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Ivan D. Frantz III, MD, Editor, Professor of Pediatrics, Tufts University School of Medicine, Boston
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Review of Conventional Mechanical Ventilation in Premature Infants

By Andrea L. Lampland, MD and Mark C. Mammel, MD**

A quick glance at the history of neonatal mechanical ventilation reveals that tremendous strides have been made since the 1950s and 1960s, when mechanical ventilation to treat neonatal respiratory distress syndrome (RDS) was first reported.[1,2] Before the 1970s, mechanical ventilation of premature infants was often considered to be an heroic and experimental intervention. The mechanical ventilators of that time were either hand-built or modified adult ventilators that used intermittent gas flow only during mechanical breaths, with high ventilator rates and pressures. With a closed ventilator circuit, many of the infant's spontaneous breaths received no fresh gas flow; they simply rebreathed their previously exhaled gases (Figure 1). In addition, the key concept relating positive end-expiratory pressure (PEEP) and mean airway pressure to lung volume and oxygenation was still in the future.[3,4]

An important turning point in neonatal mechanical ventilation came in the early 1970s when Kirby and deLemos developed a ventilator circuit that allowed

What's Inside

**Andrea L. Lampland, MD, is a neonatologist and Co-director of the Infant Diagnostic & Research Center at Children's Hospitals and Clinics of Minnesota–St. Paul, and Assistant Professor in the Department of Pediatrics at the University of Minnesota. Mark C. Mammel, MD, is a neonatologist and Director of the Infant Diagnostic & Research Center at Children's Hospitals and Clinics of Minnesota–St. Paul, and Professor of Pediatrics and Co-director of the Neonatal-Perinatal Fellowship Program at the University of Minnesota.*

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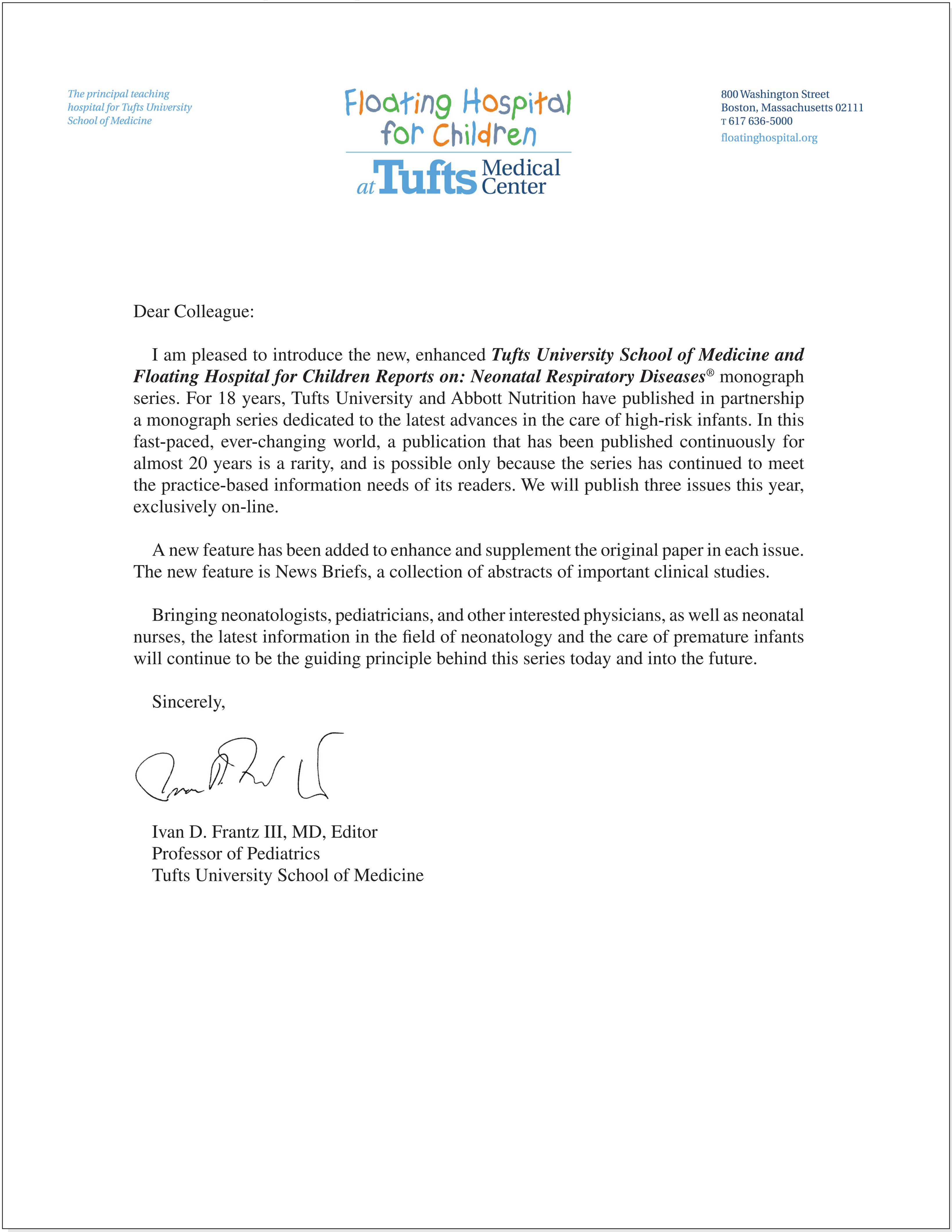

