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Neonatology Today (NT) is a monthly newsletter for BC/BE neonatologists and perinatologists that provides timely news and information regarding the care of newborns and the diagnosis and treatment of premature and/or sick infants.

Visual Light Spectrography (VLS) for Detecting Alterations in Tissue Oxygenation with Administration of Packed Red Blood Cells (PRBC) in Very Low Birth Weight (VLBW) Premature Infants

By V. Bronshtein, MD; E. F. LaGamma, MD; J. M. Curry, NNP; J. Garcia Hoffman, MD and B. Parvez, MD

Abstract:

Background: Sixty to eighty percent of all VLBW infants receive PRBC transfusions with a goal of improving tissue oxygen delivery. Yet no firm consensus exists regarding individualized Hb trigger levels or the best method to assess the efficacy of blood transfusion. Clinical signs and blood tests are late indicators and the latter contribute to iatrogenic anemia. Visible light spectroscopy (VLS) can non-invasively assess tissue saturation (StO_2) in small segments of tissue and reliably obtain recording during poor perfusion states.

Objective: To investigate the effect of PRBC on StO_2 in patients with anemia.

Design/Methods: Tissue oxygen and pulse oximeter saturations were measured continuously and compared at the following time epochs: 1 hour before, at the beginning, hourly during and 1 hour after blood transfusion. The difference between pulse and tissue saturation was calculated ($\Delta P = SpO_2 - StO_2$), as a marker of tissue perfusion. Vital signs and Neonatal Therapeutic Intervention Scoring System (NTISS) severity of the disease scores were assessed.

Results: Five neonates without evidence of hypovolemia receiving PRBC transfusions to increase RBC mass were studied. Despite an absence of changes in vital signs and SpO_2, there was statistically significant decrease in tissue oxygenation and worsening of pulse (P) at 2nd, 3rd and 4th hours of transfusion indicating compromised tissue oxygenation.

Conclusions: The decrease in StO_2 and increase in ΔP during blood transfusion was

"VLS is easy to use and non invasive method of assessment of tissue saturation in VLBW neonates with various severity of illness."

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an unexpected, but transient event which occurred in all patients regardless of severity of illness and Hb levels and without any changes in pulse oximetry or vital signs. VLS may be helpful in identifying patients at risk for developing transfusion related injury.

Blood transfusion is common in hospitalized patients with more than 14 million units of PRBC transfused every year in the Unites States [1]. Sixty to eighty percent of all VLBW infants receive blood transfusions during their hospital course [2]. PRBC are given to improve tissue oxygen delivery. There is currently no firm consensus regarding Hb level for transfusion in neonates. Various methods have been tried to assess adequacy of tissue oxygenation: clinical signs, blood tests, use of invasive and non invasive monitoring devices. However, clinical signs such as tachycardia, low blood pressure, decrease in urine output and apnea are non-specific, and often late indication of poor tissue oxygenation. Blood tests, indicating metabolic and lactic acidosis and increased arterio - venous oxygen saturation difference are also late and non-specific findings, invasive and may exacerbate iatrogenic anemia.

Methods of measurement of Superior Vena Cava (SVC) flow to assess upper body/brain perfusion require expertise, appropriate equipment and can not be done on a continuous basis [3]. Other methods such as gastric tonometry can not be used in infants receiving feeds [4]. Moreover, in conditions associated or caused by poor gut perfusion, such as NEC, gut tonometers may interfere with the medical management of gut decompression.

Near Infrared Spectrography (NIRS) is a well established method of assessing brain oxygenation. However, a splanchnic probe was only recently developed. As such, there are no known normative values for premature infants. Also of note, the NIRS probe can stay on the infant's skin for no longer then 24 hours [5].

