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Time to Lung Volume Stability After Pressure Change During High-Frequency Oscillatory Ventilation

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OBJECTIVES: Clinicians have little guidance on the time needed before assessing the effect of a mean airway pressure change during high-frequency oscillatory ventilation. We aimed to determine: 1) time to stable lung volume after a mean airway pressure change during high-frequency oscillatory ventilation and 2) the relationship between time to volume stability and the volume state of the lung.

DESIGN: Prospective observational study.

SETTING: Regional quaternary teaching hospital neonatal ICU.

PATIENTS: Thirteen term or near-term infants receiving high-frequency oscillatory ventilation and muscle relaxants.

INTERVENTIONS: One to two cm H_2O mean airway pressure changes every 10 minutes as part of an open lung strategy based on oxygen response.

MEASUREMENTS AND MAIN RESULTS: Continuous lung volume measurements (respiratory inductive plethysmography) were made during the mean airway pressure changes. Volume signals were analyzed with a biexponential model to calculate the time to stable lung volume if the model R^2 was greater than 0.6. If volume stability did not occur within 10 minutes, the model was extrapolated to maximum 3,600 s. One-hundred ninety-six mean airway pressure changes were made, with no volume change in 33 occurrences (17%). One-hundred twenty-five volume signals met modeling criteria for inclusion; median (interquartile range) R^2, 0.96 (0.91–0.98). The time to stable lung volume was 1,131 seconds (718–1,959 s) (mean airway pressure increases) and 647 seconds (439–1,309 s) (mean airway pressure decreases), with only 17 (14%) occurring within 10 minutes and time to stability being longer when the lung was atelectatic.

CONCLUSIONS: During high-frequency oscillatory ventilation, the time to stable lung volume after a mean airway pressure change is variable, often requires more than 10 minutes, and is dependent on the preceding volume state.

KEY WORDS: high-frequency oscillatory ventilation; infant; lung mechanics; mechanical ventilation

The safe and effective delivery of high-frequency oscillatory ventilation (HFOV) depends on achieving an optimal lung volume (1). During HFOV, the principal determinant of lung volume is the applied mean airway pressure (P_{AW}) (2). Optimally applied, P_{AW} maximizes oxygenation (3–5) and lung mechanics (6–8), whereas an inappropriate P_{AW} increases adverse events (9) and cardiovascular compromise (10) due to either atelectasis or overdistension. The most recent European guidelines on the management of preterm respiratory distress syndrome (RDS) recommend using an open lung strategy on initiation of HFOV (11). Open lung strategies involve mapping the quasi-static pressure-volume relationship of the lung using a series of increasing, and then decreasing, P_{AW} steps applied over a fixed period of time, with the

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purpose of identifying the point of optimal oxygenation upon the deflation limb of the pressure volume relationship of the lungs. Usually, Spo_2 and Fio_2, as indirect indicators of lung volume, are used to guide the response (3, 12, 13). Critical to the practical application of open lung strategies is an understanding of how rapidly lung volume stabilizes after each P_{AW} changes.

Due to the nonlinear mechanical properties of the respiratory system, changes in lung volume follow an exponential plateau pattern after an adjustment in P_{AW} (14–16). The time required to achieve a new steady-state lung volume is determined by the time constant of the respiratory system. An understanding of this relationship has important clinical implications for the application of open lung strategies during HFOV. Adequate time must be allowed for achievement of the desired new lung volume with changes in Spo_2 reflecting the new volume (7). In preterm infants with early RDS receiving HFOV as first intention invasive respiratory support, lung volume stabilizes within 5 minutes of a 2-cm H_2O P_{AW} change and varies based on the volume state of the lung; well recruited lungs require less time than partially recruited lungs (17). Many infants receiving HFOV do not have acute RDS, and many are not preterm (18). Thus, the poor lung compliance and short time constants associated with acute RDS in preterm infants are unlikely to be translatable to the majority of infants being managed with HFOV whether as elective or rescue therapy, or younger children with acute respiratory distress syndrome (ARDS).

