invasive Therapies Group, Medtronic, The Technopole Centre, Edinburgh EH26 0PJ, Scotland, United Kingdom

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ABSTRACT

The potential for a simple, non-invasive measure of respiratory effort based on the pulse oximeter signal - the photoplethysmogram or 'pleth' – was investigated in a pilot study. Several parameters were developed based on a variety of manifestations of respiratory effort in the signal, including modulation changes in amplitude, baseline, frequency and pulse transit times, as well as distinct baseline signal shifts. Thirteen candidate parameters were investigated using data from healthy volunteers. Each volunteer underwent a series of controlled respiratory effort maneuvers at various set flow resistances and respiratory rates. Six oximeter probes were tested at various body sites. In all, over three thousand pleth-based effort–airway pressure (EP) curves were generated across the various airway constrictions, respiratory efforts, respiratory rates, subjects, probe sites, and the candidate parameters considered. Regression analysis was performed to determine the existence of positive monotonic relationships between the respiratory effort parameters and resulting airway pressures. Six of the candidate parameters investigated exhibited a distinct positive relationship ($p < 0.001$ across all probes tested) with increasing upper airway pressure repeatable across the range of respiratory rates and flow constrictions studied. These were: the three fundamental modulations in amplitude (AM-Effort), baseline (BM-Effort) and respiratory sinus arrhythmia (RSA-Effort); two pulse transit time modulations - one using a pulse oximeter probe and an ECG (P2E-Effort) and the other using two pulse oximeter probes placed at different peripheral body sites (P2-Effort); and baseline shifts in heart rate, (BL-HR-Effort). In conclusion, a clear monotonic relationship was found between several pleth-based parameters and imposed respiratory loadings at the mouth across a range of respiratory rates and flow constrictions. The results suggest that the pleth may provide a measure of changing upper airway dynamics indicative of the effort to breathe.

1. Introduction

Respiratory Effort is recognized as an important clinical parameter. However, the term, although relatively ubiquitous, is defined and measured in a number of different ways depending upon the clinical setting, including: maximal inspiratory and expiratory pressures [1]; pleural pressures, esophageal pressures and work of breathing [2] changes in nasal cannula pressures [3]; changes in blood pressures or pulse transit times [4,5]; changes in EMG signals [6]; chest band extensions [7]; visual observation of signs of distress and muscle use [8]; changes in coloration [9]; and respiratory sounds [10]. These measurements may involve invasive procedures, spot checks, distant proxies for effort, or visual or aural cues. In fact, the patient often may simply be asked to respond to questioning regarding their ability to breathe easily.

The manifestation of respiratory components in the photoplethysmogram (pleth) has been well documented in the literature [11–15]. Much of the current activity in this area has focused on the derivation of respiratory rate (RR) which may be determined from an analysis of the *periodicity* of respiratory modulations present in the signal [16,17]. However, it has been noticed that the *strength* of these modulations may be indicative of thoracic pressure changes, associated with the effort to breathe, that are transmitted through the vasculature to peripheral probe sites [18]. In the study reported here we do not consider the pleth-based measurement of *respiratory rate*, but rather focus on the potential for the pleth waveform to provide an indication of the *effort to breathe*. In addition, in contrast to previous studies on respiratory effort from the photoplethysmogram, a wide range of photoplethysmogram-based parameters are considered (13 parameters in total from a range of modalities).

It was hypothesized that a positive monotonic relationship exists between respiratory effort and the strength of the pleth modulations. In fact, respiratory effort may manifest in the pleth in a variety of different ways. This has led to the development of a number of promising candidate pleth-based technologies

E-mail address: paul.addison@medtronic.com

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Table 1
The candidate respiratory effort parameters.

Parameter type	Candidate parameter name	Description	Required number of probes
Pleth modulations	**AM-Effort**	Pleth amplitude modulation	1
	BM-Effort	Pleth baseline modulation	1
	RSA-Effort	Respiratory Sinus Arrhythmia	1
Transit time modulations	**P2E-Effort**	PTT-based (Requires ECG)	2 (Pleth+ECG)
	P2-Effort	DPTT-based	2 (Pleth+Pleth)
	P1_DPTT-Effort	Single probe DPTT-based	1
	P1_STT-Effort	Single probe STT-based	1
Baseline shifts	**BL_HR-Effort**	Baseline shifts in heart rate	1
	BL_PP-Effort	Baseline shifts in pleth	1
	BL_P2E-Effort	Baseline shifts in PTT	2 (Pleth+ECG)
	BL_P2-Effort	Baseline shifts in DPTT	2 (Pleth+Pleth)
	BL_P1_DPTT-Effort	Baseline shifts in single probe DPTT	1
	BL_P1_STT-Effort	Baseline shifts in STT	1

for its measurement. In the present study, computer algorithm code modules were developed for thirteen candidate pleth-based parameters: seven modulation parameters and six baseline shift parameters as described in the following section. The performance of each parameter was evaluated over a range of sensors using data from an in-house trial involving a range of respiratory rates and flow constrictions.

2. Method

2.1. Technological basis of the candidate respiratory effort parameters

This work aimed to characterize the properties of the selected candidate pleth-based respiratory parameters. These are summarized in Table 1 and described below. The parameters are subdivided into three classes: pleth waveform-based modulations, transit time modulations and baseline shifts.

2.1.1. Pleth modulations: AM-Effort, BM-Effort and RSA-Effort

The photoplethysmographic signal comprises a repeating smooth, double-humped, cardiac 'pulse' waveform riding on a more constant baseline component (often called the DC component). This is depicted in Fig. 1(a). Respiratory activity may cause the pleth to modulate in three fundamental ways: Baseline Modulation, Pulse Amplitude Modulation and Pulse Frequency Modulation (Respiratory Sinus Arrhythmia or RSA). These are illustrated in Fig. 1(b)–(d) and have been more fully described in [16] and [19]. From previous experience working with the pleth, it has been noticed that changes in these modulations strengths may be indicative of changes in the effort to breathe. Fig. 1(e) contains a plot of an actual pleth collected during the study reported here with these three fundamental modulations indicated.