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Sincerely,

Ivan D. Frantz III, MD, Editor
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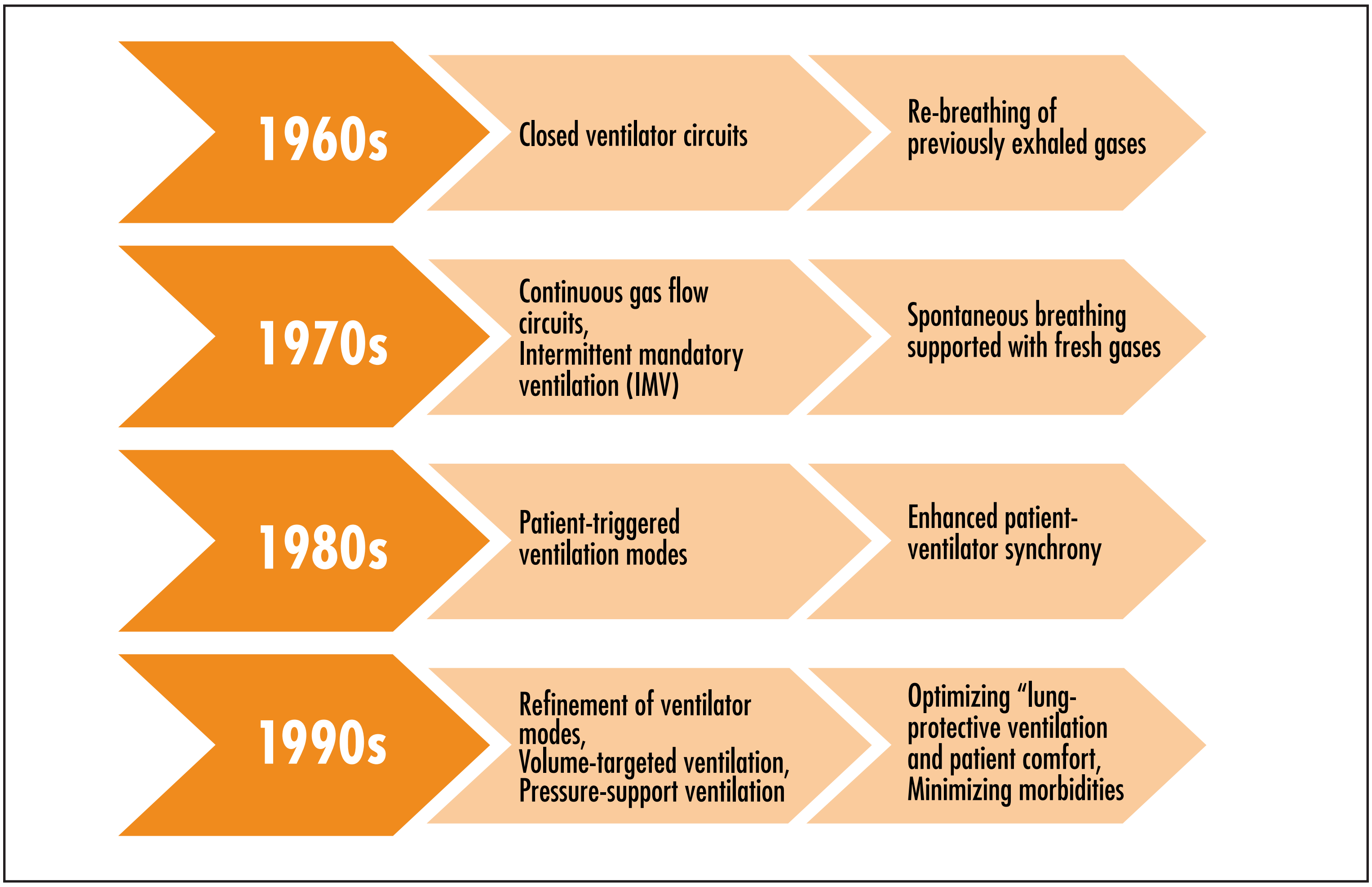

Figure 1: *Decade-by-decade advances in mechanical ventilation techniques for neonates.*

for continuous gas flow throughout the respiratory cycle.[5,6] This background of continuous gas flow combined with the ventilator's ability to deliver time-cycled, mechanically assisted breaths allowed patients to breathe spontaneously between machine breaths and receive fresh, humidified gases with each breath. This was the inception of intermittent mandatory ventilation (IMV). Although IMV did not allow for directed synchrony of mechanical assistance with patient respirations, it was a huge step forward and allowed for simplification and consistency of neonatal mechanical ventilatory support.

The 1980s and 1990s were decades of revisions and fine-tuning of ventilator mechanics aimed at enhancing patient tolerance and decreasing pulmonary morbidities related to mechanical ventilation (Figure 1). Patient-triggered ventilation modes, including assist/control (A/C) and synchronized intermittent mandatory ventilation (SIMV), were introduced to address specific pulmonary morbidities related to patient-ventilator asynchrony. In particular, patient-triggered modes of ventilation allowed for improved synchrony of ventilator assistance with patient inhalation and therefore improved gas exchange at lower inflating pressures. Net results of these improvements might be expected to lead to a reduction in pulmonary morbidities such as pulmonary air leaks and chronic lung tissue injury. In preterm babies, patient-triggered modes of ventilation have been associated with lower clinical distress scores and stress hormone concentrations.[7] Meta-analyses comparing patient-triggered ventilation to IMV have demonstrated that patient-triggered modes of ventilation do tend to reduce air leaks and duration of mechanical ventilation. However, there is no compelling evidence that these modes have significant effects on long-term outcomes such as death, chronic lung disease (CLD), or intracranial hemorrhage (ICH).[8]

The advances in synchronized, patient-triggered mechanical ventilation coincided with many other advances in neonatal medicine. In particular, routine use of antenatal steroids and of exogenous surfactant replacement decreased neonatal mortality and morbidity in premature infants.[9-11] All told, much progress has been made in the treatment of RDS over the past few decades. However, despite these advancements in neonatal mechanical ventilation strategies, RDS continues to be a source of significant morbidity and mortality in preterm infants. Ventilator-induced lung injury and other pulmonary morbidities secondary to mechanical ventilation remain ongoing problems in the care of premature infants. Of most concern, CLD develops in up to one third of preterm infants with RDS who receive positive pressure mechanical ventilation.[12]

Noninvasive Management Versus Mechanical Ventilation for RDS

Because RDS and CLD continue to be major sources of morbidity in premature infants, clinicians are still searching for the "optimal" treatment plan, and are particularly asking these questions: which interventions and when? The first question is whether the benefits to intubation, surfactant administration, and mechanical ventilation in infants with RDS outweigh the risks. The answer to this question seemed obvious after the initial surfactant trials. However, since the babies in these trials, who weighed ≤1250 g and were electively intubated, then randomized to either prophylactic or rescue therapy, the particular scenario of the infant who is able to establish spontaneous respirations without intubation was not evaluated. Subsequently, an alternative treatment plan to elective mechanical ventilation, application of noninvasive continuous positive airway pressure (CPAP), has been shown to be both feasible and effective in premature infants as young as 25 weeks' gestation. However, this approach obviously does not allow for surfactant administration.[13-15] The international, multicenter CPAP or Intubation at Birth (COIN) trial, published by Morley and colleagues in 2008, investigated the question of which treatment intervention, CPAP versus mechanical ventilation, is preferable in the treatment of RDS. They randomized infants born at 25-28 weeks' gestation to CPAP versus intubation for treatment of respiratory distress and found mixed results.[16] Use of CPAP did not significantly reduce the rate of death or CLD compared to intubation. The CPAP group did have less oxygen need at 28 days and fewer days of mechanical ventilation; however, the CPAP group also had a higher incidence of pneumothorax than did the intubated group. The use of surfactant and caffeine was not defined, and extubation criteria were similarly left to local practice. Therefore, especially in the smallest babies, we must await results from other ongoing, large, multicenter, randomized trials.

The data regarding the timing of intubation and surfactant administration for spontaneously breathing premature infants with RDS are better defined. Early intervention with intubation, surfactant administration, and planned extubation to CPAP within an hour of intubation is associated with less time on mechanical ventilation, fewer air leak syndromes, and less CLD.[17] Similarly, using a fraction of inspired oxygen (F_{IO_2}) of <0.45 as an indication for intubation and surfactant therapy confers an even greater advantage in reducing air leak syndromes and CLD.

> ...the data thus far do not suggest a "right way" in the treatment of RDS, but do suggest a potential "right time" if intubation and surfactant administration are deemed necessary.