We aimed to determine: 1) time to stable lung volume after a P_{AW} change during HFOV and 2) the relationship between time to stable lung volume and the volume state of the lung. These aims are addressed by applying different exponential models of the volumetric behavior of the lung against time from a series of infants we have previously reported as part of another study, in which the clinical and volume response to an open lung strategy was measured (3, 8).

MATERIALS AND METHODS

This study was performed at the Neonatal Unit of the Royal Children's Hospital, Melbourne, and was approved by the Royal Children's Hospital Human Research and Ethics Committee (number 23022B). Prospective, written, informed parental consent was obtained for each infant prior to enrollment in the study. The dataset used for this study was recorded from infants studied from 2004 to 2006. A detailed methodology has been published previously (3, 8).

Study Population

Infants receiving HFOV, using the Sensormedics 3100A oscillator (Sensormedics, Yorba Linda, CA), and muscle-relaxants were studied. Infants were not eligible if they had congenital heart or lung disease (such as congenital diaphragmatic hernia or cystic lung lesions), a known chromosomal anomaly, refractory hypotension despite maximal inotrope and fluid support, or an Fio_2 of greater than 0.9.

Measurements

Proximal P_{AW} was measured at the airway opening using a Florian respiratory monitor (Acutronic Medical Systems, Zug, Switzerland). Real-time relative changes in lung volume were measured with a low-pass-filtered, direct current (DC)-coupled respiratory induction plethysmograph (RIP; Respitrace 200, Noninvasive Monitoring Systems, North Bay Village, FL) using the technique we have described previously to derive an uncalibrated volume signal in volts (3, 19), following signal thermal stability (20).

The pressure-volume relationship of the lung was mapped in all infants as part of another study (3). To summarize this protocol: after achieving an Fio_2 that maintained a stable Spo_2 of 90–94%, a series of 2-cm H_2O P_{AW} increases were made every 10 minutes (inflation limb) from the P_{AW} in clinical use ($P_{initial}$) until no further improvement in Spo_2 was noted over two consecutive P_{AW} increments (P_{max}; functional total lung capacity). The deflation limb was then mapped by decreasing P_{AW} in 1–2 cm H_2O steps every 10 minutes (deflation limb) until the P_{AW} was identified that resulted in Spo_2 less than 85% for 5 minutes (P_{final}; closing pressure of the lung) (3, 4, 21).

Data Collection and Analysis

P_{AW} and V_{RIP} were recorded at 200 Hz, and digitized and analyzed using the custom-built software (LabVIEW, National Instruments, Austin, TX). From the RIP recording for each P_{AW} step, the amplitude (V_{TRIP}; volts) and trough of each tidal oscillation were determined, with the trough voltage defining end-expiratory volume (V_{LRIP}). P_{AW} and V_{LRIP} were normalized to the

values at P_{max} (100%) and P_{final} (0%) (3). Initially, the time course of the V_{LRIP} signal was analyzed to determine if any volume change occurred within the 10-minute period (**Fig. 1**). A detectable change was defined as a difference between the initial and final V_{LRIP} voltages of at least 1/3 of the average oscillatory amplitude (V_{TRIP} value) at that P_{AW}. This definition was chosen to account for the facts that RIP cannot be reliably calibrated to a known volume during HFOV and has a 3–6% measurement error, and that V_{TRIP} would represent 1–3 mL/kg (22). The P_{AW} steps associated with identification of P_{max} and P_{final} were excluded as, by definition, these are associated with significant Spo_2 (and volume) changes related to clinically apparent overdistension and atelectasis.

In the recordings in which V_{LRIP} did change, a second-order biexponential model was applied to the time course signal (23):

$$\text{Inflation Limb: } y = y_0 + a(1 - e^{-t/\tau 1}) + b(1 - e^{-t/\tau 2})$$

$$\text{Deflation Limb: } y = y_f + a.e^{-t/\tau 1} + b.e^{-t/\tau 2}$$

where y is V_{LRIP}, y_0 is initial V_{LRIP} for each time signal recording and y_f final V_{LRIP}, t is time since P_{AW} change(s), a and b define the magnitude of volume such that final $V_{LRIP} = y_0 + a + b$, and τ_1 and τ_2 are time constants.

