Infant tidal flow–volume parameters and arousal state

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Abstract

Background Infant lung function can be assessed with tidal flow–volume (TFV) loops. While TFV loops can be measured in both awake and sleeping infants, the influence of arousal state in early infancy is not established. The aim of the present study was to determine whether TFV loop parameters in healthy infants differed while awake compared to the sleeping state at 3 months of age.

Methods From the population-based Scandinavian Preventing Atopic Dermatitis and ALLergies in children (PreventADALL) birth cohort, 91 infants had reproducible TFV loops measured with Exhalyzer® D in both the awake and sleeping state at 3 months of age. The TFV loops were manually selected according to a standardised procedure. The ratio of time to peak tidal expiratory flow (t_{PTEF}) to expiratory time (t_E) and the corresponding volume ratio (V_{PTEF}/V_E), as well as tidal volume (V_T) and respiratory rate were compared using nonparametric tests.

Results The mean (95% CI) t_{PTEF}/t_E was significantly higher while awake compared to the sleeping state: 0.39 (0.37–0.41) *versus* 0.28 (0.27–0.29); with the corresponding V_{PTEF}/V_E of 0.38 (0.36–0.40) *versus* 0.29 (0.28–0.30). The V_T was similar, while the respiratory rate was higher while awake compared to the sleeping state: 53 (51–56) breaths·min^{-1} *versus* 38 (36–40) breaths·min^{-1}.

Conclusion Higher t_{PTEF}/t_E, V_{PTEF}/V_E and respiratory rate, but similar V_T while awake compared to the sleeping state suggests that separate normative TFV loop values according to arousal state may be required in early infancy.

Introduction

Lung function is an important indicator of respiratory health. Impaired lung function in early infancy tracks into later life with increased risk of future respiratory diseases [1]. Although several techniques to measure infant lung function exist, few are feasible in clinical settings or larger epidemiological studies, if sleep or sedation is necessary to obtain sufficient collaboration for reproducible measurements. Tidal flow–volume (TFV) loop measurements require minimal cooperation beyond a calm infant [2], presenting compound measurements of lung function including the size of the conducting airways, mechanical characteristics of the lung [3] and respiratory control [4]. In addition, the technique may expose abnormal breathing patterns and airway obstruction [5]. To reduce intra-individual variation, lung function measurements should be standardised and performed under similar circumstances [6], including arousal state, which beyond infancy usually is in the awake state. Infants and children with obstructive airways diseases generally reach peak tidal expiratory flow (PTEF) earlier (and consequently after a smaller expiratory volume (V_E)) during the expiratory phase [7]. The most commonly used TFV loop parameter is the ratio of time to peak tidal expiratory flow (t_{PTEF}) to expiratory time (t_E) [8], of which lower ratios have been demonstrated to capture

airway obstruction [9, 10], associated with the development of asthma [8]. In a Norwegian longitudinal birth cohort study, reduced lung function in adolescents with asthma, atopic dermatitis and allergic rhinitis was present already at birth, observed as a lower ratio of t_{PTEF}/t_E measured in the awake state [11]. Another closely related TFV loop parameter is the ratio of volume at peak tidal expiratory flow (V_{PTEF}) to V_E, of which lower values have been reported in children with airway obstruction [7, 12].

Historically, TFV loop measurements have mostly been performed in sleeping or sedated infants [13], and according to existing guidelines measurements are commonly obtained during quiet sleep to enable the recording of undisturbed regular breathing [6]. Yet, there is a need for research on lung function techniques allowing for repeated measurements in awake young children [2]. One study from the early 1990s reported that TFV loop measurements in 19 infants appeared more stable in the awake, rather than in the sleeping arousal state [14]. The methodology at the time allowed sampling of maximum four loops per test, in contrast to present software, allowing longer sampling periods of representative TFV loops. The authors are unaware of other studies assessing the influence of arousal state on the t_{PTEF}/t_E and V_{PTEF}/V_E ratio in healthy infants. Therefore, this study aimed to determine if TFV loop parameters differed in the awake compared to sleeping state at 3 months of age, focusing on the most commonly used parameters including the t_{PTEF}/t_E and V_{PTEF}/V_E ratios.

