



How best to capture the respiratory consequences of prematurity?

Francesca Ciuffini^{1,2,3}, Colin F. Robertson^{1,3,4} and David G. Tingay^{4,5,6}

Affiliations: ¹Respiratory Research, Murdoch Children's Research Institute, Melbourne, Australia. ²NICU, Dept of Clinical Sciences and Community Health, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, Milan, Italy. ³Respiratory Medicine, Royal Children's Hospital, Parkville, Australia. ⁴Dept of Paediatrics, University of Melbourne, Melbourne, Australia. ⁵Neonatal Research, Murdoch Children's Research Institute, Melbourne, Australia. ⁶Neonatology, Royal Children's Hospital, Melbourne, Australia.

Correspondence: Francesca Ciuffini, Neonatal Research, Dept of Clinical Sciences and Community Health, University of Milan, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Via Della Commenda 12-20122, Milan, Italy. E-mail: francesca.ciuffini@unimi.it



@ERSpublications

Better measures are needed to predict chronic respiratory morbidity in survivors born prematurely
<http://ow.ly/1L3n30ihq9C>

Cite this article as: Ciuffini F, Robertson CF, Tingay DG. How best to capture the respiratory consequences of prematurity? *Eur Respir Rev* 2018; 27: 170108 [<https://doi.org/10.1183/16000617.0108-2017>].

ABSTRACT Chronic respiratory morbidity is a common complication of premature birth, generally defined by the presence of bronchopulmonary dysplasia, both clinically and in trials of respiratory therapies. However, recent data have highlighted that bronchopulmonary dysplasia does not correlate with chronic respiratory morbidity in older children born preterm. Longitudinally evaluating pulmonary morbidity from early life through to childhood provides a more rational method of defining the continuum of chronic respiratory morbidity of prematurity, and offers new insights into the efficacy of neonatal respiratory interventions. The changing nature of preterm lung disease suggests that a multimodal approach using dynamic lung function assessment will be needed to assess the efficacy of a neonatal respiratory therapy and predict the long-term respiratory consequences of premature birth. Our aim is to review the literature regarding the long-term respiratory outcomes of neonatal respiratory strategies, the difficulties of assessing dynamic lung function in infants, and potential new solutions.

Introduction

Premature birth is a significant cause of long-term respiratory morbidity, with many infants developing chronic respiratory complications. The most frequently used clinical predictor of long-term respiratory risk is the presence of bronchopulmonary dysplasia (BPD). The definition of BPD has changed considerably since the first histopathological definition of NORTHWAY *et al.* [1] in 1967 based on fibrosis, alveolar inflammation and dysplastic airways. In the post-surfactant and gentle ventilation era, these processes were rarely seen and chronic respiratory morbidity better reflected a disruption of lung growth, resulting in a combination of structural airways damage, failure of alveolarisation and vascular development, with resultant impairment of gas exchange [2]. Following broad international consensus, BPD was redefined to reflect the need for oxygen therapy beyond 28 days after birth [3]. As neonatal respiratory care become more refined, this BPD definition also failed to reflect the physiological consequences of preterm birth. In order to develop more interinstitutional consistency, in 2003 WALSH *et al.* [4] published a "physiological" definition of BPD standardising the determination of oxygen requirement at 36 weeks. In 2006, QUINE *et al.* [5] tried to quantify the severity of gas exchange impairment, defining BPD as reduced ventilation/

Received: Sept 20 2017 | Accepted after revision: Jan 31 2018

Provenance: Submitted article, peer reviewed.

Copyright ©ERS 2018. ERR articles are open access and distributed under the terms of the Creative Commons Attribution Non-Commercial Licence 4.0.

perfusion ratio. Despite the evolution of BPD from a histological to physiological clinical entity, common to all these definitions is a single resultant dichotomous diagnosis made near term-corrected gestation.

Over the past 50 years BPD has been used as a surrogate for identifying infants at risk of later respiratory morbidity. Consequently, BPD has become the primary respiratory outcome in the assessment of respiratory strategies adopted in neonatal intensive care units (NICUs). While medical advances, including artificial surfactant, antenatal corticosteroids, lung protective strategies of mechanical ventilation and noninvasive respiratory support techniques improve survival of extremely premature infants, BPD remains a major clinical problem with little change in prevalence over the past 20 years, suggesting that it may lack the precision to delineate the true differences in the long-term implications of modern NICU respiratory therapies [6].

Recently, a high incidence of respiratory morbidity in children born preterm, even in the absence of BPD, has been described [7–9]. Irrespective of BPD diagnosis, children born prematurely have altered lung function with at least partially reversible airflow obstruction (high airways resistance and gas trapping) and increased airway reactivity, but with little evidence of eosinophilic inflammation. Lung parenchymal abnormalities on thoracic imaging, hospital readmissions for respiratory problems and increased respiratory symptoms are common in preterm survivors [10–13]. The high incidence of later pulmonary morbidity among children born preterm, independent of a diagnosis of BPD, highlights the shortcomings of BPD as a surrogate for long-term pulmonary morbidity. The dichotomous nature of modern BPD definitions lacks the ability to describe the evolution of the functional and pathophysiological multifactorial continuous disease processes that increasingly clinicians are aware extend into childhood.

We contend that preterm lung disease represents a pathophysiological continuum requiring repeated evaluation throughout life. As such, BPD, a single time-based dichotomous measure of defining the long-term impact of preterm birth is inadequate. Sensitive and repeatable early-life measures of lung function and structure should inform outcomes of clinical interventions, allow identification of those at risk and follow lung development through childhood.

This review aims to provide a perspective from a literature review of 1) the long-term outcomes of neonatal respiratory therapies; and 2) the current state of neonatal respiratory assessment tools as outcome measures of chronic respiratory morbidity of prematurity.

Search strategy and selection criteria

References for this review were identified through PubMed searches using the terms “bronchopulmonary dysplasia”, “premature”, “prematurity”, “preterm”, “follow up”, “long term”, “respiratory outcomes”, “lung function”, “pulmonary imaging”, “ventilation”, “nasal continuous positive airway pressure” and “high flow nasal cannula”. Articles relating to the specific aims of the review and relevant references cited in those articles were reviewed. All authors repeatedly reviewed the entire manuscript until a consensus was reached. Articles published in English, French and Italian were included.

Long-term outcomes of neonatal respiratory therapies: lessons from literature

There have been many well-designed large clinical trials exploring different aspects of preterm respiratory management in early life. Generally, these studies have used death and/or BPD as the primary outcome measure, which may not inform clinicians accurately about the long-term implications of each therapy. This section summarises some of the major advances and controversies in the respiratory support of the preterm lung and describes whether the trial data allow interpretation of the long-term respiratory implications.

Oxygen and mechanical ventilation: predictors of long-term respiratory impairment?

It is well known that higher oxygen needs are associated with ventilator-induced lung injury, as well as directly inducing acute lung injury [2, 3]. Prolonged neonatal oxygen exposure has been identified as a prognostic indicator for subsequent long-term airway obstruction [14–16]. Duration of oxygen supplementation, especially if lasting >1 month, was associated with impairment of forced expiratory volume in 1 s (FEV₁) in 10–18-year-old children and with respiratory resistance and reactance assessed using the forced oscillatory technique (FOT) in preschool children who had BPD [17]. Duration of oxygen exposure in neonatal life was found to be predictive of later pulmonary abnormalities on high-resolution computed tomography (HRCT) imaging [18].

Oxygen exposure requires consideration of dose as well as duration. STEVENS *et al.* [19], using an area under the curve analysis of cumulative oxygen exposure, identified that the accumulated oxygen exposure at 72 h of life predicted respiratory symptoms and respiratory-related health service and medication use during infancy in a dose-dependent manner. This suggests that the dose of early-life oxygen supplementation, rather than its duration, may be a stronger and earlier prognostic respiratory predictor. A

reproducible and simple to use oxygen cumulative score to indicate magnitude of injury, correlated to later respiratory function is needed.

