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Citation

Foglia, E. E., Kirpalani, H., Ratcliffe, S. J., Davis, P. G., Thio, M., Hummler, H., ... Pas, A. B. te. (2021). Sustained inflation versus intermittent positive pressure ventilation for preterm infants at birth: respiratory function and vital sign measurements. *The Journal Of Pediatrics*, 239, 150-154.e1. doi:10.1016/j.jpeds.2021.08.038

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Note: To cite this publication please use the final published version (if applicable).



Sustained Inflation Versus Intermittent Positive Pressure Ventilation for Preterm Infants at Birth: Respiratory Function and Vital Sign Measurements

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Objective To characterize respiratory function monitor (RFM) measurements of sustained inflations and intermittent positive pressure ventilation (IPPV) delivered noninvasively to infants in the Sustained Aeration of Infant Lungs (SAIL) trial and to compare vital sign measurements between treatment arms.

Study design We analyzed RFM data from SAIL participants at 5 trial sites. We assessed tidal volumes, rates of airway obstruction, and mask leak among infants allocated to sustained inflations and IPPV, and we compared pulse rate and oxygen saturation measurements between treatment groups.

Results Among 70 SAIL participants (36 sustained inflations, 34 IPPV) with RFM measurements, 40 (57%) were spontaneously breathing prior to the randomized intervention. The median expiratory tidal volume of sustained inflations administered was 5.3 mL/kg (IQR 1.1-9.2). Significant mask leak occurred in 15% and airway obstruction occurred during 17% of sustained inflations. Among 34 control infants, the median expiratory tidal volume of IPPV inflations was 4.3 mL/kg (IQR 1.3-6.6). Mask leak was present in 3%, and airway obstruction was present in 17% of IPPV inflations. There were no significant differences in pulse rate or oxygen saturation measurements between groups at any point during resuscitation.

Conclusion Expiratory tidal volumes of sustained inflations and IPPV inflations administered in the SAIL trial were highly variable in both treatment arms. Vital sign values were similar between groups throughout resuscitation. Sustained inflation as operationalized in the SAIL trial was not superior to IPPV to promote lung aeration after birth in this study subgroup. (*J Pediatr* 2021;239:150-4).

Trial Registration [Clinicaltrials.gov](https://clinicaltrials.gov): NCT02139800.

See related article, p 143

Lung aeration is essential for successful newborn transition after birth,¹ and almost all extremely preterm infants require support to achieve this goal. Intermittent positive pressure ventilation (IPPV) is recommended to support lung aeration for apneic or bradycardic newborns.² Sustained inflation, in which the inflation is maintained >5 seconds, is a proposed alternative.³ A respiratory function monitor (RFM) uses an in-line flow sensor between the gas flow and respiratory interface to calculate data on delivered inflations during positive pressure ventilation. A direct comparison of sustained inflation and IPPV on respiratory function with simultaneous vital sign measurements after birth has not been described.

The Sustained Aeration of Infant Lungs (SAIL) trial ([Clinicaltrials.gov](https://clinicaltrials.gov): NCT02139800) was designed to determine if sustained inflation is superior to IPPV to prevent bronchopulmonary dysplasia or death among extremely preterm infants.⁴ In a subgroup of SAIL trial participants, RFM and vital sign measurements were recorded during the study intervention and subsequent resuscitation. The objective of the present study was to identify the effects of sustained inflation and IPPV on real-time objective measurements of respiratory function and vital signs.

IPPV	Intermittent positive pressure ventilation
RFM	Respiratory function monitor
SAIL	Sustained Aeration of Infant Lungs
Vte	Expiratory tidal volume
Vti	Inspiratory tidal volume

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Supported by the National Institutes of Health and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD): R03HD 086655-01A1 (to E.F.), K23HD084727-01A1 (to E.F.), and U01-HD072906-01A1 (to H.K.). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The authors declare no conflicts of interest.

Portions of this study were presented at the Pediatric Academic Societies annual meeting, April 24-May 1, 2019, Baltimore, Maryland.

0022-3476/\$ - see front matter. © 2021 Elsevier Inc. All rights reserved.
<https://doi.org/10.1016/j.jpeds.2021.08.038>

Methods

This was an ancillary study to the multisite international SAIL trial.⁴ SAIL randomized eligible infants born between 23 and 26^{6/7} weeks of gestation to receive up to 2 sustained inflations for 15 seconds each with peak inspiratory pressures of 20-25 cm H₂O, or IPPV with an initial peak inspiratory pressure of 20 cm H₂O that was then titrated. Subsequent interventions were based on local protocols. All participants with RFM data recorded from 5 SAIL trial sites were included in this ancillary study. Local Institutional Review Boards approved the SAIL trial, including RFM measurements. Parental informed consent was obtained for all participants. An external data and safety monitoring board was convened to ensure RFM data collection did not impose undue risk.