This model is superior to other nonlinear models in a population of spontaneously breathing adults with and without lung disease (23). Using an extra sum-of-square F test comparison against a simpler single-order exponential equation (15), this model is valid in over 90% of recordings. The time to achieve stable lung volume (defined as 95% of total ΔV_{LRIP} predicted by the model) was only calculated from those V_{LRIP} data in which the model had a goodness-of-fit of R^2 greater than or equal to 0.6. Acknowledging that the 10-minute duration at each P_{AW} step may not have allowed V_{LRIP} stability, if stability had not occurred within the 10-minute recording period, the time extrapolation was permitted to a maximum of 3,600 s. Statistical analysis was performed with Prism 9.0 (GraphPad, San Diego, CA) and a p value of less than 0.05 was considered significant.

RESULTS

Thirteen predominantly term or ex-preterm infants were studied. All infants completed the protocol without complications. Their demographic and clinical characteristics are summarized in **Table 1**. Seven infants were receiving HFOV to treat meconium aspiration syndrome, four infants had pneumonia, and the remaining two infants required HFOV following abdominal surgery. One of these infants was ex-preterm and had evolving chronic lung disease. Twelve of the infants met the criteria for neonatal ARDS (24).

A total of 196 P_{AW} changes were made (54 inflation limb, 142 deflation limb; **Supplementary Fig. 1**, http://links.lww.com/CCX/A623). During the deflation series, the P_{AW} decrements were of magnitude 2 cm H_2O (n = 41) or 1 cm H_2O (n = 101). The time for P_{AW} to stabilize after a change was 9 seconds (2–27 s) (median [range]). One-hundred sixty-three P_{AW} changes (83%) resulted in a volume change that met the predefined ΔV_{LRIP} criterion for inclusion in the analysis. During the deflation series, a ΔV_{LRIP} satisfying the inclusion criterion was more likely following a 1 cm H_2O change

