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Imaging the Respiratory Transition at Birth: Unravelling the Complexities of the First Breaths of Life

Tingay, David G ; Farrell, Olivia ; Thomson, Jessica ; Perkins, Elizabeth J ; Pereira-Fantini, Prue M ; Waldmann, Andreas D ; Rüegger, Christoph ; Adler, Andy ; Davis, Peter G ; Frerichs, Inéz

Abstract: Rationale: The transition to air-breathing at birth is a seminal respiratory event common to all humans, but the intrathoracic processes remain poorly understood. Objectives: The objectives of this prospective, observational study were to describe the spatiotemporal gas flow, aeration and ventilation patterns within the lung in term neonates undergoing successful respiratory transition. Methods: Electrical impedance tomography was used to image intrathoracic volume patterns for every breath until six minutes from birth in neonates born by elective cesarean section and not needing resuscitation. Breaths were classified by video data, and measures of lung aeration, tidal flow conditions and intrathoracic volume distribution calculated for each inflation. Measurements and Main results: 1401 breaths from 17 neonates met all eligibility and data analysis criteria. Stable functional residual capacity was obtained by median (IQR) 43 (21, 77) breaths. Breathing patterns changed from predominantly crying (80.9% first minute) to tidal breathing (65.3% sixth minute). From birth tidal ventilation was not uniform with the lung, favouring the right and non-dependent regions; $p < 0.001$ versus left and dependent (mixed effects model). Initial crying created a unique pattern with delayed mid-expiratory gas flow associated with intrathoracic volume redistribution (pendelluft flow) within the lung. This preserved functional residual, especially within the dorsal and right regions. Conclusions: The commencement of air-breathing at birth generates unique flow and volume states associated with marked spatiotemporal ventilation inhomogeneity not seen elsewhere in respiratory physiology. At birth neonates innately brake expiratory flow to defend functional residual capacity gains and redistribute gas to less aerated regions.

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Imaging the Respiratory Transition at Birth: Unravelling the Complexities of the First Breaths of Life

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Author Contributions: DGT developed the concept and designed the experiment. DGT, OF, JT, EJP, CR enrolled and studied all infants. AW, IF, AA, DGT developed the image reconstruction and analysis methods used in the study. DGT, OF, JT, PP-F were involved in data analysis. DGT, PGD, IF, AA interpreted the data. DGT wrote the first draft of the manuscript and all authors contributed to redrafting the manuscript.

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Competing Interests: AW was an employee of Swisstom AG (Landquart, Switzerland), who initially developed the EIT hardware and software systems (Swisstom was acquired by Sentec AG after the study was completed). Swisstom was not involved in study design, implementation, analysis, interpretation or reporting. IF and AW were investigators in an European Union Horizon 2020 Research and Innovation program grant to develop an infant EIT chest imaging system (CRADL project, Grant ID 668259). IF also reports funding from another European Union Horizon 2020 project (WELMO, Grant ID 825572) and reimbursement of soeaking fees, congress and travel costs by Dräger Medical (a company that produces a commercial EIT unit). No author received an honorarium, grant, or other form of payment to produce the manuscript. The study was not commissioned and no commercial agencies were involved in any aspect of this study. The authors have no other competing interests to declare.

Ethics Approval: The Royal Women’s Hospital Human Research and Ethics Committee (#16-33), and registered with the Australian New Zealand Clinical Trials Registry (ACTRN12618000128291).

Data Sharing: Individual participant data collected during the study, after de-identification, 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 intermediatry”) identified for purpose. Data is 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.

Some of the results of these studies have been previously reported in the form of a preprint (medRxiv, [30 July 2020] <https://doi.org/10.1101/2020.07.29.20161166>).

At a Glance Commentary

Scientific Knowledge on the Subject

Birth requires the rapid transition from a fluid-filled to aerated lung that is poorly understood. Limited human and animal studies suggest high intrathoracic pressure and flow states are required to attain functional residual capacity and support tidal ventilation.

What this Study Adds to the Field

In the first breath-by-breath imaging of the lungs of term neonates undergoing successful respiratory transition at birth we identified highly inhomogeneous, spatiotemporal aeration and ventilation patterns during. Crying at birth preserved functional residual capacity by allowing intrathoracic volume redistribution (pendelluft flow) within the lung. Newborns defend aeration from intrathoracic lung-fluid shifts at birth by innately braking expiratory flow using the glottis and diaphragm.

ABBREVIATIONS:

AU	Arbitrary Units
CoV	Centre of Ventilation
EIT	Electrical Impedance Tomography
FRC	Functional Residual Capacity
PEF	Peak Expiratory Flow
PIF	Peak Inspiratory Flow
SpO ₂	Peripheral oxygen saturation
τ	Time constant (tau)
Ti	Inspiratory time
Te	Expiratory time
V _T	Tidal Volume

ABSTRACT

Rationale: The transition to air-breathing at birth is a seminal respiratory event common to all humans, but the intrathoracic processes remain poorly understood.

Objectives: The objectives of this prospective, observational study were to describe the spatiotemporal gas flow, aeration and ventilation patterns within the lung in term neonates undergoing successful respiratory transition.

Methods: Electrical impedance tomography was used to image intrathoracic volume patterns for every breath until six minutes from birth in neonates born by elective cesarean section and not needing resuscitation. Breaths were classified by video data, and measures of lung aeration, tidal flow conditions and intrathoracic volume distribution calculated for each inflation.

Measurements and Main results: 1401 breaths from 17 neonates met all eligibility and data analysis criteria. Stable functional residual capacity was obtained by median (IQR) 43 (21, 77) breaths. Breathing patterns changed from predominantly crying (80·9% first minute) to tidal breathing (65·3% sixth minute). From birth tidal ventilation was not uniform with the lung, favouring the right and non-dependent regions; $p < 0·001$ versus left and dependent (mixed effects model). Initial crying created a unique pattern with delayed mid-expiratory gas flow associated with intrathoracic volume redistribution (pendelluft flow) within the lung. This preserved functional residual, especially within the dorsal and right regions.

Conclusions: The commencement of air-breathing at birth generates unique flow and volume states associated with marked spatiotemporal ventilation inhomogeneity not seen elsewhere in respiratory physiology. At birth neonates innately brake expiratory flow to defend functional residual capacity gains and redistribute gas to less aerated regions.