Methods

Study design and study population

In the present study we included 91 infants with TFV loops measured both in the awake and sleeping state at the 3-month clinical investigations in the Preventing Atopic Dermatitis and ALLergies in children (PreventADALL) study, a Scandinavian multicentre population-based prospective birth cohort described elsewhere [15]. Briefly, infants were recruited antenatally by enrolling their pregnant mothers in connection with the national routine ultrasound examination at ~18 weeks gestational age (GA) at hospitals and separate maternal clinics at Oslo University Hospital and Østfold Hospital Trust (Norway) and in the region of Stockholm (Sweden). Mothers were recruited between December 2014 and October 2016, while their singleton or twin infants born without severe disease at a gestational age of ⩾35 weeks were enrolled at birth. Infants attended regular follow-up visits after birth, the first at 3 months of age [15].

Informed written consent was collected from the mothers at enrolment, and parents at infant inclusion. The PreventADALL study was approved by the regional committee for medical and health research ethics in South-Eastern Norway (2014/518) and in Sweden (2014/2242-31/4), as well as registered at clinicaltrials.gov (NCT02449850).

Data collection

Lung function measurements

In the PreventADALL study, 1183 infants had at least one acceptable TFV loop measurement at 3 months of age: 899 in the awake state, 375 in the sleeping state, and 91 in both the awake and sleeping state. Overall, lung function measurements were performed prior to other investigations, in the arousal state in which the infants arrived at the study site, in order to ensure that infants were calm. If the first TFV measurement was conducted while the infant was asleep, a second test was attempted in the awake state. Infants were positioned in a supine position in the caregiver's lap or the cot, whichever was successful. Using the Exhalyzer® D (Eco Medics, Duernten, Switzerland), TFV loops were sampled through an ultrasound flow head and a dead-space reducer, with a carefully fitted face mask with an air-inflated rim, by a stable grip over the mouth and nose of the infant, using fingers to control for minimal leakage from the mask, according to existing guidelines [6, 16]. When the infant breathed calmly and evenly into the mask, loop sampling started, aspiring to record at least 10 consecutive breaths. Infants were considered "awake" if they were quietly alert (open eyes, lively face, quiet body movements) or actively alert (active face and body movements). Infants were considered "sleeping" if drowsy (closed eyes, dozing), lightly sleeping (moving while sleeping, startling at noises) or deeply sleeping (laying quietly without body movements). A dedicated group of trained personnel performed the TFV loop measurements, and three reviewers manually selected acceptable TFV loops using a set of standardised criteria according to a previously described method [17]. Infant arousal state was added as a comment in each test in the software programme, and therefore blinded evaluation of the TFV measurements and loop selection was not feasible.

Outcomes and definitions

The primary outcomes were the t_{PTEF}/t_E and corresponding V_{PTEF}/V_E ratios.

TABLE 1 Outcomes and definitions	
Time parameters	
t_{PTEF}	Time to peak tidal expiratory flow (s)
t_E	Expiratory time (s)
t_{PTEF}/t_E	Time to peak tidal expiratory flow to expiratory time
Volume parameters	
V_{PTEF}	Volume at peak tidal expiratory flow (mL)
V_E	Expiratory volume (mL)
V_{PTEF}/V_E	Volume at peak tidal expiratory flow to expiratory volume
V_T	Tidal volume (mL)

The secondary outcomes were the additional time and volume parameters, given in seconds and millilitres, as outlined in table 1. Additionally, the number of breaths available in each test, as well as respiratory rate and the mean intra-individual variation (given as standard deviation) are reported in the awake and sleeping state.

A t_{PTEF}/t_E <0.20 was pre-defined as a ratio value of interest, based on previous studies in awake infants identifying clinical and epidemiological associations to subsequent obstructive airway disease [8, 18, 19]. Ratios >0.25 in awake [18], sleeping [20, 21] or sedated [21–23] infants have previously been reported as normal [18, 20–23]. As we were interested in the lower range of the ratio t_{PTEF}/t_E, comparison of ratios below 0.20 and 0.25 between the awake and sleeping measurements were reported.

Statistical analyses

Data are presented in numbers and percentages or mean (95% CI) or mean±SD. Comparisons between measurements with skewed distribution in the awake and sleeping state were performed by Wilcoxon signed-rank tests of paired samples. The McNemar test was conducted to compare cut-off values of the t_{PTEF}/t_E and V_{PTEF}/V_E ratios between the two arousal states. Conditional logistic regression was used to estimate odds and probability for defined cut-off values of the two ratios between paired awake and sleeping measurements. The statistical significance was set to 0.05. Statistical analyses were conducted using IBM SPSS Statistics 26 software. This project used data from the PreventADALL project database at the Service for Sensitive Data at Oslo University, which comply with General Data Protection Regulation legislation.