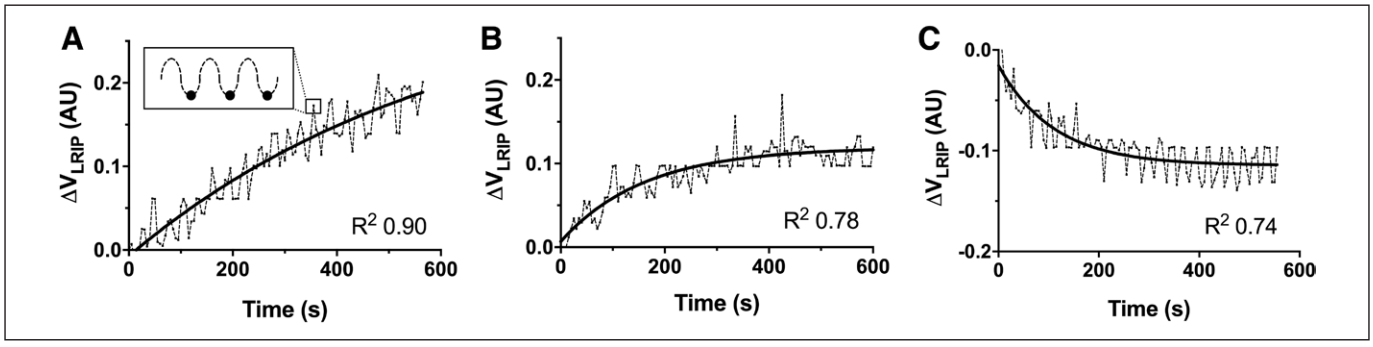

Figure 1. Fitting of second-order biexponential model to VLRIP data. Representative examples of individual lung volume changes (ΔV_{LRIP}, arbitrary units [AU]) over 10 min following a single adjustment in P_{AW} of 2 cm H_2O during the inflation (**A** and **B**) and deflation (**C**) limb. *Dotted line*: V_{LRIP}, plotted using sequential trough values from the oscillatory waveform (see inset; *black dots* indicate trough of oscillatory V_{LRIP} time course); *solid line*: fitted biexponential model. In (**B**) and (**C**), stable lung volume was achieve before 600 s; 241 s ($R^2 = 0.78$) and 168 s ($R^2 = 0.74$), respectively. In (**A**), stable lung volume was not achieved by 600 s.

TABLE 1.
Subject Characteristics at Study Commencement ($n = 13$)

					Initial HFOV settings				Gas Exchange Indices		
Age (d)	Weight (kg)	GA (wk)	Corrected GA (wk)	Time on HFOV (hr)	Mean Airway Pressure (cm H_2O)	Amplitude (cm H_2O)	Frequency (Hz)	FIO_2	$PaCO_2$ (mm Hg)	Alveolar-Arterial Oxygen Difference (mm Hg)	Oxygenation Index
2 (1–42)	3.4 (1.1–3.7)	40 (23–42)	40 (28–42)	24 (4–54)	14.3 (9.8–17.4)	33 (21–42)	8 (6–12)	0.5 (0.21–0.9)	48 (37–100)	197 (35–526)	9.6 (5.5–31.6)

GA = gestational age, HFOV = high-frequency oscillatory ventilation.
All data are represented as median (range).

(82% vs 66%), as 1 cm H_2O changes were made around P_{final} where volume state was less stable (7, 8). The exponential model could be fitted to the V_{LRIP} data with a R^2 greater than 0.60 for 125 P_{AW} alterations; median (interquartile range [IQR]) R^2, 0.96 (0.91–0.98).

Figure 1 shows examples of inflation and deflation limb recordings. Only three inflation limb (6%) and 14 deflation limb (18%) recordings ($n = 125$) achieved stable V_{LRIP} within the 10-minute recording time ($p = 0.067$, chi-square test). Stabilization time was predicted by extrapolation to be within 3,600 seconds (60 min) in a further 66 recordings (53%). Using the model, the median (IQR) time to stable lung volume was 1,311 seconds (718–1,959 s) in the inflation limb, and 647 seconds (439–1,309 s) in the deflation limb ($p = 0.023$, Mann-Whitney U test). The time constant of the first phase of the biphasic exponential model (τ_1) was median 8 seconds (3–21 s).

Figure 2 shows the frequency distribution of all ΔV_{LRIP}, with 56% (inflation) and 31% (deflation) of all P_{AW} changes requiring at least 30 minute until stable V_{LRIP} (both $p < 0.0001$; chi-square). Stable ΔV_{LRIP} was more likely to be obtained quickly during the first third of P_{AW} changes and the last third more likely to require more than 30 minutes during the deflation limb ($p < 0.0001$; chi-square). **Figure 3** summarizes the time to stable ΔV_{LRIP} within different regions of the pressure-volume relationship.

DISCUSSION

HFOV is used in the neonatal ICU for a diverse range of conditions (18) and most often as a rescue therapy when conventional modes of mechanical ventilation are not effective. In our population of predominantly term infants receiving rescue HFOV, we found that lung

