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SHORT REPORT

Novel Insights into Preterm Respiratory Physiology: Celebrating the 100th Birthday of Dr. Mildred T. Stahlman

Changes in respiratory mechanics in response to crystalloid infusions in extremely premature infants

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Abstract

Extremely premature infants are at a higher risk of developing respiratory distress syndrome and circulatory impairments in the first few weeks of life. Administration of normal saline boluses to manage hypotension is a common practice in preterm infants. As a crystalloid, a substantial proportion might leak into the interstitium; most consequently the lungs in the preterm cohorts, putatively affecting ventilation. We downloaded and analyzed ventilator mechanics data in infants managed by conventional mechanical ventilation and administered normal saline bolus for clinical reasons. Data were downloaded for 30 min prebolus, 60 min during the bolus followed by 30 min postbolus. Sixteen infants (mean gestational age 25.2 ± 1 wk and birth weight 620 ± 60 g) were administered 10 mL/kg normal saline over 60 min. The most common clinical indication for saline was hypotension. No significant increase was noted in mean blood pressure after the saline bolus. A significant reduction in pulmonary compliance (mL/cmH_2O/kg) was noted (0.43 ± 0.07 vs. 0.38 ± 0.07 vs. 0.33 ± 0.07, $P = 0.003$, ANOVA). This was accompanied by an elevation in the required peak inspiratory pressure to deliver set volume-guarantee (19 ± 2 vs. 22 ± 2 vs. 22 ± 3 mmHg, $P < 0.0001$, ANOVA), resulting in a higher respiratory severity score. Normal saline infusion therapy was associated with adverse pulmonary mechanics. Relevant pathophysiologic mechanisms might include translocation of fluid across pulmonary capillaries affected by low vascular tone and heightened permeability in extremes of prematurity, back-pressure effects from raised left atrial volume due to immature left-ventricular myocardium; complemented by the effect of cytokine release from positive pressure ventilation.

NEW & NOTEWORTHY Administration of saline boluses is common in premature infants although hypovolemia is an uncommon underlying cause of hypotension. This crystalloid can redistribute into pulmonary interstitial space. In the presence of an immature myocardium and diastolic dysfunction, excess fluid can also be "edemagenic." This study on extremely premature infants (25 wk gestation) noted adverse influence on respiratory physiology after saline infusion. Clinicians need to choose judiciously and reconsider routine use of saline boluses in premature infants.

compliance; hypotension; normal saline; preterm respiratory physiology

INTRODUCTION

Infants born at extremes of prematurity are at high risk of respiratory distress syndrome (RDS). The primary underlying pathogenesis is inadequate pulmonary surfactant; manifesting as diffuse alveolar atelectasis, pulmonary edema, and cell injury. Other factors contributing to dysfunction include increased water content of the premature lung, immature mechanisms for lung fluid clearance, and the presence of hemodynamically significant patent ductus arteriosus (hsPDA) (pulmonary over-circulation). Recovery from RDS is characterized by spontaneous diuresis (reflecting clearance of lung fluid) whereas excessive fluid administration may contribute to pulmonary edema, either by itself or via a higher occurrence of an hsPDA (1). Putatively, the use of normal saline boluses in preterm infants may slow down the spontaneous recovery and affect lung compliance. Investigators have previously noted an association between excess fluid intake in preterm infants and important clinical outcomes such as bronchopulmonary dysplasia, hsPDA, and intraventricular hemorrhage (2–4). This cohort is also at a higher risk of circulatory impairment in the initial postnatal weeks of life. This may present as hypotension, metabolic acidosis, and poor perfusion, with bolus of normal saline (oftentimes multiple) a common initial intervention (5–7). However, infant's volume status (presence of hypovolemia) is rarely ascertained echocardiographically, highlighting a lacuna in neonatal clinical practice.

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The volume kinetics and distribution of isotonic crystalloids in preterm neonates may be influenced by the rate of infusion, infant's physiological condition, and vascular permeability and tone. Given its high chloride concentration, 0.9% sodium chloride is an unbalanced isotonic crystalloid (8, 9). Although neonatal information is scarce, data indicate that up to 50% of the intravascular volume effect can be lost in as little as 30 min in adults with normal transcapillary fluid dynamics (i.e., no hypotension or altered capillary permeability). The volume of distribution of isotonic crystalloids between the intravascular and interstitial spaces in healthy adults approximates the relative size of respective compartments (~25% will stay intravascular whereas ~75% interstitial) (10, 11). Among preterm infants, the interstitial space of concern where fluid might redistribute is the lungs, affecting respiratory physiology and pulmonary compliance.

