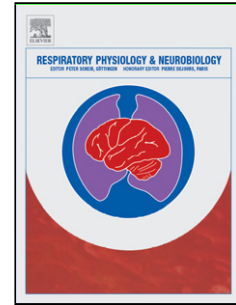# Accepted Manuscript

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The relationship between partial upper-airway obstruction and inter-breath transition period during sleep

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Running Head: Partial upper airway obstruction and breath transition time

Highlights

- Short pauses (transition periods) between breaths are often observed during sleep.

- We hypothesized that the transition period reduces as inspiratory period increases.

- Unobstructed breathing and events with partial airway obstruction were identified.

- We observed an increase in the inspiratory period during upper airway obstruction.

- A reduction in the transition period rather than the expiratory period was observed.

Abstract

Short pauses or "transition-periods" at the end of expiration and prior to subsequent inspiration are commonly observed during sleep in humans. However, the role of transition periods in regulating ventilation during physiological challenges such as partial airway obstruction (PAO) has not been investigated. Twenty-nine obstructive sleep apnea patients and eight controls underwent overnight polysomnography with an epiglottic catheter. Sustained-PAO segments (increased epiglottic pressure over ≥5 breaths without increased peak inspiratory flow) and unobstructed reference segments were manually scored during apnea-free non-REM sleep. Nasal pressure data was computationally segmented into inspiratory (T_I, shortest period achieving 95% inspiratory volume), expiratory (T_E, shortest period achieving 95% expiratory volume), and inter-breath transition period (T_{Trans}, period between T_E and subsequent T_I). Compared with reference segments, sustained-PAO segments had a mean relative reduction in T_{Trans} ($-24.7\pm17.6\%$, $P<0.001$), elevated T_I ($11.8\pm10.5\%$, $P<0.001$), and a small reduction in T_E (-3.9 ± 8.0, $P\leq0.05$). Compensatory increases in inspiratory period during PAO are primarily explained by reduced transition period and not by reduced expiratory period.

Keywords: Obstructive sleep apnea, ventilatory duty cycle, breath timing, breath segmentation, upper airway resistance.

INTRODUCTION

Clinical assessment of human respiration is focussed upon the two mechanically defined phases of inspiration and expiration. While the inspiratory airflow period is in concert with the neural inspiratory phase, expiratory airflow occurs throughout two neural phases: Stage-1 (or post-inspiration), and Stage-2 expiration. During sleep in humans, Stage-2 expiration is typically passive with expiratory flow rate and lung volume falling exponentially, driven by the mechanical time constant of the respiratory system. If the time constant and respiratory drive are sufficiently low, an end-expiratory pause (preceding the next inspiration) is often observed in higher vertebrates (Milsom, 1991). Such end-expiratory pauses, typically greater than a breath-period in duration, have been observed and characterised during apparently normal tidal breathing in neonates (Ellingson et al., 1982), as a hallmark of apnoea of prematurity (Barrington and Finer, 1991), and following augmented breaths in both adults (Vaschillo et al., 2015) and neonates (Fleming et al., 1984). In contrast, shorter end-expiratory pauses (i.e. less than one breath period) have also been observed in adult humans (Shee et al., 1985). While there is clearly a continuum of pause durations, animal models showing continued lumbar spinal cord output to the abdomen throughout the late-expiratory period (Bautista and Dutschmann, 2016) suggest these shorter pauses may be distinct from true central apnoeic pauses. However to date, these shorter end-expiratory pauses - henceforth referred to as the end-expiratory transition period to distinguish from true central pauses - remain largely uncharacterised. In particular, there have been no investigations to determine the role that these short quiescent periods in the mechanical respiratory cycle may play in regulating ventilation during physiological challenges such as the partial upper airway obstruction that characteristically occurs in patients with obstructive sleep apnea (OSA).

