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Functional residual capacity measurements in healthy infants: ultrasonic flow meter *versus* a mass spectrometer

J.J. Pillow*,#,¶, H. Ljungberg*,+, G. Hülskamp*,§,ƒ, J. Stocks*,§

Functional residual capacity measurements in healthy infants: ultrasonic flow meter versus *a mass spectrometer. J.J. Pillow, H. Ljungberg, G. Hülskamp, J. Stocks.* ©*ERS Journals Ltd 2004.*

ABSTRACT: Accurate, reproducible and portable bedside monitoring of lung volume could potentially facilitate the early recognition of both under and overinflation of the lungs in ventilated and nonventilated subjects. This study asked whether a prototype portable ultrasonic flow meter provided valid and reliable measurements of functional residual capacity (FRCUS) when compared to those obtained using a mass spectrometer (FRCMS) in nonventilated healthy infants.

Paired, randomised measurements of FRCMS and FRCUS were obtained using the sulphur hexafluoride (SF_6) multiple-breath washout technique in 23 healthy infants with a median (range) postnatal age of 34.6 (1.3–92.6) weeks and weight of 8.3 (3.9–11.7) kg.

FRCUS was on average 5.7% (95% CI: 1.0–10.4%) less than FRCMS equating to a difference of approximately 1 $mL \cdot kg^{-1}$. The 95% limits of agreement (LA) between the two techniques were relatively wide (95% LA: -17.5% to 29%), although in keeping with previously reported within-patient variability for lung volume measurements. There was no significant difference between the within subject coefficient of variation for FRCMS (3.7%) and FRCUS (5.2%).

The ultrasonic flow meter used in this study provides repeatable measurements of functional residual capacity in spontaneously breathing healthy infants that approximate those obtained during mass spectrometry.

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*Portex Unit: Respiratory Physiology, Institute of Child Health, #Dept of Neonatology, University College London Hospital NHS Trust, and §Neonatal Unit, Homerton Hospital NHS Trust, London, UK. ¶Centre for Child Health Research, Perth, Australia. +Dept of Paediatric Clinical Physiology, Queen Silvia Children's Hospital, Göteborg, Sweden. ƒUniversitäts-Kinderklinik, Münster, Germany.

Correspondence: J.J. Pillow, Neonatal Clinical Care Unit, King Edward Memorial Hospital, P.O. Box 134, Subiaco Perth, Western Australia, 6904.
Fax: 61 893817559
E-mail: janep@ichr.uwa.edu.au

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The recognition of both under and overinflation of the lung may provide important information to the clinician during treatment of the infant with respiratory illness and facilitate earlier institution of treatments that could prevent further clinical deterioration. Despite a general awareness of the potentially adverse consequences of volutrauma, the lack of readily available, portable and noninvasive clinical tools that accurately detect either overinflation or atelectasis has hampered attempts to achieve this goal. There is an urgent need for technological developments that will facilitate accurate measurement of functional residual capacity (FRC) in infants and young children.

Although body plethysmography is considered the gold-standard measurement of FRC, it is sensitive to environmental conditions and not easily used at the bedside where gas dilution techniques provide an alternative approach. The multiple-breath washout technique has recently gained popularity due to the potential for concomitant assessment of indices of ventilation inhomogeneity [1]. The mass spectrometer is often regarded as the gold standard of gas dilution techniques, although the size and sensitivity of most mass spectrometers to environmental conditions usually precludes their use as a portable device.

A recent development in this field has been the ultrasonic flow meter. Initially reported in 1986 by BUESS *et al.* [2], studies using a prototype system for measurement of lung volume and indices of ventilation inhomogeneity have recently been published in experimental animal models [3] and in both nonventilated [4] and ventilated [3] infants and children. Whilst accuracy of the measured volumes has been confirmed *in vitro* [4, 5], validation of this technique has not been reported in a healthy infant population. This study aimed to establish whether valid and reliable measurements of FRC are obtainable in healthy infants using an ultrasonic sensor during multiple-breath washout (FRCUS) by comparing them to FRC measured within the same test occasion using a mass spectrometer (FRCMS).

Methods

Study population, ethics and background data

Healthy infants without congenital abnormalities or neonatal respiratory compromise were recruited from the Homerton Hospital and the University College London Hospital as controls for ongoing epidemiological studies [6, 7]. The local research ethics committees approved these studies, and written informed parental consent was obtained prior to lung function testing. Infants were tested when clinically free from respiratory tract infections for at least three weeks.