We hypothesize that normal saline bolus may adversely affect respiratory physiology. The objective of this study was to evaluate the evolution of pulmonary compliance when normal saline bolus was administered to mechanically ventilated extremely premature infants.

METHODS

This observational study was approved by the institution ethics review committee (HREC RES-22-0000-291Q—86554). Since the data were already being recorded, no formal consent was required. The study included preterm infants ≤28 wk gestational age (GA) being administered normal saline bolus (10 mL/kg over 60 min) for reasons determined by the clinical team. Infants were ≤7 days of postnatal age and ventilated by conventional mechanical volume-controlled PC-AC (Assist Control-every infant initiated breath is supported) ventilation using the Drager Babylog VN500 ventilator with Infinity C500 touchscreen control and display. A flow sensor is routinely attached between the circuit and the end of the endotracheal tube that continuously feeds back flow and volume information to the ventilator. This system uses hot wire anemometer placed between y-piece and the endotracheal tube to measure flow, two internal pressure sensors installed in inspiratory and expiratory line to measure the airway pressure, thermal conductivity is used to measure O_2 concentration, and light absorption is used to measure CO_2 concentration internally. Fisher and Paykel 950 humidifier and the corresponding breathing circuit is used with the Babylog VN500 (12). We downloaded pulmonary mechanics data (being continuously recorded by the ventilator) for a period of 30 min preinfusion, 60 min during the infusion, followed by 30 min postinfusion (total 2 h). Self-ventilating infants, those on other modes of ventilation (continuous positive airway pressure or high frequency) and infants >7 days old were excluded. One infant was studied for observation only once and at the time of the initial infusion.

Statistics

This was a hypothesis-generating study providing preliminary data. Descriptive statistics were used to characterize baseline characteristics. Continuous variables were analyzed using Student's *t* test. Pair-wise comparisons versus baseline (preinfusion readings) were performed using the Holm–Sidak method. Analysis of covariance testing was used to analyze serial change over time. Two-tailed significance was set at $P < 0.05$.

Table 1. *Study population demographics*

Variable	*n* = 16
Gestational age at birth, wk	25.2 ± 1
Birthweight, g	620 ± 60
Age at saline bolus (day of life)	3.7 ± 1.2
Gestational age at saline bolus, wk	25.6 ± 1
Weight at saline bolus, g	602 ± 54
Antenatal steroids, *n* (%)	14 (90)
Mode of delivery (vaginal), *n* (%)	13 (65)
Male sex, *n* (%)	11 (55)
Surfactant, *n* (%)	20 (100)
Last dose of caffeine, h	7.1 ± 1.6
Documented reason*	^Hypotension 9 ↑lactate 5 ↓perfusion 4 ↓urine output 4 metabolic acidosis 3

*Multiple in some; ^mean blood pressure < gestational age.

RESULTS

Sixteen extremely preterm infants formed the study cohort. The GA and birthweight of the cohort were 25.2 ± 1 wk and 620 ± 60 g, respectively. Table 1 depicts other clinical and demographic characteristics. None of the infants had an obvious cause of hypovolemia (such as feto-maternal hemorrhage, twin-to-twin transfusion, or pulmonary hemorrhage). No infants were on inotropes before or during the 2-h period. All infants were supine and no endotracheal suction was performed during the observations. No change was made to ventilator settings except nurse controlled change in fractional inspired oxygen to maintain saturations within the nominated range (91–95%). The most common documented reason for saline bolus was hypotension (mean blood pressure [BP] <GA) (multiple reasons in some) (Table 1). The net volume of normal saline infused (10 mL/kg) was 6.4 ± 0.6 mL. There was no significant improvement in mean BP on reassessment (24 ± 2 vs. 26 ± 3 mmHg, $P = 0.2$).

Table 2 depicts ventilator data over the 2-h period. The set volume guarantee in the cohort was median 5 mL/kg (range 4.5–5). A significant reduction in compliance was noted (0.26 ± 0.03 preinfusion to 0.2 ± 0.03 mL/cmH_2O postinfusion, $P < 0.0001$). To be able to deliver the set tidal-volume via volume guarantee, the ventilator generated higher peak inspiratory pressures. Alongside a trend in increased oxygen requirements, an increase in respiratory severity score (mean airway pressure × fractional inspired oxygen) was noted. Figure 1 depicts the trends in compliance, inspiratory pressures, and oxygen requirements, before, during, and after the saline infusion.