Results

The 91 infants, of whom 51 (56.0%) were girls had a mean±SD gestational age of 40.0±1.3 weeks at birth and a mean±SD age of 91.0±7.3 days at the time of the 3-month investigation. The birth and background characteristics of the infants are given in table 2. The mean (95% CI) number of breaths available for analyses was significantly lower, and the respiratory rate was significantly higher while awake compared to the sleeping state (table 3).

The mean (95% CI) t_{PTEF}/t_E of 0.39 (0.37–0.41) in the awake state was significantly higher than that in the sleeping state (0.28, 0.27–0.29), as shown in table 3 and figure 1a. While the mean t_{PTEF} was similar

TABLE 2 Background characteristics of the study population (n=91) with tidal flow–volume loop measurements in both the awake and sleeping arousal state	
Birth characteristics	
Girls (n=91)	51 (56.0)
Gestational age at birth (weeks) (n=91)	40.0±1.3
Birth weight (kg) (n=91)	3.5±0.5
Birth length (cm) (n=82)	50.3±2.0
Infants at 3-month investigation	
Age (days) (n=91)	91.0±7.3
Weight (kg) (n=91)	6.1±0.8
Length (cm) (n=89)	61.5±2.3
Parents	
Mother's age (years) (n=91)	32.7±3.6
Nordic origin of mothers[#] (n=87)	82 (94.3)
Asthma reported in mother (n=87)	19 (21.8)
Asthma reported in father (n=85)	8 (9.4)

Data are presented as n (%) or mean±SD. [#]: based on maternal country of origin.

TABLE 3 Tidal flow–volume loop parameters in the awake and sleeping state (n=91). The mean of the individual standard deviation is given to demonstrate variability related to arousal state and number of breaths

	Awake	Sleeping	p-value[#]
Lung function parameters			
Number of loops included	21 (18–24)	33 (30–37)	**<0.001**
Respiratory rate (breaths·min^{-1})	53 (51–56)	38 (37–40)	**<0.001**
Standard deviation	5.93 (5.26–6.61)	4.27 (3.74–4.81)	**<0.001**
PTEF (mL)	110 (105–116)	84.1 (80.0–88.2)	**<0.001**
Standard deviation	17.2 (15.3–19.0)	12.1 (10.9–13.4)	**0.006**
Time parameters			
t_{PTEF}/t_E ratio	0.39 (0.37–0.41)	0.28 (0.27–0.29)	**<0.001**
Standard deviation	0.06 (0.05–0.06)	0.05 (0.05–0.05)	**0.006**
t_{PTEF} (s)	0.24 (0.23–0.26)	0.25 (0.24–0.26)	0.402
Standard deviation	0.04 (0.04–0.04)	0.04 (0.04–0.04)	0.332
t_E (s)	0.65 (0.61–0.68)	0.93 (0.88–0.98)	**<0.001**
Standard deviation	0.08 (0.07–0.09)	0.13 (0.12–0.14)	**<0.001**
Volume parameters			
V_{PTEF}/V_E ratio	0.38 (0.36–0.40)	0.29 (0.28–0.30)	**<0.001**
Standard deviation	0.53 (0.48–0.58)	0.52 (0.48–0.56)	0.675
V_{PTEF} (mL)	18.4 (17.2–19.6)	14.2 (13.5–15.0)	**<0.001**
Standard deviation	4.07 (3.69–4.45)	2.89 (2.68–3.10)	**<0.001**
V_E (mL)	49.1 (46.4–51.7)	49.7 (47.4–51.9)	0.834
Standard deviation	8.16 (7.46–8.86)	6.17 (5.60–6.73)	**<0.001**
V_T (mL)	49.4 (46.7–52.1)	50.5 (48.2–52.8)	0.598
Standard deviation	7.76 (7.07–8.46)	6.00 (5.41–6.59)	**<0.001**

Data are presented as mean (95% CI), unless otherwise stated. PTEF: peak tidal expiratory flow; t_{PTEF}: time to peak tidal expiratory flow; t_E: expiratory time; V_{PTEF}: volume at peak tidal expiratory flow; V_E: expiratory volume; V_T: tidal volume. Bold type represents statistical significance. [#]: Wilcoxon signed-rank test of paired samples.

between the arousal states, the mean t_E was significantly shorter while awake compared to the sleeping state (table 3). The corresponding volume ratio (V_{PTEF}/V_E) was significantly higher while awake compared to the sleeping state, as shown in table 3 and figure 1b. The mean tidal volume (V_T) and V_E were similar in the awake and sleeping states, whereas mean V_{PTEF} was significantly higher while awake (table 3). The mean standard deviation for the time parameter ratio t_{PTEF}/t_E, reflecting the loop-to-loop variability, was larger in awake compared to sleeping measurements (p=0.006), while the variability for the volume parameter ratio V_{PTEF}/V_E was similar between the two arousal states.