2.1.2. Transit time modulations: P2E-Effort, P2-Effort, P1Effort, STT-Effort

It is well known that transit time of the pulse wave from the heart to the peripheries varies inversely with blood pressure. As transit time varies inversely with pressure it is expected that during the respiratory cycle it will vary cyclically with the pressure changes induced by respiratory activity. During inhalation, where the intrathoracic pressure reduces thus lowering arterial pressure, the transit time is expected to increase [4]. Correspondingly, during exhalation, where the intrathoracic pressure increases thus increasing arterial pressure, the transit time is expected to decrease. In the present study four types of transit time were examined and are described below:

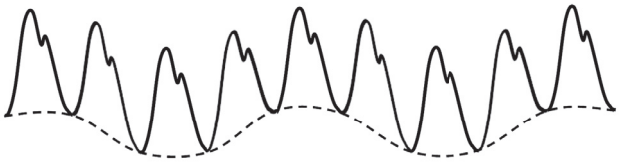
(1) *P2E-Effort from Pulse Transit Time (PTT):* This is a temporal measure from the ECG to the pleth as shown in Fig. 2. PTT may be measured from a fiducial point on the ECG signal to a fiducial point on a photoplethysmographic signal arriving at the sensor site. The example shown here defines PTT as the time from the arrival of the peak of the ECG R-wave to the peak of the pleth pulse. In practice, a variety of fiducial points may be identified on the ECG and pleth to derive a number of PTTs. PTT was extracted in this study by measuring the time period between the QRS peak and the trough of the arriving pleth wave.

(2) *P2-Effort from Differential Pulse Transit Time ($DPTT_2$):* A two-probe differential pulse transit derived from two pleth cardiac pulses arriving at different sites on the body [20]. This is also shown schematically in Fig. 2. $DPTT_2$ is derived by examining the relative timings between selected fiducial points on two pleth cardiac pulses arriving at different sites on the body (e.g., finger-ear, finger-toe, ear-toe, finger-forehead, etc. In this pleth-only method, no ECG is used. DPTT only considers the difference in arrival times at the peripheries and therefore does not contain the time associated with electromechanical delay (or pre-ejection period) that PTT, as defined above, suffers from. $DPTT_2$ was measured from the trough to trough period of the corresponding pulse waves arriving at each site.

(3) *P1-Effort from Single Pulse Differential Pulse Transit Time ($DPTT_1$):* This may be extracted from a single pleth pulse as depicted in Fig. 2. $DPTT_1$ is calculated from a single pleth pulse by considering the relative timings of internal reflection components that make up the single pulse waveform such as those shown in the figure. For this work, $DPTT_1$ was actually measured from the peak of the first derivative of the signal to the next trough.

(4) *STT-Effort from Single Pulse-Single Point Slope Transit Time (SST):* During the work it was realized that through the respiratory cycle the effect of change in pulse period and changes in the period of internal pulse components, making up the pulse waveform, act in opposition to each other. This observation led to the development of a novel single pulse-single slope transit time to mitigate this effect, as depicted in Fig. 3. The pulse waveform arriving at the sensor site is made up of an initial wave plus a series of reflected waves which combine to form the aggregated pulse waveform observed in practice. This aggregated waveform has two competing temporal elements: during exhalation, as the arterial blood pressure increases, the internal pulse waves travel faster, thus reducing PTT, and are of shorter period (P_1). However, the inter-beat pulse period, P_2, lengthens as the heart rate decreases due to RSA. During inhalation the opposite occurs. These two temporal effects, from blood pressure and heart rate changes, therefore oppose each within the pleth waveform. Hence, as PTT increases and correspondingly P_1 increases it can be seen from geometrical consid-

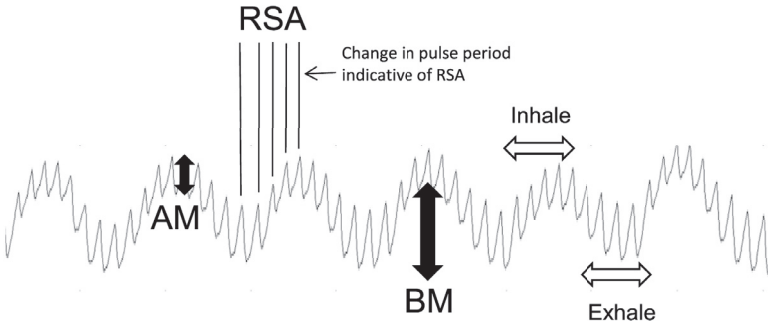
(a) **Non-Modulated Pleth Waveform**



(b) **Baseline Modulation:** A dashed line has been added to the Fig. to highlight the modulating nature of the signal baseline. The baseline modulation was extracted by filtering around the respiratory rate and measuring peak to trough amplitudes.

(c) **Pulse Amplitude Modulation:** Inspiration leads to a decreased pulse amplitude during this phase of respiration (Fig. 1c). The amplitude modulation was extracted by measuring the peak to trough amplitudes of the cardiac pulses.

(d) **Respiratory Sinus Arrhythmia:** This is a well-documented variation in heart rate that occurs throughout the respiratory cycle where heart rate increases during inspiration and decreases during expiration. The respiratory sinus arrhythmia modulation was extracted by measuring peak to peak time periods.



(e)

Fig. 1. (a–d):Schematic of pleth modulation components due to respiration.
(a), (b), (c) and (d) reprinted from: Addison PS, Watson JN, Mestek ML, Mecca RS. 'Developing an algorithm for pulse oximetry derived respiratory rate (RRoxi): a healthy volunteer study'. J Clin Mon Comp. 2012;26:45–51.
(e): A real pleth exhibiting all three modulations due to respiration reprinted from: Addison PS, Watson JN, Mestek ML, Ochs J.P., Uribe A.A., Bergese S.D. 'Pulse Oximetry-Derived Respiratory Rate in General Care Floor Patients'. J Clin Mon Comp. 2014; May, Published Online.

erations that the gradient (m) of the upslope of the initial pulse wave component should decrease. Further, $k = 1/m$ where k may be thought of as a 'temporal gradient', i.e., the time change per unit amplitude rather than m, which is an amplitude change per unit time. k is proportional to transit time and is not dominated by HR effects but rather follows a slope transit time (STT). It was therefore hypothesized that STT, and hence k, would prove a more appropriate single probe proxy for PTT than $DPTT_1$ (and hence a better measure for respiratory effort). Note that in practice m may be taken as the amplitude of the first peak of the first derivative of the pleth signal (i.e., maximum gradient of the upslope): a measure easily extracted from the current computer code and the inverse of which provides k. Full details of this novel measure are given in [21].