In conclusion, the data thus far do not suggest a "right way" in the treatment of RDS, but do suggest a potential "right time" if intubation and surfactant administration are deemed necessary. Not surprisingly, with the incidence of CLD remaining relatively stagnant over the past few decades and mechanical ventilation's clear association with lung injury, the debate continues on whether or not to use mechanical ventilation in the treatment of each premature baby with respiratory distress.

Ventilation Modes and Strategies

There are too many neonatal ventilators to mention individually in this review, but most incorporate similar design features and can be used for multiple purposes. In general, mechanical ventilators produced since the early1970s provide continuous gas flow throughout the circuit and deliver tidal volumes by time-cycled, pressure-limited gas bursts. The delivered tidal volume is a function of the change in proximal airway pressures from the baseline PEEP to the peak inspiratory pressure (PIP). The PIP is constant and therefore the tidal volume that can be delivered at the fixed PIP varies with the lung compliance and airway resistance of the infant. This type of ventilatory mode, often called IMV or intermittent positive pressure ventilation (IPPV), is simple to use and standard on all ventilators. The addition of patient-triggered flow mechanisms, as used in SIMV, A/C, and pressure support (PSV) modes, allow for synchronization of mechanical breaths with patient effort and deliver synchronized, time-cycled, pressure-limited ventilation. However, clinicians must be aware that these pressure-preset modes do not maintain constant or reliable tidal volume delivery in the face of changing resistances or compliances, which may have a significant impact on patient management.[18]

The most recent investigations into ventilator-induced lung injury have pointed toward high lung volumes with alveolar overdistention and repetitive alveolar collapse/expansion cycles, also known as "volutrauma" and "atelectrauma," respectively, as critical determinants of lung damage and risk factors for the development of CLD.[19,20] With this in mind, many neonatal intensive care unit (NICU) physicians have targeted their mechanical ventilation strategies in preterm infants toward the use of low tidal volumes with adequate PEEP to try to mitigate the known effects of volutrauma and atelectrauma.[21-23] This strategy of combining low tidal volume ventilation, adequate PEEP, and recruitment maneuvers to reopen collapsed alveoli has now been coined "lung-protective ventilation."[24] Despite substantial experimental data to suggest that the use of lung-protective ventilation strategies should decrease ventilator-induced lung injury, these findings have not been as obvious in the clinical setting.[25]

With the goal of minimizing volutrauma, newer volume-targeted ventilation (VTV) modes have been investigated. VTV delivers a preset tidal volume for each mechanical breath, and different ventilators use different strategies to achieve volume targeting by varying peak pressure delivery, inflation time, and airway pressure waveforms. When compared with standard modes of synchronized, pressure-limited ventilation, the addition of volume targeting has been shown to be feasible, safe, and effective in the premature population. These short-term studies have demonstrated effective gas exchange with more consistent tidal volume delivery, less inadvertent hypocarbia, and lower levels of acute inflammatory markers in the airway when using volume-targeted modes of ventilation compared to pressure-limited modes.[26-31] Volume targeting has been shown to result in a significant reduction in PIP and thus a reduction in overall mean airway pressure exposure.[28] The 2005 Cochrane Review meta-analysis of four randomized,

An established record of safety and efficacy.

SURVANTA is indicated for prevention and treatment ("rescue") of Respiratory Distress Syndrome (RDS) (hyaline membrane disease) in premature infants. SURVANTA significantly reduces the incidence of RDS, mortality due to RDS and air leak complications.

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SURVANTA CAN RAPIDLY AFFECT OXYGENATION AND LUNG COMPLIANCE. Therefore, its use should be restricted to a highly supervised clinical setting with immediate availability of clinicians experienced with intubation, ventilator management, and general care of premature infants. Infants receiving SURVANTA should be frequently monitored with arterial or transcutaneous measurement of systemic oxygen and carbon dioxide.

DURING THE DOSING PROCEDURE, TRANSIENT EPISODES OF BRADYCARDIA AND DECREASED OXYGEN SATURATION HAVE BEEN REPORTED. If these occur, stop the dosing procedure and initiate appropriate measure to alleviate the condition. After stabilization, resume the dosing procedure.

*IMS DDD Lung Surfactant Market Purchases July 1991 through January 2009. On file, Abbott Nutrition Marketing Research.

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DESCRIPTION

SURVANTA® (beractant) Intratracheal Suspension is a sterile, non-pyrogenic pulmonary surfactant intended for intratracheal use only. It is a natural bovine lung extract containing phospholipids, neutral lipids, fatty acids, and surfactant-associated proteins to which colfosceril palmitate (dipalmitoylphosphatidylcholine), palmitic acid, and tripalmitin are added to standardize the composition and to mimic surface-tension lowering properties of natural lung surfactant. The resulting composition provides 25 mg/mL phospholipids (including 11.0-15.5 mg/mL disaturated phosphatidylcholine), 0.5-1.75 mg/mL triglycerides, 1.4-3.5 mg/mL free fatty acids, and less than 1.0 mg/mL protein. It is suspended in 0.9% sodium chloride solution, and heat-sterilized. SURVANTA contains no preservatives. Its protein content consists of two hydrophobic, low molecular weight, surfactant-associated proteins commonly known as SP-B and SP-C. It does not contain the hydrophilic, large molecular weight surfactant-associated protein known as SP-A.

Each mL of SURVANTA contains 25 mg of phospholipids. It is an off-white to light brown liquid supplied in single-use glass vials containing 4 mL (100 mg phospholipids) or 8 mL (200 mg phospholipids).

CLINICAL PHARMACOLOGY

Endogenous pulmonary surfactant lowers surface tension on alveolar surfaces during respiration and stabilizes the alveoli against collapse at resting transpulmonary pressures. Deficiency of pulmonary surfactant causes Respiratory Distress Syndrome (RDS) in premature infants. SURVANTA replenishes surfactant and restores surface activity to the lungs of these infants.

Activity

In vitro, SURVANTA reproducibly lowers minimum surface tension to less than 8 dynes/cm as measured by the pulsating bubble surfactometer and Wilhelmy Surface Balance. *In situ*, SURVANTA restores pulmonary compliance to excised rat lungs artificially made surfactant-deficient. *In vivo*, single SURVANTA doses improve lung pressure-volume measurements, lung compliance, and oxygenation in premature rabbits and sheep.

Animal Metabolism

SURVANTA is administered directly to the target organ, the lungs, where biophysical effects occur at the alveolar surface. In surfactant-deficient premature rabbits and lambs, alveolar clearance of radio-labelled lipid components of SURVANTA is rapid. Most of the dose becomes lung-associated within hours of administration, and the lipids enter endogenous surfactant pathways of reutilization and recycling. In surfactant-sufficient adult animals, SURVANTA clearance is more rapid than in premature and young animals. There is less reutilization and recycling of surfactant in adult animals.

Limited animal experiments have not found effects of SURVANTA on endogenous surfactant metabolism. Precursor incorporation and subsequent secretion of saturated phosphatidylcholine in premature sheep are not changed by SURVANTA treatments.