The reduction in upper airway muscle tone, and subsequent increase in the upper airway resistance during the inspiratory portion of the breath cycle is a normal physiological response in the transition from wake to sleep (Kay et al., 1994; Kay et al., 1996). In some individuals, a complex interaction of physiological phenotypes (including the upper airway anatomy, respiratory control stability, arousal response, and upper airway muscle activity), leads to instability of the upper airway and dynamic changes in the inspiratory upper airway resistance (Eckert et al., 2013; Wellman et al., 2004). This behaviour is most obvious clinically in patients where an upper airway obstruction is not compensated for, and ventilation is compromised in the form of apneas and hypopneas (Gleadhill et al., 1991; Sanders and Moore, 1983). Two compensatory mechanisms can be induced in an attempt to maintain desired ventilation during partial airway obstruction with a consequent increase in inspiratory upper airway resistance: (1) Increase inspiratory muscle pressure or effort (i.e. increasing the work of

breathing) (Badr et al., 1990; Younes and Riddle, 1981); and (2) increase the duty cycle of the inspiratory portion of the breath to maintain an equal tidal volume despite a reduced peak flow (Hoshino et al., 2009; Poon, 1989). The latter has been quantified by calculating the fractional inspiratory time (Jordan et al., 2007; Schneider et al., 2003); with the increase in the inspiratory period presumed to be associated with a reduced expiratory period (Onal and Lopata, 1986). However, typically studies either do not detail how the short transition periods between breaths were handled (Neder et al., 2003; Noble et al., 1987); or alternatively, may exclude patients exhibiting this breath feature from analysis (Shee et al., 1985).

As such, we hypothesized that the end-expiratory transition period between breaths will decrease during partial airway obstruction. Recognising that there was no uniform standard for the definition of the mechanical transition period, we aimed to first develop an objective and robust algorithm for breath segmentation that enables calculation of the end-expiratory transition period using nasal pressure recordings during sleep. Then, using data from patients studied simultaneously with full overnight polysomnography and epiglottic manometry, we identified transient periods of partial upper-airway obstruction using definitions similar to those proposed in literature: (1) a steady and progressively more negative peak end-inspiratory epiglottic pressure, referred to as a "crescendo" segment; and (2) a sudden increase followed by sustained duration of increased epiglottic pressure, referred to as a "sustained partial airway obstruction" segment (Black et al., 2000; Guilleminault et al., 2001). The change in end-expiratory transition period over the course of crescendo segments were examined, and the transition period during sustained partial airway obstruction segments were compared with reference segments.

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METHODS

Patients and data

We examined 37 studies with high quality nasal pressure recording out of a larger dataset of overnight polysomnogram recordings. Briefly, recruited subjects included controls from the community and recently diagnosed but untreated OSA patients. The in-laboratory polysomnogram included a standard clinical montage for the evaluation of OSA (electroencephalogram, electrooculogram, sub-mental and leg electromyogram, electrocardiogram, nasal pressure and thermistor, piezo-electric bands placed around the chest and abdomen, body position, arterial oxygen saturation monitored at the finger), with the addition of an epiglottic pressure catheter (model MCP-500; Millar Inc. Houston TX, USA). Patients were asked to sleep in the supine position, and were given an 8 hour sleep opportunity. All signals were sampled at 125Hz via a Power1401 interface and displayed using Spike 2 software (Cambridge Electronic Design Ltd, Cambridge, UK) (Edwards et al., 2014). Patients were not included for this analysis if there was <2 hours non-REM sleep, or if there was an absence of a clear expiratory signal on the nasal pressure recording. The previously applied standard criteria for sleep staging (Iber C, 2007) and scoring of arousals and respiratory events (AASM, 1999) were maintained. The current study examined 8 Controls (Apnea-hypopnea index [AHI] < 5 events/hour), 6 patients with mild OSA (5-14.9 events/hour), 7 with moderate OSA (15-29.9 events/hour), and 16 with severe OSA (≥30 events/hour). The Partners Internal Review Board approved all procedures in the initial protocol; and the University of Queensland Human Research Ethics Committee subsequently approved the retrospective analysis.

Definition and scoring of crescendo and sustained partial airway obstruction segments

Manual scoring in the current protocol was conducted in Spike2 using a custom written script. A zero-phase low-pass filter at 5Hz was applied to the on-screen display of both nasal pressure and epiglottic pressure signals. The nasal pressure signal was used as a surrogate for airflow (Ayappa et al., 2000; Heitman et al., 2002; Thurnheer and Bloch, 2004). By definition, upper airway resistance (R_{AW}) can be established through interpretation of flow and epiglottic pressure signals as $R_{AW} =$ Pressure $\div$ Flow. The use of nasal pressure rather than a calibrated mask pneumotachograph means that airway resistance cannot strictly be calculated. However, it is possible to infer transient increases in the instantaneous resistance at peak inspiratory flow, and therefore the presence of partial airway

obstruction, by identifying increased inspiratory epiglottic pressure nadir without a corresponding increase in peak inspiratory flow.