Mechanical ventilation has an important role in early lung injury. Duration of mechanical ventilation, but not duration of oxygen supplementation, correlates with increased ventilation/perfusion mismatch (single photon emission computed tomography) at 37 weeks postmenstrual age in infants with BPD [20]. In later childhood, duration of mechanical ventilation is associated with reduced forced vital capacity, increased functional residual capacity and bronchial hyperresponsiveness [20–24].

Both oxygen supplementation and ventilator support have a strong link to long-term respiratory outcomes. However, current BPD definitions are limited to the duration of oxygen supplementation and mechanical ventilation, rather than oxygen dose or type mechanical ventilation.

High-frequency oscillatory ventilation: time for a well-designed study of long-term outcomes?

High-frequency oscillatory ventilation (HFOV) aims to correct atelectasis while minimising exposure to barotrauma/volutrauma, using subanatomical dead space tidal volumes, and thus was originally proposed as an effective method of reducing BPD. Despite 19 randomised controlled trials (RCTs) of first-intention HFOV in preterm infants and extensive meta-analyses, the theoretical lung protective potential of HFOV over conventional mechanical ventilation (CMV) has not been demonstrated [25, 26]. In many NICUs, HFOV is used as a rescue therapy rather than first-intention treatment. Rescue HFOV has only been evaluated in a single RCT [27]. The investigation of first-intention HFOV serves as an example of the complexity of neonatal respiratory trial interpretation. With >15 years between the early and later trials of HFOV, NICU care has changed considerably. Throughout this period CMV strategies, such as the availability of synchronisation and volume targeting, have improved, and it has become evident that mode of support is of lesser importance than how clinicians apply it. Favourable BPD outcomes from HFOV were only observed when HFOV was applied using a high lung volume approach, and only if CMV was not applied optimally [26].

Long-term respiratory outcomes have been reported from some trials (table 1). The HIFI (High-Frequency Ventilation in Premature Infants) trial, the first large RCT to compare CMV with HFOV in an era without antenatal steroids or surfactant, found no difference in BPD and mortality, but higher rates of air leak and intraventricular haemorrhage attributed to the low lung volume HFOV strategy [28]. There was no subsequent difference in respiratory morbidity and function or morbidity at 9 months, 2 years and 8–9 years in survivors [29–31]. A similar longitudinal finding was reported by LISTA and colleagues [7, 32] in a more recent small cohort of infants followed-up to 7 years, in whom antenatal steroid exposure, prophylactic surfactant therapy and high lung volume HFOV were used.

In contrast, the Provo multicentre high lung volume HFOV trial reported significantly less obstructive lung function and maldistribution of ventilation in 6-year-old children ventilated with HFOV during the neonatal period [33, 34]. It is possible that HFOV preserves small airway function better than CMV once long-term injury is established, with higher maximal flow at functional residual capacity observed at 12 months in a small series of infants with BPD [35]. More recently, the UKOS (United Kingdom Oscillatory Study) trial reported better small airway function and less airway obstruction in a cohort of 319 adolescent survivors randomised to a high lung volume HFOV strategy than those managed with CMV, although no difference in BPD was reported [36–39]. Prophylactic surfactant and antenatal steroids were well established in NICU practice when the UKOS trial was performed [40]. The trial was criticised for its pragmatic trial design, short duration (72 h) of HFOV use and lack of aggressive lung recruitment during HFOV [41]. A second, large HFOV trial with stricter ventilation strategies, high study compliance and longer durations of HFOV use showed a greater benefit of HFOV in reducing BPD, but did not report long-term outcomes [42]. Irrespective of this, the data from the PROVO and UKOS trials suggest that HFOV may confer long-term respiratory benefits that are not being realised with current reliance on BPD as an outcome.

Volume-targeted ventilation: still few data regarding long-term outcomes

Volume-targeted ventilation (VTV) is now widely used during CMV support of premature infants. There is a strong physiological rationale to limit excessive tidal volume exposure, and VTV achieves this by dynamically adapting to changing disease state [43]. Meta-analysis has shown that VTV reduces BPD, as well as survival without BPD, compared to support without VTV in preterm newborns [44–46]. Whether this benefit is a result of shorter duration of mechanical ventilation or a reduction in volutrauma exposure is unclear. SINGH and co-workers [47, 48] reported that significantly fewer children required administration of inhaled steroids and/or bronchodilators at 2 years old if supported with VTV (table 2). Further studies are needed to confirm whether the physiological rationale of VTV in early life confers long-term respiratory benefits.

TABLE 1 Studies assessing short- and long-term respiratory outcomes of high-frequency oscillatory ventilation (HFOV) compared to conventional ventilation (CV) for acute pulmonary dysfunction in preterm infants

First author [ref.]	Patients n	Birthweight; GA	Age at time of study [#]	Methods	Primary outcome	Results	Criticisms
HIFI trial							
RIGATTO [28]	673 [346 CV + 327 HFOV]	750–2000 g; 24–31 weeks (mean 28 weeks)	Neonatal period	Multicentre (11 centres) RCT. Patients assigned within 12 h of life to HFOV (low-volume strategy) or CV (intermittent mandatory ventilation)	Death or BPD (need for oxygen and pathological radiography at 28 days)	No differences in BPD, mortality or level of ventilation support in the two groups. Increased incidence of IVH, PVL and pneumoperitoneum in HFOV group	Many centres had no experience with HFOV. No strategies to optimise lung volume on HFOV and CV, or antenatal steroids, or surfactant were used. Infants relatively mature
RIGATTO [30]	223 [118 CV + 105 HFOV]	As above	9 months	Not detailed; only abstract available	Respiratory morbidity and function	No differences between the two groups in growth, respiratory morbidity and mechanics (FEF, peak-to-peak oesophageal pressure, compliance and resistance)	As above
MANNINO [29]	673 [346 CV + 327 HFOV]	As above	2 years	Not detailed; only abstract available	Respiratory morbidity and neurodevelopmental outcome	No differences between the two groups in survival, growth and respiratory morbidity. Worse neurodevelopmental outcome in the HFOV group (hydrocephalus, Bayley score)	As above
PIANOSI [31]	32 [20 CV + 12 HFOV] + 15 term controls	As above	8–9 years	Observational study. PFT: lung volumes, FEF rates and single-breath <i>D</i> _{LCO} , in a body plethysmograph; repeated after salbutamol	Respiratory function	Mildly obstructive pattern in children born preterm and with asthma. No difference of pulmonary function in two groups of ventilation mode or between children with or without neonatal BPD	As above
UKOS trial							
JOHNSON [39]	797 [397 CV + 400 HFOV]	Mean 705 g at 23–25 weeks; mean 930 g at 26–28 weeks	Neonatal period	Multicentre (25 centres) RCT. Patients assigned within 1 h of life to CV (time-cycled, PLV) or HFOV (high-volume strategy). Administration of antenatal steroids and surfactant therapy (no specified dose)	Death or BPD (dependence on supplemental oxygen at 36 weeks PMA)	No significant difference in the two groups in terms of death or BPD and secondary outcomes	Infants received HFOV for a median 3 days, then the majority were switched to CV for weaning. Protective strategies of CV (triggered modes and volume-targeted ventilation) were not used
THOMAS [38]	76 [34 CV + 42 HFOV]	As above	1 year (11–14 months)	Single-centre, observational study. PFT: tidal breathing spirometry, whole-body plethysmography and helium dilution	Respiratory function	No significant difference in pulmonary function in HFOV and CV groups: FRC, RR and inspiratory/expiratory airway resistance	Sample size fell below the statistical target. Unequal group sizes. Tests of small airway function were not assessed