DISCUSSION

Although there is no consensus on how best to treat hypotension in preterm infants, the use of saline boluses remains the initial intervention by most clinicians (13). Detrimental clinical effects (such as PDA, necrotizing enterocolitis, bronchopulmonary dysplasia, and death) of liberal administration

Table 2. *Evolution of ventilator parameters*

Parameter	Before Infusion (30 min) T1	During Infusion (60 min) T2	After Infusion (30 min) T3	*P* T1 vs. T2	*P* T2 vs. T3	*P* T1 vs. T3	ANOVA
Pulmonary compliance nett, mL/cmH_2O	0.26 ± 0.03	0.23 ± 0.03	0.2 ± 0.03	0.02	0.03	<0.0001	0.0002
Pulmonary compliance, mL/cmH_2O/kg	0.43 ± 0.07	0.38 ± 0.07	0.33 ± 0.07	0.08	0.08	0.001	0.003
PIP, cmH_2O	19 ± 2	22 ± 2	22 ± 3	<0.0001	0.3	<0.0001	<0.0001
MAP, cmH_2O	9.3 ± 1.4	10.5 ± 1.3	11.1 ± 1.2	0.02	0.2	0.0008	0.001
Oxygen requirement, %*	34 (24, 58)	43 (34, 70)	47 (38, 82)	0.2	0.4	0.06	0.1
RSS (MAP × FI_{O_2})	4 ± 2.6	5.5 ± 3.1	6.5 ± 3.2	0.1	0.4	0.03	0.08
Time constant expiratory, s	0.15 ± 0.04	0.12 ± 0.03	0.11 ± 0.03	0.02	0.8	0.01	0.01
Tidal volume, mL	3.1 ± 0.3	3 ± 0.3	2.9 ± 0.2	0.4	0.1	0.1	0.3

ANOVA, analysis of variance; FI_{O_2}, fractional inspired oxygen; MAP, mean airway pressure; PIP, peak inspiratory pressure; RSS, respiratory severity score. *Median (interquartile range).

of fluids are known (14–17). Our study noted adverse effects on preterm lung mechanics in association with saline boluses, putatively related to redistribution into extravascular (interstitial) space. Clinicians need to be cognizant of such effects and decide on fluid replenishment judiciously.

Use of Normal Saline as Therapy for Hypotension in Extremely Preterm Infants

Preterm ventilated infants are affected by certain maturational peculiarities that include delayed closing of PDA, immaturity of the myocardium, and the imperfection in peripheral chemo and baroreceptors. Clinical manifestations include reduced BP, reduced perfusion, metabolic acidosis, oliguria and tachycardia (18, 19). Although there could be other reasons for reduced preload (such as high mean airway pressure), and absolute hypovolemia from acute hemorrhage is a less common cause, fluid bolus therapy represents an established component of management in preterm infants. Most clinicians use mean BP < GA to define and treat hypotension in preterm infants (20–22), normal saline being the most commonly used crystalloid (6, 13). A Canadian survey of 95 neonatologists reported that clinicians routinely treated suspected hemodynamic compromise in premature infants with a fluid bolus, most commonly using 0.9% sodium chloride (21). An international observational study in preterm infants who received a fluid bolus for the management of hemodynamic compromise noted the most common fluid used was 0.9% sodium chloride (most commonly 10 mL/kg) (6). The most common indication was hypotension, followed by poor perfusion and metabolic acidosis. Minimal or no clinical improvement was reported by clinicians in 40% cases (6). These data echo the findings of our study in terms of indications, choice and the amount of fluid bolus, and the lack of response to numerical hypotension. Investigators have previously noted that infants who received ≥30 mL/kg volume expansion in the initial 48 h were more likely to die versus those who received less fluid (15). A Cochrane review found no evidence to determine if preterm infants with clear hemodynamic compromise benefitted from volume expansion compared with no volume expansion (17).