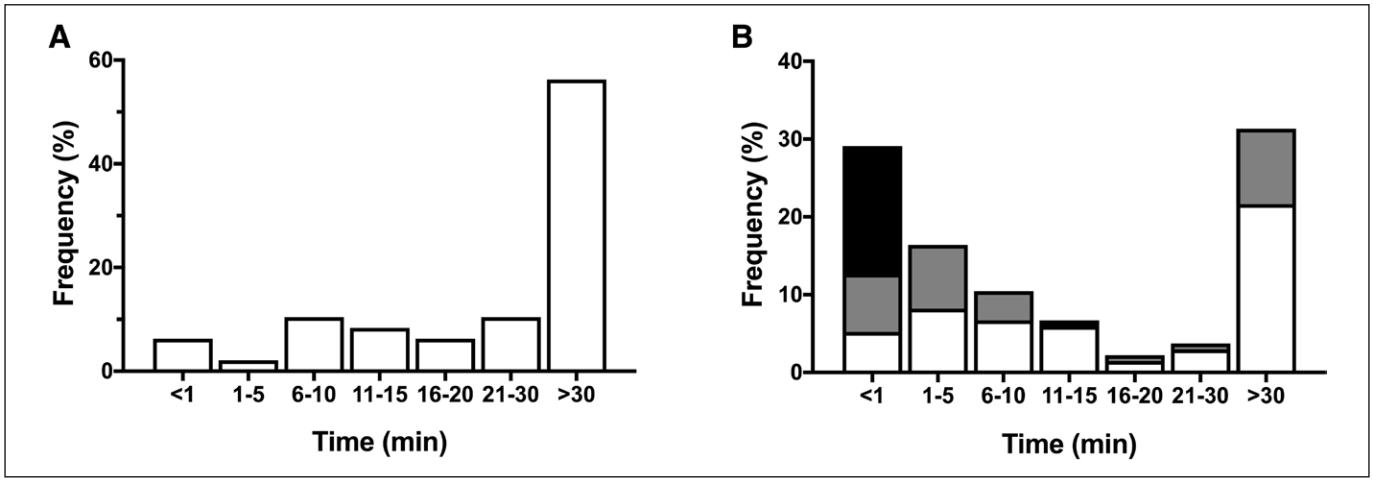

Figure 2. Frequency distribution of time to stable lung volume following a P_{AW} change. **A**, Inflation limb ($n = 54$ P_{AW} changes). **B**, Deflation limb ($n = 142$ P_{AW} changes). During the deflation limb, P_{AW} changes were analyzed for the first third (*black*), middle third (*gray*), and last third (*white*) of sequential P_{AW} changes from P_{max} to P_{final}. V_{LRIP} recordings that did not meet the criterion for volume change after the P_{AW} change are included in the less than 1-min groups.

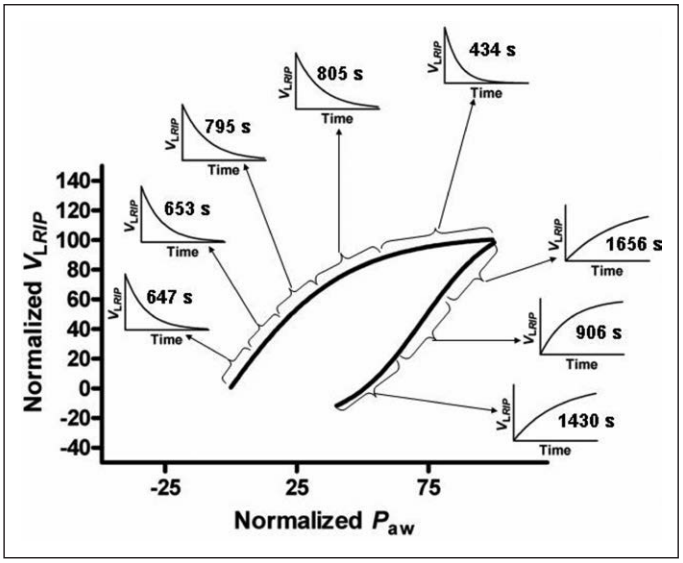

Figure 3. Schematic showing the median time to stable lung volume and representative exponential model of lung volume change over time, for different sections of the normalized pressure-volume relationship of the lung measured during the study (3). Regions of the pressure-volume relationship are separated by volume into equal thirds of the inflation limb and into equal fifths of the deflation limb.

volume had not fully stabilized within 10 minutes after a P_{AW} change in most cases. The time to stability was related to the volume state of the lung, reflecting that volume attainment is a continual and regional process, taking longer in poorly recruited lungs. These findings have implications for the application of open lung strategies during HFOV. Unlike the preterm infant with RDS, clinicians using HFOV in more mature infants will need to allow longer time before interpreting the clinical response to P_{AW} changes. We are not aware of any current clinical guidelines that recognize the differences in time required to apply an open lung strategy during HFOV between primary RDS of prematurity and other neonatal lung conditions, such as neonatal ARDS.