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INTRODUCTION

The rapid adaptation to air-breathing at birth (aeration) is one of the most important, but least understood, physiological events in humans. Much of our understanding is inferred from preclinical studies (1-4) or invasive observational studies.(5-8) These studies suggest that creating a functional residual capacity (FRC) during the initial process of lung aeration requires first clearing the airways of fetal lung liquid using high intra-thoracic pressure gradients.(1,2,5) Subsequent tidal ventilation must prevent influx of fluid back into the alveoli during expiration.(1) Animal studies have demonstrated that these processes exhibit a high degree of spatiotemporal variability within the lung.(2,9) For most newborns, fluid clearance and the transition from placenta to lung as the organ of gas exchange is achieved through the spontaneous onset of breathing. When this process fails, especially in preterm infants, death or significant morbidity may result. Due to an inability to define the processes of aeration and ventilation at birth, effective evidence-based interventions to support breathing after birth are lacking.(10,11)

The development of effective delivery room interventions first requires an understanding of the physiological processes defining success or failure of aeration at birth. Adapting physiological concepts from preclinical studies have limited utility as instrumentation restricts the ability to emulate respiratory mechanics and the neurological state of the breathing human infant.(1-3,12) The delivery room further creates a challenging research environment, the time critical and dynamic nature of birth itself hampers physiological measurements.(13) Lung volume changes at birth have been intermittently imaged using chest radiography(14) and ultrasound(15), and pressure and flow patterns measured invasively at the mouth or pharynx.(5,16) These studies identified unique breath types associated with high intra-thoracic pressure gradients during successful respiratory transition in term infants, specifically crying

and grunting.(5,17,18) Importantly, these studies failed to directly define the fundamental dynamic spatiotemporal processes of aeration and subsequent ventilation within the lung.

To address this gap in knowledge, we used electrical impedance tomography (EIT), an emerging radiation-free imaging modality.(19) EIT uses the differential electrical properties of aerated and fluid-containing tissue to measure the tidal and end-expiratory volume changes in lung regions within a transverse chest slice.(19) We adapted our EIT techniques for measuring the respiratory transition in preclinical studies.(2-4,12,20-23) This allowed non-invasive, and non-hazardous, direct imaging of the dynamic breath-to-breath regional process of aeration at birth in human infants without interfering with normal physiology or clinical care. The objective of this study was to describe the spatiotemporal respiratory patterns associated with the successful transition to air-breathing after birth in term infants. The specific aims were to 1) characterise the inspiratory and expiratory time and flow characteristics within the lung at birth, and 2) describe the resultant spatiotemporal ventilation and volume patterns by breath type and time.

METHODS

A detailed methodology can be found in the online supplement. This prospective observational study was conducted at the Royal Women's Hospital, Melbourne, Australia.

Infants were eligible for enrolment if they were delivered by elective caesarean section via spinal anaesthesia for non-fetal reasons at $\geq 36^{+0}$ weeks gestation, and written prospective parental consent obtained. Infants were not included if placement of an EIT belt would interfere with clinical care,(24-26) or the fetus had a known congenital condition that would alter EIT interpretability. Infants who received resuscitative interventions were excluded from analysis.

Measurements

Heart rate and peripheral oxygen saturation (SpO_2) were measured with a Radical 7 pulse oximeter (Massimo Corporation, Irvine CA). Regional lung volume changes were imaged at 48 frames/s with the Pioneer EIT system using an ultrasound gel-coated NeoSensor Belt (Sentec AG, Landquart, Switzerland).(2,12,24-26) Audio and video were recorded at 30 frames/s (Logitech webcam, Lausanne, Switzerland).

Delivery room protocol

As the infant was being placed supine on the resuscitaire the NeoSensor Belt was secured (velcro tab) around the chest at nipple level (**Supplementary Video 1**). The pulse oximetry sensor was applied to the right hand. There was no other interference with routine clinical care. Infants were managed in a supine position in accordance with local guidelines, including timing of umbilical cord clamping. Data were only recorded during care on the resuscitaire.

Data acquisition and analysis

EIT, video, audio and pulse oximetry data were continuously recorded digitally during resuscitaire management, and timing of critical events from birth documented. SpO_2 and heart rate data were reviewed for loss of signal or movement artefact. EIT data were recorded in a custom-built infant imaging package,(27) and images reconstructed post hoc(19,28) using the vendor-provided human model chest atlas, with non-lung regions excluded.(2,23,24,26) Each potential tidal volume (V_T) change due to breathing was identified from the global lung signal. Analysis of the EIT change associated with a breath was only performed if there was 1) video confirmation of a breath; and 2) no movement interference on the video. All included breaths were classified by the presence of an audible cry, grunt or no breathing noise (tidal breath). If audio classification was not possible the breath was excluded (Supplementary Figure 1).

For included breaths, the pre and post-breath FRC, inspiratory time (T_i), expiratory time (T_e), time constant of the respiratory cycle (τ) and relative peak inspiratory (PIF) and expiratory flow (PEF) were calculated for the global signal and right, left, ventral and dorsal lung regions.(19) The shape of the impedance change during each breath was classified by an investigator (DGT) unaware of the breath type or time from birth. The centre of ventilation along the ventrodorsal (CoV_{VD}) and right-left (CoV_{RL}) planes were calculated to determine spatiotemporal distribution of V_T within the chest slice.(19,29) The percentage of the global V_T signal was calculated for the most dependent, central and non-dependent thirds of the right and left lung regions, and the percentage and location of lung regions without any V_T signal.(19,24)

Sample size and statistical analysis

Based on a previous study of respiratory parameters at birth (16), a convenience sample of thirty infants was estimated to provide data for breath-by-breath classification. and analysis of 100-150 breaths/infant per 5-6 minute period in 15-20 infants. Continuous data were analysed with a mixed-effects linear regression model, with robust standard error and cluster analysis to adjust for multiple breaths from each infant. A p value <0.05 was considered statistically significant.

RESULTS

A visual abstract of the main study findings is available in **Supplementary Video 2**.

Study population

Thirty-three families were approached on the day of the delivery, with three declining to participate. Two studied infants received resuscitative support after birth and were excluded. Of the remaining 28 infants, EIT data were obtained in 27 infants (EIT belt incorrectly placed).

Complete audio or video data were not acquired in ten infants (technical failure in delivery room, camera obstructed, excessive background noise or inability to delineate any audio/video breaths). The characteristics of the final 17 infants with matched EIT, video and audio data are described in Supplemental Table 1. All were singleton pregnancies and no mother received antenatal corticosteroids.

Pulse oximetry

A pulse oximetry signal could be acquired in 15 infants, with a median (range) of 17 (3, 198)s between applying the probe and signal acquisition. The first SpO₂ signal was acquired at 52 (12, 97)s, but then lost for >10s at least once in ten infants. SpO₂ increased with time from 53 (48, 72)% at 60s to 78 (60, 96)% by 360s ($p=0.029$; mixed-effects model, Supplementary Figure 2). Heart rate was stable throughout the study period ($p=0.25$).

Time to image acquisition

The median (range) time from birth to first EIT image was 36 (20, 62)s, with the longest periods being in the two infants born with delayed cord clamping (60 and 62s). The time between cutting of umbilical cord and first EIT image was 31 (20, 48)s. In all infants the time between applying the EIT belt and first images was <12 s, with no subsequent signal loss.