Visible light spectroscopy (VLS) is a relatively new, non-invasive method for detecting hypoxemia and ischemia. VLS, as well as NIRS, is based on reflectance spectrophotometry, a method utilizing the process of interaction between light photons of different wavelengths with biological tissues. NIRS utilizes 500-1000 nm wave length while VLS uses 475-600 nm. In contrast, the traditional Pulse Oximeter utilizes red and infrared light (660 and 910 nm). The higher the wave length, the deeper the light penetrates the biological tissue.

A VLS probe placed on, in, or near various tissue emits white light and collects any light returning to the probe. The collected light is separated by wavelength into 2,048 bins, measured simultaneously. The blue-to-yellow (400 – 625 nm) portion of the visible spectrum, is used to solve for light scattering and for the concentration of each of the major forms of hemoglobin (deoxyhemoglobin, oxyhemoglobin), using first differential spectroscopy and least squares fitting to known hemoglobin spectra. Tissue hemoglobin oxygen saturation (StO_2) is determined as the proportion of oxyhemoglobin from the total hemoglobin (oxyhemoglobin/oxyhemolgobin+deoxyhemoglobin). The measurements are continuous, each typically requiring five to 50 ms, depending on the intensity of the reflected light. The data is saved on an internal hard drive within the VLS oximeter [6]. T-Stat® Spectros CA uses the methodology of VLS to measure tissue oxygenation. T – Stat has been used in animals and adults [11-17]; however, despite FDA approval for use of VLS since 2004, it has been used primarily in adults and there is currently only one published VLS study on five neonates with congenital heart disease undergoing cardiac surgery [18] since approval of the infant buccal probe in 2006.

The objective of this study was to investigate the effect of PRBC on tissue oxygenation in VLBW premature neonates before, during and after blood transfusion, using VLS.

Design/Methods:

This is a prospective, observational, non randomized pilot study.

VLBW neonates receiving PRBC transfusion ordered by the medical team were studied.

An infant buccal probe (Spectros Corporation T-Stat® 303) was applied on the infant cheek with the light emitting probe suspended in the mouth close to the buccal mucosa. Continuous data from the T-Stat Visual Light Spectrograph for tissue oxygenation oxyhemoglobin and total Hb content was recorded.

The data for HR and SpO_2 were extracted from the cardio-respiratory monitor used in our NICU (Phillips Intell Vue MP-70 Neonatal). Preductal SpO_2, StO_2, and HR were measured continuously and then compared at the following five-minute time epochs: 1 hour before, at the beginning, hourly during and 1 hour after blood transfusion. SpO_2 and HR recordings were integrated over 10 seconds, sampled every 1 minute and averaged over the observational epochs. Tissue oxygen saturation (StO_2) recordings from VLS were integrated over 2 second intervals, sampled every 1 minute and then averaged over the observational epochs. ΔP was calculated as the difference between pulse and tissue saturation ($\Delta P = SpO_2 - StO_2$).

The clinical data was extracted from the medical records and the reasons for blood transfusion were recorded.

Neonatal Therapeutic Intervention Scoring System (NTISS) was used to assess the severity of the illness of the study patients. Neonatal Therapeutic Intervention Scoring System assesses patients by the level of support and intervention required throughout their hospital stay. Eighty-two data variables are used for the calculation of the NTISS score, which has an advantage over other neonatal severity scores that assess the infant only at the time of birth. Scores of <9 indicate mild, 10-19 moderate and >20 severe clinical course [19].

Table 1. Patient demographics							
	NTISS score	Hct before	Hct after	GA (wks)	BW (g)	DOL (d)	Reason for transfusion
	6	22	35	30	1270	33	Asymptomatic anemia
	8	27	36	30	1365	77	Asymptomatic anemia
	10	27	34	26	820	43	Anemia+Apnea
	11	25	36	24	670	65	Anemia+Apnea
	28	38	44	33	1670	2	Hypoplastic Left Heart Syndrome
Avg	12.6	27.8	37	28.6	1159	44	
SD	8.8	6	4	3.6	409	29	
Median	10	27	36	30	1270	43	