Continued

TABLE 1 Continued

First author [ref.]	Patients n	Birthweight; GA	Age at time of study [#]	Methods	Primary outcome	Results	Criticisms
MARLOW [37]	428 (217 CV + 211 HFOV)	As above	2 years (22–28 months)	Multicentre (25 centres), observational trial. Routine assessments by local paediatricians and parental questionnaire	Respiratory morbidity and neurodevelopment outcome	Mode of ventilation had no effect on respiratory morbidity (wheeze, cough, inhaled medication and readmission to hospital) and neurological outcomes	The low response rate (73% of survivors) could introduce bias; however, the perinatal variables between the two groups were similar
ZIVANOVIC [36]	319 (159 CV + 160 HFOV)	As above	11–14 years	Multicentre (23 centres), observational trial. PFT: spirometry, impulse oscillometry, plethysmography, multiple-breath, helium-dilution, single-breath techniques, fraction of exhaled nitric oxide. Family history of asthma, skin-prick test. Questionnaires to children, parents and teachers: behavioural and academic achievement and quality of life	Respiratory function and morbidity. Primary outcome: small airway function by measure of FEF ₇₅	The two groups had similar respiratory morbidity. HFOV group had significantly superior lung function: FEF ₂₅ , FEF ₅₀ , FEV ₁ , FEV ₁ /FVC ratio, FVC, VC, PEF, diffusing capacity and impulse-oscillometric findings. The HFOV group was rated significantly higher in three school subjects: art and design, information technology and design and technology	Children recruited were more likely to have a mother who was white and who did not smoke during pregnancy. The CV group had had a higher mean birthweight and GA and were more likely to have received surfactant. Full health assessment was possible in only 248 patients of the 319 enrolled
Provo multi-centre trial							
GERSTMANN [33]	125 (61 CV + 64 HFOV)	Mean 1510 g; <36 weeks (mean 30.9 weeks)	Neonatal period	Multicentre (three centres), prospective RCT. Patients assigned within 12 h of life to HFOV (high-volume strategy) or CV (time-cycled, PLV, not synchronised). Surfactant administration (100m g·kg ⁻¹ dose)	Death or BPD (defined on clinical parameters at 30 days of life and discharge oxygen use and level)	HFOV demonstrated less vasopressor support, surfactant redosing, oxygen or ventilator support, treatment failure, BPD, NEC, hearing abnormality and hospital costs. No differences between the two study groups in other secondary outcomes (PDA, air leak, ROP, IVH, length of hospitalisation and survival)	Surfactant dose of 100 mg·kg ⁻¹ . Only 24% received antenatal steroids. Few immature newborn, only 21 patients weighed 1000 g. No attempt was made to minimise tidal breathing before initiation of HFOV. CV not synchronised and without Vt guarantee. Many infants who failed CV were changed to HFOV for rescue
GERSTMANN [24]	69 (33 CV + 36 HFOV)	As above	6.4 years	Single-centre study. PFT: whole-body plethysmography, spirometry, single-breath technique, bronchodilation challenge. Mental and motor testing, social and health questionnaires	Respiratory function and morbidity. Neurodevelopmental outcomes	CV group had significantly poorer pulmonary function: decreased PEF, increased RV and greater maldistribution of ventilation. No differences between the two groups for pulmonary morbidity and neurodevelopment outcomes	Sample size. Larger percentage of infants in the HFOV group were exposed to household smoking

Continued

TABLE 1 Continued

First author [ref.]	Patients n	Birthweight; GA	Age at time of study [#]	Methods	Primary outcome	Results	Criticisms
HOFHUIS [35]	36 (18 CV + 18 HFOV)	<1250 g (mean 837 g); mean 26.8 weeks	6 months and 12 months	Single-centre study. Inclusion criteria: 1) VLBW; 2) need for CV/HFOV from day 1 for ≥7 days; 3) need for supplemental oxygen at 28 days and/or at 36 weeks GA; 4) chest radiograph at 1 month. Surfactant (100 mg·kg ⁻¹ dose) and dexamethasone administered. PFT: rapid thoracoabdominal compression technique, whole-body plethysmography	Respiratory function. Primary outcomes: FRC and V _{max} FRC	VLBW infants with BPD have decreased V _{max} FRC that worsens during the first year of life. At 12 months, the mean V _{max} FRC was lower for children treated with CV, which may reflect abnormal development of airways. FRC was within the normal range	Ventilation strategy was not randomised. No description of the ventilation mode. Excluding very preterm neonates who did not develop BPD. In HFOV group, infants had lower birthweight and received fewer doses of surfactant
LISTA [32]	40 (19 CV + 21 HFOV)	<1250 g (mean 1010 g); 25–32 weeks (mean 27 weeks)	Neonatal period	Single-centre RCT. A/C ventilation plus VG versus HFOV (high-volume strategy). Patients randomised within 1 h of life, maintained until the 96th hour (when neonates in HFOV started switching to A/C and then breathing spontaneously). Antenatal steroids and surfactant (200 mg·kg ⁻¹ dose) administered	Pulmonary inflammation (IL-6, IL-8 and TNF in tracheal aspirate on days 1, 3 and 7 of life) and respiratory outcome (short term)	In the HFOV group IL-6 levels were significantly higher on day 3 and duration of oxygen dependency was significantly longer. No significant differences were observed in duration of ventilation, surfactant administration, PVL, IVH, ROP, BPD or mortality between the two groups	Relatively small sample size. Early crossover from HFOV to A/C+VG ventilation
LISTA [7]	25 (13 CV + 12 HFOV)	As above	7 years	Observational study. PFT: whole-body plethysmography, spirometry and reversibility test. Only non-BPD infants were enrolled	Respiratory function and morbidity	No differences between the two groups for respiratory disorders and obstructive deficit (elevated values of airway resistance, RV and TLC)	Small number of patients. Only infants without BPD were involved

GA: gestational age; HIFI: High-Frequency Ventilation in Premature Infants; UKOS: United Kingdom Oscillatory Study; RCT: randomised controlled trial; BPD: bronchopulmonary dysplasia; IVH: intraventricular haemorrhage; PVL: periventricular leukomalacia; FEF_n: forced expiratory flow at n% of the forced vital capacity (FVC); DLCO: diffusing capacity of the lung for carbon monoxide; PLV: pressure-limited ventilation; PMA: postmenstrual age; PFT: pulmonary function test; FRC: functional residual capacity; RR: respiratory rate; FEV₁: forced expiratory volume in 1 s; VC: vital capacity; PEF: peak expiratory flow; NEC: necrotising enterocolitis; PDA: patent ductus arteriosus; ROP: retinopathy of prematurity; V_t: tidal volume; RV: residual volume; VLBW: very low birthweight; V_{max}FRC: maximal flow at FRC; A/C: assist-control; VG: volume guarantee; IL: interleukin; TNF: tumour necrosis factor; TLC: total lung capacity. [#]: ages at the study time are given in corrected age.

Can BPD capture the respiratory consequences of early noninvasive ventilation?

Recent large longitudinal cohort data from DOYLE *et al.* [8] found the same or worse lung function in 8-year-old ex-preterm children born in 2005 compared with those born in 1991 and 1997. Importantly, children in the more recent cohort were managed in an era of greater noninvasive ventilation (NIV). This raises the fascinating hypothesis that the early lung-protective effects of NIV may not confer protection from long-term respiratory impairment. Although early stabilisation with continuous positive airway pressure (CPAP) has demonstrated beneficial short-term outcomes, with reductions in death, BPD and important secondary respiratory outcomes [49, 50], its long-term efficacy has only been investigated in two follow-up studies of the large the COIN (Continuous Positive Airway Pressure or Intubation at Birth) and SUPPORT (Surfactant, Positive Pressure, and Oxygenation Randomized Trial) trials (table 3) [9, 50–52].