Breathing patterns

A total of 1401 inflations met the inclusion criteria (Table 1). Only 14 breaths (1%) had audible grunting (all during periods of crying), and were included within the 787 crying breaths. Overall, crying was more prominent early in the respiratory transition, representing 80.9% of all included inflations within the first minute, then decreasing to 34.7% by the sixth minute ($p<0.0001$; chi-squared test for trend).

Breaths could be classified as following two distinct EIT volume patterns; 1) linear inspiratory and expiratory volume change consistent with tidal ventilation of already-aerated lungs, or 2) an expiratory phase with a distinct bifid expiratory wave and a transient increase or preservation in lung volume (Figure 1 and **Supplementary Video 2**). During these bifid waves there was a subtle redistribution of ventilation seen on fEIT images consistent with pendelluft flow. 70.8% of all crying breaths had a bifid wave, but only 2.5% of tidal breaths.

Ti increased over the first minutes of life for both breath types; $p < 0.0001$ (Figure 2A). Crying generated shorter Ti than tidal breaths in the first 60s, mean (95% CI) difference 101 (56, 147) ms. In contrast, Te and τ were longer during crying than tidal breaths (both $p < 0.0001$; Figure 2B and C), especially between 61-180s (Te) and after 120s (τ). Overall, Te and τ did not change significantly with time for crying or tidal breaths.

PIF was greater at all time epochs during crying compared to tidal breaths (all $p < 0.0001$). Overall, PIF increased with time for tidal breaths ($p < 0.0001$; Figure 2D), but not during crying. PEF was greater during crying than tidal breaths for the first 180s (all $p < 0.0001$; Figure 2E), with the greatest difference in the first 60s (1.4 (0.9, 1.8) AU/s). PEF decreased with time during crying ($p < 0.0001$), whilst tidal breaths were unchanged.

The detailed spatiotemporal behaviour of Ti, Te, τ , PIF and PEF in the right, left, ventral and dorsal regions are provided in the supplemental results (Supplemental Figures 3-7). Overall, Ti, Te and τ were similar within all regions for both breath types. Crying resulted in faster PIF and PEF in the dorsal and right regions compared to ventral and left respectively. Tidal breaths resulted in less right-left and ventral-dorsal heterogeneity in PIF and PEF than crying.

Functional residual capacity

Overall, FRC increased, and was quickly established, after birth, with the maximum recorded FRC value for each infant occurring at a median (IQR) 43 (21, 77) of included breaths after birth; 67.8 (51.9, 94.5)% of the analysed sequential breaths (Figure 3 and Supplemental Figure 8). During an infant's first 100 breaths (or total if <100), 48% of FRC change occurred by the fifth breath.

Regional ventilation patterns

Ventilation redistributed towards the dorsal regions with time for both crying and tidal breaths (Figure 1); CoV_{VD} $p=0.045$ and $p<0.0001$ respectively. Overall, CoV_{VD} favoured the ventral regions during crying compared to tidal breaths by a mean (95% CI) 1.6 (0.3, 2.9)%, although the differences were not significant within each minute. The redistribution of V_T towards the dorsal regions was predominantly due to increased V_T within central l regions during crying, and the dorsal region during tidal breaths ($p=0.0004$), both at the expense of ventral V_T .

Both breath types resulted in greater ventilation in the right lung (Figure 4). During crying a mean (SD) 82.2 (15.3)% of total V_T occurring in the right lung during the first 60s (CoV_{RL} 3.0 (9.1)%; ideal 46%), increasing within the left lung with time ($p=0.011$). By 240s 64.3 (11.4)% of V_T occurred within the right lung (CoV_{RL} 43.1 (6.5)%). The right lung accounted for predominance of 59.5 (14.3)% of V_T (CoV_{RL} 46.4 (9.3)%) during tidal breaths within the first 60s, and this predominance did not change over time ($p=0.10$). Crying resulted in greater right-left lung inhomogeneity, with CoV_{RL} being a mean (95% CI) 2.0 (0.5, 3.5)% less overall than tidal breaths, and the difference greatest in the first minute; 13.4 (6.7, 20.1)%.

Approximately 10% of predefined lung regions were unventilated for both tidal and crying breaths, with not difference in the ventrodorsal pattern of unventilated regions (Supplementary Figure 9). After 240s there was less unventilated lung regions, especially during tidal breathing, suggesting increasing aeration resulted in greater engagement of the distal lung in ventilation.

DISCUSSION

The transition to air-breathing at birth is a seminal physiological event essential to life in all humans. In our observational study we provide the first detailed description of the volumetric processes within the lung at birth. We found that the transition to air-breathing is characterised by complex spatiotemporal patterns of aeration and ventilation initially mediated by high PIF rates and prolonged expiration. Overall this results in rapid lung aeration that moves from the central to distal lung, with the right lung engaging in ventilation earlier than the left. Crying, the dominant breathing pattern at birth, creates greater PIF and complex expiratory volume patterns, including pendulluft flows, more suited to both rapid aeration and maintenance of FRC than tidal breathing, at a time the lung is still likely to be partially fluid-filled. That these findings occurred in healthy term infants without instrumentation or active intervention is important, providing the first human evidence that successful aeration at birth is dependent on actively engaging in expiratory mechanisms to protect FRC (**Figure 5**).

Clearing the respiratory system of fetal lung liquid, and establishing aeration is essential to physiological success at birth. We showed that the majority of lung aeration is rapidly achieved at birth, similar to chest radiography studies during the first seconds after birth in term infants.(7,8) Unlike these studies we were able to continuously follow the process of aeration beyond the first inflations. Although there was considerable inter-subject variability, aeration conformed with an exponential pattern reported in preclinical studies,(3,4,23,30,31) and during lung recruitment in the already-aerated lung.(32,33) Aeration was also associated with a temporal increase in distal lung ventilation. Our study is the first in humans to confirm the sequential central-distal movement of the air-fluid interface during aeration from the major airways to the distal alveoli reported in animal studies is ongoing beyond the first few breaths.(1,9) EIT can not directly measure airspace fluid, but the markedly different electrical

properties of air and fluid make EIT ideally suited to mapping the air-fluid interface and tracking lung aeration clinically.

The patterns of ventilation indicate that spatiotemporal aeration after birth is more complex than only a central-distal process. The preferential ventilation of the right lung was unexpected but biologically plausible. At birth the lung is fluid filled, and airways (and tissue) have a high resistance.⁽³⁴⁾ The left main bronchus exits the carina acutely, and is encumbered by the heart. This may create preferential flow states towards the right lung, especially during the higher inspiratory flows of crying. Resistance falls in those areas of the lung that aerate first, further potentiating ventilation compared to unaerated regions. Our data also suggests that ventilation initially follows a gravity-dependent pattern, similar to that seen in parenchymal lung diseases.^(35,36) Once aerated the lung rapidly develops the anatomical ventrodorsal pattern of ventilation reported in healthy older infants, favouring the dorsal lung with its increased lung mass and greater diaphragmatic tidal movement.^(19,37) These changing spatiotemporal patterns across multiple planes make applying respiratory support without risking lung injury particularly challenging.