Respiratory interventions were administered via neonatal facemask or a nasopharyngeal tube connected to T-piece resuscitator. RFM measurements were made with the New-Life Box RFM (Advanced Life Diagnostics) using a sensor (Avea VarFlexFlow Transducer; Vyair) placed in line between the respiratory device and interface. The sensor signals are used to calculate flow, pressure, volume, mask leak, and respiratory rate. The RFM display was masked or visible to clinicians based on the local practice and/or concurrent enrollment in an ongoing trial (Monitoring Neonatal Resuscitation Trial).⁵

RFM and vital sign signals were synchronized and recorded from the time positive pressure respiratory support was initiated until 5 minutes elapsed or the infant was successfully transitioned to continuous positive airway pressure. One investigator performed breath by breath analysis of all recordings using Pulmochart software (Advanced Life Diagnostics) to ensure signal quality and assess for spontaneous breathing during and between inflations. Only delivered inflations were analyzed. If a spontaneous breath coincided with a delivered inflation, the entire combined inflation was reported as a superimposed breath.

To distinguish IPPV provided as the randomized intervention from IPPV administered during ongoing resuscitation, we defined an intervention phase of IPPV for control infants. This corresponded temporally with the upper 75% distribution of the duration of sustained inflation interventions for infants in the experimental arm.

Operational definitions were as follows: (1) Discrepancy in tidal volumes: $[(\text{inspiratory tidal volume, Vti} - \text{expiratory tidal volume, Vte}) / \text{Vti}] * 100$; (2) Significant mask leak: Supraphysiologic inspiratory tidal volume (Vti >60 mL/kg), with $\geq 60\%$ discrepancy between Vti and Vte; and (3) Airway obstruction: Inflations with Vti <2 mL/kg, as this volume represents dead space ventilation.

Statistical Analyses

Using R-3.6.3 (R Project) and Stata/SE 15 (StataCorp), we summarized RFM measures during the randomized intervention for each group. Because of differences in the timing and duration of sustained inflation and IPPV inflations, we did not directly compare RFM values between treatment

groups during the intervention phase. We used simple linear or logistic regression with infant level clustered sandwich estimators to compare RFM measurements between groups in the postintervention phase and vital signs at each minute of resuscitation. A *P* value of < .05 was considered statistically significant.

Results

Of 70 SAIL participants included in this study from August 2014 to September 2017, 34 were randomized to the control arm and 36 to the sustained inflation arm. Baseline characteristics were similar between groups (Table I). Providers delivered 75 sustained inflations to the 36 infants randomized to the intervention arm (Table II; available at www.jpeds.com). Significant mask leak occurred in 15% of sustained inflations and obstruction in 17% of sustained inflations (Figure 1, A). Among 34 infants allocated to the control arm, a median of 67 IPPV inflations were provided during the 120 second intervention phase (Table III; available at www.jpeds.com). Significant mask leak occurred in 3% of IPPV inflations and obstruction was present in 17% of inflations (Figure 1, B).

Characteristics of postintervention IPPV for both groups are shown in Table IV. Spontaneous breathing during the postintervention phase was observed in 83% of infants in the control group and 90% of infants in the sustained inflation group (*P* = .47). Vital sign measurements did not significantly differ between groups (Figure 2; available at www.jpeds.com).

Discussion

We report physiologic responses to respiratory interventions delivered during the SAIL trial. Expiratory tidal volumes were highly variable in both groups, and spontaneously breathing was common before and during treatment interventions. Pulse rate and oxygen saturation values were similar between groups.