Impact of Saline Boluses on Physiology

Experimental data from studies in piglets indicated lack of efficacy of crystalloids toward volume expansion. Five groups of premature piglets were infused with saline (10 or 20 mL/kg) or packed red cells (10 or 20 mL/kg) over 1 h and compared with no treatment (23). Blood volume, blood pressure, central venous pressure, heart rate, and carotid flow were measured alongside cerebral oxygenation, pH, base excess, and serum lactate for 6 h after start of treatment. Both packed red cell cohorts noted significant increases in blood volume and improved measures of cardiovascular function, cerebral oxygenation, and reduction in metabolic acidosis. Saline infusion did not significantly alter any of the aforementioned measures; the most likely explanation for the ineffectiveness is the rapid leakage of saline out of the systemic vasculature. Similar evidence is available from studies in sheep where at 10 min after infusion of 0.9% saline, only 15% remained within the circulation (24).

Total body water accounts for ∼60% of total body weight though infants possibly have a higher percentage of water by weight than adults. Normal saline (when compared with plasma) rapidly distributes as the membrane between the vascular and interstitial space is permeable to most electrolytes. The distribution within the extracellular fluid is quite identical to that of water, i.e., ∼25% vascular and 75% interstitial; the time frame for this to occur clinically is ∼30 min (25). A study on adults noted that one liter of crystalloid resulted in an increase in plasma volume of only 194 mL. Plasma volume was maximal at the end of the infusion time of 1 h; gradually decreasing over the next 45 min (26). In essence, pulmonary edema as a consequence of crystalloid fluid administration is a distinct possibility, especially in preterm infants with already immature vascular tone and permeability. This might explain the decreased pulmonary compliance we observed in our cohort. Higher cardiac filling is associated with injury to the endothelial glycocalyx, contributing to increased endothelial permeability (27, 28). Figure 2 summarizes various mechanistic linkages.

The use of normal saline could contribute to iatrogenic fluid overload. This is further complicated by the distinct developmental differences in the premature myocardium (inefficient contractile apparatus, lack of elastic tissue, high proportion of stiff fibers) (29, 30) (Fig. 2). In contrast to the adult heart where ∼60% of the myocardium is muscular, in extremely premature infants contractile tissue only accounts for ∼30% (31), with over-representation of relatively disorganized mitochondria (32). In such a scenario, the ability of the myocardium to respond to additional stress (e.g., changing loading conditions, volume boluses) may be severely

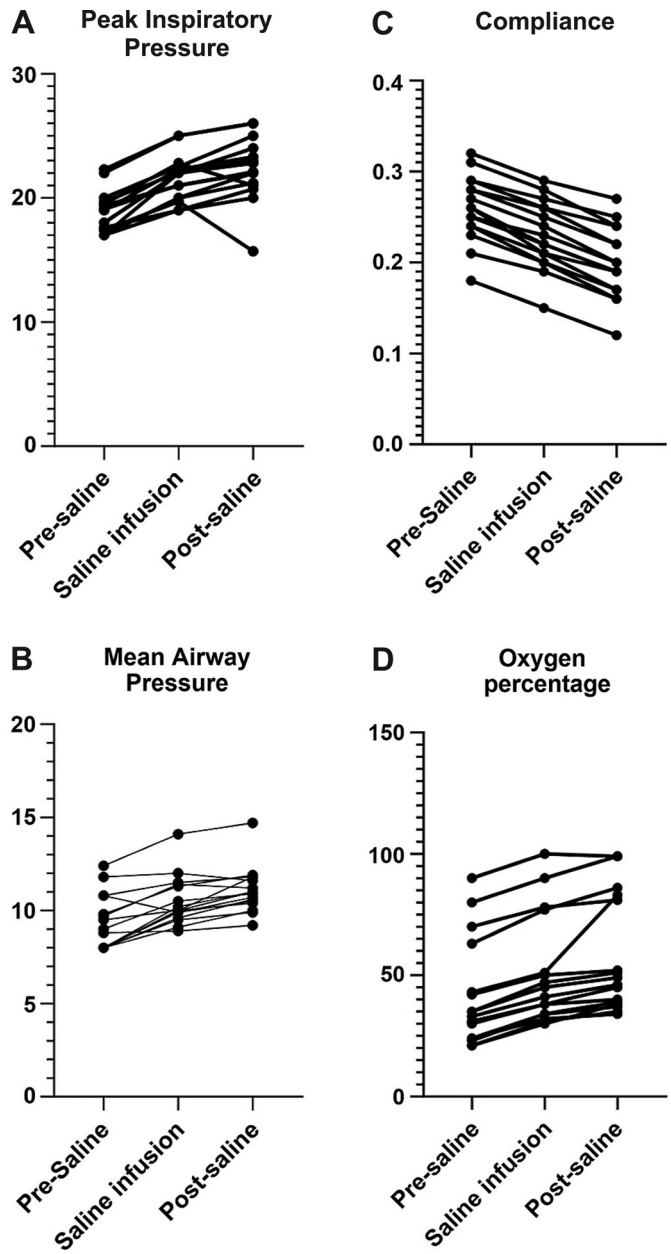

Figure 1. Line graphs showing evolution of mean values of peak inspiratory pressure (in cmH_2O; *A*), mean airway pressure (in cmH_2O; *B*), compliance (in $mL/cmH_2O/kg$; *C*), and oxygen (in %; *D*) at three time points (30 min of presaline, 60 min of saline infusion, 30 min of postsaline).