Both COIN and SUPPORT trials found that early CPAP did not significantly reduce the rate of death or BPD [50, 51]. In a single-centre subcohort study of the COIN trial, improved lung mechanics and decreased work of breathing at 8 weeks corrected age were found in the CPAP group [52]. In the Breathing Outcomes Study, a secondary study to SUPPORT, patients in the CPAP group had lower rates of several important respiratory morbidities at 18–22 months, including respiratory illnesses, treatment with oxygen or diuretics at home and overnight hospitalisation for breathing problems [9]. Despite observing no difference in the incidence of BPD, both COIN and SUPPORT follow-up studies found better long-term respiratory outcomes using early CPAP [9, 52]. In addition, DOYLE *et al.* [8] reported a longer duration of oxygen therapy in the 2005 cohort, attributing this to a combination of NIV use and greater availability of oximetry monitoring. This may account for the differences of the protocolised NIV strategies in COIN and SUPPORT trials.

Surfactant: long-term efficacy beyond the NICU?

Exogenous surfactant replacement therapy has revolutionised the management of hyaline membrane disease [53]. While short-term effectiveness of surfactant treatment is well established, data on respiratory long-term outcomes remain evidence-poor (table 4). Initial long-term follow-up studies of surfactant therapy against placebo produced contradictory results, illustrating the limitation of small sample sizes [54–59]. Historical cohort comparisons of infants managed before (1980s) and after (1990s) the introduction of surfactant reported similar respiratory morbidity and function (airway obstruction, hyperresponsiveness and pulmonary hyperinflation) in childhood and early adulthood [60–63]. However, these trials studied children born when the surfactant replacement had just been introduced and other potentially beneficial therapies (VTV, HFOV and NIV) were not in routine use [60, 63]. Two large cohort follow-up programmes, the Victorian Infant Collaborative Study and that of VOLLSÆTER *et al.* [64, 65], reported similar lung function in children who were born prematurely in 1991–1992 and 1997–2000. It is important to note that many of the infants born in 1997–2000 would not have survived if born in 1991–1992, suggesting that the combination of more protective ventilation approaches with near universal surfactant use had a positive effect. A recent meta-analysis of the neonatal respiratory outcomes between the pre- and the post-surfactant era found better

TABLE 2 Study assessing long-term respiratory outcomes of volume-targeted ventilation *versus* pressure-controlled mechanical ventilation in preterm infants

	Patients n	Birthweight; GA	Age at time of study [#]	Methods	Primary outcome	Results	Criticisms
SINGH [47]	85 (45 VTV + 40 PLV)	600–1500 g (mean 1000 g); 24–31 weeks (mean 27 weeks)	2 years (mean 22 months)	Randomised within 6 h of MV to receive either PLV or VTV. Parental questionnaire and local paediatricians' records. Respiratory outcomes: cough and wheeze, inhaled medications and hospital admissions for respiratory illnesses. Neurodevelopmental outcome: cerebral palsy, deafness or blindness	Neurodevelopmental outcome and pulmonary morbidity	VTV children, compared to PLV children, required significantly fewer inhaled steroids/bronchodilators. No significant difference in readmission rates, frequency of respiratory illness or neurodevelopmental outcomes	No respiratory functional test. PLV group assessed at a later time (24 months) than the VTV group (18 months). The original study was not powered to look at long-term outcomes

GA: gestational age; VTV: volume-targeted ventilation; PLV: pressure-limited ventilation; MV: mechanical ventilation. #: ages at the study time are given in corrected age.

TABLE 3 Studies assessing long-term respiratory outcomes of early noninvasive ventilation strategies in preterm infants

First author [ref.]	Patients n	Birthweight; GA	Age time of study [#]	Methods	Primary outcome	Results	Criticisms
COIN trial							
ROEHR [52]	39 (17 nCPAP + 22 MV)	Mean 950 g; 25–28 weeks	8 weeks	Single-centre, subcohort study. Randomised after birth to nCPAP <i>versus</i> intubation, surfactant and MV. PFT: dead-space free flow, occlusion test and body plethysmography	Pulmonary function and morbidity	CPAP group had lower RR, minute ventilation, better compliance, higher respiratory time constant and improved elastic WOB. No differences in FRC and morbidity	Sample size. CPAP group had fewer doses of surfactant, days of MV and shorter total respiratory support and oxygen supplementation
SUPPORT trial							
STEVENS [9]	918 (474 nCPAP + 444 MV)	Mean 850 g; 24–27 weeks	At hospital discharge, at 6, 12 and 18–22 months	Prospective secondary, multicentre (20 centres) study. Randomised after birth to one of two respiratory strategies: lower (85–89%) <i>versus</i> higher (91–95%) oxygen saturation targets and early CPAP <i>versus</i> early intubation and surfactant administration by 1 h of life. Parental questionnaires	Pulmonary morbidity	At 6 months, the lower oxygen saturation target group had less wheezing and use of nebulised medications. nCPAP group had less respiratory morbidities at 6 and 18–22 months (respiratory illnesses, treatment with oxygen or diuretics at home and hospitalisation). Significant differences in respiratory outcomes for infants with and without BPD	Data were obtained by parental report, which has the potential for classification and recall bias
GA: gestational age; COIN: Continuous Positive Airway Pressure or Intubation at Birth; SUPPORT: Surfactant, Positive Pressure, and Oxygenation Randomized Trial; nCPAP: nasal continuous positive airway pressure (CPAP); MV: mechanical ventilation; PFT: pulmonary function test; RR: respiratory rate; WOB: work of breathing; FRC: functional residual capacity; BPD: bronchopulmonary dysplasia. [#] : ages at the study time are given in corrected age.							

FEV₁ at school age and early adulthood of subjects born prematurely in the post-surfactant era, especially those with BPD [11, 66]. Furthermore, neonatal exogenous surfactant administration reduced respiratory hospitalisation within the first 3 years post-discharge [67].

Although it is likely that surfactant is beneficial to the preterm lung in the long term, it is unfortunate that longitudinal pulmonary function evaluation was not a feature of many surfactant trials. This would have allowed exploration of the mechanistic role of exogenous surfactant, specifically whether these benefits were due to alterations in lung growth or simply prevention of injury due to reduction in mechanical ventilation duration and need. This is especially important as less invasive surfactant therapy during NIV becomes more popular. Long-term pulmonary follow-up of less-invasive surfactant methods may provide valuable insight into whether surfactant function is altered during NIV.

The current state of neonatal respiratory assessment tools as outcome measures of chronic respiratory morbidity of prematurity

Despite the rationale for the use of childhood functional respiratory status, rather than BPD (by any diagnostic criteria), as the principal method of assessing the efficacy of neonatal respiratory therapies, traditional pulmonary function tests are impractical in neonates. Thus, new functional measures that can be performed in early life and then repeated during childhood, are urgently needed. Ideally such measurements would provide a standardised functional definition of pathological lung state that correlates with later respiratory morbidity, and at a resolution that would allow interrogation of the hypothesised differences between current respiratory therapies. Very early measures of the immature and developing airways of preterm infants need to delineate specific developmental lung states. The availability of such

TABLE 4 Studies assessing long-term respiratory outcomes of surfactant treatment in preterm infants