Study design

The study was designed as a randomised comparative observational study of two different methods of measuring FRC.

Equipment and test protocol

FRC was measured in unsedated and sedated infants using the multiple-breath washout technique by means of both a mass spectrometer (FRCMS; Amis 2000; Innovision, Odense, Denmark) with customised software (TestPoint; Capital Equipment Corp., Billerica, MA, USA) and the current, commercially available prototype ultrasonic flow meter (FRCUS; Eco Medics, Duernten, Switzerland) using acquisition and analysis software (Wbreath v3.8.22; Ndd, Zurich, Switzerland). Subjects were studied in the supine position during behaviourally determined quiet sleep [8]. Infants older than 6 weeks post-term were sedated with an oral or rectal dose of 50–100 $mg \cdot kg^{-1}$ chloral hydrate. FRC measurements were performed consecutively prior to any other lung function tests and the order of commencement (FRCMS *versus* FRCUS) was random. Both sets of measurements were completed within ~20 min in sedated infants, while unsedated studies took up to 1 h.

Mass Spectometer. FRCMS was obtained using equipment and procedure as previously described [9]. Flow was recorded using a tube pneumotachograph (Fleisch No.0; Fleisch, Lausanne, Switzerland). A Rendell-Baker Size 1 or 2 mask was used according to the infant's age (table 1) and the gas concentration was sampled from the mask using a respiratory mass spectrometer (fig. 1a). The delay between gas sampling and measurement and the flow signal was incorporated in the calibration procedure. A test gas mixture (4% sulphur hexafluoride (SF_6), 4% He, 21% O_2 and balance N_2) was administered *via* a T-piece bias flow system connected to the external end of the pneumotachograph, until expired and inspired SF_6 concentrations had equilibrated. The bias flow delivering the tracer gas was then disconnected during

Table 1. – Deadspace of mask and flow meter assemblies

Ultrasonic flow meter	
Set 1 (<8 kg)	
VolSen1	0.5
VolSen2	0.5
VolSen3+mask	0.5+7.5[#]
Total deadspace	9.0
Set 2 (⩾8 kg)	
VolSen1	1.7
VolSen2	1.7
VolSen3+mask	4.1+10[+]
Total deadspace	17.5
Mass spectrometer	
<3 months	
Post-capillary	5.0
Pre-capillary (mask only)	7.5[¶]
Total deadspace	12.5
⩾3 months	
Post-capillary	5.0
Pre-capillary (mask only)	10.0[+]
Total deadspace	15.0

All values are in mL. VolSen: deadspace (DS) volume of ultrasonic sensor (US) (see fig. 1), [#]: laerdal size 0/1, [¶]: Rendell-Baker size 1 and [+]: Rendell-Baker size 2 masks. Effective mask dead space was taken to be 50% of water displacement volume [10]. Expired tracer gas volumes were corrected for re-inspired gas within VolSen1 (US) and the post-capillary dead space (mass spectrometer). Functional residual capacity (FRC) was corrected during software analysis (FRCUS) or following analysis (FRCMS) for the dead space between lips and point of gas sampling (50% VolSen2+VolSen3+mask for FRCUS and pre-capillary DS for FRCMS).