No information is available about the metabolic fate of the surfactant-associated proteins in SURVANTA. The metabolic disposition in humans has not been studied.

CLINICAL STUDIES

Clinical effects of SURVANTA were demonstrated in six single-dose and four multiple-dose randomized, multi-center, controlled clinical trials involving approximately 1700 infants. Three open trials, including a Treatment IND, involved more than 8500 infants. Each dose of SURVANTA in all studies was 100 mg phospholipids/kg birth weight and was based on published experience with Surfactant TA, a lyophilized powder dosage form of SURVANTA having the same composition.

Prevention Studies

Infants of 600-1250 g birth weight and 23 to 29 weeks estimated gestational age were enrolled in two *multiple-dose* studies. A dose of SURVANTA was given within 15 minutes of birth to prevent the development of RDS. Up to three additional doses in the first 48 hours, as often as every 6 hours, were given if RDS subsequently developed and infants required mechanical ventilation with an $FiO_2 \geq 0.30$. Results of the studies at 28 days of age are shown in Table 1.

TABLE 1

Study 1

	SURVANTA	Control	*P*-Value
Number infants studied	119	124	
Incidence of RDS (%)	27.6	63.5	<0.001
Death due to RDS (%)	2.5	19.5	<0.001
Death or BPD due to RDS (%)	48.7	52.8	0.536
Death due to any cause (%)	7.6	22.8	0.001
Air Leaks[a] (%)	5.9	21.7	0.001
Pulmonary interstitial emphysema (%)	20.8	40.0	0.001

Study 2[b]

	SURVANTA	Control	*P*-Value
Number infants studied	91	96	
Incidence of RDS (%)	28.6	48.3	0.007
Death due to RDS (%)	1.1	10.5	0.006
Death or BPD due to RDS (%)	27.5	44.2	0.018
Death due to any cause[c] (%)	16.5	13.7	0.633
Air Leaks[a] (%)	14.5	19.6	0.374
Pulmonary interstitial emphysema (%)	26.5	33.2	0.298

[a] Pneumothorax or pneumopericardium
[b] Study discontinued when Treatment IND initiated
[c] No cause of death in the SURVANTA group was significantly increased; the higher number of deaths in this group was due to the sum of all causes.

Rescue Studies

Infants of 600-1750 g birth weight with RDS requiring mechanical ventilation and an $FiO_2 \geq 0.40$ were enrolled in two *multiple-dose* rescue studies. The initial dose of SURVANTA was given after RDS developed and before 8 hours of age. Infants could receive up to three additional doses in the first 48 hours, as often as every 6 hours, if they required mechanical ventilation and an $FiO_2 \geq 0.30$. Results of the studies at 28 days of age are shown in Table 2.

TABLE 2

Study 3[a]

	SURVANTA	Control	*P*-Value
Number infants studied	198	193	
Death due to RDS (%)	11.6	18.1	0.071
Death or BPD due to RDS (%)	59.1	66.8	0.102
Death due to any cause (%)	21.7	26.4	0.285
Air Leaks[b](%)	11.8	29.5	<0.001
Pulmonary interstitial emphysema (%)	16.3	34.0	<0.001

Study 4

	SURVANTA	Control	*P*-Value
Number infants studied	204	203	
Death due to RDS (%)	6.4	22.3	<0.001
Death or BPD due to RDS (%)	43.6	63.4	<0.001
Death due to any cause (%)	15.2	28.2	0.001
Air Leaks[b] (%)	11.2	22.2	0.005
Pulmonary interstitial emphysema (%)	20.8	44.4	<0.001

[a] Study discontinued when Treatment IND initiated
[b] Pneumothorax or pneumopericardium

Acute Clinical Effects

Marked improvements in oxygenation may occur within minutes of administration of SURVANTA.

All controlled clinical studies with SURVANTA provided information regarding the acute effects of SURVANTA on the arterial-alveolar oxygen ratio (a/APO_2), FiO_2, and mean airway pressure (MAP) during the first 48 to 72 hours of life. Significant improvements in these variables were sustained for 48-72 hours in SURVANTA-treated infants in four single-dose and two multiple-dose rescue studies and in two multiple-dose prevention studies. In the single-dose prevention studies, the FiO_2 improved significantly.

INDICATIONS AND USAGE

SURVANTA is indicated for prevention and treatment (“rescue”) of Respiratory Distress Syndrome (RDS) (hyaline membrane disease) in premature infants. SURVANTA significantly reduces the incidence of RDS, mortality due to RDS and air leak complications.

Prevention

In premature infants less than 1250 g birth weight or with evidence of surfactant deficiency, give SURVANTA as soon as possible, preferably within 15 minutes of birth.

Rescue

To treat infants with RDS confirmed by x-ray and requiring mechanical ventilation, give SURVANTA as soon as possible, preferably by 8 hours of age.

CONTRAINDICATIONS

None known.

WARNINGS

SURVANTA is intended for intratracheal use only.

SURVANTA CAN RAPIDLY AFFECT OXYGENATION AND LUNG COMPLIANCE. Therefore, its use should be restricted to a highly supervised clinical setting with immediate availability of clinicians experienced with intubation, ventilator management, and general care of premature infants. Infants receiving SURVANTA should be frequently monitored with arterial or transcutaneous measurement of systemic oxygen and carbon dioxide.

DURING THE DOSING PROCEDURE, TRANSIENT EPISODES OF BRADYCARDIA AND DECREASED OXYGEN SATURATION HAVE BEEN REPORTED. If these occur, stop the dosing procedure and initiate appropriate measures to alleviate the condition. After stabilization, resume the dosing procedure.

PRECAUTIONS

General

Rales and moist breath sounds can occur transiently after administration. Endotracheal suctioning or other remedial action is not necessary unless clear-cut signs of airway obstruction are present.

Increased probability of post-treatment nosocomial sepsis in SURVANTA-treated infants was observed in the controlled clinical trials (Table 3). The increased risk for sepsis among SURVANTA-treated infants was not associated with increased mortality among these infants. The causative organisms were similar in treated and control infants. There was no significant difference between groups in the rate of post-treatment infections other than sepsis.

Use of SURVANTA in infants less than 600 g birth weight or greater than 1750 g birth weight has not been evaluated in controlled trials. There is no controlled experience with use of SURVANTA in conjunction with experimental therapies for RDS (eg, high-frequency ventilation or extracorporeal membrane oxygenation).

No information is available on the effects of doses other than 100 mg phospholipids/kg, more than four doses, dosing more frequently than every 6 hours, or administration after 48 hours of age.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been performed with SURVANTA. SURVANTA was negative when tested in the Ames test for mutagenicity. Using the maximum feasible dose volume, SURVANTA up to 500 mg phospholipids/kg/day (approximately one-third the premature infant dose based on $mg/m^2/day$) was administered subcutaneously to newborn rats for 5 days. The rats reproduced normally and there were no observable adverse effects in their offspring.