compromised. Circulatory instability among preterm infants may be due to higher capillary permeability of immature vessels, raised hydrostatic pressure gradient, and lower oncotic pressure gradient, alongside reduced lymphatic return and inappropriate vasodilatation (lower vasomotor tone) and a limited capacity to vasoconstrict (33, 34). In the presence of myocardial dysfunction (common in extremely premature infants), a rapid increase in preload can result in pulmonary venous congestion, especially if there is inadequate diastolic function due to the aforementioned developmental factors. Finally, positive pressure ventilation coupled with the need for higher pressures in response to decreasing compliance could initiate a cascade of cytokine-mediated vasomotor permeability (35). These mediators include interleukins and histamine/bradykinin, and may contribute to the other mechanisms of pulmonary congestion/edema highlighted earlier (Fig. 2).

Relevance of Lung Mechanics in Preterm Infants

To deliver set tidal volume (volume-guarantee), a significant increase in ventilator pressures (peak and mean airway pressures) was noted, accompanied by decreased pulmonary compliance and expiratory time constant in association with normal saline bolus in extremely preterm infants.

Lung compliance describes how much volume will change for a given pressure differential. In premature infants, a low compliance generally implies higher surface tension, generated as water molecules cluster together, reducing exposure to oxygen in the alveolar space. This coalescing produces a force that tends to pull the alveolar walls inward, necessitating a larger outward pressure to inflate the alveoli (Fig. 2). Although extremely preterm infants are at the late canalicular or early saccular stage of pulmonary architecture development, it is the later saccular stage where the extracellular matrix matures, stabilizing elastin-collagen arrangement, leading to improved lung compliance (36–38). Decrease in pulmonary compliance is undesirable because it becomes more difficult to inflate the lungs, the consequent barotrauma leading to higher respiratory support requirements due to an overall adverse effect on alveolar distensibility. The expiratory time constant is a dynamic measurement of respiratory mechanics and is useful for diagnosing the lung condition and its severity, optimizing the ventilator settings and understanding respiratory physiology. Lower expiratory time constant indicates lowering of compliance, which will require a higher inspiratory transpulmonary pressure. A stiff lung with low compliance, whether due to RDS or fluid translocation into the pulmonary interstitium, will empty quickly on expiration. For instance, in adult patients with acute RDS, it is typically in the range of 0.4–0.6 s. It is shorter in patients with more severe acute RDS, indicating low compliance and a small volume of aerated lung (39). The need for higher ventilator pressures to deliver guaranteed volume in volume-controlled mode of ventilation could propagate barotrauma (Fig. 2). This is associated with the activation of a complex inflammatory cascade and colonizing the airway with pathogens (35).

Way Forward: Better Assessment-Judicious Management

Hemodynamic management of preterm infants requires appreciation of the aforementioned physiology, and point-of-care echocardiography could enhance (complement) diagnostic accuracy and select physiologically appropriate medications. Volume responsiveness is evaluated as an increase in echocardiographic stroke volume by 5–10% in response to fluid bolus (40). However, dynamic indices of fluid responsiveness such as BP variation are mainly studied in adults and older children but are not applicable in daily practice in neonatal intensive care (41–44). Echocardiographic markers of hypovolemia such as end-diastolic left ventricular and left atrial diameter, and the diameter/collapsibility of the inferior vena cava (IVC) are subjective and unreliable (45–47). Generally, a