2.1.3. Baseline shift measures: BL_HR-Effort, BL_PP-Effort, BL_P2-Effort, BL_P2E-Effort, BL_P1_DPTT-Effort, BL_P1_STT-Effort

These candidate effort parameters are distinctly different from those described above. The parameters above correspond to a

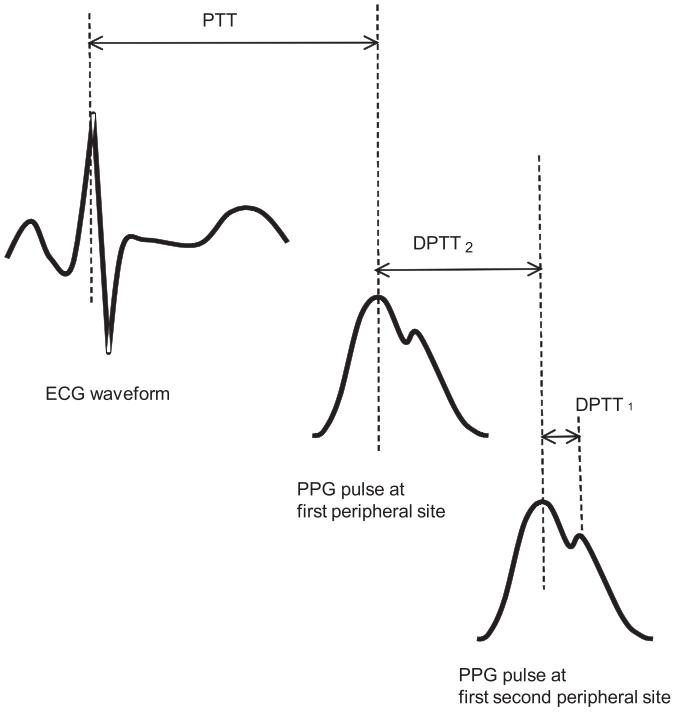


Fig. 2. Schematic of transit time modalities used in the study.
Note that here the standard orientation of pleth is depicted with the onset of the systolic wave at the start (trough) of the waveform, and the peak indicating maximum volume at the probe site. This is the orientation displayed on a monitor screen and is the inverse of the collected signal.

change in amplitude of a signal *modulation* whereas the baseline shift measures correspond to a distinct change in the underlying *baseline* of the signal. (For example RSA, a measure of modulation strength of heart rate, may change without changing the mean heart rate. However, if the mean heart rate changes, then this is counted as a baseline shift in heart rate.) This is depicted in the schematic of Fig. 4. In this study, baseline shifts of six pleth-based parameters were analyzed, these were: heart rate (BL_HR-Effort), the pleth itself (BL_PP-Effort) and the four pulse transit time parameters (BL_P2-Effort, BL_P2E-Effort, BL_P1_DPTT-Effort, BL_P1_STT-Effort).

2.2. Study

With institutional review board approval and written informed consent, a convenience sample of 7 healthy adult volunteers (4 female, 3 male) was enrolled at the Covidien RMS clinical laboratory in Boulder, CO. These had been pre-screened and completed physical exams. The subjects had a mean age of 32.3 yr (range 21–46 yr); a mean weight of 68.1 kg (range 49–83 kg); and a mean height of 169.6 cm (range 157.0–184.5 cm).

During the trials, the subjects were positioned comfortably in a chair with the pulse oximeter sensors attached. A facemask was attached to each subject consisting of a pneumotach containing a number of interchangeable flow resistors (5, 20 and 50 cm H_2O/L/s linear resistors, (Hans Rudolf Inc., Kansas City, MO)). Airway pressure signals at the mouth and pleth waveforms were synchronized and recorded via a custom data acquisition system. Three commercial pulse oximeter probes from Nellcor pulse oximeter hardware (Nell-1 OEM boards, Covidien, Boulder, CO.) were attached to the (1) right index finger (Nellcor Max-A), (2) forehead (Nellcor Max-Fast) and (3) right ear (Nellcor D-YSE) and an analog signal acquired from each. The analog signals allowed synchronization with the ECG for pulse transit time analysis. However, these signals have the main pleth DC component removed. Another three probes were attached to (1) the left ear (Nellcor D-YSE), (2) the left index finger (Nellcor Max-A) and (3) the left ring finger (Nellcor Max-N). From these, digital ('SHIP') data was acquired which contained the full pleth baseline and were therefore useful in determining effort measures related to baseline shifts in the pleth which could not be achieved using the analog signals.

The study involved breathing over a number of RRs at a number of set resistances. RRs of 8, 15 and 24 BrPM were used in the current study. These were chosen as they represent relatively low breathing rates, near average breathing rates, and relatively high breathing rates respectively in the general adult population. The subjects performed three separate runs, one at each flow resistance: 5, 20 and 50 cm H_2O/L/s linear resistors. After assuring an adequate mask seal, subjects were coached to breathe in synchrony with a metronome for 1 minute periods against the resistor. A 2 minute recovery period was provided between each trial where the subjects were allowed to breathe freely. The protocol is summarized in Table 2. Each run shown in the table lasted 41 minutes and was repeated for each of the three flow resistors.

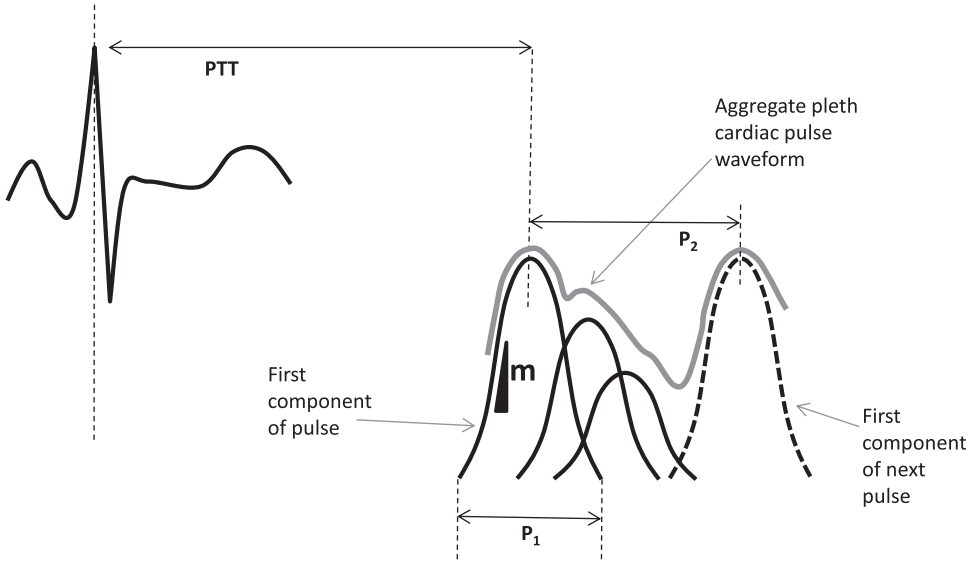


Fig. 3. Schematic of the opposing effects on internal components and pulse period during the respiratory cycle.