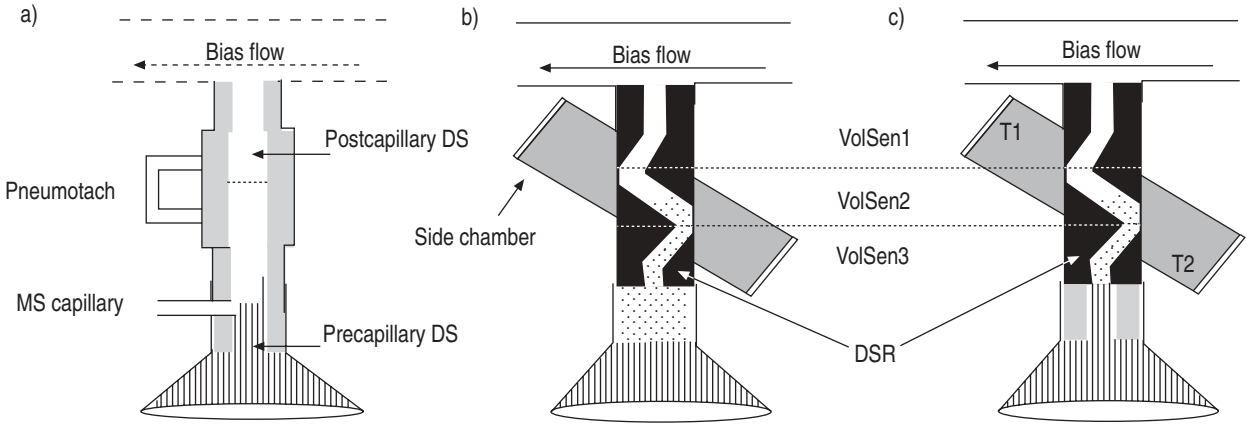

Fig. 1. – Equipment configuration of flow meter and mask during multiple-breath washout measurements: a) mass spectrometer (MS; with either size 1 or size 2 Rendell-Baker mask); b) ultrasonic flow meter in infants >8 kg; and c) ultrasonic flow meter in infants <8 kg. VolSen: ultrasonic sensor deadspace volume; DSR: dead space (DS) reducer; T1 and T2: ultrasonic transducers 1 and 2. The neck of the Rendell-Baker masks (a and b) fitted around the outside of the flow sensor, while the Laerdal 0/1 mask occupied most of the space within the end of the flow sensor (c). Re-inspired gas in post-capillary space (mass spectrometer) and VolSen1 (ultrasonic flow meter) was subtracted from the exhaled gas volume for each breath, prior to computation of functional residual capacity (FRC). Vertical stripes indicate volume subtracted from FRC due to mask, spotted area shows volume of sensor subtracted from FRC measurements (ultrasonic flow meter only). Dotted lines show division of dead-space compartments.

Table 2. – Outcome of analysis of functional residual capacity (FRC) and variability

	Mass spectrometer	Ultrasonic flow meter	Mean difference (95% CI)
FRC mL	146 (62.1–301)	136 (60.5–279)	-9.9 (-3.3–-16.5)
FRCCV %	3.7 (0.4–9.7)	5.2 (0.8–13.0)	1.40 (0.93–2.11)$^{+}$
VT mL·kg^{-1}	8.3 (6.4–11.1)	8.4 (6.4–11.6)	0.05 (-0.33–0.43)
RR breaths·min^{-1}	33 (24–52)	31 (22–50)	-2 (-0.7–-3.3)
MV mL·kg^{-1}·min^{-1}	274 (197–397)	257 (177–367)	-17 (-30–-4)

Data are presented as mean (range) unless otherwise stated. MS: mass spectrometer; US: ultrasonic flow meter; CV: coefficient of variability; VT: tidal volume; RR: respiratory rate; MV: minute volume. $^{+}$: ratio of geometric means.

expiration so that washout with room air commenced with the next inspiration and continued until the end-tidal SF_6 was <2.5% of the starting concentration (*i.e.* 0.1% SF_6 at end expiration). Computations were limited to the washout phase.

Prototype ultrasonic flow meter. The ultrasonic flow meter design included two side chambers within which the ultrasonic transducers were located, in free communication with, but on opposing sides of, the main flow path (fig. 1b and c). The flow path traversed through a deadspace reducer inserted into the flow meter. Two different deadspace reducers and face masks were used according to whether the infant′s weight was below (set 1) or above (set 2) 8 kg (fig. 1, table 1). A disposable bacterial filter (Spirette^{TM}) surrounded the dead space reducer. Additional tape was applied to the Spirette^{TM} prior to assembly to improve the seal, and the absence of leak was confirmed up to 2 kPa. Multiple-breath washouts were performed using a bias flow mixture that contained 4% SF_6 and 21% O_2. Measurements differed from those obtained using the mass spectrometer in that there was no delay between molecular mass and flow measurements and a constant bias flow was maintained throughout the measurement (4% SF_6 during washin, air during washout), and the length of the recorded trace was slightly longer (including at least five breaths after end-tidal SF_6 reached <2.5% of the starting concentration). Flow was computed from the difference in the time of flight for ultrasonic pulses emitted from each transducer, whilst molar mass is a function of the absolute time of flight [3], thereby permitting estimation of the concentration of a tracer gas. Only washout data was used for comparison with the mass spectrometer FRC measurements.