As expected in healthy infants, during the first two minutes 80% of breaths were cries. In a similar population of 13 infants, 77% of the analysed 749 breaths within the first 90 seconds after birth were classified as cries or grunts, but breath classification was performed post hoc from face mask measurements without auditory or visual confirmation, limiting interpretability.⁽¹⁶⁾ Our study is the first to classify volume changes with flow and breathing behaviour. Crying created different flow characteristics than tidal breathing, quickly inflating the lung with faster T_i and PIF. This is advantageous within the highly resistive fluid-filled lung at birth,⁽³⁴⁾ but once aerated provides little mechanical or gas exchange benefit. We postulate that crying has a *de novo* physiological purpose, and not simply due to the noxious

stress response of birth. Once aerated the high PIF conditions of crying increase unventilated lung tissue, with infants switching to the more advantageous tidal breaths.

Importantly, crying is also an expiratory phenomenon, being associated with slow expiratory flows, longer T_e and τ . Volume loss during expiration followed a unique bifid pattern, occurring in 71% of all cries and rarely in tidal inflations. This pattern of volume change represents transient periods of minimal airway flow despite the chest wall being in a state of expiratory recoil. In this state reducing expiratory flow could only be achieved via active means, such as glottic closure or diaphragmatic hold; both seen in radiological imaging at birth.(8) The lung is in a state of flux in early ex-utero life; the alveoli maybe air-filled but fetal lung fluid remains in the interstitium, and fluid can influx back into alveoli if the intrathoracic pressure gradient falls, compromising FRC.(4,9,34) It has been proposed that ‘expiratory braking’ is essential during this period,(1,5,7,8,17,18,38) and flow patterns measured at the airway opening support this, but have not been correlated to temporal FRC change.(16) Our study provides the first evidence that expiratory braking does more than just prevent egress of gas from the lungs. It also facilitates the volumetric conditions needed to preserve FRC, and importantly redistributes gas within the lungs (pendelluft flow). We propose that this provides a simple visual indicator of an infant’s independent ability to independently support respiratory transition. Further studies are warranted to determine if the same breath types, and patterns, are present in at risk and preterm infants.

Reports of the cardiorespiratory processes at birth are sparse, mainly due to challenges in measurement. Following chest radiology studies in the 1960s,(7,8) instrumentation within the mouth, initially with bulky equipment,(5,17,18,38) and more recently, face masks(16,39,40) have measured airway opening flow, V_T , expired CO_2 and/or pressure changes, and infer intrathoracic conditions. Face masks are frequently applied with a leak,(41,42) application

interferes with normal breathing efforts,(43) and cannot identify important spatiotemporal events, limiting usefulness during spontaneous breathing. Ideally measurements should be obtained from the thorax without impacting respiratory effort. Recently respiratory inductive plethysmography(39) and lung ultrasound(15) have been used in the delivery room. Inductive plethysmography requires two belts and determines lung volume from measuring the cross-sectional areas of the chest and abdomen, which may not change between fluid- and air-filled states.(32) Lung ultrasound is ideal for imaging the air-fluid interface, is simple to use, but lacks regional resolution, and continuous imaging has not been possible.(15) In this context, EIT is attractive. EIT is an established and validated method of measuring relative change in multiple spatiotemporal respiratory parameters.(19) EIT is radiation-free and available with a simple non-invasive belt (25) that could be applied as quickly, and more reliably, than pulse oximetry. EIT also confirmed the physiological patterns seen in humans and preclinical studies using these other measurement tools.(2,9,23) We contend that EIT is currently the best method of monitoring the respiratory system at birth.

Limitations

Our study was limited to birth via elective caesarean section, and measuring were not made from delivery of the chest. The birth experience is uniquely personal, and we intentionally limited our study to a period of clinical mother-baby separation. Consequently, we missed the first few inflations in most infants. We content that these inflations are unlikely to be markedly different from those we captured. The unique volumetric, flow and FRC characteristics we identified indicate fluid clearance was still ongoing during the first 120s. It is unlikely that the enhanced lung liquid clearance provided by delivery through the vaginal canal would alter the respiratory findings in our healthy term population with active vigorous breathing. Respiratory effort was not suppressed, but data on all modes of delivery are needed in less vigorous infants.

We have demonstrated that EIT can be practically applied earlier and during vaginal delivery. Our study of 1401 inflations from 17 infants is one of the largest, but, like previous studies,(16,17) exclusions were necessary and may have included potentially important breaths. In part this was intentional; our methodology was designed to minimise artefact and ensure correct breath classification lacking in previous studies. It is possible that respiratory drive occurred with an occluded airway. This would not result in a volume change on EIT but is an important physiological finding that should be seen on video. Like all other imaging tools used to describe the respiratory transition, EIT is limited to a single slice of the lung. However, single slice EIT has been shown to represent whole lung patterns in infants.(19) EIT cannot measure intrathoracic pressure. To do so would require invasive instrumentation, but is unnecessary as flow patterns reflect intrathoracic pressure states.

Conclusions

This study provides the first detailed description of the respiratory behaviour of the healthy human lung during the transition to air-breathing after birth. Birth requires rapid aeration of the lung, and is achieved predominately via crying. Crying creates unique flow and volume states not seen elsewhere in respiratory physiology, and is characterised by high peak inspiratory flow and expiratory braking to preserve attained FRC and allow volume redistribution. The right lung ventilates before the left lung after birth, and the lung quickly develops an anatomical pattern of ventrodorsal ventilation once aerated. Understanding how the human lung successfully commences breathing at birth is the first step in developing tools to identifying when intervention is required.

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FIGURE LEGENDS

Figure 1. A. Relative Volume change (ΔV_L) over time within the whole lung during the two representative breaths for crying (**i**; 25 s) and tidal breaths (**ii**; 5 min). **B.** ΔV_L during the same breaths within the ventral (blue) and dorsal (red) hemithoraces. **C.** Ventrodorsal centre of ventilation (CoV_{VD}) by minute after birth for crying and tidal breaths. CoV_{VD} of 55% represents uniform ventilation, with values <55% indicating relatively greater ventilation in the ventral lung and >55% the dorsal lung. Grey dots represent individual breath data, and black line and bars mean $\pm$ SD. **C.** Relative distribution of ventilation (% total V_T) along the gravity dependent plane for crying and tidal breaths in the most gravity dependent third of the lung (black bars), central third (grey bars) and non-gravity dependent third (white bars), with solid bars being right lung region and dotted bars left lung. All data mean $\pm$ SD. * p <0.05, ** p <0.01, *** p <0.0001 against first 60s (mixed-effects model).