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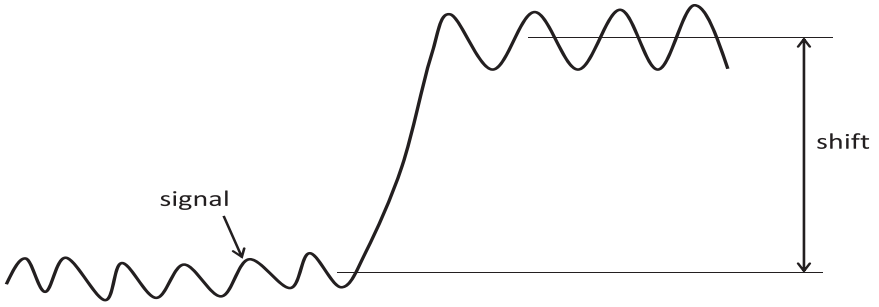

Fig. 4. Schematic of a baseline shift.
Baseline shift parameters quantify permanent displacements in baseline or 'DC' components of values of a parameter rather than changes in the amplitude of its modulation.

Table 2
Trial regimen for one value of constriction (C). Total duration = 41 min. This was repeated for each of the 3 flow resistors used in the study. RR in breaths per minute or free breathing recovery.

RR	free	8	free	8	free	8	free	8	free	15	free	15	free	15	free	15	free	24	free	24	free	24	free	24	free
Effort		M		H		S		M		M		H		S		M		M		H		S		M	
Duration	6	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	1

Effort: H = Hard; M = Moderate; S = Soft.
Duration in minutes.

Table 3
The subject data sets. Of a possible 63 data sets (7 subject, 3 resistance, 3 respiratory rates) 52 were acquired due to subjects not completing tasks.

Subject ID	Inhalation (C-20)	Inhalation (C-5)	Inhalation (C-50)	Inhalation/Exhalation
RE002	**Y**	**Y**	**Y***	Inhalation
RE003	**Y**	**Y**	**Y***	Exhalation
RE005	**Y**	**Y**	**N**	Inhalation
RE006	**Y**	**Y**	**Y**	Exhalation
RE008	**Y**	**Y**	**Y***	Inhalation
RE009	**Y**	**Y**	**Y**	Inhalation
RE011	**Y**	**Y**	**Y**	Inhalation

Legend:
Y = Regimen data collected. Subject completed all tasks.
Y* = Subject did not complete all tasks.
N = Subject did not complete any tasks at this value of constriction.

A number of benchtop test runs were conducted before the final protocol was formulated where it was found that it is extremely challenging for an individual to sustain a forced respiratory effort with any degree of consistency for more than one minute. This is an inherent problem with such respiratory effort studies and distinguishes such trials from respiratory rate trials where usually free breathing is monitored which may be sustained over substantial periods of time [19]. Thus, the final protocol used in the study reported here only contained four one-minute effort periods at each resistance and respiratory rate separated by a two-minute recovery period. Hence, only four data points were generated for each subject for each respiratory rate/flow resistance combination.

Each subject was initially asked to breathe through the set flow resistor at a consistent effort for a 1 minute period at what they felt appropriate for that resistance. This is labeled 'M' in Table 2. At the second effort period, the subject was asked to breathe with more effort through the resistor. This is labeled 'H'. During the third period the subject was asked to breathe with less effort through the resistor than the initial effort 'S', and during the fourth period the subject was asked to breathe in a similar manner to the first attempt ('M'). This provided four data points of mouth air pressure against pleth–based respiratory effort for a given respiratory rate. This was repeated for the same resistor for two more respiratory rates during the run. The equipment also allowed for the option to set the flow resistance only on inhalation or only on exhalation. The regimes undertaken by the seven subjects are summarized in Table 3, where it can be seen that five subjects encountered flow resistance on inhalation and two on exhalation.

2.3. Analysis of the data

Each four point data set (per RR/flow resistance combination for each subject and probe) was plotted separately. As an example, Fig. 5(a) shows all such four-point effort-pressure (EP) sets for the BM_Effort parameter for the analog finger probe. (There were 66 such plots generated in the study: the full list is given in Table 4 below in the results section.) A regression line was fitted to each set of points and the gradient determined. This is depicted in Fig. 5(b) for three example point sets taken from Fig. 5(a). The fitted regression lines are shown dashed in Fig. 5(b), from which the gradients were determined. The expectation is for a positive relationship between pleth-based effort and airway pressure for these sets. This was tested using a Binomial test with the null hypothesis that there is no relationship between the pleth-based effort parameter and airway pressure and hence positive and negative gradients are equally likely to occur on lines fitted to the data points, i.e., H_0: $p = 0.5$. A significance level $\alpha = 0.05$ was assumed. A Bonferroni correction was applied to the significance level to account for multiple testing.

In addition, a new method to aggregate the data through a linearization and gradient normalization process for each subset of data points was employed during the study (recently reported by [22]). The method aims to account for the spread in gradients of