We adopted definitions from literature to score two categories of breathing segments with partial airway obstruction: (1) crescendo segments; and (2) sustained partial airway obstruction segments (Black et al., 2000; Guilleminault et al., 2001). Individual segments were constrained to a single scored sleep state (non-REM stages N1, N2 or N3); and segments occurring during AASM defined apnea were excluded to ensure the breath analysis algorithm was able to be reliably applied (i.e. breath segmentation cannot be reliably applied when flow is zero).

<u>Definition and Scoring of Crescendo Segments:</u> Crescendo segments were defined as a progressive increase in the magnitude of the inspiratory epiglottic pressure nadir without an increase in peak inspiratory nasal pressure, and terminated by a sudden reduction in epiglottic pressure swing to pre-event levels (epiglottic pressure reversal). Segments may be terminated with or without a scored EEG arousal. The sudden epiglottic pressure reversal distinguished these segments from the characteristic crescendo-decrescendo fluctuations of Cheyne-Stokes respiration. Figure 1 illustrates an example Crescendo segment.

<u>Definition and Scoring of Reference and Sustained Partial Airway Obstruction Segments:</u> Sustained partial airway obstruction segments (sustained-PAO segments) were scored in conjunction with a temporally related reference segment. Reference segments of normal breathing were selected from continuous periods satisfying all of the following criteria: (1) no scored respiratory events (and therefore no reductions in ventilation of greater than 30% below eupnea); (2) no scored EEG events; (3) a minimum duration of 30 seconds; (4) a minimum of five complete breaths; (5) a maximum duration of three minutes; (6) a steady epiglottic pressure nadir; (7) no other obvious indicators of flow-limited breathing (flattening or scooping of breath shape); (8) and occurring in the same sleep stage as the temporally associated sustained-PAO segment. Sustained-PAO segments were defined as a clear and sudden increase in epiglottic pressure nadir (at least two standard deviations above the mean of the reference segment) which: last for five or more successive breaths; is terminated by epiglottic pressure reversal; and does not satisfy crescendo segment criteria. Breaths marked as EEG arousal were permitted in the scored sustained-PAO segments; however, the associated breaths were identified and excluded during analysis so that values associated with these breaths did not contribute to the results. Figure 2 illustrates example reference and sustained-PAO segments.

Data analysis

Original (unfiltered) signals and scoring data were imported into MATLAB (The MathWorks, Inc., Natick, Massachusetts, United States) using the MATLAB/SON library interface (http://ced.co.uk/upgrades/spike2matson) and resampled at 100Hz. We calculated breath timing measurements for every non-arousal breath within each scored crescendo segment, reference segment and sustained-PAO segment. To control for variability in the breath cycle duration, we also calculated ratios of transition period, inspiratory time and expiratory time to total breath time.

Breath Segmentation into Inspiratory, Expiratory and Transition Periods: There was no consistent definition for either the manual or automated scoring of the end-expiratory inter-breath transition period. As such, we propose a definition for the objective estimation of the transition period using nasal pressure data. This was implemented as a computerized algorithm, detailed in the following six-step process. (1) To account for potential DC baseline shift and asymmetry in nasal pressure recordings, the unfiltered nasal pressure signal was offset so that the baseline is coincident with the start of inspiration as determined by the inspiratory deflection in the epiglottic pressure trace. (2) The baseline-corrected 100 Hz nasal pressure signal was low-pass filtered with a zero-phase 10-point moving average filter (cut-off frequency approximately 4.4 Hz) to produce NAP_{LPF}. (3) Preliminary breaths were isolated by locating zero-crossing points immediately before and after each extrema in the NAP_{LPF} signal. The locations of these extrema were confirmed using an additional signal, NAP_{smooth}, which identified breath excursions by inspiratory maxima and expiratory minima. The NAP_{smooth} signal was produced by applying a heavy filter to the NAP_{LPF} signal (zero-phase 2nd order Butterworth band-pass, with coefficients determined by the interpolated peak locations of a quadratic polynomial seeded within the predominant frequency from the NAP_{LPF} signal, as determined by Welch's power spectral density estimate). (4) Outlier breaths were classified if the preliminary inspiratory and expiratory durations and volumes, and the breath-by-breath minute ventilation were beyond three standard deviations of the respective means. Large outlier breaths (i.e. greater than upper limit) were identified and removed as artefactual. Small outlier breaths (i.e. smaller than lower limit, resulting from transient zero crossings) were considered as part of the transition period between surrounding breaths. (5) For each of the initial inspiration periods (and subsequently for each initial expiration period) the shortest continuous time period that would account for 95% of the total air volume for that breath movement is calculated to define the final inspiratory and expiratory periods (i.e. predominant inspiratory and predominant expiratory periods). (6) The end-expiratory transition time was defined as the interval between the end of the predominant expiratory period and the commencement of the subsequent predominant inspiratory period. Figure 3 shows the application of breath segmentation method to a sample nasal pressure trace. This method also produces a separate