A t_{PTEF}/t_E <0.20 was observed in none of the 91 infants in the awake state and in six (6.6%) in the sleeping state, while six (6.6%) infants had a t_{PTEF}/t_E <0.25 while awake compared to 33 (36.3%) in the sleeping state (p<0.001). Three out of the six awake infants with a t_{PTEF}/t_E <0.25 had a t_{PTEF}/t_E <0.25 in the sleeping state. A V_{PTEF}/V_E <0.20 was observed in none of the awake infants and one (1.1%) of the sleeping infants, whereas three (3.3%) infants had a V_{PTEF}/V_E <0.25 while awake compared to 19 (20.9%) in the sleeping state (p<0.001). None of the three infants with a V_{PTEF}/V_E <0.25 while awake had a V_{PTEF}/V_E <0.25 in the sleeping state.

Compared to awake infants, the OR (95% CI) for having a ratio of t_{PTEF}/t_E and V_{PTEF}/V_E <0.25 was significantly higher among sleeping infants: unadjusted OR 10.0 (3.05–32.8) and 6.33 (1.87–21.4), respectively (p<0.005) (figure 2). Stratified by arousal state, the distribution of the t_{PTEF}/t_E and V_{PTEF}/V_E ratios are shown in supplementary figure S1.

Discussion

Lung function parameters were influenced by arousal state among 91 healthy 3-month-old infants, with higher t_{PTEF}/t_E and V_{PTEF}/V_E in the awake *versus* sleeping state. In the awake compared to the sleeping state t_E was shorter while t_{PTEF} was similar, whereas for the volume parameters, V_E was similar while the V_{PTEF} was higher. Infants had 10 and six times higher odds, respectively, of a t_{PTEF}/t_E and V_{PTEF}/V_E <0.25 while awake compared to the sleeping state.

The higher t_{PTEF}/t_E ratio while awake compared to the sleeping state is in line with a study from 1992 demonstrating a higher mean t_{PTEF}/t_E in awake compared to sleeping state in 19 healthy newborn
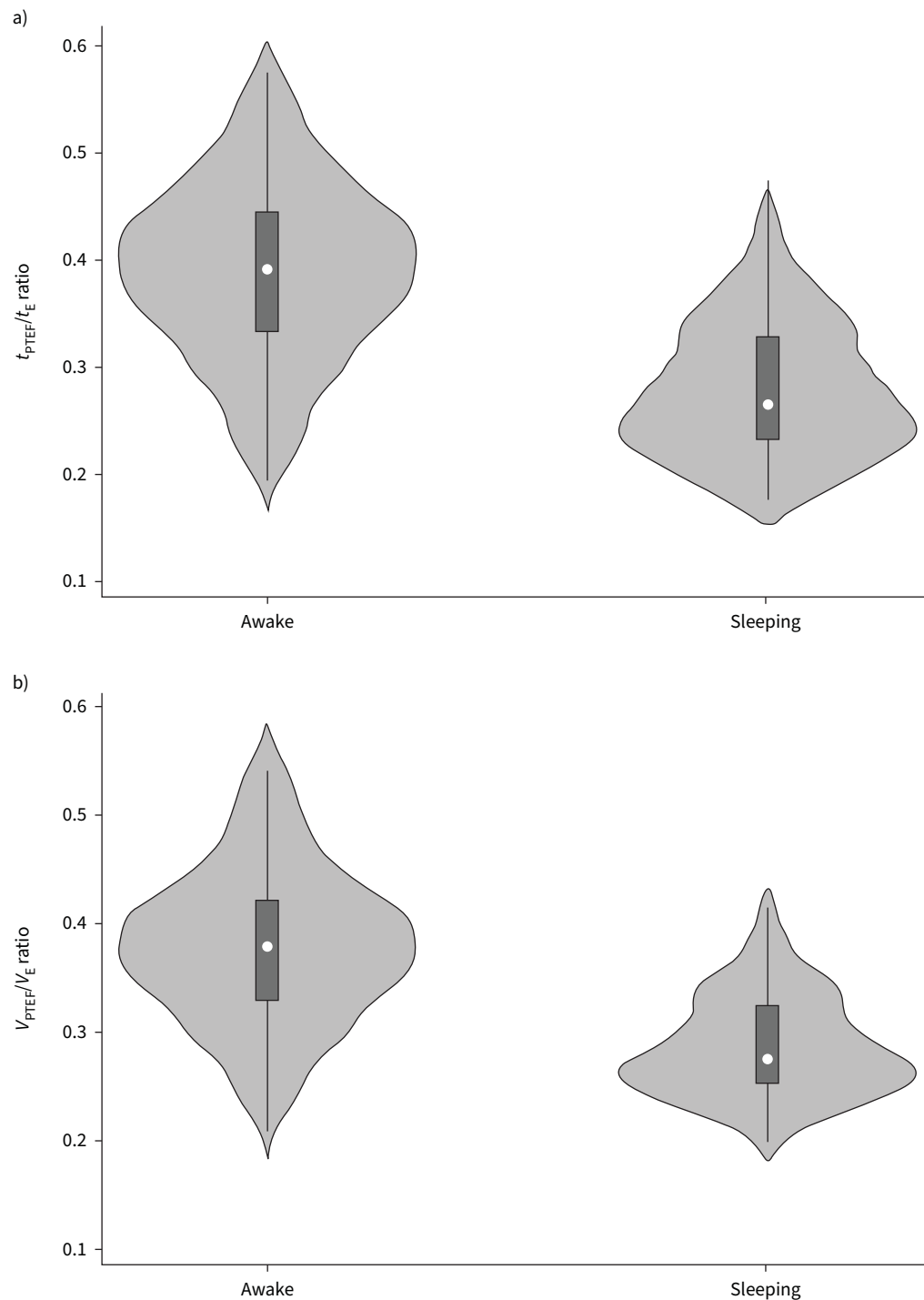
a)