ADVERSE REACTIONS

The most commonly reported adverse experiences were associated with the dosing procedure. In the multiple-dose controlled clinical trials, each dose of SURVANTA was divided into four quarter-doses which were instilled through a catheter inserted into the endotracheal tube by briefly disconnecting the endotracheal tube from the ventilator. Transient bradycardia occurred with 11.9% of *doses*. Oxygen desaturation occurred with 9.8% of *doses*.

Other reactions during the dosing procedure occurred with fewer than 1% of doses and included endotracheal tube reflux, pallor, vasoconstriction, hypotension, endotracheal tube blockage, hypertension, hypocarbia, hypercarbia, and apnea. No deaths occurred during the dosing procedure, and all reactions resolved with symptomatic treatment.

The occurrence of concurrent illnesses common in premature infants was evaluated in the controlled trials. The rates in all controlled studies are in Table 3.

TABLE 3

	All Controlled Studies		
Concurrent Event	**SURVANTA (%)**	**Control (%)**	***P*-Value**[a]
Patent ductus arteriosus	46.9	47.1	0.814
Intracranial hemorrhage	48.1	45.2	0.241
Severe intracranial hemorrhage	24.1	23.3	0.693
Pulmonary air leaks	10.9	24.7	<0.001
Pulmonary interstitial emphysema	20.2	38.4	<0.001
Necrotizing enterocolitis	6.1	5.3	0.427
Apnea	65.4	59.6	0.283
Severe apnea	46.1	42.5	0.114
Post-treatment sepsis	20.7	16.1	0.019
Post-treatment infection	10.2	9.1	0.345
Pulmonary hemorrhage	7.2	5.3	0.166

[a] *P*-value comparing groups in controlled studies

When all controlled studies were pooled, there was no difference in intracranial hemorrhage. However, in one of the single-dose rescue studies and one of the multiple-dose prevention studies, the rate of intracranial hemorrhage was significantly higher in SURVANTA patients than control patients (63.3% *v* 30.8%, $P = 0.001$; and 48.8% *v* 34.2%, $P = 0.047$, respectively). The rate in a Treatment IND involving approximately 8100 infants was lower than in the controlled trials.

In the controlled clinical trials, there was no effect of SURVANTA on results of common laboratory tests: white blood cell count and serum sodium, potassium, bilirubin, creatinine.

More than 4300 pretreatment and post-treatment serum samples from approximately 1500 patients were tested by Western Blot Immunoassay for antibodies to surfactant-associated proteins SP-B and SP-C. No IgG or IgM antibodies were detected.

Several other complications are known to occur in premature infants. The following conditions were reported in the controlled clinical studies. The rates of the complications were not different in treated and control infants, and none of the complications were attributed to SURVANTA.

Respiratory: lung consolidation, blood from the endotracheal tube, deterioration after weaning, respiratory decompensation, subglottic stenosis, paralyzed diaphragm, respiratory failure.

Cardiovascular: hypotension, hypertension, tachycardia, ventricular tachycardia, aortic thrombosis, cardiac failure, cardio-respiratory arrest, increased apical pulse, persistent fetal circulation, air embolism, total anomalous pulmonary venous return.

Gastrointestinal: abdominal distention, hemorrhage, intestinal perforations, volvulus, bowel infarct, feeding intolerance, hepatic failure, stress ulcer.

Renal: renal failure, hematuria.

Hematologic: coagulopathy, thrombocytopenia, disseminated intravascular coagulation.

Central Nervous System: seizures.

Endocrine/Metabolic: adrenal hemorrhage, inappropriate ADH secretion, hyperphosphatemia.

Musculoskeletal: inguinal hernia.

Systemic: fever, deterioration.

Follow-Up Evaluations

To date, no long-term complications or sequelae of SURVANTA therapy have been found.

Single-Dose Studies

Six-month adjusted-age follow-up evaluations of 232 infants (115 treated) demonstrated no clinically important differences between treatment groups in pulmonary and neurologic sequelae, incidence or severity of retinopathy of prematurity, rehospitalizations, growth, or allergic manifestations.

Multiple-Dose Studies

Six-month adjusted age follow-up evaluations have been completed in 631 (345 treated) of 916 surviving infants. There were significantly less cerebral palsy and need for supplemental oxygen in SURVANTA infants than controls. Wheezing at the time of examination was significantly more frequent among SURVANTA infants, although there was no difference in bronchodilator therapy.

Final twelve-month follow-up data from the multiple-dose studies are available from 521 (272 treated) of 909 surviving infants. There was significantly less wheezing in SURVANTA infants than controls, in contrast to the six-month results. There was no difference in the incidence of cerebral palsy at twelve months.

Twenty-four month adjusted age evaluations were completed in 429 (226 treated) of 906 surviving infants. There were significantly fewer SURVANTA infants with rhonchi, wheezing, and tachypnea at the time of examination. No other differences were found.

OVERDOSAGE

Overdosage with SURVANTA has not been reported. Based on animal data, overdosage might result in acute airway obstruction. Treatment should be symptomatic and supportive.

Rales and moist breath sounds can transiently occur after SURVANTA is given, and do not indicate overdosage. Endotracheal suctioning or other remedial action is not required unless clear-cut signs of airway obstruction are present.

DOSAGE AND ADMINISTRATION

For intratracheal administration only.

SURVANTA should be administered by or under the supervision of clinicians experienced in intubation, ventilator management, and general care of premature infants.

Marked improvements in oxygenation may occur within minutes of administration of SURVANTA. Therefore, frequent and careful clinical observation and monitoring of systemic oxygenation are essential to avoid hyperoxia.

Review of audiovisual instructional materials describing dosage and administration procedures is recommended before using SURVANTA. Materials are available upon request from Abbott Nutrition.

Dosage

Each dose of SURVANTA is 100 mg of phospholipids/kg birth weight (4 mL/kg). The SURVANTA Dosing Chart shows the total dosage for a range of birth weights.

SURVANTA DOSING CHART

WEIGHT (grams)	TOTAL DOSE (mL)	WEIGHT (grams)	TOTAL DOSE (mL)
600- 650	2.6	1301- 1350	5.4
651- 700	2.8	1351- 1400	5.6
701- 750	3.0	1401- 1450	5.8
751- 800	3.2	1451- 1500	6.0
801- 850	3.4	1501- 1550	6.2
851- 900	3.6	1551- 1600	6.4
901- 950	3.8	1601- 1650	6.6
951- 1000	4.0	1651- 1700	6.8
1001- 1050	4.2	1701- 1750	7.0
1051- 1100	4.4	1751- 1800	7.2
1101- 1150	4.6	1801- 1850	7.4
1151- 1200	4.8	1851- 1900	7.6
1201- 1250	5.0	1901- 1950	7.8
1251- 1300	5.2	1951- 2000	8.0

Four doses of SURVANTA can be administered in the first 48 hours of life. Doses should be given no more frequently than every 6 hours.

Directions for Use

SURVANTA should be inspected visually for discoloration prior to administration. The color of SURVANTA is off-white to light brown. If settling occurs during storage, swirl the vial gently (DO NOT SHAKE) to redisperse. Some foaming at the surface may occur during handling and is inherent in the nature of the product.