First author [ref.]	Patients n	Birthweight; GA	Age at time of study [#]	Methods	Primary outcome	Results	Criticisms
WALTI [56]	43 (13 surfactant + 9 nonsurfactant + 21 control)	N/A	1 year	Not detailed; only abstract is available	Pulmonary function	Surfactant does not affect long-term pulmonary function at 1 year of age	Not detailed; only abstract is available
COUSER [57]	47 (30 surfactant + 17 control)	N/A	2 years	Not detailed; only abstract is available	Pulmonary function and morbidity	No differences between the two groups in terms of respiratory morbidity and function (FRC, V _T , compliance, resistance and time constant)	Not detailed; only abstract is available
YUKSEL [44]	17 (7 surfactant + 10 control)	N/A	7 months	Not detailed; only abstract is available	Pulmonary function	Surfactant group had lower resistance and higher conductance	Not detailed; only abstract is available
ABBASI [55]	47 (34 surfactant + 13 control)	N/A	3–6 months and 9–12 months	Not detailed; only abstract is available	Pulmonary function	Surfactant group had lower resistance and resistive WOB and airflow obstruction	Not detailed; only abstract is available
PELKONEN [59]	60 (40 preterm + 20 term control)	<30 weeks	7–12 years	Bicentre study. Randomised into three groups: surfactant at birth (prophylactic), after development of RDS (rescue) and placebo group. Parental questionnaires and prick tests. PFT: bronchodilation test (twice daily for 4 weeks) and spirometry	Pulmonary function	No significant differences in spirometric measurements between the three groups	Small sample size. Children born in 1983–1987. The strategy of ventilation support used was not described
GAPPA [58]	40 (22 surfactant + 18 term control)	Mean 1100 g; 25–30 weeks	6 years	Observational study. Surfactant versus placebo. Parent questionnaires. PFT: spirometry, whole-body plethysmography and test of bronchial hyperreactivity	Pulmonary function and morbidity	No difference between the two groups in pulmonary morbidity, FRC, resistance, FEV ₁ or bronchial hyperreactivity. Only FEF ₂₅ was significantly lower in surfactant group	Sample size. Children born in 1987–1988. Lack of statistical power for no cooperation during lung function tests
HALVORSEN [16]	162 (81 preterm + 81 term control)	<1000 g; <28 weeks	10–18 years	Population-based, controlled study. Children born in 1982–1985 (no surfactant) and in 1991–1992 (49% received surfactant). BPD definition proposed by JOBE and BANGALARI [3]. Test for atopy: skin prick test and specific IgE. Parental questionnaires. PFT: spirometry, body plethysmography and methacholine provocation	Pulmonary function and morbidity	Preterms had similar long-term decreases in lung outcome: BPD incidence, airway obstruction, hyperresponsiveness and pulmonary hyperinflation. Similar significant airway obstruction in the two birth cohorts: oxygen supplementation was associated with long-term negative effects on FEV ₁ only if lasting >1 month approximately	Low experience in surfactant therapy, administered as rescue therapy. Pulmonary function was assessed at a mean age of 17.7 years in children born in 1980s and at a mean age of 10.4 years in children born in 1990s
PALTA [61]	625 (265 VLBW + 360 term control)	<1500 g (mean 1123 g); mean 29 weeks	10 years	Multicentre (six centres) prospective study. During 1988–1991, three surfactant periods: 1) sporadic RCTs; 2) investigational new drug; and 3) general release. Parental respiratory questionnaires. PFT: electronic peak flow meter	Pulmonary function and morbidity	Respiratory abnormalities persist to age 10 years for VLBW children born in the surfactant era. Baseline test results did not differ across birth years, but PEF variation and FVC were less in the postsurfactant era	The study may have been insufficiently powered to statistically detect a decrease in FVC postsurfactant

Continued

TABLE 4 Continued

First author [ref.]	Patients n	Birthweight; GA	Age at time of study [#]	Methods	Primary outcome	Results	Criticisms
VICS trial							
DOYLE [60]	448 [240 preterms + 208 term control]	<1000 g; <28 weeks	8 years	Observational study. Children born in 1991–1992. Surfactant as rescue therapy. BPD defined as oxygen dependency at 36 weeks PMA. Parental questionnaires. PFT: spirometry, whole-body plethysmography	Pulmonary function and morbidity	Abnormalities in respiratory function and asthma incidence in very preterm children compared with control subjects described in the presurfactant era persisted in the 1990s, especially in those who had BPD	Low experience in surfactant therapy (surfactant has been used in Victoria since 1991). Surfactant used only as rescue therapy and only in with the most severe lung disease
HACKING [64]	1991–1992 cohort: 448 [240 preterm + 208 term control] 1997 cohort: 299 [150 preterm + 149 term control]	As above	8 years	Two population cohorts born in 1991–1992 and 1997, when higher rates of antenatal corticosteroids and surfactant were administered. Parental questionnaires. PFT: spirometry, whole-body plethysmography	Pulmonary function and morbidity	Preterm children born in both eras had substantially reduced lung function compared with controls for FEV ₁ , FVC, FEF _{25–75%} , and FEV ₁ /FVC	As above. Absence of exercise testing
DOYLE [63]	363 [209 preterms + 154 term control]	As above	18 years	Observational study. Children born in 1991–1992. Patient questionnaires. PFT: spirometry at baseline and postbronchodilator	Pulmonary function	Preterms had a greater small airway obstruction between 8 and 18 years. Within the preterm group, those who had BPD and were smokers had even more airway obstruction increased over time. Within the preterm group, only those with BPD, but not smokers, had a larger response in FEV ₁ to salbutamol	As above. Low follow-up at age 18 years and incomplete data for smoking from the patients' questionnaires
VOLLSTÆTER [62]	1982–1985 cohort: 92 [46 preterm + 46 term control] 1991–1992 cohort: 70 [35 preterm + 35 term control]	<1000 g; <28 weeks	1982–1985 cohort: at 18 and 25 years 1991–1992 cohort: at 10 and 18 years	Prospective longitudinal study. Two population cohorts born in 1982–1985 and 1991–1992, when surfactant was for selective administration in the Osiris trial. BPD defined as oxygen dependency at 36 weeks PMA. Parental questionnaires. PFT: spirometry	Pulmonary function and morbidity	No differences between the two population cohorts born in 1982–1985 and 1991–1992. Preterm-born cohorts, particularly those with BPD, had significantly lower FEV ₁ and FEF _{25–75%} . FEV ₁ was stable at ages 10–18 years and at ages 18–25 years in all subgroups	Besides surfactant, other significant changes from 1982–1985 to 1991–1992: fewer ventilator days, more use of antenatal and postnatal steroids and lower GA
VOLLSTÆTER [65]	1991–1992 cohort: 70 [35 preterm + 35 term control] 1999–2000 cohort: 111 [57 preterm + 54 term control]	As above	1991–1992 cohort: at 10 and 18 years 1999–2000 cohort: at 11 years	As above. Parental or patient respiratory questionnaires. PFT: spirometry, F _e NO and DLCO	Pulmonary function and morbidity	For children with BPD, important lung function variables were better in 1999–2000 compared to 1991–1992 and improvements were related to more use of antenatal corticosteroids and surfactant treatment	Besides surfactant, other significant changes from 1991–1992 to 1999–2000: more extensive use of antenatal corticosteroids, better perinatal care and better exploitation of technologies, such as A/C ventilation and HFOV. Sample size

GA: gestational age; VICS: Victorian Infant Collaborative Study; N/A: not available; FRC: functional residual capacity; Vt: tidal volume; WOB: work of breathing; RDS: respiratory distress syndrome; PFT: pulmonary function test; IgE: immunoglobulin E; FEV₁: forced expiratory volume in 1 s; FEF_n: forced expiratory flow at n% of the forced vital capacity (FVC); BPD: bronchopulmonary dysplasia; VLBW: very low birthweight; RCT: randomised controlled trial; PEF: peak expiratory flow; PMA: postmenstrual age; F_eNO: exhaled nitric oxide fraction; DLCO: diffusing capacity of the lung for carbon monoxide; A/C: assist-control; HFOV: high-frequency oscillatory ventilation. [#]: ages at the study time are given in corrected age.

measures would benefit clinical trial design and offer potential to address the role of later life childhood respiratory events, such as respiratory infections and environmental factors, on lung growth and development.