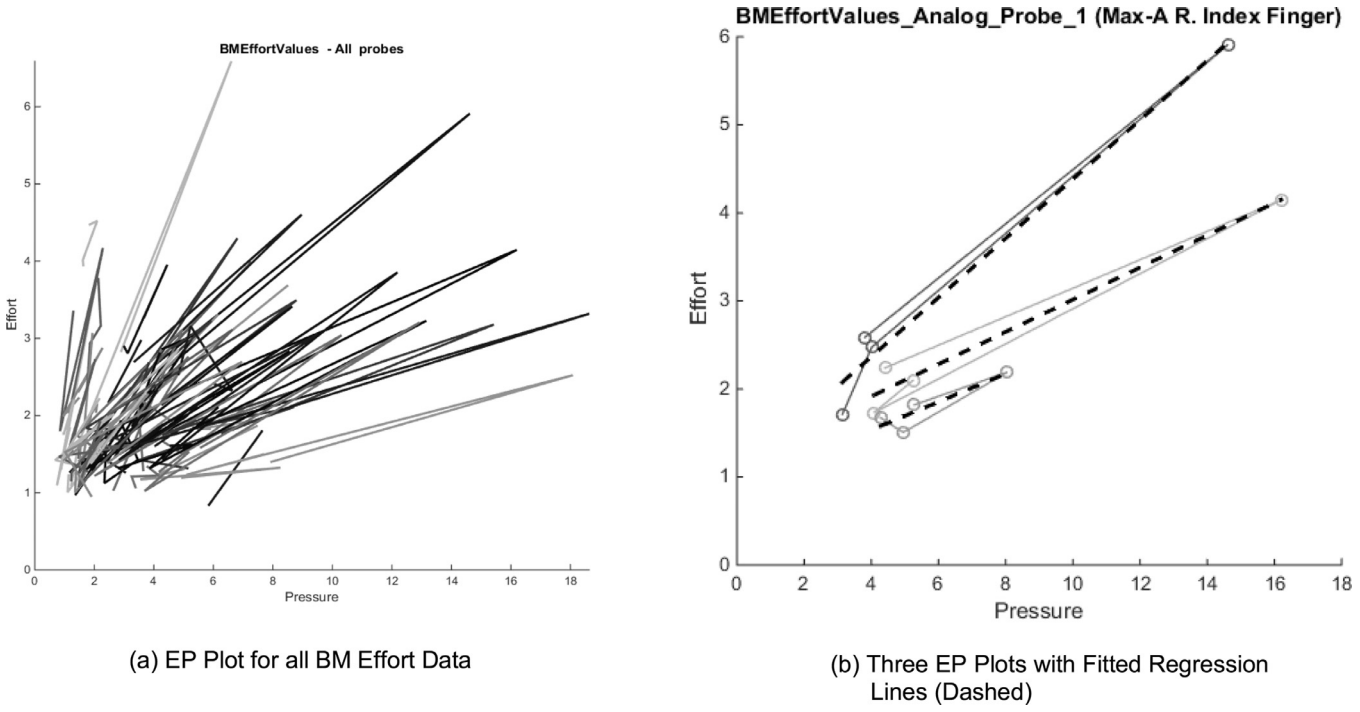

Fig. 5. Pleth-based Effort against Airway Pressure (EP) Plots for the Analog Finger Probe.
(Pressure units: cm H_2O. Effort Units: arbitrary. Note that the units are arbitrary as the photoplethysmogram value is a function of light intensity, tissue properties and hardware.)

Table 4
Test for positive gradients.
Number of positive gradients/total number of EP curves. (Binomial test).
Note that, for example, the BM-Effort for analog finger probe shown in the table corresponds to the data in Fig. 5(a). Similar data plots lie behind each of the entries in the table.
Note also that total numbers vary from a maximum of 52 (see legend Fig. 3) down to 47. This is caused by algorithmic failures due to difficulties in selecting fiducial points in noisy data. Missing information in table box corresponds to: (1) a lack of DC component in the pleth baseline of the analog signal and hence no BL_PP-Effort can be calculated; (2) an inability to accurately synchronize pleth and ECG signals using the digital pleth, and hence no P2E-Effort and BL_P2E-Effort can be computed; and where (3) only HR was computed for the analog signal. (The HR signals were almost identical for all probes – as expected). Hence, no BL-HR-Effort was computed. The table lists the results of all 3300, 4-point EP curves used in the analysis.
A Bonferroni correction was applied to the results in the table to account for multiple testing where conservatively all 66 tests were considered one family, thus the significance level, α, was reduced to 0.000758. This brought the two results indicated by an asterisk in the table above the significance level.

Effort	Analog			Digital		
	1-fin	2-for	3-ear	A-ear	B-fin	C-fin
AM-Effort	48/52 ($p < 0.001$)	47/52 ($p < 0.001$)	51/52 ($p < 0.001$)	45/47 ($p < 0.001$)	43/47 ($p < 0.001$)	45/47 ($p < 0.001$)
BM-Effort	51/52 ($p < 0.001$)	52/52 ($p < 0.001$)	50/52 ($p < 0.001$)	47/47 ($p < 0.001$)	43/47 ($p < 0.001$)	43/47 ($p < 0.001$)
RSA-Effort	46/52 ($p < 0.001$)	42/52 ($p < 0.001$)	50/52 ($p < 0.001$)	45/47 ($p < 0.001$)	39/47 ($p < 0.001$)	45/47 ($p < 0.001$)
P2E-Effort	46/52 ($p < 0.001$)	39/52 ($p < 0.001$)	46/52 ($p < 0.001$)	/	/	/
P2-Effort	38/50 ($p < 0.01$)	40/50 ($p < 0.001$)	42/50 ($p < 0.001$)	43/50 ($p < 0.001$)	39/50 ($p < 0.001$)	47/50 ($p < 0.001$)
P1_DPTT-Effort	37/50 ($p < 0.01$)	34/50 ($p < 0.05$)*	30/50 ($p > 0.05$)	41/50 ($p < 0.001$)	39/50 ($p < 0.001$)	35/50 ($p < 0.05$)*
P1_STT-Effort	27/50 ($p > 0.05$)	30/50 ($p > 0.05$)	36/50 ($p < 0.01$)	41/50 ($p > 0.05$)	44/50 ($p < 0.05$)	45/50 ($p < 0.01$)
BL_HR-Effort	41/52 ($p < 0.001$)	41/52 ($p < 0.001$)	42/52 ($p < 0.001$)	/	/	/
BL_PP-Effort	/	/	/	17/47 ($p > 0.05$)	16/47 ($p > 0.05$)	15/47 ($p > 0.05$)
BL_P2E-Effort	14/52 ($p > 0.05$)	5/52 ($p > 0.05$)	8/52 ($p > 0.05$)	/	/	/
BL_P2-Effort	39/50 ($p < 0.001$)	26/50 ($p > 0.05$)	37/50 ($p < 0.01$)	31/50 ($p > 0.05$)	18/50 ($p > 0.05$)	28/50 ($p > 0.05$)
BL_P1_DPTT-Effort	33/50 ($p > 0.05$)	28/50 ($p > 0.05$)	28/50 ($p > 0.05$)	30/50 ($p > 0.05$)	20/50 ($p > 0.05$)	18/50 ($p > 0.05$)
BL_P1_STT-Effort	14/50 ($p > 0.05$)	8/50 ($p > 0.05$)	8/50 ($p > 0.05$)	4/50 ($p > 0.05$)	28/50 ($p > 0.05$)	27/50 ($p > 0.05$)

each pleth-based effort – airway pressure (EP) curve by producing a single normalized relationship of all collected data and thus be amenable to more traditional descriptors for pulse oximeter parametric data. The method is shown schematically in Fig. 6. In doing so, Mean Bias, Precision and Accuracy statistics, as per the essential performance specified by the ISO80601-2-61 standard, Annex CC [23], may be employed to characterize the data. (This general pulse oximeter standard was adopted by the author in lieu of a specific standard for pulse oximetry-derived respiratory effort.) The accuracy was computed for each probe–parameter combination which is defined as the root mean squared deviation (RMSD) of the data from the line of unity. This combines both systematic and random errors.