The SAIL trial was stopped early due to increased mortality in the first 48 hours of life among infants in the sustained

Table I. Demographic characteristics of SAIL participants with respiratory function monitor recordings

Characteristics	Control arm (n = 34)	Sustained inflation arm (n = 36)	<i>P</i> value
Gestational age, wk; mean (SD)	25.1 (0.9)	25.4 (0.8)	.23
Birth weight, g; mean (SD)	769 (160)	817 (184)	.17
Antenatal corticosteroids (complete), n (%)	28 (82%)	32 (89%)	.51
Cesarean delivery, n (%)	20 (59%)	23 (64%)	.81
Multiple birth, n (%)	5 (15%)	9 (25%)	.37
1-min Apgar score; median (IQR)	3.5 (2-5)	4 (2-5)	.79
5-min Apgar score; median (IQR)	7 (6-8)	7 (5-9)	.70
Spontaneously breathing prior to intervention, n (%)	22 (65%)	18 (50%)	.24

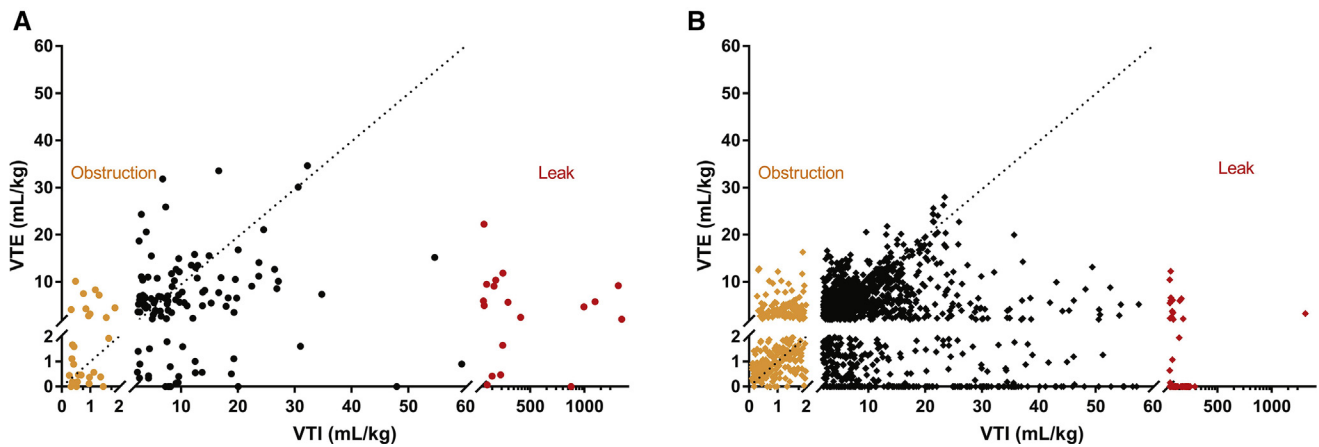


Figure 1. Vti and Vte for inflations delivered in the intervention phase. **A**, Sustained inflations. **B**, IPPV inflations. *IPPV*, intermittent positive pressure ventilation.

Table IV. Characteristics of IPPV inflations applied during the postintervention phase

Characteristics	Control arm (n = 2077 inflations)	Sustained inflation arm (n = 2855 inflations)	P value*
Peak inspiratory pressure, cm H ₂ O; mean (SD)	24.9 (4.0)	26.2 (2.8)	.13
Spontaneous breathing during IPPV, n (%)	491 (24)	556 (20)	.49
Vte, mL/kg; median (IQR)	5.7 (2.5-10.0)	6.3 (3.6-9.9)	.53
Discrepancy between Vti and Vte, %; median (IQR)	12.0 (0-76.3)	0 (0-19.5)	.003
Inflations with significant leak, n (%)	75 (4%)	30 (1%)	.072
Inflations with airway obstruction, n (%)	128 (6%)	441 (15%)	.059

IPPV, intermittent positive pressure ventilation.

*P values from simple linear or logistic regression models with adjustment for clustering by infant. Variables were transformed to normality, as required.

inflation arm, but no causal pathway was identified. Speculative explanations included excessive tidal volumes causing lung injury on the one extreme vs inadequate inflations delaying effective resuscitation and prolonging bradycardia on the other.^{6,7} Granular physiologic data recorded in this subset of SAIL participants do not confirm either of these proposed explanations. Consistent with other reports,⁸⁻¹¹ Vte of delivered sustained inflations varied widely. However, we did not observe systematic patterns of sustained inflation RFM measures likely to cause morbidity or mortality.