A variety of clinical sequelae, functional tests and thoracic imaging methods have been proposed to assess later pulmonary outcomes in infants born prematurely. Many of these are based on techniques developed to capture and track early lung disease in other chronic paediatric pulmonary diseases, particularly cystic fibrosis and recurrent wheezing. Although the ability of specific tests to detect abnormalities varies according to the underlying disease pathophysiology, this common interest has led to furthering our understanding of respiratory outcome measures in preschool children generally [68].

Dynamic lung function tests

Objective dynamic physiological measures may have a key role in the early diagnosis of chronic respiratory morbidity in preterm patients, but measuring lung function in early life is challenging. The American Thoracic Society reviewed safe, feasible and potentially clinically useful lung function tests in preschool children in 2009–2010 [68]. The application to the clinical management of six lung function tests (infant raised-volume rapid thoracic compression and plethysmography, spirometry, specific airway resistance, FOT, the interrupter technique and multiple-breath washout) was reviewed in children aged <6 years with cystic fibrosis, BPD and recurrent wheeze. Spirometry, specific airway resistance and the interrupter resistance technique were identified as potentially useful methods for identifying obstructive lung disease, a feature of BPD. Plethysmography and raised-volume rapid thoracic compression may prove more insightful given the potential to measure trapped gas. FOT, which measures dynamic respiratory mechanics directly, offers a sensitive method of identifying disturbances of the more peripheral airways, but commercial infant systems are lacking. The utility of using multiple-breath washout techniques to quantify ventilation homogeneity in infants remains controversial [17, 68, 69]. Although insufficient evidence was found to recommend the incorporation of these tests into the routine diagnostic evaluation and clinical monitoring of children affected with these diseases, the potential to address specific concerns, such as ongoing symptoms or monitoring response to treatment, and as research tools was recognised [68]. However, published evaluation of all these techniques in preterm preschoolers is very limited and further studies are needed to identify whether these methods are able to reliably identify the early prodromal features of chronic respiratory morbidity following preterm birth. The multimodal nature of preterm lung disease suggests that no single dynamic measure will be useful. A more appropriate approach may be to develop and evaluate a composite suite of measures.

Uncalibrated plethysmography techniques, such as respiratory inductance plethysmography [70], electromagnetic impedance plethysmography [71] and electrical impedance tomography (EIT) [72], have been used widely as research tools to evaluate the neonatal ventilator–lung interaction, and potentially guide respiratory care. Of these, EIT is the most established, and dedicated infant EIT systems have been developed recently [72, 73]. EIT is a noninvasive, radiation free and, importantly, continuous measure of multiple regional measures of tidal ventilation, end-expiratory and breathing pattern homogeneity [72]. EIT has been used widely to define short-term respiratory status of specific neonatal therapies, including NIV, HFOV, VTV and surfactant administration [74–79]. Recent international consensus guidelines [72], including standardised methodology, terminology and recommendations for use in infants and children during NICU and ambulatory care, offer the potential for EIT to be a powerful dynamic function tool, especially if combined with other methods of assessing ventilation homogeneity (multiple breath washout) and lung mechanics (FOT). As EIT can be performed independent of age, clinical care and without instrumentation of the respiratory system we would suggest that future studies using EIT in the NICU include longitudinal measurements.

Structural lung imaging

Structural lung abnormalities have been explored as long-term outcome measures in patients born prematurely. Chest HRCT is the most sensitive tool for assessing early structural lung abnormalities in infants with cystic fibrosis, and may predict risk of later symptomatic lung disease in preterm infants [80]. The association between abnormality on HRCT scans and the severity of lung function impairment has been demonstrated in preterm survivors. However, it is important to note important limitations of HRCT scanning in clinical practice, specifically radiation exposure and need for general anaesthesia in younger children [18, 80].

Magnetic resonance-based imaging (MRI), although traditionally considered not suitable to quantify lung disease, has been shown to detect abnormal lung structure and perfusion in young children with cystic fibrosis, without the need for a general anaesthetic. These results suggest that MRI may be suitable for non-ionising long-term respiratory monitoring from early childhood in preterm infants. Pulmonary MRI

has been shown to reveal quantifiable abnormalities in premature patients; however, further validation studies are needed [81]. The alveolar structure itself can be observed by hyperpolarised helium MRI, which has demonstrated catch-up of alveolar structural growth following preterm birth [82].

Despite limited information, and often a lack of standardisation, chest imaging is already providing new insight into the nature and development of long-term respiratory function in children born prematurely. As our knowledge increases regarding the significance of structural lung imaging at different ages, there may be a role for routine scanning to determine prognosis and appropriate follow-up. Ideally structural assessment should be paired with functional measures.

Conclusion

Future trials of neonatal respiratory therapies should include long-term respiratory outcomes. However, both the techniques and the outcomes need to be standardised. Dynamic lung function tests offer the most potential for capturing the respiratory consequences of prematurity. It is unlikely that any one test will be robust or practical enough to serve all ages. A combination of methods, combined with intermittent imaging of structural lung growth and disease, would allow for meaningful assessment of neonatal novel therapies or prevention strategies, and offer the potential to titrate neonatal respiratory care individually for the best respiratory health outcomes.

Author contributions: F. Ciuffini developed the concept and wrote the first draft under guidance from C.F. Robertson and D.G. Tingay. All authors contributed to redrafting the manuscript including tables.

Conflict of interest: None declared.

Support statement: This study is supported by the Victorian Government Operational Infrastructure Support Program (Melbourne, Australia). D.G. Tingay is supported by a National Health and Medical Research Council Clinical Career Development Fellowship (Grant ID 11123859). Funding information for this article has been deposited with the Crossref Funder Registry.

References

- 1 Northway WH Jr, Rosan RC, Porter DY. Pulmonary disease following respirator therapy of hyaline-membrane disease. Bronchopulmonary dysplasia. *N Engl J Med* 1967; 276: 357–368.
- 2 Jobe AJ. The new BPD: an arrest of lung development. *Pediatr Res* 1999; 46: 641–643.
- 3 Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *Am J Respir Crit Care Med* 2001; 163: 1723–1729.
- 4 Walsh MC, Yao Q, Gettner P, et al. Impact of a physiologic definition on bronchopulmonary dysplasia rates. *Pediatrics* 2004; 114: 1305–1311.
- 5 Quine D, Wong CM, Boyle EM, et al. Non-invasive measurement of reduced ventilation:perfusion ratio and shunt in infants with bronchopulmonary dysplasia: a physiological definition of the disease. *Arch Dis Child Fetal Neonatal Ed* 2006; 91: F409–F414.
- 6 Latini G, De Felice C, Giannuzzi R, et al. Survival rate and prevalence of bronchopulmonary dysplasia in extremely low birth weight infants. *Early Hum Dev* 2013; 89: Suppl. 1, S69–S73.
- 7 Lista G, Castoldi F, Bianchi S, et al. Lung function and respiratory health at school age in ventilated very low birth weight infants. *Indian J Pediatr* 2014; 81: 275–278.
- 8 Doyle LW, Carse E, Adams AM, et al. Ventilation in extremely preterm infants and respiratory function at 8 years. *N Engl J Med* 2017; 377: 329–337.
- 9 Stevens TP, Finer NN, Carlo WA, et al. Respiratory outcomes of the surfactant positive pressure and oximetry randomized trial (SUPPORT). *J Pediatr* 2014; 165: 240–249.
- 10 Bolton CE, Bush A, Hurst JR, et al. Lung consequences in adults born prematurely. *Thorax* 2015; 70: 574–580.
- 11 Gibson AM, Doyle LW. Respiratory outcomes for the tiniest or most immature infants. *Semin Fetal Neonatal Med* 2014; 19: 105–111.
- 12 Ronkainen E, Dunder T, Kaukola T, et al. Intrauterine growth restriction predicts lower lung function at school age in children born very preterm. *Arch Dis Child Fetal Neonatal Ed* 2016; 101: F412–F417.
- 13 Pike KC, Davis SA, Collins SA, et al. Prenatal development is linked to bronchial reactivity: epidemiological and animal model evidence. *Sci Rep* 2014; 4: 4705.
- 14 Simpson SJ, Hall GL, Wilson AC. Lung function following very preterm birth in the era of ‘new’ bronchopulmonary dysplasia. *Respirology* 2015; 20: 535–540.
- 15 Kennedy JD, Edward LJ, Bates DJ, et al. Effects of birthweight and oxygen supplementation on lung function in late childhood in children of very low birth weight. *Pediatr Pulmonol* 2000; 30: 32–40.
- 16 Halvorsen T, Skadberg BT, Eide GE, et al. Better care of immature infants; has it influenced long-term pulmonary outcome? *Acta Paediatr* 2006; 95: 547–554.
- 17 Udomittipong K, Sly PD, Patterson HJ, et al. Forced oscillations in the clinical setting in young children with neonatal lung disease. *Eur Respir J* 2008; 31: 1292–1299.
- 18 Aukland SM, Rosendahl K, Owens CM, et al. Neonatal bronchopulmonary dysplasia predicts abnormal pulmonary HRCT scans in long-term survivors of extreme preterm birth. *Thorax* 2009; 64: 405–410.
- 19 Stevens TP, Dylag A, Panthagani I, et al. Effect of cumulative oxygen exposure on respiratory symptoms during infancy among VLBW infants without bronchopulmonary dysplasia. *Pediatr Pulmonol* 2010; 45: 371–379.
- 20 Kjellberg M, Björkman K, Rohdin M, et al. Bronchopulmonary dysplasia: clinical grading in relation to ventilation/perfusion mismatch measured by single photon emission computed tomography. *Pediatr Pulmonol* 2013; 48: 1206–1213.