SURVANTA is stored refrigerated (2-8°C). Date and time need to be recorded in the box on front of the carton or vial, whenever SURVANTA is removed from the refrigerator. Before administration, SURVANTA should be warmed by standing at room temperature for at least 20 minutes or warmed in the hand for at least 8 minutes. ARTIFICIAL WARMING METHODS SHOULD NOT BE USED. If a prevention dose is to be given, preparation of SURVANTA should begin before the infant's birth.

Unopened, unused vials of SURVANTA that have been warmed to room temperature may be returned to the refrigerator within 24 hours of warming, and stored for future use. SURVANTA SHOULD NOT BE REMOVED FROM THE REFRIGERATOR FOR MORE THAN 24 HOURS. SURVANTA SHOULD NOT BE WARMED AND RETURNED TO THE REFRIGERATOR MORE THAN ONCE. Each single-use vial of SURVANTA should be entered only once. Used vials with residual drug should be discarded.

SURVANTA DOES NOT REQUIRE RECONSTITUTION OR SONICATION BEFORE USE.

Dosing Procedures

General

SURVANTA is administered intratracheally by instillation through a 5 French end-hole catheter. The catheter can be inserted into the infant's endotracheal tube without interrupting ventilation by passing the catheter through a neonatal suction valve attached to the endotracheal tube. Alternatively, SURVANTA can be instilled through the catheter by briefly disconnecting the endotracheal tube from the ventilator.

The neonatal suction valve used for administering SURVANTA should be a type that allows entry of the catheter into the endotracheal tube without interrupting ventilation and also maintains a closed airway circuit system by sealing the valve around the catheter.

If the neonatal suction valve is used, the catheter should be rigid enough to pass easily into the endotracheal tube. A very soft and pliable catheter may twist or curl within the neonatal suction valve. The length of the catheter should be shortened so that the tip of the catheter protrudes just beyond the end of the endotracheal tube above the infant's carina. SURVANTA should not be instilled into a mainstem bronchus.

To ensure homogenous distribution of SURVANTA throughout the lungs, each dose is divided into four *quarter-doses*.

Each quarter-dose is administered with the infant in a different position. The recommended positions are:

- Head and body inclined 5-10° down, head turned to the right
- Head and body inclined 5-10° down, head turned to the left
- Head and body inclined 5-10° up, head turned to the right
- Head and body inclined 5-10° up, head turned to the left

The dosing procedure is facilitated if one person administers the dose while another person positions and monitors the infant.

First Dose

Determine the total dose of SURVANTA from the SURVANTA dosing chart based on the infant's birth weight. Slowly withdraw the entire contents of the vial into a plastic syringe through a large-gauge needle (eg, at least 20 gauge). DO NOT FILTER SURVANTA AND AVOID SHAKING.

Attach the premeasured 5 French end-hole catheter to the syringe. Fill the catheter with SURVANTA. Discard excess SURVANTA through the catheter so that only the total dose to be given remains in the syringe.

BEFORE ADMINISTERING SURVANTA, assure proper placement and patency of the endotracheal tube. At the discretion of the clinician, the endotracheal tube may be suctioned before administering SURVANTA. The infant should be allowed to stabilize before proceeding with dosing.

In the prevention strategy, weigh, intubate and stabilize the infant. Administer the dose as soon as possible after birth, preferably within 15 minutes. Position the infant appropriately and gently inject the first quarter-dose through the catheter over 2-3 seconds.

After administration of the first quarter-dose, remove the catheter from the endotracheal tube. Manually ventilate with a hand-bag with sufficient oxygen to prevent cyanosis, at a rate of 60 breaths/minute, and sufficient positive pressure to provide adequate air exchange and chest wall excursion.

In the rescue strategy, the first dose should be given as soon as possible after the infant is placed on a ventilator for management of RDS. In the clinical trials, immediately before instilling the first quarter-dose, the infant's ventilator settings were changed to rate 60/minute, inspiratory time 0.5 second, and FiO_2 1.0.

Position the infant appropriately and gently inject the first quarter-dose through the catheter over 2-3 seconds. After administration of the first quarter-dose, remove the catheter from the endotracheal tube and continue mechanical ventilation.

In both strategies, ventilate the infant for at least 30 seconds or until stable. Reposition the infant for instillation of the next quarter-dose.

Instill the remaining quarter-doses using the same procedures. After instillation of each quarter-dose, remove the catheter and ventilate for at least 30 seconds or until the infant is stabilized. After instillation of the final quarter-dose, remove the catheter without flushing it. Do not suction the infant for 1 hour after dosing unless signs of significant airway obstruction occur.

AFTER COMPLETION OF THE DOSING PROCEDURE, RESUME USUAL VENTILATOR MANAGEMENT AND CLINICAL CARE.

Repeat Doses

The dosage of SURVANTA for repeat doses is also 100 mg phospholipids/kg and is based on the infant's birth weight. The infant should not be reweighed for determination of the SURVANTA dosage. Use the SURVANTA DOSING CHART to determine the total dosage.

The need for additional doses of SURVANTA is determined by evidence of continuing respiratory distress. Using the following criteria for redosing, significant reductions in mortality due to RDS were observed in the multiple-dose clinical trials with SURVANTA.

> Dose no sooner than 6 hours after the preceding dose if the infant remains intubated and requires at least 30% inspired oxygen to maintain a PaO_2 less than or equal to 80 torr.
>
> Radiographic confirmation of RDS should be obtained before administering additional doses to those who received a prevention dose.

Prepare SURVANTA and position the infant for administration of each quarter-dose as previously described. After instillation of each quarter-dose, remove the dosing catheter from the endotracheal tube and ventilate the infant for at least 30 seconds or until stable.

In the clinical studies, ventilator settings used to administer repeat doses were different than those used for the first dose. For repeat doses, the FiO_2 was increased by 0.20 or an amount sufficient to prevent cyanosis. The ventilator delivered a rate of 30/minute with an inspiratory time less than 1.0 second. If the infant's pretreatment rate was 30 or greater, it was left unchanged during SURVANTA instillation.

Manual hand-bag ventilation should not be used to administer repeat doses. DURING THE DOSING PROCEDURE, VENTILATOR SETTINGS MAY BE ADJUSTED AT THE DISCRETION OF THE CLINICIAN TO MAINTAIN APPROPRIATE OXYGENATION AND VENTILATION. AFTER COMPLETION OF THE DOSING PROCEDURE, RESUME USUAL VENTILATOR MANAGEMENT AND CLINICAL CARE.

Dosing Precautions

If an infant experiences bradycardia or oxygen desaturation during the dosing procedure, stop the dosing procedure and initiate appropriate measures to alleviate the condition. After the infant has stabilized, resume the dosing procedure.

Rales and moist breath sounds can occur transiently after administration of SURVANTA. Endotracheal suctioning or other remedial action is unnecessary unless clear-cut signs of airway obstruction are present.