The technical realities of providing noninvasive respiratory support in the delivery room are complex. Airway obstruction and mask leak are known impediments,¹²⁻¹⁶ and both were observed in the present study. Mask leak is generally calculated as the difference between Vti and Vte, divided by Vti. A “significant” mask leak is not standardly

defined; published definitions range from 30% to 75%.^{13,15-17} In addition, some delivered gas remains in the lungs as air replaces liquid to form a functional residual capacity immediately after birth.^{1,18} Therefore, when Vti and Vte differ during immediate transition, it is difficult to attribute the cause to leak vs functional residual capacity formation. In this study, we report the difference between Vti and Vte simply as discrepancy. Significant leak (defined more stringently as $\geq 60\%$ discrepancy between Vti and Vte when a supraphysiologic Vti was recorded) was more commonly observed during sustained inflation. This is likely because delivering a prolonged (‘sustained’) inflation with constant inspiratory gas flow allowed more time to release a supraphysiologic Vti when mask leak was present, compared with brief IPPV inflations.

Spontaneous breathing patterns may impact the effectiveness of both sustained inflation and IPPV.^{10,19} Laryngeal closure during apnea is one cause of airway obstruction that prevents gas delivery to the lung.¹⁹ Further, facemask application precedes apnea in some preterm infants.²⁰ Spontaneous breathing with an open glottis may therefore be a modifying factor for sustained inflation to effectively promote lung aeration.^{10,11,21} In the present study, 57% of infants were breathing spontaneously after facemask application before receiving either sustained inflation or IPPV, and many breathed during post-intervention IPPV. These findings suggest that spontaneous breaths taken during transition allowed lung aeration and sufficient gas delivery for most SAIL trial participants.

Preclinical models demonstrated sustained inflation to be more effective than IPPV for uniform lung aeration after birth.^{22,23} However, there are key differences between the laboratory and clinical environment: experimental animals were anesthetized, and interventions were provided via endotracheal tube (bypassing the upper airway) rather than facemask. Results from controlled animal models may not

adequately reflect the dynamic delivery room setting. In addition, preclinical studies used phase contrast imaging to assess lung aeration, which is not possible clinically. During neonatal transition, rise in heart rate is considered the best and earliest clinical indicator of lung aeration,²⁴⁻²⁶ which is typically followed by rising oxygen saturation. We found pulse rate and pulse oximetry values to be similar at all time points, suggesting that neither sustained inflation nor IPPV provided superior lung aeration and oxygenation.

We acknowledge several limitations to this analysis. This study included 70 out of 426 (16%) of SAIL participants born when RFM recording was feasible and may not represent all infants enrolled in SAIL. However, RFM recording immediately after birth is not yet uniformly available in all clinical settings. Further, this sample may not provide adequate power to detect more subtle differences in RFM data or vital signs between groups. In addition, many infants were breathing prior to and during delivered inflations; spontaneous breathing efforts could reduce or augment the effectiveness of both sustained inflation and IPPV. Ultimately, this reflects both the pragmatic nature of the SAIL trial and the reality of how respiratory interventions are applied in standard delivery room practice. Finally, we did not adjust for multiple comparisons in this exploratory analysis.

Study strengths include a relatively large compilation of RFM recordings across multiple sites with breath by breath analyses to ensure signal quality. These data contribute to understanding how SAIL trial interventions were administered. Future investigators may consider recording RFM and vital sign measurements as objective outcomes and indicators of how interventions are delivered in the delivery room.

In conclusion, expiratory tidal volumes of sustained inflation and IPPV inflations delivered to infants in the SAIL trial were highly variable, and airway obstruction and mask leak impeded ventilation in both groups. Pulse rate and oxygen saturations were similar between groups throughout the first five minutes of resuscitation. These data suggest that sustained inflation delivered noninvasively does not promote lung aeration better than IPPV in extremely preterm infants. ■

We thank the members of the data safety monitoring board: Drs Myra Wyckoff (chair), Dirk Bassler, and Elaine Boyle.

Submitted for publication Apr 30, 2021; last revision received Jul 30, 2021; accepted Aug 19, 2021.

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50 Years Ago in *THE JOURNAL OF PEDIATRICS*

Phototherapy: From Novelty to Routine

Kaplan E, Herz F, Schere E, Robinson LD. Phototherapy in ABO hemolytic disease of the newborn infant. *J Pediatr* 1971;91:1-4.