b)

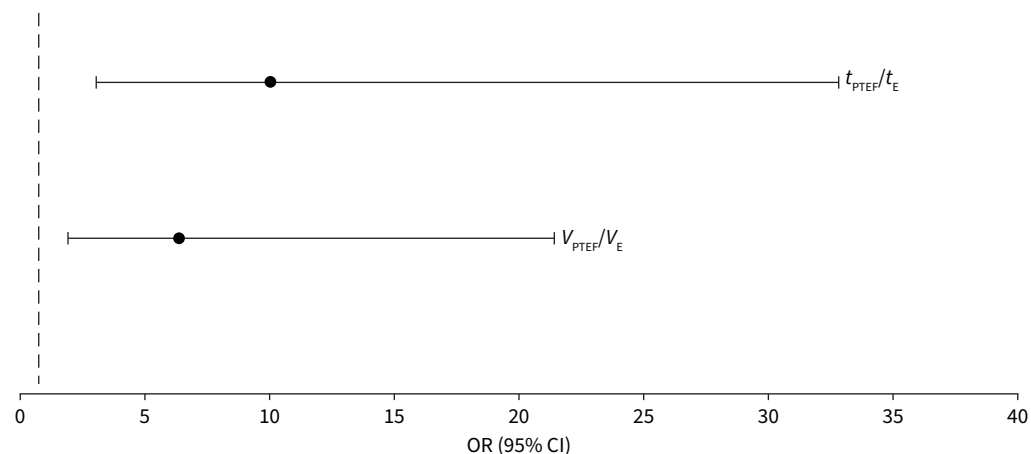FIGURE 1 Distributions of a) the ratio of time to peak tidal expiratory flow (t_{PTEF}) to expiratory time (t_E) and b) the volume at peak tidal expiratory flow (V_{PTEF}) to expiratory volume (V_E) in awake and sleeping tidal flow–volume loop measurements (n=91).

infants [14]. We are not aware of other studies comparing tidal lung function measures in awake and sleeping infants, older children or adults. The t_{PTEF} was similar, while the t_E, was longer in sleeping compared to awake state, possibly explained by the physiological inhibition of skeletal muscle tone during sleep that may lead to increased diaphragmatic work of breathing, and subsequently a longer expiratory time compared to the awake state [24]. In a study examining the effect of sleep phases on TFV loop measurements in sedated wheezing infants, t_{PTEF}, t_E and t_{PTEF}/t_E varied during sleep and lower values were

FIGURE 2 OR (95% CI) for ratios of time to peak tidal expiratory flow (t_{PTEF}) to expiratory time (t_E) and volume at peak tidal expiratory flow (V_{PTEF}) to expiratory volume (V_E) <0.25 among sleeping compared to awake tidal flow–volume loop measurements (n=91).

probably related to decreased respiratory muscle tone [25]. Interestingly, breathing during sleep is more prone to airway obstruction [26], and nocturnal worsening of asthma related symptoms is common [27]. Thus, it is possible that asthma symptom thresholds are lower in the sleeping compared to the awake state, reflected in the overall lower t_{PTEF}/t_E in sleeping infants.