Figure 2. T_i (**A**), T_e (**B**), respiratory system time constant (τ ; **C**), PIF (**D**) and PEF (**E**). Black circles indicate crying breaths and white diamonds tidal breaths. All data mean $\pm$ SD. * p <0.05, ** p <0.01, *** p <0.0001 cry vs tidal inflation; † p <0.01 within breath type (all mixed-effects model).

Figure 3. A. Change (Δ) in FRC from first measured inflation for all breaths (**A**) and for the first 100 inflations (maximum)(**B**). ΔFRC normalised to the FRC before the first breath (0%) and maximum FRC (100%) for each infant. **A.** Blue line represents line of best fit (dashed lines 95% CI) using a one-phase exponential association; $y=y_{plateau} \cdot [1-e^{x \cdot \tau^{-1}}]$; plateau (95% CI) 56.2 (54.0, 58.6)%, τ 8.0 (6.0, 10.5) inflations (R^2 0.14, RSME 24.5%, replicates test discrepancy (F) 0.82 [p =0.96]). Grey dashed lines demonstrate ΔFRC at 50% of FRC_{max} and 50 inflations.

B. Black circles represent the mean ΔFRC every 5 inflations for each infant, and dashed lines 95% CI.

Figure 4. A. Relative Volume change (ΔV_L) over time within the right (blue) and left (red) lung during the two representative breaths for crying (**i**; 25 s) and tidal breaths (**ii**; 5 min). **B.** Functional EIT images of volume change within the lungs for the same breaths using the colour scale defined in Supplementary Video 2. **C.** Relative distribution of ventilation (% total V_T) in the right (black bars) and left (white bars) lung for crying and tidal breaths. **D.** Centre of ventilation (CoV_{RL}) along the right-left plane for all inflations by minute after birth for crying and tidal breaths. CoV_{RL} of 46% represents uniform ventilation, with values <46% indicating relatively greater ventilation in the right lung, and >46% greater ventilation in the left lung. All data mean $\pm$ SD, and dots individual breath data. Panel A and C; * p <0.05, *** p <0.0001 (mixed-effects model). Panel B and D; * p <0.05, ** p <0.01 against first 60s. † p <0.05 against 181-240s.

Figure 5. Summary of main findings and hypothesised explanation of the criteria which define the respiratory events within the lungs at birth. Representative global lung volume change during a single cry at 14 s after birth (Infant 6; **Panel A**) demonstrating the dynamic volume change during inspiration and expiration, and resultant increase in end-expiratory FRC. The breath has been divided into five phases related to the mechanistic events identified during the respiratory transition from a fluid-filled to aerated lung (**Panel B**), and the respective fEIT images for each shown in **Panel C**. At the start of the inflation the airways and alveoli are fluid filled (**Column 1**). A cry initiates a rapid and large contraction of the diaphragm with a resultant rapid inspiratory flow (slope of the time-volume curve) and high inflating (driving) pressure within the lung generating aeration by moving fluid from the proximal airways to the alveoli (enlarged) and then the lung interstitium (**Column 2**). Expiration begins with rapid contraction of the diaphragm (**Column 3**). The fall in intra-thoracic pressure during expiration lowers intra-

alveolar pressure, and in some lung units this fall allows fetal fluid to influx back into the alveoli spaces. To counteract this effect the neonate slows (brakes) diaphragmatic contraction and partially closes the glottis, thus transiently re-pressurising the lung and allowing pendulluft gas flow between aerated to poorly aerated lung units (**Column 4**). When expiration continues it does so against a partially closed glottis which mediates slower expiratory gas flow and allows some gas to remain in the lungs, thus generating a greater end-expiration FRC (**Column 5**) and more favourable lung conditions at the start of the next inflation.

Table 1. Type of breath by time

n=1401 included inflations	Time from birth (s)					
	0-60	61-120	121-180	181-240	241-360	Total
Cry	55	186	221	188	137	787
Tidal	13	48	106	189	258	614
Cry (%)*	80.9%	79.5%	67.6%	49.9%	34.7%	56.2%
Median (minimum, maximum) cry/infant	6 (2,21)	13 (3,22)	13 (3,52)	12 (1,63)	15 (1,48)	11 (1,63)
Median (minimum, maximum) tidal/infant	7 (4,9)	4 (1,13)	9 (1,20)	11 (2,44)	15 (4,102)	9 (1,102)

*p<0.0001; chi-squared test for trend.

Figure 1

183x220mm (300 x 300 DPI)

Figure 2
68x272mm (300 x 300 DPI)

Figure 3

249x91mm (300 x 300 DPI)

Figure 4

190x231mm (300 x 300 DPI)

Figure 5

Imaging the Respiratory Transition at Birth: Unravelling the Complexities of the First Breaths of Life

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Online Supplementary Materials

1. Detailed Methods
2. Supplementary Results
3. Description of Supplementary Videos
4. Reference List for Online Supplementary Materials

1. DETAILED METHODS

Study Population

Recruitment was conducted in the operating theatres of The Royal Women's Hospital, Melbourne, Australia (a tertiary obstetric hospital) between February to May 2017. The study was approved by the hospital's Ethics in Human Research Committee, and registered with the Australian New Zealand Clinical Trials Registry (ACTRN12618000128291).

Infants were eligible for enrolment if they were delivered by elective caesarean section via spinal anaesthesia for non-fetal reasons at $\geq 36^{+0}$ weeks post menstrual age and there was a low likelihood of neonatal intervention in the delivery room. Potentially eligible infants were identified from elective surgical lists and written prospective consent was obtained from parents before delivery. Timing of cord clamping was at the discretion of the clinical team. Infants were not included if 1) the mother received any analgesia, sedation or anaesthesia that could suppress the infants respiratory behaviour at birth, 2) the placement of an electrical impedance tomography (EIT) belt in the standard position would interfere with clinical care,(E1-3) 3) the fetus was known to have a congenital condition or disease that may alter interpretability of the EIT data or 4) the clinical team requested the infant not be studied. If an enrolled infant received resuscitative interventions in the delivery room, data were recorded but excluded from analysis.