end-inspiratory transition period. These periods were substantially shorter, and were not included in further analysis.

Analysis of Crescendo Segments: The number of breaths in each crescendo segment were divided into tertiles with each non-overlapping section comprising an integer number of breaths. Breath timing measurements (including inspiratory, expiratory and transition periods and ratios) were averaged for each of the three sections, and represented as both: (a) raw values, and (b) relative change from the first tertile. Each crescendo segment was then analyzed independently, with values pooled for each patient.

Analysis of reference and sustained-PAO segments: Breath timing measurements were averaged for all of the breaths within each sustained-PAO segment and within each reference segment. The average values from sustained-PAO segments were compared with those from the temporally associated reference segments. Analysis was also repeated using a mean detrended nasal pressure signal, rather than the offset corrected nasal pressure signal (as determined in Step 1 of breath segmentation) to examine whether these measurements could be made in standard clinical studies without epiglottic catheter.

Statistical Analysis: All statistical analyses were performed using MATLAB Statistics Toolbox. Values are presented as mean and standard deviation (SD); or median and inter-quartile range (IQR) as appropriate. Statistical comparisons were made using the Paired T-test with significance $P < 0.05$.

RESULTS

In total, 192 crescendo segments were identified and analyzed from 18 patients (AHI median 14.6, IQR 4.4-27.9 events/hour). Nineteen patients (51%) had either no crescendo segments, or the segments were in concert with apneic episodes. The number of crescendo segments occurring per patient ranged from 1 to 35 (median 8.5, IQR 3-17 segments/patient), with the number of breaths per crescendo segment ranging from 5 to 33 (median 7, IQR 5.3-9 breaths per crescendo segment). Figure 4 shows a statistically significant reduction in the transition period and transition period ratio across each tertile, as well as between the first and last tertile of crescendo segments.

In total, 124 reference segments and 258 sustained-PAO segments were analysed from 23 patients (AHI median 12.8, IQR 3.8-25.8 events/hour). Fourteen patients (38%) had either no sustained-PAO segments, or potential segments failed to satisfy the relevant criteria for one or more reasons (e.g. in concert with apneic episodes). The number of sustained-PAO segments per reference segment ranged from 1 to 12 (median 1, IQR 1-2 sustained-PAO segments per reference segment). The number of sustained-PAO segments per patient ranged from 1 to 40 (median 10, IQR 5-14.8 sustained-PAO segments per patient), with the number of breaths per sustained-PAO segment ranging from 5 to 434 (median 22, IQR 10.3-61 breaths sustained-PAO segment). 91% of sustained-PAO segments occurred within 10-minutes of their associated reference segment.

Inspiratory duty cycle for breaths within reference segments ranged from 31-48% (percent of total breath time), with expiratory duty cycle ranging from 33-52%, and transition duty cycle 12-31%. Breaths within sustained-PAO segments ranged from 36-56% for inspiratory duty cycle, 36-45% for expiratory duty cycle, and 9-26% for transition duty cycle.