The importance of achieving an optimal lung volume during mechanical ventilation is well understood (1, 2, 25, 26). During HFOV, P_{AW} is the principal determinant of lung volume, but clinicians have few guidelines on setting P_{AW}. We found that the time to a stable lung volume after a 1–2 cm H_2O P_{AW} change exhibited high inter- and intrasubject variabilities. The largest determinant of ΔV_{LRIP} was the volume state of the lung, with the time to stable V_{LRIP} being twice as long during the inflation limb compared with deflation limb. This was expected. During the deflation limb, the lung was initially well recruited ("open"), and HFOV occurred on the deflation limb of the pressure-volume relationship. On the deflation limb, alveoli are already recruited, and the lung is in a state of uniform volume. This creates alveolar stability, and changes will be smaller and more rapid as long as the volume state remains above the closing pressure (8, 27–29). During the inflation limb, recruitment is ongoing with some alveoli atelectatic, others recruiting or recruited, and some potentially overdistended. This heterogeneity of alveolar state, along with poorer lung compliance, increases time constants (8, 27–29). Our data suggest that clinicians should consider the volume state of the lung when anticipating the clinical response to a P_{AW} change.

Only 14% of P_{AW} changes resulted in a stable lung volume within 10 minutes. Thus, in many instances, lung volume recruitment or derecruitment may still be ongoing after the next P_{AW} change. This may have had an impact on the finding that stability was predicted to require more than 60 minutes to stabilize in 42 changes (34%; 21 inflation and 37 deflation limb). In contrast, a similar study in spontaneously breathing preterm infants receiving an open lung approach to HFOV for acute RDS reported stable lung volumes (measured with real-time continuous electrical impedance tomography [EIT]) and a simple monophasic exponential model, within approximately 5 minute of a P_{AW} change (17). Thome et al (30) reported a large time range of 2–25 minutes (median, 9 minutes) for lung volume stabilization in preterm infants following P_{AW} changes. In this study, lung volume was measured intermittently with the SF_6 washout technique (30). This required temporary conventional ventilation for 1 minute, which may have influenced the findings. Our study involved larger and more mature infants, all of whom were receiving rescue HFOV. None of the infants had primary RDS but rather pathologies often more analogous to neonatal ARDS (24). Absolute lung volume, resistance, and compliance are likely to be greater than preterm infants with RDS. With the recent recommendation to use an open lung approach on initiation of HFOV in preterm RDS (11), clinicians must be aware that the recommended 2–3 minute P_{AW} step changes cannot be extrapolated to other neonatal respiratory conditions (5, 12).

Furthermore, as we reported previously in this group of infants, Spo_2 had stabilized during most of the 10-minute periods (3, 8). With Spo_2 generally only

being unstable when the lung was rapidly decruiting (P_{final}) or overdistended at P_{max}. Our extrapolated data suggest that during other P_{AW} changes, V_{LRIP} may still be changing, whereas Spo_2 had stabilized. Open lung strategies require clinicians to apply a dynamic physiologic feedback system to optimize P_{AW}, but this must also be practical. Open lung approaches often require 10 or more P_{AW} changes. It may not be practical for clinicians to allow longer than 10 minutes per P_{AW} change if an improvement in gas exchange is being observed.