Calculations and statistical analysis

FRCMS and FRCUS data were analysed independently by two investigators (J.P. and H.L.), each of whom was blinded to the results obtained from the alternative technique. Data were only accepted for analysis if obtained during regular breathing, with a stable end-expiratory level [7] and if there was no evidence of leak. Leak was excluded by testing the sensor in accordance with published guidelines [11], observation of flow-volume loops after achievement of mask seal over the patient′s nares and mouth, and by inspection of test traces for sudden changes in inspired molar mass on washin and diminished flow during either washin or washout. Recorded flows and volumes were converted to body temperature and pressure, saturated (BTPS) conditions. The analysis of the ultrasonic washouts included correction for a side chamber reservoir effect and the effects of within-cycle changes in temperature on molecular mass were accounted for using a temperature model as previously described [3].

Comparisons of FRC between the two systems were undertaken on the first three (minimum two) technically acceptable SF_6 washouts. FRC was calculated from the cumulative volume of expired SF_6 divided by the difference between end-tidal gas concentration at the start and completion of the washout. The volume of exhaled tracer gas was automatically corrected for re-inspired gas between the bias flow and the point of measurement of the tracer gas in each software package. Software reported FRC measurements were further corrected for the deadspace present between the airway opening and the point at which the tracer gas was measured, including the "effective" deadspace of the facemask [10]. For the mass spectrometer this included the mask volume between the lips and the sampling capillary, while for the ultrasonic flow meter this included the mask volume, VolSen3 and 50% of VolSen2 (fig. 1, table 1).

Deadspace corrected FRC values obtained from the prototype ultrasonic flow meter were compared to those obtained using the "gold-standard" mass spectrometer using the method of Bland and Altman [12]. As the within-subject coefficient of variability (CV=100×SD/mean) data were not normally distributed, these data were log transformed and their difference determined (logFRCCV,US–logFRCCV,MS). The difference between the logarithms of two geometric means gives the logarithm of their ratio, not of their difference. Back transformation of these data to obtain the ratio of the geometric mean is achieved by obtaining the antilog. If there was no difference, the 95% CI of this ratio would span 1 [13]. The current authors considered that FRCUS would be a reasonable alternative to FRCMS if there was $\leqslant$5% difference between the two measures of FRC and if the limits of agreement (LA: mean difference $\pm$1.96 SD) on any given test occasion were within $\pm$20% of the measured difference in the means [14, 15].

Results

Study population

Technically satisfactory parallel measurements of FRC were obtained in 23 healthy infants (12 male) on 27 occasions. The infants had a median (range) gestation of 39.7 (31.4–42.4) weeks, postnatal age corrected for expected delivery date of 34.6 (1.3–92.6) weeks, weight of 8.3 (3.9–11.7) kg and length of 70 (52.5–87) cm. Seven studies (<6 weeks corrected postnatal age) were performed in natural sleep without sedation.

Comparison between functional residual capacity from the mass spectrometer and ultrasonic flow meter

The relevant physiological data for comparisons between FRCMS and FRCUS are presented in table 2. Highly reproducible results were obtained using both techniques with a mean (range) within-subject CV of 3.7% (0.4–9.7%) for FRCMS and 5.2% (0.9–14.1%) for FRCUS. There was no significant difference between the CV or measured tidal volume for the two techniques. The mean respiratory rate and

minute volume were slightly lower during studies with the ultrasonic flow meter.

There was a small statistically significant difference between FRC measurements obtained from the two techniques, with FRCUS being an average (95% CI) 5.7 % (1.0–10.4%) lower than FRCMS (table 2 and fig. 2). The limits of agreement (mean difference ±1.96 SD) were between -29.0% and 17.5% (*i.e.* ±23.2% of -5.7%). Only two out of the 27 studies exceeded the predefined acceptable limit of agreement of ±20% of the difference between the means.