Measurements

Heart rate and peripheral oxygen saturation (SpO_2) were displayed and measured with a Massimo Radical 7 pulse oximeter and newborn SET sensor (Massimo Corporation, Irvine CA). Regional lung volume changes were imaged with the Pioneer EIT system using 33 cm NeoSensor Belt and custom made neonatal connector system (Sentec AG, Landquart,

Switzerland), containing a positional gyroscope placed in a supine position on an existing shelf of the neonatal resuscitaire.(E1-5) The Pioneer system is an open-source EIT platform designed to be modified for bespoke research purposes. We have previously used the system in the Neonatal Intensive Care Unit (E1, 3) and to image the respiratory transition in preterm lambs.(E4-11) The NeoSensor Belt consisted of a striped electrically conductive (Ag) non-adherent textile cover enclosing a 3D space fabric wrapped around a flexible printed circuit board containing 32 electrodes to allow unobstructed chest wall movement.(E2) Electrical conductance with the skin is achieved with warmed ultrasound gel applied to the belt before placement. EIT images were measured at 48 frames per second using a current injection amplitude of 3 mA_{rms} at a frequency of 200 kHz. Audio and video were recorded at 30 frames per second with a high-definition webcam (Logitech, Lausanne, Switzerland).

Delivery room protocol

Prior to birth the measurement equipment was placed on a neonatal resuscitaire and the study protocol reaffirmed with the clinical team caring for the infant. To ensure that the exact time of birth was digitally recorded in all systems, EIT and video/audio imaging recording commenced with the resuscitation clock. As the infant was being placed supine on the resuscitaire, the NeoSensor Belt was secured around the chest at nipple level, and below the armpit, using a Velcro tab, as shown in the **Supplementary Video 1**. We have used this system and method of attachment in preterm lambs, and refined the process in a pilot study (n=3 infants).(E4, 5, 8, 12) The pulse oximetry sensor was applied to the right hand. Apart from the application of the EIT belt and pulse oximetry sensor there was no interference with routine clinical care, and the infants were managed in a supine position in accordance with local guidelines. Data were recorded only during care on the resuscitaire. Measuring equipment was

removed when the clinical staff deemed the infant ready to be given to her/his parents, or transferred to another setting for ongoing clinical care.

The following time points were documented: the time the umbilical cord was cut, the infant was placed on the resuscitator, the first breath, the EIT belt was applied (and duration of application), first EIT signal was acquired, pulse oximetry was applied and first oximetry signal acquired.

EIT remains a research tool in neonatal medicine (E13), and has never previously been used in the delivery room. Introduction of any new research technology into a clinical environment must only be done so without impacting clinical care or the patient wellbeing and experience. To allow staff to become familiar with the technology, and ensure that we did not impose on the unique mother-baby experience in the first few minutes after birth, we intentionally elected to limit the study population to infants receiving a period of separation from their mother as part of standard care (resuscitator).

Data acquisition and analysis

Video, audio and pulse oximetry data were continuously recorded and analysed in LabChart (AD Instruments, Sydney, Australia). SpO₂ and heart rate data was manually reviewed for loss of signal or movement artefact, and the mean and range of included data determined for each minute after birth. The following clinical data were collected: gestational age, birth weight, sex, Apgar score, need for stimulation and/or resuscitation after birth, reason for caesarean section and type of maternal anaesthesia. EIT data was recorded in real-time into the same computer (to ensure matched time-stamp signals) using a custom-built infant imaging package (Sentec AG) built using the EIDORS platform.(E14) This software provides a simple graphic interface to indicate electrode contact quality, real-time waveform of whole lung impedance change and a functional EIT image.

Supplementary Figure 1 summarises the data analysis workflow. EIT data were only analysed if matched video and audio signals were present. Included time-course EIT images were reconstructed using the vendor-provided human model atlas with thoracic shape and lung and heart regions defined from a collection of computerised tomography images in the GREIT algorithm to minimise shape deformation.^(E13, 15) Non-lung regions were excluded during post-processing and the pixel EIT signals filtered to the respiratory domain (IbeX software package, Sentec AG) as described previously.^(E1, 3, 5, 11) Within the entire lung region ('global' signal), each potential tidal volume (V_T) change due to breathing was identified. Analysis of the EIT change associated with a breath was only performed if there was 1) video confirmation of a breath (defined as chest wall or abdominal movement); and 2) there was no movement interference on the video (for example due to drying or wrapping), even if a breath was visualised. The audio signal was then reviewed for all included artefact-free and video-confirmed breaths and each classified by the presence of a cry, grunt or no breathing noise (tidal breath). If audio classification was not possible the breath was excluded.

For included breaths, the pre and post minima of the global impedance change was defined as the relative FRC before and after the breath. Inspiration time and subsequent relative V_T were defined as the time and the signal difference from the pre-inflation minima to the maxima, and expiration time and expiratory V_T change from the maxima to next minima. The pre and post-breath FRC, breath duration, inspiratory time (T_i), expiratory time (T_e), time constant of the respiratory cycle (τ) and relative peak inspiratory (PIF) and expiratory flow (PEF) were calculated for the global signal and right, left, ventral and dorsal lung regions. The shape of the time-volume impedance change for each breath was visually reviewed by an investigator (DGT) blinded to the breath type and time from birth, and coded as consistent or not with volume change during tidal breathing (triangular shape with linear volume change during

inspiration and expiration), to determine if breathing patterns during the respiratory transition differed from those seen in the already aerated lung.

To define the spatiotemporal distribution, and homogeneity, of V_T within the chest the centre of ventilation along the ventrodorsal (CoV_{VD}) and right-left (CoV_{RL}) planes were calculated and expressed as a percentage (0% representing all V_T in the most ventral or right and 100% in the most dorsal or left lung regions).(E13, 16) Due to the uneven contribution of each lung to the total lung volume, homogeneous ventilation occurs at CoV_{VD} 55% and CoV_{RL} 46%. The percentage of the global V_T signal was also calculated for the most dependent, central and non-dependent thirds of the right and left lung, and the percentage and location of lung regions without any apparent V_T signal determined.

Sample size and statistical analysis

In previous prospective observational studies of respiratory parameters after birth approximately 40% of studied infants needed to be excluded for technical reasons.(E17) It was also estimated that 5% of infants would require resuscitation in the delivery room. A convenience sample of thirty infants was required to provide data for breath-by-breath classification and analysis of 15-20 infants. A median of 62 inflations/infant over 90s were recorded in a study of facemask flow, volume and pressure characteristics (without video/audio) in a study of 13 term infants immediately after birth (the previous largest study of breath-by-breath characteristics at birth).(E17) As our study included stricter analysis criteria we anticipated 20-30 breaths/minute/infant would be included for breath-by-breath classification and analysis (100-150 breaths per 5-6 minute period per infant).

Data were analysed for each minute after birth (up to a maximum of 6 minutes). All data were analysed for outliers using a 1% threshold (ROUT). Continuous data were tested for normality and analysed with a mixed-effects linear regression model, with robust standard error and

cluster analysis to adjust for multiple breaths from each infant if appropriate. Due to the variable end point, breaths during the fifth and sixth minute (241-360s) of the study were pooled for statistical analysis. Statistical analysis was performed using Prism (v8.2.1, GraphPad Software, San Diego, CA) or Stata (v16.0, StataCorp, College Station, TX), and a p value <0.05 considered statistically significant.