3. Results

Table 4 contains the number of positive gradients found for each data set split by probe type and effort parameter with corresponding *p*-values from the Binomial test. The table contains the results of 3300 EP curves from 13,200 (M,H,S,M) effort data points. Note that in two cases, (i.e., BM_Effort for analog finger and digital ear probes) the gradients were found to be positive for all

Table 5
Summary of gradient normalization RMSDs.

Renormalization RMSD's	Analog			Digital			Mean
	1-fin	2-for	3-ear	A-ear	B-fin	C-fin	
AM-Effort	1.62	3.94	1.50	1.14	1.69	1.77	1.94
BM-Effort	1.05	0.81	1.60	1.48	1.66	1.69	1.38
RSA-Effort	1.58	2.13	1.42	1.25	1.64	1.64	1.61
P2E-Effort	2.21	2.38	1.96	\	\	\	2.18
P2-Effort	1.96	1.65	1.95	1.91	1.15	1.82	1.74
P1_DPTT-Effort	2.38	2.62	3.22	2.66	2.12	2.80	2.63
P1_STT-Effort	2.94	3.24	2.88	2.28	2.23	2.25	2.64
BL_HR-Effort	2.43	2.44	2.43	\	\	\	2.43
BL_PP-Effort	\	\	\	2.66	2.76	2.75	2.72
BL_P2E-Effort	2.55	2.57	2.60	\	\	\	2.57
BL_P2-Effort	2.88	3.01	2.26	2.47	2.29	2.46	2.56
BL_P1_DPTT-Effort	2.53	2.52	2.61	2.86	2.68	2.56	2.62
BL_P1_STT-Effort	2.60	2.75	2.83	3.06	2.43	2.54	2.70

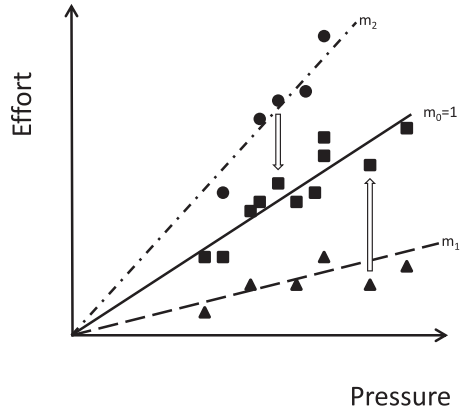

Fig. 6. Gradient normalization method.
The figure depicts two candidate results by circles and triangles. Each of these is associated with a true 'underlying' curve of gradient m_1 and m_2. In order to compare each curve, and aggregate their points, the positions of the points are rescaled according to the slope of the best fit line of each data set. Thus, the data is rescaled to a single slope, shown as m_0. This may be of arbitrary value. Here, however, a slope of unity was chosen for simplicity and ease of viewing. The data denoted by the triangles and circles are moved to the points indicate by the boxes, which all lie around the m_0 line. Note that in the method the data is assumed to follow an underlying linear relationship (i.e., it would be linear in the absence of noise) which passes through the origin. Hence a least squares technique is used to determine m_1, m_2, etc., but with the y-intercept forced to pass through the origin (i.e., regression through the origin.) Thus, by rescaling in this way, aggregate measures for the combined data may be determined.

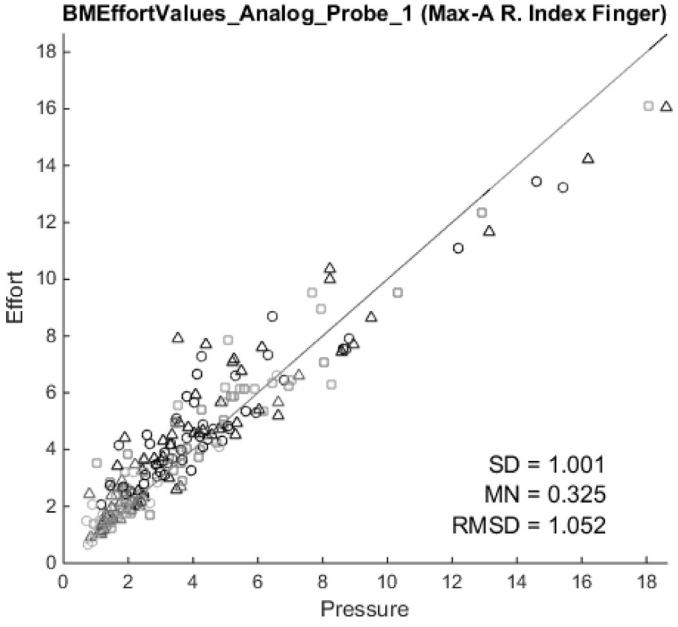

Fig. 7. Gradient normalization plot for BM effort and analog finger probe.
Effort=SD of baseline modulations. Arbitrary units. Pressure=mean absolute pressure in cm H_2O. Note: the gradient normalization technique results in both axes having the same units (of pressure).

calculated individual plots of pleth-based effort and airway pressure (EP curves). The associated gradient renormalization RMSDs for all effort parameters are provided in Table 5. Fig. 7 contains a gradient normalization plot for BM-Effort as an example. It can be seen that a clear monotonic relationship is exhibited for this normalized EP plot. Inspection of Tables 4 and 5 reveals that the probes with the lowest six RMSDs correspond to those who all exhibit $p < 0.001$ for all six probe sites: AM-Effort, BM-Effort and RSA-Effort, P2E-Effort P2-Effort and BL_HR_Effort. Of the modulation strength parameters, it was found that, in general, the pleth waveform-based measures resulted in lower RMSDs than those based on transit times. The baseline shift parameters generally produced higher RMSDs than both modulation parameter type with the exception of BL_HR_Effort. It was noticeable from visual inspection of the time series plots that heart rate demonstrated a distinct shift in value with increasing mouth pressure which was clearly visible in the heart rate tracing, whereas the pleth baseline shift showed no obvious correlation with mouth pressure for this protocol. In addition, no obvious difference in the form of the results was found between the results for constriction on inhalation and those for constriction on exhalation.