Discussion

Summary

FRC obtained using the ultrasonic flow meter were slightly albeit significantly lower than those obtained using the mass spectrometer for SF_6 multiple-breath washout estimations of FRC in healthy infants aged 1.3 to 92.6 weeks corrected postnatal age. Measurements using the ultrasonic flow meter were repeatable, although the within subject agreement with measurements obtained using the mass spectrometer just exceeded the study's predefined nominal limits of acceptability. The considerable scatter in the paired measurements of FRC is indicative of an underlying variability in the measurement of FRC. The causes for this variability may be methodological, technical or physiological.

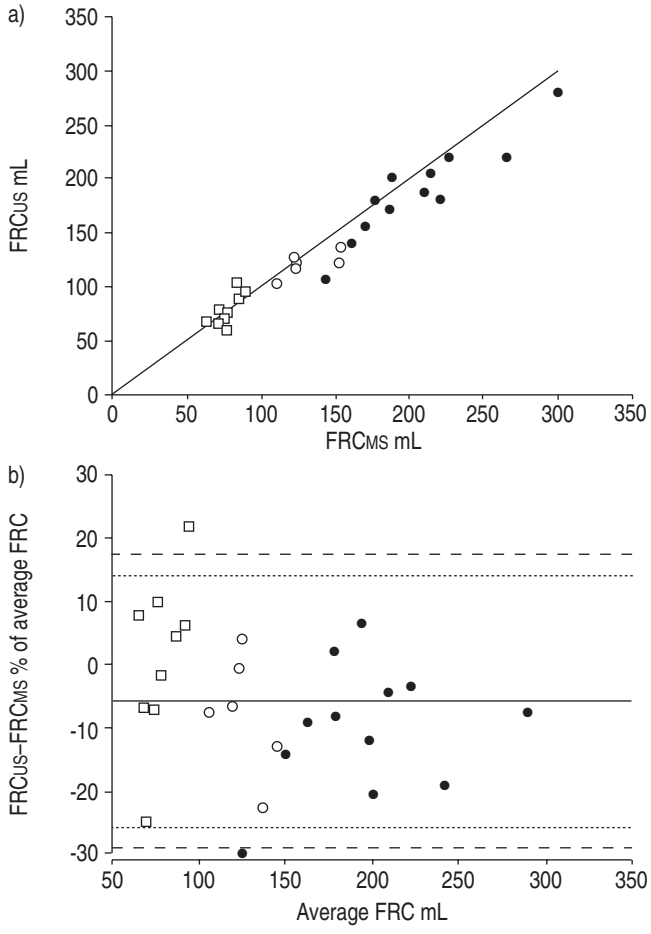

Fig. 2.–Comparison of functional residual capacity (FRC) obtained with the mass spectrometer (FRCMS) and the ultrasonic flow meter (FRCUS). a) Absolute measurements of FRCUS plotted against FRCMS. Solid line represents line of identity. b) Bland-Altman plot of the % difference in FRC obtained using the mass spectrometer and ultrasonic flow meter plotted against the average FRC. Solid line indicates mean difference while the dashed line indicates 95% limits of agreement (mean difference±1.96SD). The dotted line demarcates ±20% of the mean difference between the two techniques. □: FRCMS with Rendell-Baker 1 Mask and FRCUS with Laerdal 0/1 Mask; ○: FRCMS with Rendell-Baker 2 Mask and FRCUS with Laerdal 0/1 Mask; ●: FRCMS with Rendell-Baker 2 Mask and FRCUS with Rendell-Baker 2 Mask.