Supplementary Figure 1. Data analysis workflow. Simultaneous video and audio recordings were made with EIT imaging once the infant was placed on the resuscitaire as demonstrated in **Supplementary Videos 1 and 2**. Time-course EIT data was only included for breath-by-breath analysis if matched signals for EIT, video and audio were obtained. Volume changes in the global time-course EIT signal (IbeX Software package, Sentec AG, Landquart, Switzerland) were identified (red and blue boxes). Any EIT volume change was only classified as a breath if there was visual confirmation of a breath on video (chest wall and/or abdominal movement) and no movement artefact (for example handling). Finally, each video confirmed breath on EIT

was then classified as a cry, grunt or tidal breath based on the noise, or lack thereof, on audio signal. If no audio classification was possible (for example too much background noise) the breath was excluded from analysis.

2. RESULTS

Presented in order mentioned in main manuscript results section.

Online Supplemental Material Table 1. Infant Characteristics (n=17)

GA (weeks)	BW (kg)	Gender (F:M)	DCC	Cried at birth	Stimulation at birth	Apgar Score	
						1 min	5 min
39 (36, 39)	3.26 (2.77, 3.86)	7:10	2 (11)%*	15 (88%)	8 (47%)	9 (7,9)	9 (9,9)
Anaesthesia		Reason for caesarean section					
16 spinal; 1 general anaesthesia		16 previous caesarean section (3 gestational diabetes, 1 maternal muscular dystrophy, 1 breech), 1 suspected macrosomia, 1 previous stillbirth					

Abbreviations: GA; Gestational age at birth (completed weeks), BW; birth weight, DCC;

Delayed Cord Clamping.

*Umbilical cord was cut at 30 and 40 s. All data median (range) unless stated.

Supplementary Figure 2. Heart rate (HR; **A**) and peripheral saturation of oxygen (SpO₂; **B**) for each minute from birth until six minutes after birth. Boxes median and 10-90th percentile and error bars range. Numbers below each box represent the number of infants with complete SpO₂ or heart rate data for that minute. *p=0.029 (mixed effects model).

Regional breathing patterns

Inspiratory Time

Ti behaved similarly in the ventral ($p=0.25$, mixed-effects model) and dorsal ($p=0.53$) lung during crying (Supplementary Figure 3). During tidal breaths the Ti was variable in the ventral lung over time ($p=0.003$), but not the dorsal lung ($p=0.56$). In the ventral lung Ti during tidal breaths was a mean (95% CI) 140 (55, 245) ms longer after 240s compared to 121-240s. There was no difference in the ventrodorsal behaviour of Ti at each time epoch for either crying or tidal breaths. After 120s, Ti was shorter during crying in the ventral and dorsal lungs, with the greatest difference being 138 (38, 239) ms and 70 (19, 121) ms respectively after 240s.

Both the right and left lung Ti was the same over time during crying and tidal breaths. Ti was shorter during crying compared to tidal breaths after 121s in both the right and left lung; mean (95% CI) difference for the right lung at -112 (14, 209) ms (121-180s) and -125 (61, 189) ms (after 180s), with similar differences in the left lung.

Supplementary Figure 3. Spatiotemporal behaviour of Ti during crying (**A** and **C**) and tidal (**B** and **D**) breaths along the ventrodorsal (**A** and **B**) and right-left (**C** and **D**) lung planes. Black circles represent right or ventral lung respectively, and open diamonds left or dorsal lung. All data mean±SD. * $p<0.05$, ** $p<0.01$, *** $p<0.0001$ between lung regions at time point (mixed-effects model).

Expiratory Time

Te increased with time in the dorsal lung ($p=0.007$; mixed-effects model) during crying, but did not change in the ventral lung (Supplementary Figure 4). After 180s Te was a mean (95% CI) 234 (102, 367) ms longer in the dorsal lung. Te did not change in the ventral ($p=0.73$) or

dorsal ($p=0.49$) lung over time, or between regions. The type of breath did not influence Te at any time epoch within the ventral and dorsal lung.

During crying Te did not change with time in the right ($p=0.19$; mixed-effects model) and left ($p=0.35$) lungs during cries, and both the right and left lung Te were similar. Te was unchanged with time in the right lung during tidal breaths ($p=0.12$), but decreased in the left lung, being a mean (95% CI) 179 (6, 353) ms shorter after 240s compared to the first two minutes. Tidal breath Te was not different between the right and left lung at each time epoch.

Supplementary Figure 4. Spatiotemporal behaviour of Te during crying (A and C) and tidal (B and D) breaths along the ventrodorsal (A and B) and right-left (C and D) lung planes. Symbols as per OSM Figure 3. All data mean $\pm$ SD.

Respiratory system time constant

The respiratory time constant was a mean (95% CI) 111 (3, 192) ms longer after 240s compared to 121-240s in the ventral lung during crying (mixed-effects model; Supplementary Figure 5). There was no difference in τ with time in the dorsal lung ($p=0.94$) during crying, and both the ventral ($p=0.75$) and dorsal ($p=0.71$) lungs during tidal breaths. Cry and tidal breath τ were the same within the ventral ($p=0.60$) and dorsal ($p=0.77$) lung.

The right and left lung τ was similar, and did not change with time during both cries ($p=0.69$ and $p=0.50$ respectively; mixed-effects model) and tidal breath ($p=0.20$ and $p=0.41$). There was no difference in τ in the right ($p=0.26$) and left ($p=0.37$) lung between cries and tidal breaths. During crying the ventral lung PIF was greater at all time epochs than in the dorsal lung ($p<0.0001$), with the greatest difference of 0.95 (0.81, 1.10) AU/s occurring between 121-240s.

Supplementary Figure 5. Spatiotemporal behaviour of τ during crying (**A** and **C**) and tidal (**B** and **D**) breaths along the ventrodorsal (**A** and **B**) and right-left (**C** and **D**) lung planes. Symbols as per OSM Figure 3. All data mean $\pm$ SD.

Peak Inspiratory Flow

PIF did not change over time in the ventral and dorsal lung during crying (Supplementary Figure 6), but was always faster in the dorsal lung at all time epochs (all $p < 0.0001$). During tidal breaths the ventral lung PIF between 121-240s was a mean (95% CI) 0.97 (0.61, 1.33) AU/s and 1.13 (0.90, 1.35) AU/s faster than during the first two minutes and after 240s respectively (mixed-effects model). The dorsal lung PIF did not change over time during tidal

breaths. During tidal breaths the ventral and dorsal lung PIF only differed after 240s; mean (95% CI) difference 0.34 (0.28, 0.39) AU/s. Within both the ventral and dorsal lung the PIF was significantly faster during crying than tidal breaths at each time epoch except ventral lung at 121-240s (both $p < 0.0001$).