4. Discussion

A rigorous coached breathing protocol was conducted in an attempt to determine the form of the relationship between imposed upper airway pressures due to flow constriction at various respiratory rates and various components of the pleth (both baseline shift and modulating components). Over three thousand EP curves were generated from over thirteen thousand data points in an unprecedented detailed study of the manifestation of respiratory effort in the pleth waveform: these resulting from controlled variations in airway constrictions, respiratory efforts, respiratory rates, subjects, probe sites and candidate parameters. The coached breathing protocol conducted in this study represents an attempt to determine the form of the relationship between imposed upper airway pressures due to flow constriction and various components of the

pleth (both baseline shift and modulating components). The protocol was constructed with particular attention paid to the difficulties in performing respiratory maneuvers of this kind, whereby subjects cannot sustain the individual tasks for long periods and where it is difficult to pre-define levels of effort. As such, the protocol allowed each subject to provide his/her own four points on an effort-pressure curve for each value of respiratory rate and flow constriction considered.

Analysis of the EP curves demonstrated that six of the candidate parameters exhibited a distinct positive relationship (which is defined as $p < 0.001$, Binomial test) with increasing upper airway pressure for all six probes across the range of respiratory rates and flow constrictions studied. However, the individual gradients of the curves varied widely across subject, respiratory rate and constriction as can be seen in Fig. 5(a). The six parameters were: the three fundamental modulations AM-Effort, BM-Effort and RSA-Effort; the two-probe pulse transit time modulations P2E-Effort and P2-Effort; and baseline shifts in heart rate, BL-HR-Effort. In addition, it had been expected that the strength of modulations would diminish significantly with increasing respiratory rate, as tidal volume decreased. However, this was not found to be the case. It appeared that the expected effect was mitigated by the increasing upper airway pressures exhibited at the higher rates, which had the compensating effect of increasing modulation strength. The remaining parameters are split into two groups: (1) those which, for a number of probes exhibited a noisy but discernable monotonic relationship (i.e., $p < 0.05$ for some probes) - P1_DPTT-Effort, P1_STT-Effort, BL_P2-Effort; and (2) those which consistently failed to produce good relationships ($p > 0.05$ all probes) - BL_PP-Effort, and the baselines of BL_P2E-Effort, BL_P1_DPTT-Effort, BL_P1_STT-Effort. For case (1) it was felt that signal noise was less of an issue in extracting the information than changing pleth morphology which made consistent detection of fiducial points challenging. For example, changing local maxima on each beat in the derivative of the pleth was found in some signals, making it difficult to detect a consistent repeatable fiducial point and upstroke gradient, and this may have adversely affected the localized, single pulse transit time-based measures in particular, i.e., P1_DPTT-Effort, P1_STT-Effort. Future improvements to fiducial detection algorithms should tackle this issue.

The key points of the study may be summarized as follows:

(1) A number of pleth-based respiratory effort parameters have been identified which exhibit a distinct monotonic relationship with airway pressure at the mouth.
(2) These parameters are derived from a wide range of manifestations of respiratory effort in the pleth waveform: amplitude modulation, baseline modulation, frequency modulation, transit time modulation and baseline shifts.
(3) Although distinctly monotonic, the scaling factor (i.e., gradient) between airway pressure and each respiratory effort parameter, varies markedly from subject to subject, across respiratory rates and flow constrictions and cannot be determined in advance. Thus it may be possible to accurately monitor trending in respiratory effort changes over time, but only in a relative manner that is context-specific.

On the third point above, a new gradient normalization method was employed in an attempt to normalize the relationships across respiratory rate and flow resistance so that a comparison could be made across probe types for each of the candidate pleth-based respiratory effort parameters. The six parameters with the lowest resulting RMSDs on their normalized EP plots corresponded to those identified as having consistent monotonic relationships ($p < 0.001$) across all probes. This provides some evidence that gradient normalization may prove to be a useful comparison methodology for analyses of this type.

It is worth highlighting here the subtle nature of the modulation effects that are resolvable within the photoplethysmographic signal using the methods discussed here. The sophisticated processing techniques developed in-house allow for the extraction of this modulation information which is, in effect, a *modulation of a modulation of a modulation*! This is explained as follows:

- The cardiac pulse component of the pleth is a small modulation of the whole signal, i.e., a small percentage of the baseline component (a modulation).
- In this study, various respiratory modulations of the cardiac pulse component of the pleth are interrogated: amplitude, baseline, RSA, or fiducial points for transit time measurements (a modulation of a modulation).
- Changes (i.e., modulations) in these respiratory modulations were extracted and used as a relative measure of respiratory effort (a modulation of a modulation of a modulation)

During the study, these pleth modulation magnitudes were controlled by varying the magnitude of upper airway pressures at the mouth to produce distinct monotonic relationships. From the work conducted here it can now be confirmed that the behavior is highly resolvable under controlled conditions. Although the author has conducted much previous research involving respiratory modulations of the pleth (e.g., [14,16,17,24–26]), the repeated clarity of many of the resulting respiratory effort relationships was quite unexpected (e.g., Fig. 5(a) and 5(b)).

There is now a realization that the pleth waveform contains much more information than previously thought, and that we are just beginning to develop methods to extract it for clinically useful purposes [27]. The current work focuses on respiratory effort and there are a number of papers in the literature which specifically describe various pleth-based parameters associated with some kind of effort to breathe. Brock et al. [4] considered pulse transit times as a measure of respiratory effort. Hartert et al. [13] used the baseline modulation – which they called the respiratory waveform variation (RWV) – as a measure of airway obstruction in a group of patients with obstructive airway disease (asthma or COPD). They found that the measure gave good separation when used it to identify those patients with abnormal pulsus paradoxus (defined as > 10 mm Hg variation during the respiratory cycle) from those with physiologic pulsus (< 10 mm Hg). In later work, Arnold et al. [12] considered the variation in both waveform area and height of the cardiac pulse through the respiratory cycle as a correlate for change in mouth pressures in a study of healthy young adults who breathed against progressively increasing levels of mouth pressure. Although a relationship was found, the plotted data appears very noisy, which could be a result of the signal processing used, or perhaps more likely, the intra-patient variability in performing these tasks (as described above for the current study). Khandoker et al [28] suggested pleth pulse amplitude and pulse period as markers of respiratory effort and Li et al [29] have found that both time period and amplitude indices from pleth and ECG measures are modulated with respiratory effort. More recently, Perel [30] even suggested an adjunct use of pleth-based fluid responsiveness measures for the detection of respiratory effort increases due to upper airway obstructions and the authors own group have followed up in this area by examining the DPOP measure of fluid responsiveness [31] in this regard. (Although note that DPOP is not a raw measure of PPG-based effort such as those considered here.) However, the author believes that the current work reported here is the first attempt to provide a rigorous and comprehensive picture of the whole spectrum of signal behaviors (modulations and shifts) associated with respiratory effort. This is combined with the extraction of the respiratory effort information using relatively advanced signal processing methods developed over the years by the author and colleagues.