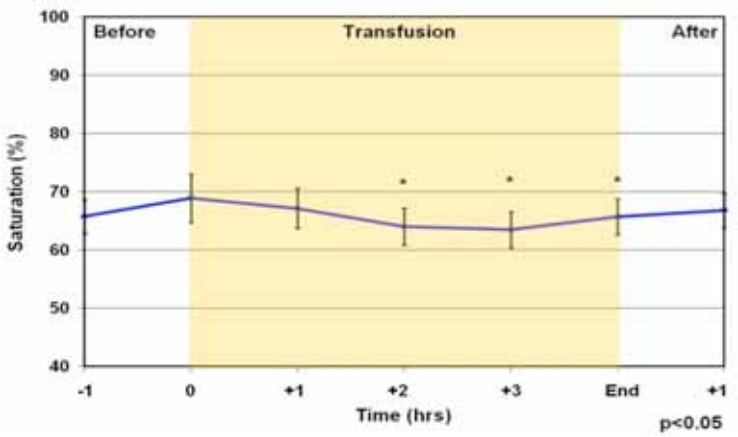

Figure 1. Tissue saturation decreased significantly at the second, third and fourth hours of the PRBC transfusion.

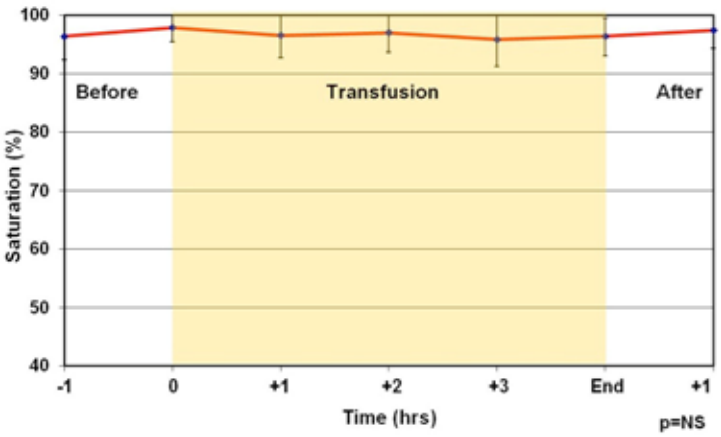

Figure 2. SpO_2 remained unchanged during the transfusion.

Descriptive statistics and mean and standard deviation were used to summarize the data for SpO_2, StO_2 and ΔP before, during and after PRBC transfusion. Analysis of Variance (ANOVA) with repeated measures was used to detect statistical differences in pulse and tissue saturations between the different epochs.

Results:

A total of 5 neonates were studied on DOL 44 ± 29: two with mild disease and asymptomatic anemia, two with moderate NTISS score, anemia and significant apneas and one patient with severe disease score and HLHS. Their demographic and clinical characteristics are summarized in Table 1.

Unexpectedly, we observed a significant decrease in tissue oxygen saturation (Figure 1) and increase in ΔP (Figure 3) at the 2nd, 3rd and 4th hour of blood transfusion, followed by recovery at the end of the transfusion. None of the neonates had any signs of hypovolemia and PRBC was given to increase oxygen carrying capacity by increasing the red cell mass.

Pulse oximetry measurements and HR remained stable, as shown in Figures 2 and 4 respectively. The decrease in tissue oxygenation during blood transfusion occurred in all patients regardless of pre transfusion Hct and NTISS score.