HOW SUPPLIED

SURVANTA (beractant) Intratracheal Suspension is supplied in single-use glass vials containing 4 mL (**NDC** 0074-1040-04) or 8 mL of SURVANTA (**NDC** 0074-1040-08). Each milliliter contains 25 mg of phospholipids suspended in 0.9% sodium chloride solution. The color is off-white to light brown.

Store unopened vials at refrigeration temperature (2-8°C). Protect from light. Store vials in carton until ready for use. Vials are for single use only. Upon opening, discard unused drug.

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Abbott Laboratories
Columbus, Ohio 43219-3034 USA

controlled trials of volume-targeted versus pressure-limited ventilation demonstrated no differences in the rates of death or CLD between the two groups.[32] The infants treated with VTV did, however, have a shorter duration of mechanical ventilation as well as lower rates of pneumothorax and IVH. Singh and colleagues have further substantiated the findings of quicker ventilator weaning and decreased duration of total mechanical ventilation when using a volume-targeted versus a pressure-limited mode.[33]

Although all studies comparing VTV versus pressure-limited ventilation have demonstrated equivalency and potential superiority of VTV with regards to some short-term pulmonary end points, as a collective the data are limited. The studies to date lack critical information about long-term pulmonary and neurodevelopmental follow-up. While many sound physiologic reasons may be advanced to support volume targeting, large, multicentered, randomized trials are warranted to further elucidate both the short-term and long-term pulmonary and neurodevelopmental outcomes before real evidence-driven recommendations can be made about the superiority of VTV over conventional pressure-limited ventilation.

Pressure support ventilation (PSV) is another newer mode of mechanical ventilation that entered the neonatal respiratory therapy arsenal in the 1990s. PSV aims to augment the patient's spontaneous respiratory effort with an inspiratory pressure boost that overcomes the imposed work of breathing from the endotracheal tube and the ventilator. PSV is thought to potentially allow for added synchrony and patient comfort throughout the patient's spontaneous breaths, since it provides patient-triggered assistance with every spontaneous breath and the support is flow-cycled, which allows the patient to control the inspiratory time. PSV can be used as a stand-alone ventilation in patients with consistent respiratory drive. In the NICU, it is more commonly combined with other modes of pressure-limited or volume-targeted synchronized mechanical ventilation to assuage difficulties encountered with patient apnea or decreased respiratory effort, as commonly seen in sick preterm infants.

Few studies have been published about the use of PSV in neonates, so there is no set of conventional "rules" for the use of PSV. Typically, if PSV is used as a stand-alone mode of ventilation, the pressure support is set at a level to deliver adequate tidal volumes. In one recent small study (N=7), Kapasi and colleagues found PSV alone achieved better patient-ventilator synchrony and decreased work of breathing when compared to SIMV and IMV, but increased work of breathing when compared to A/C.[34]

Most often, PSV has been studied in conjunction with another synchronized mode of ventilation, such as SIMV or other forms of VTV. When using PSV in this way, the pressure support is often set at 30% to 50% of the difference between PIP and PEEP set for the mechanically triggered breaths.[35,36] The largest randomized, controlled trial comparing SIMV to SIMV plus pressure support enrolled 107 preterm, extremely-low-birth-weight infants in the first week of life.[36] This study demonstrated that SIMV plus pressure support allowed for quicker extubation in the first month of life, but the rates of CLD alone or combined with death were not statistically different between the SIMV and SIMV plus pressure support groups. Other smaller, short-term studies have also shown that the addition of pressure support to other modes of synchronized ventilation can facilitate weaning from mechanical ventilation, with maintenance of adequate gas exchange and decreased work of breathing.[37,38]

The literature on PSV, as a stand-alone method or in conjunction with other modes of synchronized ventilation, demonstrates that it is safe and feasible to use in neonates. In particular, the addition of PSV during the weaning phase of mechanical ventilation may be beneficial. However, thus far, there are no large randomized, controlled trials that focus on long-term pulmonary or neurodevelopmental outcomes with PSV, and further data are needed to make the best clinical decision about the optimal employment of PSV in the NICU.

New Frontiers

As computer technology continues to advance, the ability to deliver highly automated respiratory support gains attention. These advances are aimed at enhancing the patient-ventilator interaction while the patient's clinical status is acutely changing. The goal is to optimize patient comfort as well as to improve timely responses to changes in ventilatory support needs. Claure and Bancalari recently reviewed some of the newly developed automated modes of mechanical ventilatory support and supplemental oxygen delivery.[39] Some of these newer modes of ventilation use servo-controlled assessment of respiratory parameters with automatic adjustments in ventilator settings to achieve the desired minute ventilation. Preliminarily, these servo-controlled ventilation modes have demonstrated equal gas exchange in the face of fewer mechanical breaths and lower airway pressure exposure.[40,41] Other modes allow for the use of PSV with the addition of apnea back-up ventilation if the patient's respiratory drive fails, a safety feature that counteracts the major drawback to using PSV as a stand-alone mode. Hybrid modes of assessment that include evaluation of respiratory rate, tidal volume, and pulse oximetry may allow for a multifactorial, computer-based assessment and subsequent targeted-ventilator changes. Nonventilator-based technology also continues to advance. In particular, there is now exploration of the use of electrode-studded esophageal catheters to sense diaphragmatic electrical activity, providing neurally adjusted ventilatory assistance (NAVA).[42,43] NAVA allows the electrical activity of a patient's diaphragm during active breathing to adjust the timing and pressure of mechanical breaths according to the neural input and patient needs. Initial studies suggest improved respiratory timing and synchronization using this mode. The potential for new technologies appears to be endless; their effects on important neonatal outcomes remain uncertain.

Conclusions

As perinatal and neonatal care has continued to improve, respiratory support of preterm neonates continues to be critical for their survival. In some ways, we have come full circle, returning to the noninvasive therapies that revolutionized early neonatal care. Importantly, our focus has shifted to an ongoing quest for techniques and technologies that will also improve morbidities related to abnormal pulmonary development. Chronic lung disease, if not inevitable, is still all too common following extremely preterm birth and relates both to the state of lung development and to the therapies we inflict upon the immature lung. Since the introduction of continuous gas flow in the respiratory circuit, technologies designed for the tiny baby have made application of mechanical ventilation more physiologic, in the sense that current devices allow the neonate to actively participate in the delivery of support. This may be through triggering breaths, altering flow based on effort, establishing their own respiratory rate and breath timing, and varying their tidal and minute ventilation.

Yet the evidence that directs us towards one mode as compared to another is remarkable for its paucity. Although we believe that lung-protective ventilatory strategies are important, in fact there is little data to guide us in the implementation of these strategies with any of our current modes of conventional ventilation. Perhaps one important reason for the inconclusive nature of current research can be found in our inability to easily measure lung volume, a key variable during respiratory support. Current evidence suggests that in addition to targeting tidal volume, maintenance of adequate end-expiratory lung volume during mechanical ventilation is critical for lung protection. In the laboratory and in small clinical studies, the use of respiratory inductive or electrical impedance plethysmography to measure changes in lung volume appears promising.[44,45] The integration of this type of measurement into routine clinical practice could greatly enhance our ability to tailor support to each patient's condition.