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Table 6
Pleth-derived parameters and their physiological associations.

Candidate parameter type	Parameter name	Description	Measure associated with:
Candidate parameters used in respiratory effort study			
Pleth modulations	**AM-Effort**	Pleth amplitude modulation	**Stroke volume variation** and **vasoconstriction/compliance change/peripheral resistance**
	BM-Effort	Pleth baseline modulation	**Short term venous return/cardiac output modulations**
	RSA-Effort	RSA	**Cardio-respiratory feedback mechanism** indicative of **autonomic nervous system**
Transit time modulations	**P2E-Effort**	PTT-based (Requires ECG)	
	P2-Effort	DPTT-based	**Blood pressure modulations** indicative of **thoracic pressure modulations (WOB)**
	P1_DPTT-Effort	Single probe DPTT-based	and/or **upper airway pressures due to obstructions** or **vessel compliance changes**
	P1_STT-Effort	Single probe STT-based	
Baseline shifts	**BL_HR-Effort**	Baseline shifts in heart rate	**Physiological work of breathing**
	BL_PP-Effort	Baseline shifts in pleth	**Long term changes in venous draining & pooling** indicative of **change in cardiac output**
	BL_P2E-Effort	PTT-based (requires ECG)	
	BL_ P2-Effort	DPTT-based	**Blood pressure changes** indicative of **physiological work of breathing** and/or
	BL_P1_DPTT-Effort	Single probe DPTT-based	**vessel compliance changes**
	BL_P1_STT-Effort	Single probe STT-based	

As discussed in detail by Addison [19], the determination of a clinically useful physiological parameter is a distinctly non-trivial task where a sophisticated algorithmic infrastructure is required to take the raw biosignal, process it, present it to the core algorithm, then apply further processing to the output in order to produce a value with the integrity necessary for display on the screen of a medical monitoring device. There is, therefore, still much work to do to convert the results described here into a clinically useful respiratory effort parameter.

It is well known that increased respiratory effort associated with obstructive events (e.g., sleep apnea) will, in general, be associated with cyclical drops in SpO_2 [32]. However, no noticeable changes in SpO_2 were observed during this study for any of the RR, flow restriction, or respiratory effort combinations, as the healthy subjects were well ventilated throughout. It is known from other in-house work conducted by the author and colleagues (unpublished) that respiratory rate may vary when a free breathing subject encounters a new respiratory effort regime generated through a change in flow restriction. However, in this study the respiratory rates were fixed during each task. Hence, although SpO_2 and RR are important in certain situations in practice, where changes in respiratory effort occur, they were not targeted by this study which focused on the direct effect of definable airway pressure changes on the pleth waveform.

The quantitative analysis assumed a linear relationship between each pleth-derived parameter and mouth pressure. This allowed gradient extraction of the data in each case. However, linearity is unlikely to rule in practice, especially at the extremes of pressures. Also, the baseline shifts appeared less linear in nature, although monotonic, and hence this possibly caused their RMSD values to be higher than those for the fundamental modulations (AM, BM, RSA). Further work in this area should attempt to assess the nature of the individual parameter-specific relationships.

The waveform of the PPG varies significantly due to many confounding factors, such as sensors, reflection/transmission method of measurement, the clip pressure or the sensor pressure on the skin surface, and motion artefact. Although worthy of consideration in separate subsequent studies, these were not the focus of this early-stage study. The pulse oximeter probes were attached to each subject by a clinician as standard practice and the patient was asked to remain as motionless as possible during the acquisition. It would be interesting to look further at the effect of clip pressure as some of the measurements, e.g., pulse amplitude modulation, could be suppressed with higher clip pressures at the site of measurement; on the other hand, RSA-based effort measures should not be affected as they are both frequency based and originate at the cardio-thoracic core (i.e., distant from the measurement site).

Note that there was no a priori power analysis to determine sample size as this was a pilot study using a convenience sample of 7 subjects to test proof of principle. Subsequent studies further down the product development chain would require sample size determination based in part on results of such proof of principle studies. As stated earlier, the study was highly controlled employing a protocol constructed with particular attention paid to the difficulties in performing respiratory maneuvers in healthy subjects. This study raises many questions on how it would perform in the critically ill patient and especially those patients with intrinsic lung disease, or with diaphragm atrophy. However, the increased thoracic pressures associated with the mechanics of respiration may enhance the modulations in such cases, whereas, a patient vasoconstricted at the peripheries may exhibit lower amplitude modulations, especially those associated with the cardiac pulse. In addition, the study investigated the mouth pressures exhibited when breathing against flow resistors placed at the mouth, rather than esophageal pressures where lung compliance and resistance will control respiratory effort. A true test for the methods described will be a comparison with oesophageal pressures in targeted patient populations with unrestricted airflow at the mouth.

Finally, during the study an attempt was made to rationalize the underlying physiological mechanisms underpinning each candidate parameter. This is summarized in Table 6. The results of the investigation, together with this appreciation of physiological underpinnings of the parameters, were used to drive the in-house identification and technical risk profiling of potential clinical applications for a pleth-based respiratory effort parameter. Initial potential applications considered include: the monitoring of respiratory dysfunction; the monitoring of goal directed respiratory therapy; as a parameter used within clinical predictive scoring systems; monitoring during ventilator weaning; and incorporation within an enhanced pleth-based fluid responsiveness measure. Further work will be conducted in order to appraise these more fully.

5. Concluding remarks

In conclusion, clear monotonic relationships were found between many of the pleth-based parameters and the imposed respiratory loadings across a range of respiratory rates and flow constrictions. The results suggest that the pleth may provide a useful measure of changing upper airway dynamics indicative of the effort to breathe. A larger cohort is required before more definitive

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conclusions can be reached. Today there is no simple, automated, continuous method of monitoring respiratory effort. The development, therefore, of a simple pleth-based non-invasive continuous measurement of the effort to breathe could enable such a respiratory effort parameter to be available across multiple areas of care. Alone, or in conjunction with other parameters such as SpO_2 and Respiration Rate (also available from the pleth), it may provide early warning of impending respiratory compromise or obstructive apneic events.

Conflict of interest

The author is an employee of Medtronic, a medical device company, who conducted the work.

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