Discussion:

The rationale for PRBC transfusion is to increase the oxygen delivery by increasing Hb level and cardiac output; therefore, the observed worsening of tissue oxygen saturation in our patients during blood transfusion was an unexpected phenomenon. Potential explanation of this phenomenon may be the

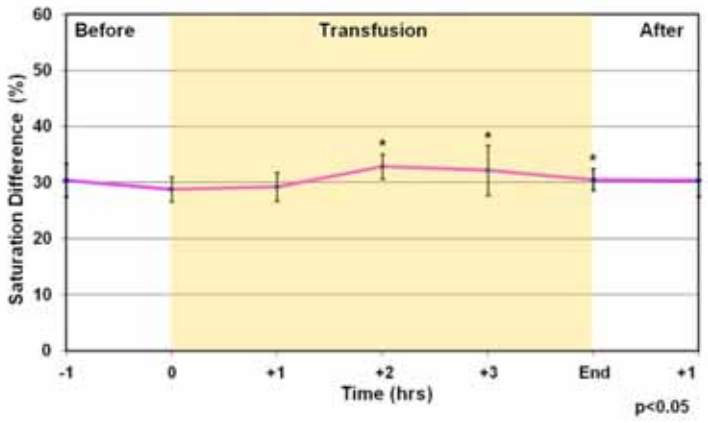

Figure 3. SpO_2-StO_2 difference increased during the PRBC transfusion, indicating decreased perfusion.

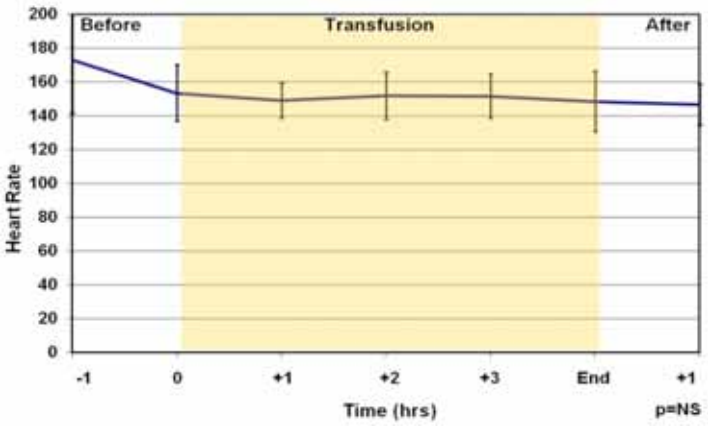

Figure 4. Heart rate remained unchanged during the transfusion.

"PRBC storage lesion." During storage, PRBC undergo hemolysis, decrease in energy stores (ATP, 2-3 DPG) and decrease in pH. Additionally, the high Hct, decrease in RBC flexibility coupled with increase in viscosity and adhesiveness may potentially lead to poor capillary perfusion. Further, the "hungry for oxygen" stored red blood cells may potentially lead to hypoxia by absorbing oxygen from "neighbor" RBCs and even from tissue. It also has been speculated that stored blood has decreased nitric oxide content (as a SNO-Hb) occurring even as soon as within 3 hours of storage and leading to local vasoconstriction [7]. Recent study of 2,872 adult patients receiving 8,802 units of blood found that the patients receiving older blood (20 days vs 11 days) had a higher rate of in–hospital mortality (2.8% vs 1.7%, p=0.004) and composite complications (7.4% vs 11%, p<0.001) [8].

Mally et al had shown that premature neonates are more prone to developing NEC within 48 hours after "elective" blood transfusion if they did not have any prior significant illness [9].

A recent meta-analysis of forty-five studies including 272,596 adult patients in intensive care, trauma, and surgery units found that 42 of the 45 analyzed studies showed increased risks of PRBC transfusions outweighing the potential benefit. The risk was neutral in two studies and only one study showed benefit of PRBC transfusion in a subgroup of elderly patients with an acute myocardial infarction and anemia (hematocrit<30%). The authors concluded that PRBC transfusions are associated with increased morbidity and mortality and, therefore, current transfusion practices may require reevaluation [10].

Our observations, showing worsening tissue oxygen saturation, are in keeping with the concerns raised by these studies. The data from our pilot study adds to the understanding of tissue "well being" during blood transfusion and the usefulness of StO_2 measurements. We also would like to underscore that neither the pulse oximeter, which measures arterial saturation, nor the HR gave any indications of the alteration of the tissue oxygenation.