Figure 5 shows a statistically significant reduction in the mean transition period and mean transition period ratio during sustained-PAO segments relative to the associated reference segments across the cohort (0.82 ± 0.28 vs 0.59 ± 0.21 seconds, $P\leq0.001$; and 0.19 ± 0.05 vs. 0.14 ± 0.04, $P\leq0.001$ respectively). Furthermore, the mean inspiratory time and mean inspiratory time ratio during sustained-PAO segments was significantly increased relative to the associated reference segments across the cohort (1.57 ± 0.27 vs 1.74 ± 0.27 seconds, $P\leq0.001$; and 0.39 ± 0.04 vs. 0.45 ± 0.05, $P\leq0.001$ respectively). The change in expiratory time from reference to sustained-PAO segments was less consistent, with the duration values reaching marginal statistical significance, and ratio values failing to meet statistical significance (1.68 ± 0.32 vs 1.60 ± 0.25 seconds, $P\leq0.05$; and 0.42 ± 0.04 vs. 0.41 ± 0.03, $P=0.22$ respectively). This corresponds with mean relative changes of $-24.7\pm17.6\%$, $P<0.001$, $11.8\pm10.5\%$, $P<0.001$, and -3.9 ± 8.0, $P\leq0.05$ for transition, inspiratory and expiratory

periods respectively, −22.4±16.1%, P<0.001, 14.6±10.9%, P<0.001, and −1.4±7.2, P>0.05 for transition, inspiratory and expiratory ratios respectively. The key trends in these results persisted when breath-segmentation was conducted using mean detrended nasal pressure signal (mean relative changes of −18.7±23.9%, P<0.01, 12.6±8.6%, P<0.001, and −13.5±11.8%, P<0.001 for transition, inspiratory and expiratory periods respectively).

Figure 6 shows a strong correlation between the transition period during reference segments and the change in transition period between reference and sustained-PAO segments (R= −0.688, P<0.001); and Figure 7 shows a significant correlation between the percentage change in minute ventilation (inspiratory area under curve of nasal pressure × respiratory rate, expressed as percentage change to reference segment) between reference and sustained-PAO segments and corresponding change in transition period and ratio (R= 0.484, P=0.031 and R= 0.535, P=0.015 respectively). There was no significant correlation between the AHI and the transition period.

DISCUSSION

The primary objective of this study was to investigate the role of mechanically defined transition periods in the regulation of ventilation during partial airway obstruction in sleep. We hypothesized that these short periods of zero or low ventilation at the end of mechanical defined expiratory period and prior to the inspiratory period would reduce during periods with partial airway obstruction, in order to increase the inspiratory duty cycle in an attempt to maintain eupneic ventilation. The results were consistent with our hypothesis, with a significant reduction in transition period over the course of crescendo breathing segments where instantaneous peak inspiratory resistance progressively increases; and a significant reduction in transition period in sustained-PAO segments relative to reference segments.

The inter-breath transition period and the relationship with neural respiratory timing

Neural respiratory timing is characterised by three phases: Inspiration, Stage-1 Expiration (or post-inspiration), and Stage-2 Expiration; each defined by respiratory motor nerve activity. However, such measurements are difficult/impossible to make in humans (particularly in long recordings such as sleep studies), and respiration in human clinical studies is generally observed and defined by the measurement of airflow or close surrogates such as nasal pressure. As such, the breath cycle is typically divided into only two mechanically defined periods in such studies: Inspiration (corresponding to the neural inspiration phase) and expiration (comprised of neural phases of Stage-1 and Stage-2 expiration). In this study, we conduct a detailed examination of a phenomena observed mechanically as a period with zero/low airflow at the end of expiration, prior to subsequent inspiration and coincident with neural Stage-2 expiratory terminus. There is no consistent definition for the transition period investigated, and previous work has relied on subjective manual scoring. We therefore proposed an objective definition and implemented an algorithm for the segmentation of breaths, which identified mechanical inspiratory and expiratory periods as the period representing the predominant transfer (95%) of the inspiratory and expiratory breath volume; subsequently leaving the transition period as the intervening time. However, there are two key considerations in the interpretation of these periods.

Firstly, this definition yields *two distinct* intervening transition periods for each breath: (i) An end-expiratory period (the focus of this study with a median 0.66 seconds, IQR 0.54-0.74 seconds) coinciding with the latter part of neural stage-2 expiration. Stage-2 expiration is characterised by exponential decay in flow and lung volume; and the calculated transition period therefore corresponds