It is as true today as it was 50 years ago that the NICU remains a laboratory, and that care of the preterm neonate remains an ongoing clinical challenge. It is up to all of us to design studies that will allow our babies to tell us how we can use these wonderful and complex technologies in ways that actually make the greatest difference for their lives after the NICU.

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News Briefs

Multiple versus single doses of exogenous surfactant to treat or prevent neonatal respiratory distress syndrome

Researchers at the University of Vermont sought to determine the effect of multiple doses of exogenous surfactant compared to single doses of exogenous surfactant on the mortality and complications of prematurity in premature infants at risk for respiratory distress syndrome (RDS). In a broad literature search of randomized, controlled clinical trials of newborn infants, the authors collected data on outcomes such as pneumothorax, patent ductus arteriosus, necrotizing enterocolitis (NEC), intraventricular hemorrhage, bronchopulmonary dysplasia, rentinopathy of prematurity, and mortality. The authors identified three trials that met the criteria. They found that in infants with established RDS, multiple doses of animal-derived surfactant resulted in greater improvements in oxygenation and ventilatory requirements, a decreased risk of pneumothorax, and improved survival. In infants at high risk of RDS, a multiple-dose regimen of synthetic surfactant was associated with greater improvements in oxygenation and ventilatory requirements, and a decreased risk of NEC and mortality. Moreover, no complications were identified with the multiple-dose regimen.

Soll R, Ozek E: Multiple versus single doses of exogenous surfactant for the prevention or treatment of neonatal respiratory distress syndrome. *Cochran Database Syst Rev* 2009;1:CD0000141.

Single 'rescue course' of antenatal corticosteroids found beneficial in preterm neonates

Previous clinical trials using repetitive courses of antenatal corticosteroids in preterm neonates found marginal or no benefit and concern over potential risk. But no prior prospective or randomized studies have evaluated the option of a single rescue course of antenatal corticosteroids on neonatal outcome. This multicenter, randomized, double-blind, placebo-controlled trial of 18 private (15) and university (3) medical centers included neonates <33 weeks' gestation who had completed a single course of antenatal corticosteroids before 30 weeks and at least 14 days before inclusion, and were considered to have a recurring threat of preterm delivery in the coming week. Patients were randomized to receive a single rescue course of betamethasone, two 12-mg doses 24 hours apart, or placebo. The exclusion criteria included premature rupture of membranes, advanced dilation (>5 cm), chorioamnionitis, and other steroid use. In all, 437 patients were randomized (223 rescue steroid group and 214 placebo group) and 55% of patients in each group delivered at <34 weeks. There was a significant reduction in neonatal morbidity <34 weeks in the rescue group vs placebo (43.9% vs 63.6%; odds ratio, 0.45; 95% confidence interval, 0.27-0.75; $P = .002$) and significantly decreased respiratory distress syndrome, ventilator support, and surfactant use. The rates of perinatal mortality and other morbidities were similar in each group. The investigators concluded that administration of a single rescue course of antenatal corticosteroids before 33 weeks' gestation improves neonatal outcome without apparent increased short-term risk.

Garite TJ, Kurtzman J, Maurel K, Clark R; Obstetrix Collaborative Research Network. Impact of a 'rescue course' of antenatal corticosteroids: a multicenter randomized placebo-controlled trial. *Am J Obstet Gynecol* 2009:200:217-218.

Very early surfactant therapy decreased the need for subsequent mechanical ventilation of premature neonates

Mechanical ventilation is a major risk factor for chronic lung disease, so the early application of nasal continuous positive airway pressure has been used to avoid mechanical ventilation in premature infants. Surfactant therapy improves the short-term respiratory status of premature infants, but its use is traditionally limited to infants being mechanically ventilated. The investigators sought to determine if the administration of very early surfactant during a brief period of intubation to infants treated with nasal continuous positive airway pressure might improve their outcome and further decrease the need for mechanical ventilation. This randomized, controlled trial included eight centers in Colombia. Infants born between 27 and 31 weeks' gestation with evidence of respiratory distress and treated with supplemental oxygen were randomly assigned within the first hour of life to intubation, very early surfactant, extubation, and nasal continuous positive airway pressure (treatment group) or nasal continuous airway pressure alone (control group). Of the 279 infants in the trial, 141were randomly assigned to the treatment group and 138 to the control group. The need for mechanical ventilation was lower in the treatment group (26%) compared with the control group (39%). In the treatment group, air-leak syndrome occurred less frequently (2%) compared with the control group (9%). The percentage of patients receiving surfactant after the first hour of life was also significantly less in the treatment group (12%) compared with the control group (26%). The incidence of chronic lung disease (oxygen treatment at 36 weeks' postmenstrual age) in the treatment group was lower (49%) than in the control group (59%), although this difference was not statistically significant. All other outcomes, including mortality, intraventricular hemorrhage, and periventricular leukomalacia, were similar between the groups. The investigators concluded that in premature infants treated with nasal continuous positive airway pressure early after birth, the addition of very early surfactant therapy without mandatory ventilation decreased the need for subsequent mechanical ventilation, decreased the incidence of air-leak syndrome, and seemed to be safe.

Rojas MA, Lozano JM, Rojas MX, et al, and Colombian Neonatal Research Network: Very early surfactant without mandatory ventilation in premature infants treated with early continuous positive airway pressure: a randomized, controlled trial. *Pediatrics* 2009;123(1):137-142.

Self Test

This self-assessment quiz is presented as an educational adjunct to the monograph. Completion of this brief quiz will help reinforce the material you have read. Answers are elsewhere on this page.

1. The pivotal development in mechanical ventilation during the 1970s that allowed for long-term mechanical ventilation of neonates was:
   a. introduction of exogenous surfactant
   b. use of continuous gas-flow circuit
   c. use of closed gas-flow circuit
   d. none of the above

2. Using an oxygen requirement of F_IO_2 <0.45 in combination with the early intervention with intubation, surfactant administration, and planned extubation to CPAP within 1 hour of intubation reduces rates of air leak syndromes and chronic lung disease in neonates with respiratory distress syndrome.
   a. true
   b. false

3. Volume-targeted ventilation, as compared to pressure-limited ventilation, has been associated with:
   a. shorter duration of mechanical ventilation
   b. lower rates of intraventricular hemorrhage
   c. lower rates of pneumothorax
   d. all of the above

4. The addition of pressure support to synchronized modes of ventilation has been shown to:
   a. facilitate weaning of mechanical ventilation
   b. increase patient work of breathing
   c. decrease rates of chronic lung disease
   d. none of the above

5. Potential benefit(s) of servo-controlled modes of ventilation are:
   a. improved patient-ventilator synchrony
   b. decreased mechanical breaths
   c. decreased airway pressure exposure
   d. all of the above

Self-Test Answers for This Issue:

1. b 2. a 3. d 4. a 5. d

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