Conclusion:

VLS is an easy-to-use and non-invasive method of assessment of tissue saturation in VLBW neonates with various severity of illness. VLS may be helpful in identifying patients at risk for developing transfusion related injury. Normative data for StO_2 and correlations between StO_2 and various Hb levels in critically ill or convalescing neonates may further guide the blood transfusion therapy.

References:

1. U.S. Department of Health and Human Services. (2005-2006). The 2005 Nationwide Blood Collection and Utilization Survey Report. Bethesda, MD: AABB Whitaker, B.I., & Sullivan, M.
2. Strauss, R. G. (1997). Practical issues in neonatal transfusion practice. American Jouranl of Clinical Pathology, 107(4), S57-S63.
3. Kluckow, M., & Evans, N. (2000). Superior vena cava flow in newborn infants: a novel marker of systemic blood flow. Archives of Disease in Childhood Fetal & Neonatal Edition, 82(3), F182-187.
4. Adams, T., & Weaver, L.T. (2003). Gastric Tonometry in the Care of the Newborn. Journal of Pediatric Gastroenterology & Nutrition, 36 (1), 1-4.

5. Johnson, B.A., & Chang A.C. (2008). Near-infrared spectroscopy and tissue oxygenation: the unremitting quest for the holy grail. Pediatric Critical Care Medicine, 9(1), 123-4.
6. Benaron, D.A., Parachikov, I.H., Cheong, W.F., Friedland, S., Rubinsky, B.E., Otten, D.M., et al. (2005). Design of a visible-light spectroscopy clinical tissue oximeter. Journal of Biomedical Optics, 10(4), 44005.
7. Bennett-Guerrero, E., Veldman, T.H., Doctor, A., Telen, M.J., Ortel, T.L., Reid, T.S., et al. (2007). Evolution of adverse changes in stored RBCs, Proceedings of the National Academy of Sciences of the United States of America, 104(43), 17063-17068.
8. Koch, C.G., Li, L., Sessler, D.I., Figueroa, P., Hoeltge, G.A., Mihaljevic, T., et al. (2008). Duration, of Red-Cell Storage and Complications after Cardiac Surgery, The New England journal of medicine, 358(12), 1229-39.
9. Mally, P., Golombek, S.G., Mishra, R., Nigam, S., Mohandas, K., Depalhma, H., et al. (2006). Perinatol, Association of necrotizing enterocolitis with elective packed red blood cell transfusions in stable, growing, premature neonates. American journal of perinatology, 23(8), 451-8.
10. Marik, Paul E et al (2008) . Efficacy of red blood cell transfusion in the critically ill: A systematic review of the literature. Critical Care Medicine. 36(9):2667-267.
11. 11.Friedland, S., Benaron, D., Parachikov, I., Soetikno, R. (2003).Measurement of mucosal capillary hemoglobin oxygen saturation in the colon by reflectance spectrophotometry, Gastrointestinal endoscopy,57(4),492-497.
12. Amir, G., Ramamoorthy, C., Riemer, R.K., Davis, C.R., Hanley, F.L., & Reddy, V.M. (2006). Visual light spectroscopy reflects flow-related changes in brain oxygenation during regional low-flow perfusion and deep hypothermic circulatory arrest. The Journal of thoracic and cardiovascular surgery, 132(6), 1307-1313.
13. Pigula, F.A., Nemoto, E.M., Griffith, B.P., & Siewers, R.D. (2000). Regional low – flow perfusion provides cerebral circulatory support during neonatal aortic arch reconstruction. The Journal of thoracic and cardiovascular surgery, 119(2), 331-9.
14. Benaron, D.A., Parachikov, I.H., Friedland, S., Soetikno, R., Brock-Utne, J., van der Starre, P.J., et al. (2004). Continuous, noninvasive, and localized microvascular tissue oximetry using visible light spectroscopy. Anesthesiology, 100(6), 1469-75.
15. Friedland, S., Benaron, D., Coogan, S., Sze, D.,& Soetikno, R.(2007). Diagnosis of chronic mesenteric ischemia by visible light spectroscopy during endoscopy. Gastrointestinal Endoscopy, 65(2), 294-300.
16. Lee, E.S., Bass, A., Arko, F.R., Heikkinen, M., Harris, E. J., Zarins, C.K et al. (2006). Intraoperative Colon Mucosal Oxygen Saturation During Aortic Surgery, Intraoperative colon mucosal oxygen saturation during aortic surgery. Journal of Vascular Surgery, 45 (5), 1086 – 1086.
17. Lee, E.S., Pevec, W.C., Link, D.P., & Dawson, D.L. (2008). Use of T-Stat to predict colonic ischemia during and after endovascular aneurysm repair: a case report. Journal of Vascular Surgery, 47(3), 632-4.
18. Heninger, C., Ramamoorthy, C., Amir, G., Kamra, K., Reddy, V.M, Hanley, F.L., et al. (2006). Esophageal saturation during antegrade cerebral perfusion: a preliminary report using visible light spectroscopy. Paediatric anaesthesia, 16(11), 1133-7.
19. Gray JE, Richardson DK, McCormick MC, Workman-Daniels K, Goldmann D. (1992). Neonatal Therapeutic Intervention Scoring System (NTISS): a therapy-based severity-of-illness index. Pediatrics, 90, 561-7.