to a quiescent period toward the end of this decay with an absence (or significant attenuation) of mechanical activity. (ii) An end-inspiratory period, poised between neural phases inspiration and post-inspiration (with median 0.22 seconds, IQR 0.19-0.26 seconds). This corresponds to the transition between active inspiration with laryngeal abductor activity assisting by opening the airway to reduce airway resistance; and the post-inspiration elastic recoil of the lungs with laryngeal adductor activity to regulate airflow. While laryngeal adductor activity has a critical role in pausing ventilation for numerous non-ventilatory functions (e.g. vocalisation, swallowing)(Dutschmann et al., 2014); activity is reduced during sleep (Henderson-Smart et al., 1982; Megirian and Sherrey, 1980), tending towards a rapid transition between these stages of the breath cycle. This is consistent with the relatively short duration of the end-inspiratory pause in our data. As such, our study has focussed on the end expiratory transition period, and did not include the end-inspiratory transition period in analyses. It is important to note that while we can infer the approximate alignment of the transition period with neural phases in general, we have not measured neural motor outputs in this study. Therefore, we cannot identify where these periods occur on a breath-by-breath basis in relation to key neurological markers.

Secondly, this definition yields a *finite* (i.e. non-zero) transition period for each breath. While according to the definition, transition periods could extend up to 10 seconds in duration, the median transition period was 0.66 seconds (IQR 0.54-0.74 seconds). As such, careful evaluation of these periods is important. Larger transition periods represent the occurrence of zero-flow periods or pauses in ventilation (i.e. a mechanically quiescent part of the respiratory cycle). In contrast, breaths not exhibiting a zero-flow period will be represented by shorter transition periods with smaller values reflecting a steep gradient at the transition between expiratory and inspiratory periods, and intermediate values reflecting a shallow gradient (possibly encapsulating a passive expiratory period - particularly those with a long expiratory time constant (Wiriyaporn et al., 2016)). It is important to note that the pauses quantified here are considerably shorter than the 3-10 second periods observed in previous neonate literature using manual segmentation (Ellingson et al., 1982; Holditch-Davis et al., 1994). This disparity reflects the distinction between the brief quiescent pauses within the breath cycle (and likely accompanied by some continued respiratory motor activity (Bautista and Dutschmann, 2016)) identified in this study; and true central apnoeic pauses. While it is likely that these longer central apnoeic pauses in neonates are related to immaturity of the respiratory network, it remains unclear whether they are primarily driven by chemo-reflex respiratory control instability (Edwards et al., 2013); or whether mechanisms underlying continuous respiratory rhythm generation also contribute (Bianchi and Gestreau, 2009).

Physiological interpretation

At a basic physiological level, there are two mechanisms that may act to maintain ventilation in the face of increased inspiratory airway resistance: (1) Increasing inspiratory muscle driving pressure; and (2) increasing the inspiratory duty cycle such that an equivalent tidal volume may be achieved over an extended inspiratory time. Indeed, increased fractional inspiratory time during periods of increased airway resistance has been well characterized (Jordan et al., 2007; Mooney et al., 2012; Schneider et al., 2003). However, in previous work, this increased inspiratory duty cycle has been presumed to occur in association with a decreased expiratory duty cycle (Onal and Lopata, 1986). Our results extend previous literature to demonstrate that the increase in inspiratory period is predominantly explained by a decrease in the transition period, with only limited reduction in the actual period of expired volume. These results are consistent with observations in a small number of interventional animal studies. Bowes et al. (1982) investigated carbon dioxide exposure in mature dogs with vagal blockade. The observed reduction in the total expiratory period was through a reduction in the mechanically defined end-expiratory pause. Similarly, Shore et al. (2000) observed an increase in total expiratory period when juvenile rats were exposed to ozone; but that this increase was primarily accounted for by an increased end-expiratory pause.

Our analysis suggests that there are both short- and longer-term mechanisms responsible for the adjustment of breath timing in response to dynamic changes in the airway resistance. Firstly, during periods of increased pharyngeal resistance, the reduced rise in lung volume leads to a reduction in the passive elastic recoil forces that normally offset inspiratory muscle activity. As such, mechanical inspiration continues beyond peak neural inspiratory activity. This acute mechanical phenomenon leads to a more negative alveolar pressure at the time that expiration normally begins. Therefore, expiration begins later, and has a higher time constant, due to the increased pharyngeal resistance. Thus, mechanical expiration would be expected to continue further into neural stage-2 expiratory phase compared with normal, culminating in a reduced mechanical transition period. Secondly, reduced transition time and increased inspiratory time may also be caused by changes in the timing of respiratory muscle activation. Indeed, there is evidence that both fast acting mechanoreceptors (Butler et al., 1995) and slow response chemoreceptors may be involved (Issa and Sullivan, 1983). In our study, we observed a modest reduction in transition period (approximately 1.5% of the breath cycle) between the first and second tertile of crescendo segments over as few as 2 breaths (median 2, IQR 2-3). The rapid nature of this response suggests a mechanical phenomenon or short latency mechanoreceptors rather than a chemo-response mechanism (Johnson et al., 2005). Reductions in the transition period in sustained-PAO segments relative to reference segments are of substantially greater magnitude (4.7% of the breath cycle), and were longer (median of 22 breaths). This duration