PIF varied with time in the right and left lung during crying, being a mean (95% CI) 0.76 (0.42, 1.10) AU/s greater between 121-240s and after 240s in the right lung, and 0.49 (0.29, 0.69) AU/s between 121-240s and 0-120s in the left lung (mixed-effects model). PIF decreased with time in the right lung ($p < 0.0001$) during tidal breaths, and was 0.52 (0.35, 0.70) AU/s slower after 240s compared to 121-240s in the left lung. During crying PIF was significantly greater at all time epochs in the right lung compared to the left lung ($p < 0.0001$), with the greatest difference of 1.67 (1.38, 1.96) AU/s occurring between 0-120s. PIF was only differed within the right and left lung between 0-120s during tidal breaths; 1.06 (0.51, 1.61) AU/s. Within the right and left lung, the PIF was greater at all time epochs during crying compared to tidal breaths (both $p < 0.0001$), with the differences being greater in the right lung.

Supplementary Figure 6. Spatiotemporal behaviour of PIF during crying (**A** and **C**) and tidal (**B** and **D**) breaths along the ventrodorsal (**A** and **B**) and right-left (**C** and **D**) lung planes. Symbols as per OSM Figure 3. All data mean $\pm$ SD.

Within the ventral lung crying and tidal breaths differed by a mean (95% CI) 0.58 (0.34, 0.82) AU/s, -0.40 (-0.63, -0.17) AU/s and 0.32 (0.27, 0.36) AU/s at 0-120s, 121-240s and after 241s respectively (mixed-effects model). Within the dorsal lung PIF was 0.57 (0.30, 0.85) AU/s, 0.79 (0.53, 1.06) AU/s and 0.55 (0.42, 0.68) AU/s greater during crying than tidal breaths at 0-120s, 121-240s and after 241s respectively. During tidal breath PIF was a 0.82 (0.55, 1.08) AU/s greater between 0-120s compared to after 240s in the right lung. Within the right lung

crying resulted in a 1.07 (0.62, 1.52) AU/s, 1.48 (0.98, 1.97) AU/s and 1.46 (1.23, 1.72) AU/s greater PIF than tidal breaths at 0-120s, 121-240s and after 240s. PIF was also greater in the left lung during crying; 0.46 (0.14, 0.77) AU/s, 0.50 (0.23, 0.77) AU/s and 0.83 (0.68, 0.98) AU/s.

Peak Expiratory Flow

PEF did not change with time in the ventral lung ($p=0.12$; mixed-effects model) but increased in the dorsal lung ($p=0.0008$) with crying (Supplementary Figure 7). PEF was similar over time in the ventral and dorsal lung. During crying PEF was always greater in the ventral lung, with a mean (95% CI) difference of 0.21 (0.12, 0.30) AU/s, 0.49 (0.42, 0.55) AU/s and 0.42 (0.32, 0.52) AU/s in each time epoch. During tidal breaths the ventral and dorsal lung PEF was only different after 240s; 0.32 (0.25, 0.38). Within the ventral lung crying resulted in greater PEF during the first two minutes and after 240s; 0.23 (0.09, 0.36) AU/s and 0.20 (0.16, 0.25) AU/s. PEF was greater during crying within the dorsal lung at all time points, increasing from a 0.27 (0.12, 0.42) AU/s difference in the first two minutes to 0.31 (0.22, 0.39) AU/s after 240s.

PEF was greater in the right lung for both crying and tidal breaths ($p<0.0001$; mixed-effects model). During crying the right lung PEF did not change with time ($p=0.06$) whilst PEF increased with time in the left lung ($p<0.0001$). The right lung PEF decreased with time during tidal breaths ($p=0.039$), and left lung increased ($p<0.0001$). In the first two minutes PEF was a mean (95% CI) -0.78 (-1.00, -0.56) AU/s greater in the right than left lung for cries, and -0.71 (-1.04, -0.37) AU/s for tidal breaths. After 240s these differences were -0.46 (-0.61, -0.31) AU/s and -0.27 (-0.41, -0.13) AU/s respectively. Within the right lung PEF was greater at all time points during cries compared to tidal breaths ($p<0.0001$). PEF was only different between cries and tidal breaths after 240s in the left lung; -0.40 (-0.53, -0.27) AU/s.

Supplementary Figure 7. Spatiotemporal behaviour of PEF during crying (**A** and **C**) and tidal (**B** and **D**) breaths along the ventrodorsal (**A** and **B**) and right-left (**C** and **D**) lung planes. Symbols as per OSM Figure 3. All data mean±SD.

Supplementary Figure 8. Change in absolute EIT values (AU; arbitrary units) from first measured breath (functional residual capacity; FRC) for all breaths. Blue line represents line of best fit (dashed lines 96% CI) using a one-phase exponential association; $y=y_{\text{plateau}} \cdot [1-e^{x \cdot \tau^{-1}}]$; plateau (95% CI) 0.99 (0.91, 1.09) AU, τ 22.3 (16.6, 29.4) breaths (R^2 0.08, RSME 0.83, replicates test discrepancy (F) 0.20 [$p>0.99$]).

Supplementary Figure 9. A. Percentage of lung regions without any apparent ventilation for crying (black) and tidal (white) breaths by minute from birth. Only tidal breaths had a significant change in unventilated lung over time; $p=0.003$ (tidal) versus $p=0.11$ (cry); mixed-effects model. 121-180s vs 241-360s: * $p=0.027$; mean (95% CI) 3.3 (0.4, 6.1)%, ** $p<0.01$; 4.3 (1.2, 7.5)%. Percentage of gravity non-dependent (black bars) and dependent (white bar)

lung regions without any apparent ventilation for crying (**B**) and tidal (**C**) breaths by minute from birth. All data mean $\pm$ SD.

3. DESCRIPTION OF SUPPLEMENTARY VIDEOS

Supplementary Video 1. Video footage and audio of the experimental methodology being applied to a representative infant during normal clinical care on the resuscitaire immediately after delivery. Video shows application of the EIT belt (chest) and pulse oximetry sensor (left hand). Video and audio delineate periods of crying and tidal breathing. The infants face and other identifiable features of participants in the video have been obscured. Written parental permission was obtained for inclusion of video footage and audio in this publication. Video recording was made at the Royal Women's Hospital (Melbourne, Victoria) on the 19th of May 2017. Video duration 05:07 min:sec.

Supplementary Video 2. Video abstract of the key findings, and differences, between crying and tidal breathing at birth and our rationale explaining the importance of these events in the respiratory transition to air-breathing at birth. Video duration 06:15 min:sec.

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Supplementary Video 1 Still

Supplementary Video 2-Still