Fifty years ago in *The Journal*, Kaplan et al described the efficacy of phototherapy for treatment of ABO hemolytic disease of the newborn (ABO-HDN) in the nursery at Sinai Hospital of Baltimore. The article was published 2 years after the hospital implemented phototherapy in 1969. Of 58 infants with ABO-HDN, researchers assigned 29 infants to receive phototherapy and 29 untreated controls. The 2 groups were further divided into mild or severe onset of disease, classified as serum bilirubin less than or greater than 0.5 mg/dL rate of rise per hour, respectively. Serum bilirubin levels were assessed at regular intervals for the first 3 days of life. Eight of the 11 untreated infants with severe onset of disease had increased serum bilirubin levels after 24 hours. In contrast, only 4 of the 13 infants with severe onset of disease who were treated with phototherapy had increased bilirubin at 24 hours. Infants who were treated with phototherapy had lower peak serum bilirubin and reached said peak earlier in their hospitalization. Despite these results, the authors cautioned that phototherapy, as a novel treatment, may carry unforeseen adverse effects. Seven untreated and 2 treated infants required exchange transfusion, accounting for 15% of the total cohort—a number that seems unthinkable in 2021.

Today, phototherapy is the standard of care for newborns with indirect hyperbilirubinemia of any origin. The technology has evolved from the “ten 20-watt daylight fluorescent bulbs” used in Kaplan’s nursery to special “bili lights” optimized for specific light wavelengths and fiberoptic blankets. Phototherapy and the introduction of intravenous immunoglobulin to reduce hemolysis have limited the use of exchange transfusion. Patients with ABO-HDN requiring exchange transfusion are sufficiently rare to merit a case report, and many neonatology fellows have never performed the procedure.^{1,2} In contrast, every pediatric intern has ordered phototherapy.

The authors may be relieved to know that most adverse effects of phototherapy are easily prevented with judicious initiation, attention to temperature control, eye coverings, and appropriate hydration, making it one of the safest interventions in the neonatal intensive care unit. The use of phototherapy to prevent the need for exchange transfusion should be considered an exemplar of progress in pediatric medicine.

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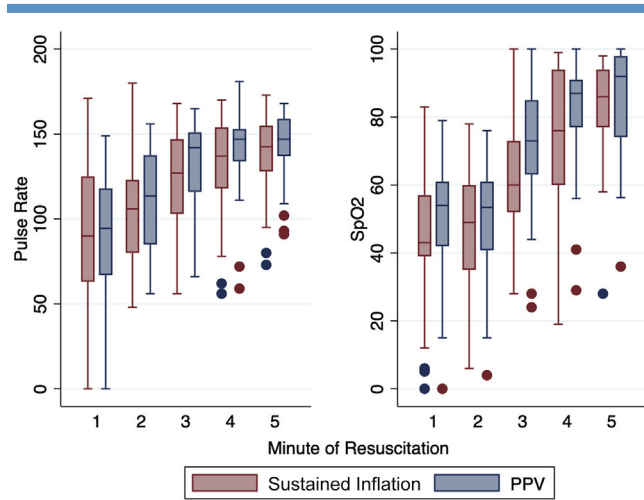


Figure 2. Pulse rate and peripheral oxygen saturation (SpO₂) for each treatment arm during first 5 minutes of resuscitation. No statistically significant differences were observed between groups for either value at any time point. *PPV*, positive pressure ventilation.

Table III. Characteristics of IPPV inflations in the control arm “intervention” phase

Characteristics	IPPV Inflations (2218 inflations in 34 infants)
Number of IPPV inflations provided per infant; median [range]	67 [4-167]
Peak pressure, cm H ₂ O; mean (SD)	22.7 (4.5)
Spontaneous breathing during IPPV, n (%)	299 (13%)
Vte, mL/kg; median (IQR)	4.3 (1.3-6.6)
Discrepancy between Vti and Vte, %; median (IQR)	6.0 (0-61.9)
Significant leak, n (%)	74 (3%)
Airway obstruction, n (%)	384 (17%)

IPPV, intermittent positive pressure ventilation.

Table II. Characteristics of sustained inflations

Characteristics	Sustained inflations (75 inflations in 36 infants)
Number of sustained inflation provided per infant; median [range]	2 [1-5]
Peak pressure of sustained inflation, cm H ₂ O; mean (SD)	24.5 (3.3)
Spontaneous breathing during sustained inflation, n (%)	34 (45%)
Number of spontaneous breaths during sustained inflation, if present; median [range]	2 [1-7]
Vte for all sustained inflation, mL/kg; median (IQR)	5.3 (1.1-9.2)
Vte of first sustained inflation, mL/kg; median (IQR)	5.0 (1.6-7.7)
Vte of second sustained inflation, mL/kg; median (IQR)	4.9 (0.9-9.8)
Discrepancy between Vti and Vte, %; median (IQR)	49.1 (0-90.5)
Significant leak, n (%)	11 (15%)
Airway obstruction, n (%)	13 (17%)