Higher respiratory rates were observed while awake compared to the sleeping state, in line with previously reported findings [28]. During sleep, in addition to the reduced tone in respiratory muscles, healthy infants' breathing patterns are typically regular with reduced respiratory rate and lung volumes, decreasing ventilation, which together with a supine position may cause airway flow restriction [29]. As all lung function measurements were performed in a supine position and the tidal volumes were similar between the arousal states, the overall lower respiratory rates in the sleeping state may also have influenced the time and volume ratios. Supporting this theory, a previous study found a positive correlation between respiratory rate and t_{PTEF}/t_E in sedated infants with a history of wheezing [30].

A swifter rise to t_{PTEF} has previously been described as a distinct feature of airway obstruction in adults and infants [12, 22, 31]. Our findings indicating that t_{PTEF} remains stable irrespective of arousal state as well as correlating with obstructive airways disease [19] suggest that t_{PTEF} may be useful as an outcome variable in future studies.

In contrast to the shortened t_E, we observed that V_E and V_T remained similar between the arousal states, while the V_{PTEF} was higher among awake infants, resulting in higher ratio V_{PTEF}/V_E in the awake measurements.

The loop-to-loop variability of the t_{PTEF}/t_E ratio was larger while awake compared to the sleeping state, in line with a previous study [14], while no significant difference in the variability of V_{PTEF}/V_E was observed between the arousal states. These differences may reflect the more irregular breathing pattern seen in healthy awake infants [29]. Moreover, the lower number of available breaths for analysis might explain the larger variation expressed as standard deviation of t_{PTEF}/t_E seen among awake infants. The t_{PTEF}/t_E and V_{PTEF}/V_E ratio showed a wider distribution of ratios in the awake tests, while a larger proportion of the sleeping infants had ratios in the lower range.

Strengths and limitations
Our findings are based upon healthy infants, standardised to 3 months of age, in a study of almost five times the number of subjects compared to the only previous study that to our knowledge reported measures in awake and sleeping infants [14]. Furthermore, our results were based upon a mean number of available TFV loops per test of 21 and 33 in the awake and sleeping states, respectively, in line with the guidelines suggesting ⩾10 loops [7].

The TFV loop measurements and subsequent loop selection were not performed by blinded reviewers unaware of infant arousal state, and may introduce expectation bias. However, the thorough loop selection

of TFV loop measurements performed according to a validated standard operating procedure [17] strengthen the reliability of our findings. Lung function was only measured at one time point in early infancy in the PreventADALL study, lacking longitudinal TFV loop data. Therefore, the authors are unable to establish whether the differences in TFV loop parameters, including the time and volume ratios, between the awake and sleeping states will remain stable or change with increasing age and decreasing respiratory rate. In a study by ANIK and UYSAL [32], the authors found a positive correlation between age and t_{PTEF}/t_E ratio among awake infants and children aged 8–23 months with recurrent wheeze, with or without high risk of atopy. Therefore, the generalisability of our findings, differences and similarities, may be limited to TFV loop measurements in young infants. Potential effect-modifying factors, such as differences in respiratory rate, might balance out between the awake and sleeping arousal state in normal growth development [28].

Clinical implications for future research

Our findings provide evidence that both awake and sleeping TFV loop measurements are feasible in infancy, while tidal breathing parameters in early infancy should be interpreted according to arousal state with separate normative values and probably different cut-off values for t_{PTEF}/t_E and V_{PTEF}/V_E. The arousal state should be stated in measurements with TFV loop measurements in both research and clinical settings.

Although impaired lung function in infancy in both awake and sleeping measurements has been associated with later obstructive airways disease, standardisation of arousal state, optimal parameters for clinical as well as research use and clinical usefulness of such parameters are yet to be determined.

Conclusion

Lung function measured by TFV loops differed according to arousal state, with higher t_{PTEF}/t_E and V_{PTEF}/V_E ratios while awake compared to the sleeping state, at 3 months of age. Future studies should focus on identifying appropriate TFV loop values in infants, in which separate normative TFV loop values according to arousal state in early infancy may be required.

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