suggests adequate time for a chemoreceptor-related mechanism whereby partial airway obstruction is accompanied by a short-term reduction in ventilation, and subsequent hypercapnia leading to a central respiratory controller adjustment in breath timing.

Clinical implications

The adjustments in breath timing during partial airway obstruction potentially explain how some patients with mildly compromised upper airway anatomy maintain stable breathing while others progress to hypopnea and/or apnea (Jordan et al., 2007; Younes, 2008). In particular, patients whose airways exhibit either starling resistor (Remmers et al., 1978; Smith et al., 1988) or negative airway dependant behaviour (Isono et al., 1997) can *only* maintain flow during increased airway obstruction by compensating with an increase in the inspiratory duty cycle (Owens et al., 2012; Schneider et al., 2009). Our results show that patients with long transition periods during reference segments have the greatest reduction during sustained-PAO segments, suggesting that these patients have a greater capacity to increase their inspiratory duty cycle without a reduction in expiratory period. This is likely to be favourable energetically (i.e. does not require an increased active expiration, i.e. through abdominal muscle recruitment). Importantly, a reduction in expiratory period may not be possible in patients who also have expiratory flow limitation consequent to diseases such as asthma, COPD or bronchiectasis (Tantucci, 2013).

The use of epiglottic pressure to identify partial airway obstruction is relatively invasive, and is generally not acquired during a standard clinical polysomnogram. Our results suggest that dynamic reduction in the transition period could indicate relative changes in airway obstruction, within an individual. As such, the transition period may complement other markers such as nasal pressure shape profiles (Mooney et al., 2012) for identifying such periods in standard sleep studies. While the breath segmentation method presented here incorporates data from the epiglottic signal, a more generalizable method using mean de-trending of the nasal pressure data yielded results consistent with our primary experiment.

Methodological considerations

While we show that the reduction in the mechanical transition period is a key distinguishing feature of increased pharyngeal resistance, we are unable to comment on the corresponding respiratory motor nerve output. Recording and examination of diaphragm EMG in future studies may shed light on this. Our analysis uses nasal pressure data as a surrogate for respiratory flow (Montserrat et al., 1997; Terrill et al., 2015). While this makes the outcomes of our work clinically generalizable and easily

comparable to other research (Hosselet et al., 1998; Series and Marc, 1999), it also has some limitations. It is not a true amplitude-calibrated proxy for flow, and it is recognized that nasal prongs themselves may increase upper airway resistance (Lorino et al., 2000). The lack of calibrated flow means that while we can identify within-patient changes in resistance, we do not have absolute measures of resistance that can be compared between patients. This, along with the multifactorial nature of OSA pathology, may explain the lack of significant correlation between AHI and transition period. Further work to elucidate these mechanisms should match patients for airway collapsibility, and measure upper airway resistance using epiglottic manometry and calibrated mask pneumotachograph. Our estimates of breath timing will be subtly influenced by amplitude scaling, however they will be far less sensitive than more direct breath shape markers. While our protocol minimized the elapsed time between reference and sustained-PAO segments, there is a possibility that subtle changes in instrumentation (e.g. nasal cannula position within the nares) may have occurred between these periods. However, the results we observed during the crescendo segments were consistent with the trends observed during sustained-PAO segments. The crescendo segments are relatively short, and as such are very unlikely to be influenced by altered instrumentation.