- 21 Gage S, Kan P, Oehlert J, *et al.* Determinants of chronic lung disease severity in the first year of life; a population based study. *Pediatr Pulmonol* 2015; 50: 878–888.
- 22 McLeod A, Ross P, Mitchell S, *et al.* Respiratory health in a total very low birthweight cohort and their classroom controls. *Arch Dis Child* 1996; 74: 188–194.
- 23 Schulzke SM, Hall GL, Nathan EA, *et al.* Lung volume and ventilation inhomogeneity in preterm infants at 15–18 months corrected age. *J Pediatr* 2010; 156: 542–549.
- 24 Mai XM, Gäddlin PO, Nilsson L, *et al.* Asthma, lung function and allergy in 12-year-old children with very low birth weight: a prospective study. *Pediatr Allergy Immunol* 2003; 14: 184–192.
- 25 Cools F, Askie LM, Offringa M, *et al.* Elective high-frequency oscillatory *versus* conventional ventilation in preterm infants: a systematic review and meta-analysis of individual patients' data. *Lancet* 2010; 375: 2082–2091.
- 26 Bollen CW, Uiterwaal CS, van Vught AJ. Cumulative metaanalysis of high-frequency *versus* conventional ventilation in premature neonates. *Am J Respir Crit Care Med* 2003; 168: 1150–1155.
- 27 HiFO Study Group. Randomized study of high-frequency oscillatory ventilation in infants with severe respiratory distress syndrome. *J Pediatr* 1993; 122: 609–619.
- 28 HiFi Study Group. High-frequency oscillatory ventilation compared with conventional mechanical ventilation in the treatment of respiratory failure in preterm infants. *N Engl J Med* 1989; 320: 88–93.
- 29 HiFi Study Group. High-frequency oscillatory ventilation compared with conventional intermittent mechanical ventilation in the treatment of respiratory failure in preterm infants: neurodevelopmental status at 16 to 24 months of postterm age. *J Pediatr* 1990; 117: 939–946.
- 30 HiFi Study Group. High-frequency oscillatory ventilation compared with conventional mechanical ventilation in the treatment of respiratory failure in preterm infants: assessment of pulmonary function at 9 months of corrected age. *J Pediatr* 1990; 116: 933–941.
- 31 Pianosi PT, Fisk M. High frequency ventilation trial. Nine year follow up of lung function. *Early Hum Dev* 2000; 57: 225–234.
- 32 Lista G, Castoldi F, Bianchi S, *et al.* Volume guarantee *versus* high-frequency ventilation: lung inflammation in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2008; 93: F252–F256.
- 33 Gerstmann DR, Minton SD, Stoddard RA, *et al.* The Provo multicenter early high-frequency oscillatory ventilation trial: improved pulmonary and clinical outcome in respiratory distress syndrome. *Pediatrics* 1996; 98: 1044–1057.
- 34 Gerstmann DR, Wood K, Miller A, *et al.* Childhood outcome after early high-frequency oscillatory ventilation for neonatal respiratory distress syndrome. *Pediatrics* 2001; 108: 617–623.
- 35 Hofhuis W, Huysman MW, van der Wiel EC, *et al.* Worsening of V_{\max}^{FRC} in infants with chronic lung disease in the first year of life: a more favorable outcome after high-frequency oscillation ventilation. *Am J Respir Crit Care Med* 2002; 166: 1539–1543.
- 36 Zivanovic S, Peacock J, Alcazar-Paris M, *et al.* Late outcomes of a randomized trial of high-frequency oscillation in neonates. *N Engl J Med* 2014; 370: 1121–1130.
- 37 Marlow N, Greenough A, Peacock JL, *et al.* Randomised trial of high frequency oscillatory ventilation or conventional ventilation in babies of gestational age 28 weeks or less: respiratory and neurological outcomes at 2 years. *Arch Dis Child Fetal Neonatal Ed* 2006; 91: F320–F326.
- 38 Thomas MR, Rafferty GF, Limb ES, *et al.* Pulmonary function at follow-up of very preterm infants from the United Kingdom Oscillation Study. *Am J Respir Crit Care Med* 2004; 169: 868–872.
- 39 Johnson AH, Peacock JL, Greenough A, *et al.* High-frequency oscillatory ventilation for the prevention of chronic lung disease of prematurity. *N Engl J Med* 2002; 347: 633–642.
- 40 Rojas-Reyes MX, Morley CJ, Soll R. Prophylactic *versus* selective use of surfactant in preventing morbidity and mortality in preterm infants. *Cochrane Database Syst Rev* 2012; 3: CD000510.
- 41 van Kaam AH, Rimensberger PC. Lung-protective ventilation strategies in neonatology: what do we know – what do we need to know? *Crit Care Med* 2007; 35: 925–931.
- 42 Courtney SE, Durand DJ, Asselin JM, *et al.* High-frequency oscillatory ventilation *versus* conventional mechanical ventilation for very-low-birth-weight infants. *N Engl J Med* 2002; 347: 643–652.
- 43 Farrell O, Perkins EJ, Black D, *et al.* Volume guaranteed? Accuracy of a volume-targeted ventilation mode in infants. *Arch Dis Child Fetal Neonatal Ed* 2017; Doi: 10.1136/archdischild-2017-312640.
- 44 Peng W, Zhu H, Shi H, *et al.* Volume-targeted ventilation is more suitable than pressure-limited ventilation for preterm infants: a systematic review and meta-analysis. *Arch Dis Child Fetal Neonatal Ed* 2014; 99: F158–F165.
- 45 Wheeler KI, Klingenberg C, Morley CJ, *et al.* Volume-targeted *versus* pressure-limited ventilation for preterm infants: a systematic review and meta-analysis. *Neonatology* 2011; 100: 219–227.
- 46 Wheeler K, Klingenberg C, McCallion N, *et al.* Volume-targeted *versus* pressure-limited ventilation in the neonate. *Cochrane Database Syst Rev* 2010; 11: CD003666.
- 47 Singh J, Sinha SK, Alsop E, *et al.* Long term follow-up of very low birthweight infants from a neonatal volume *versus* pressure mechanical ventilation trial. *Arch Dis Child Fetal Neonatal Ed* 2009; 94: F360–F362.
- 48 Singh J, Sinha SK, Clarke P, *et al.* Mechanical ventilation of very low birth weight infants: is volume or pressure a better target variable? *J Pediatr* 2006; 149: 308–313.
- 49 Fischer HS, Bühner C. Avoiding endotracheal ventilation to prevent bronchopulmonary dysplasia: a meta-analysis. *Pediatrics* 2013; 132: e1351–e1360.
- 50 Morley CJ, Davis PG, Doyle LW, *et al.* Nasal CPAP or intubation at birth for very preterm infants. *N Engl J Med* 2008; 358: 700–708.
- 51 SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Early CPAP *versus* surfactant in extremely preterm infants. *N Engl J Med* 2010; 362: 1970–1979.
- 52 Roehr CC, Proquitté H, Hammer H, *et al.* Positive effects of early continuous positive airway pressure on pulmonary function in extremely premature infants: results of a subgroup analysis of the COIN trial. *Arch Dis Child Fetal Neonatal Ed* 2011; 96: F371–F373.
- 53 Bahadue FL, Soll R. Early *versus* delayed selective surfactant treatment for neonatal respiratory distress syndrome. *Cochrane Database Syst Rev* 2012; 11: CD001456.
- 54 Yuksel B, Greenough A, Gamsu HR. Respiratory function at follow-up after neonatal surfactant replacement therapy. *Respir Med* 1993; 87: 217–221.