Methodological and technical variability

This study involved infants participating as healthy controls in two separate, ongoing longitudinal epidemiological studies. Ideally, identical facemasks would have been used for both techniques in the current methodological study, but this was precluded by the need to maintain a standard operating protocol for both epidemiological studies. One study incorporated plethysmographic measurements of lung volume for which a firm mask (*e.g.* Rendell-Baker) is essential [16]. A number of infants were also participating in a longitudinal assessment of lung growth and development in which FRC was being measured using the Laerdal mask, as this was more suitable for unsedated bedside studies. Evaluating the effect of using different masks within the same infant for the same technique was not feasible due to time constraints. As a result, the same (putty-lined) mask for both FRCMS and FRCUS measurements was only used in sedated infants >8 kg (fig. 2). Even in these infants, an additional 2.5 mL total deadspace was present during FRCUS measurements when compared to that during FRCMS (table 1). By contrast, total mask-equipment deadspace was lower during the FRCUS measurements in infants <8 kg, this difference being 3.5 mL for those <3 months and 6 mL for those >3 months (table 1). Whilst the current authors have attempted to correct for the physical differences arising from these different mask-flow meter configurations, such adjustments cannot account for any physiological changes in lung volume and breathing patterns that may occur with different deadspace and impedance loads. In the present study, a slightly lower respiratory rate was recorded during ultrasonic flow meter studies. In accordance with European Respiratory Society (ERS) guidelines [10], a standard deadspace correction was applied for all infants for any given mask (*i.e.* 50% of the water displacement volume). This approach can only represent an average and will not account for the different deadspace occupying capacity of smaller *versus* larger faces, and the variability arising from application of the mask with different degrees of pressure and/or putty. An error of only 3.5 mL in the estimated deadspace correction for an infant with a 70 mL FRC would contribute an additional 5% to the scatter of this measurement from its true value. The average series deadspace (representing the system components in which no gas exchange is evident) computed for the ultrasonic measurements with the two different setups was 7.5±4.0 mL and 12.7±2.3 mL for Set 1 and Set 2 respectively, which is less than the 8.2 mL and 15 mL used for the deadspace correction in the respective ultrasonic flow meter setups (50% VolSen2+ VolSen3+Mask for FRCUS).

Acquisition of data varied slightly for each technique. The mass spectrometer has a lower sampling frequency (33 Hz) than the ultrasonic flow (100 Hz) and molar mass signals (200 Hz) from the ultrasonic flow meter, and has yet to be validated in small infants, in whom rapid breathing rates may result in some inaccuracies. The algorithms for FRC measurement are also slightly different. The mass spectrometer provides highly specific gas analysis, whereas the molar mass signal reflects all changes in the breathing gas

composition and thus requires correction by the software for cyclic changes in the temperature, humidification and carbon dioxide content throughout each breath. FRC was calculated from washout measurements up until tracer concentration fell below 2.5% of the starting concentration for FRCMS, whereas it was derived from the final breath in the plateau for FRCUS. More importantly, however, the current side-chamber prototype of the ultrasonic flow meter (the only version currently available commercially) incorporates an empirically derived correction for the diffusion of tracer gas in and out of the transducer chambers that may contribute to the observed difference between the two methods.

Physiological variability

Despite a randomised starting order of the tests and acceptance of only those measurements obtained during behaviourally-determined quiet sleep, residual physiological variability in FRC is likely to have been present. Estimation of how this may have influenced the results is limited by the paucity of data on the short-term repeatability of either test in healthy infants. Published values of multiple breath washout FRC [17], maximal flow at FRC [14], and forced expired volumes [15] in infants [14, 17] and older children [15] suggest that the changes in such parameters are unlikely to be significant unless they exceed 20%, with even greater variability for parameters such as forced flows or resistance [18]. By any of the above standards, the agreement observed between FRCMS and FRCUS falls near currently accepted ranges for within-subject, between-test variability during lung function studies.

Clinical implications

Given that the potential utilisation of FRC measurements in clinical decision-making extends far beyond those patients physically able to visit a lung function laboratory, there is an urgent need for a valid and portable measurement of FRC. This study has demonstrated that a portable prototype ultrasonic flow meter can be used to obtain reproducible measurements of FRC at the cotside of the healthy infant that approximate those obtained from the mass spectrometer. Future modifications isolating the flow pathway from the transducer side-chambers are likely to further improve the accuracy of this device.

Whilst the technique holds promise as a useful bedside measurement of lung function, the current prototype has limitations of which the user needs to be aware. As the current authors discovered in the laboratory, the measurement and analysis software is not user-proof and collection of data with inappropriate options can influence accuracy of results. The present authors would strongly recommend saving all data in raw, unprocessed format prior to analysis to facilitate later re-analysis in the event of changes in the analysis algorithms.

Conclusions

The current study has shown that measurements of functional residual capacity obtained using a prototype ultrasonic flow meter approximate those obtained using a mass spectrometer in healthy, nonventilated infants during quiet sleep. The demonstrated reliability of such a flow meter for measurement of functional residual capacity will facilitate bedside lung volume monitoring in patients who are physically unable to attend a specialised lung function laboratory. Whilst additional development will be necessary to improve quality control during data collection and analysis, the ultrasonic flow meter represents an encouraging step forward in the development of bedside lung function applications.

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