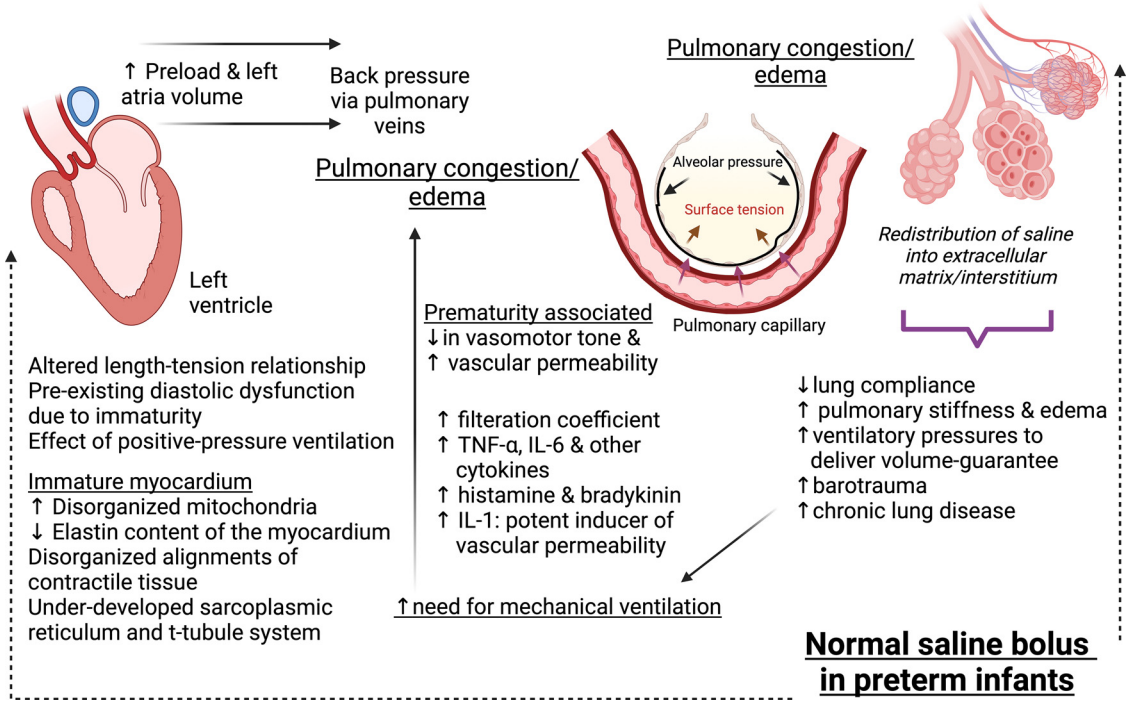

Figure 2. Mechanistic links between normal saline boluses and effects on lung compliance. IL, interleukin, TNF, tumor necrosis factor. [Image created with a licensed version of BioRender.com.]

normally filled IVC has some caliber change with cardiac cycle. An under-filled IVC will be barely visible or collapse entirely on inspiration whereas an overfilled IVC will appear distended and minimally pulsatile. This simplistic approach, however, is not valid in infants ventilated especially with high frequency ventilation as high intrathoracic pressure can effectively make the IVC appear well-filled, when the cardiac chambers themselves may be under-filled. Hence, this information needs cautious interpretation. In essence, reliable indicators of assessment of volume status in these cohorts are lacking and the use of subjective estimation of volume status (eyeballing) to decide administration of saline boluses is not evidence-based. Given hypovolemia is an uncommon cause of hypotension in neonates, routine administration of saline boluses, especially repeated, must be seriously questioned.

Limitations of the study include relatively small numbers. The recruitment was not continuous as some infants belonged to the exclusion criteria while investigator availability precluded data download in others. We did not use invasive means to measure compliance, which possibly could give a more reliable data set. Each infant acted as its own control as the primary objective was to study the evolution of parameters in response to saline bolus; we did not have a separate control population. As strength, this was a homogeneous population of extremely premature infants in the early postnatal days of life.

Conclusions and Future Research

Our preliminary data showing adverse influence on pulmonary mechanics in preterm infants is cause for scientific pause before liberal/routine use of saline boluses in the absence of hypovolemia. Similar evaluations in populations such as perinatal asphyxia and septic shock may give further physiological information. A better understanding of the alterations in neonatal respiratory physiology in response to common interventions may allow a physiology-based approach in decision making.

DATA AVAILABILITY

Data will be made available upon reasonable request.

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Figure 2 and graphical abstract image were created with a licensed version of BioRender.com.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

A.S. and B.G. conceived and designed research; A.S. and B.G. performed experiments; A.S. and B.G. analyzed data; A.S. and B.G. interpreted results of experiments; A.S. prepared figures; A.S. drafted manuscript; A.S. and B.G. edited and revised manuscript; A.S. and B.G. approved final version of manuscript.

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