CONCLUSIONS

We present a simple and reliable method for segmenting the breaths observed in nasal pressure recordings into inspiratory, expiratory and inter-breath transition periods. Consistent with previous literature, we observed an increase in the inspiratory period during sustained-PAO segments relative to reference segments; and that inspiratory period increased over the course of crescendo segments characterized by increasing instantaneous peak inspiratory resistance. However, our results show that this increase in inspiratory period is primarily explained by a reduction in the transition period rather than the expiratory period. Our results suggest that patients who have a longer transition period at baseline have a greater capacity to compensate for airway obstruction by adjusting breath timing. Long transition periods would be easy to identify in the clinic manually (identified as inter-breath pauses), or using our algorithm; and dynamic reductions in these periods may provide a useful indication of the instantaneous resistance at peak inspiratory flow, not otherwise identifiable in the standard polysomnogram.

DISCLOSURE STATEMENT

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Figures Legend

Figure 1. Example 90 second window demonstrating a defined crescendo segment. Note the increasing epiglottic pressure (Pepi) swings in association with a mild reduction in nasal pressure (Pnasal) signal, bounded by arousal activity. The crescendo segment terminates with an epiglottic pressure reversal, where epiglottic pressure swings return to pre-event levels following the final breath of the crescendo segment.

Figure 2. Example five-minute window showing a reference segment (left shaded block) with normal epiglottic pressure (Pepi) swings, and a sustained partial airway obstruction segment (sustained-PAO, right shaded block) with significantly increased epiglottic pressure swings. Despite a reduction in nasal pressure (Pnasal) signal occurring throughout this segment, a modest signal excursion remains. There may be more than one sustained-PAO segment that relates to any given reference segment, however, each subsequent sustained-PAO segment must occur within contiguous sleep (of any stage) from the reference segment. If an arousal to wake occurs, or if the reference segment criteria are (re)satisfied, a new reference segment is scored, which is then associated with sustained-PAO segments that immediately follow.

Figure 3. The Initial (upper horizontal bars) and Final (lower horizontal bars) breath segmentation for inspiratory periods (shaded green), expiratory periods (shaded blue), and transition periods (shaded magenta). The modified timing is defined as the minimum elapsed time to achieve 95% of the initial breath volume. The transition period (shaded magenta and magenta horizontal bars) is defined using the modified timing, as the period between the end expiratory marker and the subsequent start inspiratory marker.

Figure 4. The transition period (T_{Trans}) within each tertile of the scored crescendo segments. (A) The absolute transition period (seconds) for each tertile; (B) the change in the transition period relative to the first tertile of the crescendo segment; (C) the transition period ratio (T_{Trans}/T_{Tot}) for each tertile; and (D) the change in the transition period ratio relative to the first tertile of the crescendo segment. Black lines show the mean values for each individual; and dashed red lines show the population mean and confidence interval. Significance value ** is $P \leq 0.01$, *** is $P \leq 0.001$.

Figure 5. Breath timing during reference segments (Ref) and sustained partial airway obstruction segments (s-PAO). (A) The mean transition period (T_{Trans}), inspiratory time (T_I) and expiratory time (T_E); and (B) mean transition period ratio, inspiratory ratio and expiratory ratio to total breath time

(T_{Tot}). Black lines show the mean values for each individual; and dashed red lines show the population mean and confidence interval. Significance value * is $P \leq 0.05$, *** is $P \leq 0.001$.

Figure 6. Scatter plots showing (A) the transition period (T_{Trans}) during reference segments and sustained partial airway obstruction segments (s-PAO); (B) the transition period during reference segments and the change in transition period from reference to sustained-PAO segments; (C) the transition period ratio (T_{Trans}/T_{Tot}) during reference segments and the transition period ratio during sustained-PAO segments; and (D) the transition period ratio during reference segments and the change in transition period ratio from reference to sustained-PAO segments. The statistics presented are for Pearson's correlation co-efficient.

Figure 7. Scatter plots showing the percent change in minute ventilation between reference and sustained partial airway obstruction segments ($\Delta VE\%$) and: (A) the transition period (T_{Trans}) during reference segments; (B) the change in transition period from reference to sustained partial airway obstruction segments; (C) the transition period ratio (T_{Trans}/T_{Tot}) during reference segments; and (D) the change in transition period ratio from reference to sustained partial airway obstruction segments. The statistics presented are for Pearson's correlation co-efficient. While (B) and (D) show significant correlations, there is considerable variability in the data. For example, two patients in plot B show a change in T_{Trans} magnitude of greater than 0.6 seconds, however one has less than a 5% reduction in $\Delta VE\%$, while the other has a reduction in $\Delta VE\%$ of over 50%.