- 55 Abbasi S, Bhutani VK, Gerdes JS. Long-term pulmonary consequences of respiratory distress syndrome in preterm infants treated with exogenous surfactant. *J Pediatr* 1993; 122: 446–452.
- 56 Walti H, Boulé M, Moriette G, *et al.* Pulmonary functional outcome at one year of age in infants treated with natural porcine surfactant at birth. *Biol Neonate* 1992; 61: Suppl. 1, 48–53.
- 57 Couser RJ, Ferrara TB, Wheeler W, *et al.* Pulmonary follow-up 2.5 years after a randomized, controlled, multiple dose bovine surfactant study of preterm newborn infants. *Pediatr Pulmonol* 1993; 15: 163–167.
- 58 Gappa M, Berner MM, Hohenschild S, *et al.* Pulmonary function at school-age in surfactant-treated preterm infants. *Pediatr Pulmonol* 1999; 27: 191–198.
- 59 Pelkonen AS, Hakulinen AL, Turpeinen M, *et al.* Effect of neonatal surfactant therapy on lung function at school age in children born very preterm. *Pediatr Pulmonol* 1998; 25: 182–190.
- 60 Doyle LW, Victorian Infant Collaborative Study Group. Respiratory function at age 8–9 years in extremely low birthweight/very preterm children born in Victoria in 1991–1992. *Pediatr Pulmonol* 2006; 41: 570–576.
- 61 Palta M, Sadek-Badawi M, Madden K, *et al.* Pulmonary testing using peak flow meters of very low birth weight children born in the perisurfactant era and school controls at age 10 years. *Pediatr Pulmonol* 2007; 42: 819–828.
- 62 Vollsæter M, Røksund OD, Eide GE, *et al.* Lung function after preterm birth: development from mid-childhood to adulthood. *Thorax* 2013; 68: 767–776.
- 63 Doyle LW, Adams AM, Robertson C, *et al.* Increasing airway obstruction from 8 to 18 years in extremely preterm/low-birthweight survivors born in the surfactant era. *Thorax* 2017; 72: 712–719.
- 64 Hacking DF, Gibson AM, Robertson C, *et al.* Respiratory function at age 8–9 after extremely low birthweight or preterm birth in Victoria in 1997. *Pediatr Pulmonol* 2013; 48: 449–455.
- 65 Vollsæter M, Skromme K, Satrell E, *et al.* Children born preterm at the turn of the millennium had better lung function than children born similarly preterm in the early 1990s. *PLoS One* 2015; 10: e0144243.
- 66 Kotecha SJ, Edwards MO, Watkins WJ, *et al.* Effect of preterm birth on later FEV1: a systematic review and meta-analysis. *Thorax* 2013; 68: 760–766.
- 67 Hong T, Bolisetty S, Bajuk B, *et al.* A population study of respiratory rehospitalisation in very preterm infants in the first 3 years of life. *J Paediatr Child Health* 2016; 52: 715–721.
- 68 Rosenfeld M, Allen J, Arets BH, *et al.* An official American Thoracic Society workshop report: optimal lung function tests for monitoring cystic fibrosis, bronchopulmonary dysplasia, and recurrent wheezing in children less than 6 years of age. *Ann Am Thorac Soc* 2013; 10: S1–S11.
- 69 Robinson PD, Latzin P, Verbanck S, *et al.* Consensus statement for inert gas washout measurement using multiple- and single-breath tests. *Eur Respir J* 2013; 41: 507–522.
- 70 Tingay DG, Mills JF, Morley CJ, *et al.* The deflation limb of the pressure-volume relationship in infants during high-frequency ventilation. *Am J Respir Crit Care Med* 2006; 173: 414–420.
- 71 Olden C, Symes E, Seddon P. Measuring tidal breathing parameters using a volumetric vest in neonates with and without lung disease. *Pediatr Pulmonol* 2010; 45: 1070–1075.
- 72 Frerichs I, Amato MB, van Kaam AH, *et al.* Chest electrical impedance tomography examination, data analysis, terminology, clinical use and recommendations: consensus statement of the Translational EIT Development Study Group. *Thorax* 2017; 72: 83–93.
- 73 Miedema M, Waldmann A, McCall KE, *et al.* Individualized multiplanar electrical impedance tomography in infants to optimize lung monitoring. *Am J Respir Crit Care Med* 2017; 195: 536–538.
- 74 Bhatia R, Davis PG, Tingay DG. Regional volume characteristics of the preterm infant receiving first intention continuous positive airway pressure. *J Pediatr* 2017; 187: 80–88.
- 75 Armstrong RK, Carlisle HR, Davis PG, *et al.* Distribution of tidal ventilation during volume-targeted ventilation is variable and influenced by age in the preterm lung. *Intensive Care Med* 2011; 37: 839–846.
- 76 Carlisle HR, Armstrong RK, Davis PG, *et al.* Regional distribution of blood volume within the preterm infant thorax during synchronised mechanical ventilation. *Intensive Care Med* 2010; 36: 2101–2108.
- 77 Miedema M, de Jongh FH, Frerichs I, *et al.* The effect of airway pressure and oscillation amplitude on ventilation in pre-term infants. *Eur Respir J* 2012; 40: 479–484.
- 78 Miedema M, de Jongh FH, Frerichs I, *et al.* Changes in lung volume and ventilation during lung recruitment in high-frequency ventilated preterm infants with respiratory distress syndrome. *J Pediatr* 2011; 159: 199–205. e192.
- 79 Miedema M, de Jongh FH, Frerichs I, *et al.* Changes in lung volume and ventilation during surfactant treatment in ventilated preterm infants. *Am J Respir Crit Care Med* 2011; 184: 100–105.
- 80 van Mastrigt E, Logie K, Ciet P, *et al.* Lung CT imaging in patients with bronchopulmonary dysplasia: a systematic review. *Pediatr Pulmonol* 2016; 51: 975–986.
- 81 Walkup LL, Tkach JA, Higano NS, *et al.* Quantitative magnetic resonance imaging of bronchopulmonary dysplasia in the neonatal intensive care unit environment. *Am J Respir Crit Care Med* 2015; 192: 1215–1222.
- 82 Narayanan M, Beardsmore CS, Owers-Bradley J, *et al.* Catch-up alveolarization in ex-preterm children: evidence from ³He magnetic resonance. *Am J Respir Crit Care Med* 2013; 187: 1104–1109.