We applied a biphasic exponential model to describe volume change within the lung over time, the first time it has been applied to mechanically ventilated patients. This model has been previously used to describe forced expiration manoeuvres in adults (23) and passive expiration in newborn lambs (31). In our population, the biphasic exponential model described the V_{LRIP} data well and allowed extrapolation beyond the 10-minute P_{AW} application period to predict ΔV_{LRIP} behavior. Despite this caution must be applied to extrapolated modeling data, with inaccuracies likely to be higher when compared with direct modeling of real data. In contrast to simpler exponential models of volume change (17), the biphasic model allows for an initial rapid phase of volume change followed by a prolonged slow phase, generating a specific time constant for each. The model was consistent with the raw time-V_{LRIP} recordings and is biologically plausible. Open airways and alveoli have a direct connection to large airways and are, therefore, expected to change volume rapidly after a change in pressure, explaining the very rapid time constants observed in the first phase of the model. However, alveolar opening (recruitment) and closing (derecruitment) occur more slowly and are unpredictable (32), especially in the presence of the noise associated with higher frequency pressure changes within the airways (33).

Open lung approaches often report an initial increase in lung volume following reductions in initial P_{AW} from functional total lung capacity at P_{max} (3, 4, 34). We and others have postulated that this unexpected observation reflects the opening of small airways that were compressed or release of impeded venous return at higher P_{AW} (3, 4, 34). The bimodal model offers a third possibility that the slow phase of alveolar recruitment is still ongoing during the initial phase of the deflation limb. Although the lung is mechanically stable (above closing pressure) on the deflation limb, the initial V_{LRIP} reductions reflect open lung units, rapidly achieving a stable volume, with the slower recruitment of incompletely opened lung units during the previous P_{AW} steps, with longer time constants, occurring in the background.

This study and interpretation are limited to secondary analysis of a convenience sample of 13 infants from an existing data set, although similar in size to previous reports in preterm infants (4, 17). The infants in our study were all receiving muscle relaxants. It is likely that spontaneous breathing will shorten the time to stable volume but also create more uncertainty in the response. The primary diagnoses were also diverse, but in the majority, the consistent functional presentation was of neonatal ARDS (24). It is the presence of neonatal ARDS that is most likely to have contributed to the clinical need for HFOV. Measuring lung volume change in infants during HFOV is difficult. Methods validated in other populations, such as inert gas washout (30), chest radiograph (35), and computerized tomography (36), are impractical, intermittent, or involve unacceptable radiation. DC-coupled RIP is a well-validated, noninvasive, radiation-free method of continuously monitoring thoracic volume change during HFOV in animals (37) and infants (3, 8, 19, 38), but is not without some limitations (3). In particular, RIP cannot differentiate between gas and fluid changes within the chest, unlike newer technologies such as EIT (39, 40). EIT is also able to define regional volume states (41). Unfortunately, practical EIT systems were not available at the time this study was performed. We would recommend that future studies should consider EIT.

CONCLUSIONS

In term and older infants receiving rescue HFOV, the time to a stable lung volume after a P_{AW} change is variable and shorter when the lung is already recruited compared with when it is derecruited. Unlike preterm infants, greater than 10 minutes is often required for lung volume stability. Clinicians should be aware of the importance of the preceding volume state in the lung when assessing the response to a P_{AW} change and the need to allow longer for bedside monitoring to achieve a clinical response.

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Drs. Tingay, Mills, and Dargaville developed the concept and designed the study. Dr. Tingay enrolled and studied all infants. Dr. Kiraly developed the mathematical models used in the study. Drs. Tingay, Kiraly, and Dargaville were involved in data analysis and interpretation. All authors contributed to drafting the final manuscript with Drs. Tingay and Kiraly writing the first draft.

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Individual participant data collected during the study, after deidentification, and study protocols and statistical analysis code are available beginning 3 months and ending 23 years following article publication to researchers who provide a methodological sound proposal, with approval by an independent review committee ("learned intermediary") identified for purpose. Data are available for analysis to achieve aims in the approved proposal. Proposals should be directed to david.tingay@mcri.edu.au; to gain access, data requestors will need to sign a data access or material transfer agreement approved by the Murdoch Children's Research Institute.

Prospective written informed parental consent was obtained for each infant prior to enrollment in the study.

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