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Clinical Trials

Propofol Versus Midazolam as Premedication for Preterm Neonates With Respiratory Distress Syndrome (RDS)

This study is currently recruiting participants.

Purpose: The aim of the study is to compare the intubation conditions among propofol and remifentanil versus midazolam and remifentanil in premature neonates with Respiratory Distress Syndrome (RDS), and at the same time, to show the group of drugs that could let the neonates with no residual sedation after the use of surfactant (the possibility of the premature neonates to be readily extubated after the use of surfactant).

Condition: Respiratory Distress Syndrome

Intervention: Drug: propofol

Phase: IV

Study Type: Interventional

Study Design: Supportive Care, Randomized, Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor), Active Control, Parallel Assignment, Safety/Efficacy Study.

Official Title: Propofol and Remifentanil Versus Midazolam and Remifentanil as Premedication Allowing Very Early Extubation After Surfactant Treatment in Preterm Neonates With Respiratory Distress Syndrome

Further study details:
- **Primary Outcome Measures:** Time until extubation after bolus dose as premedication for tracheal intubation
  [Time Frame: within the first 3 days of life]
  [Designated as safety issue: Yes]
- **Secondary Outcome Measures:** Quality of intubation with the combination of drugs used for premedication
  [Time Frame: within the first 2 days of life]
  [Designated as safety issue: Yes]

Estimated Enrollment: 20
Study Start Date: August 2008
Estimated Study Completion Date: December 2009
Estimated Primary Completion Date: December 2009 (Final data collection date for primary outcome measure)

Intervention Details: Drug: propofol2mg/Kg IV in bolus before tracheal intubation.

Detailed Description: It has been demonstrated that remifentanil, due to its very short context-sensitive, has an interesting potential for use in premature neonates with RDS. Indeed, remifentanil allowed an adequate level of sedation and analgesia as well as rapid recovery after discontinuation. The aim of the present study was to compare the intubation conditions among propofol and remifentanil versus midazolam and remifentanil in premature neonates with respiratory distress syndrome.

Eligibility: Both genders eligible and ages up to 2 days
- Does not accept healthy volunteers

Inclusion Criteria:
- Gestational age between 28-34 wk
- Clinical and radiological features compatible with respiratory distress syndrome that required elective tracheal intubation and surfactant therapy
- Hemodynamic stability before tracheal intubation
- Signature (parents) consent form

Exclusion Criteria:
- The presence of major congenital malformations
- Birth weight less than 1000 g
- Previous use of opioid or other sedative drug for any reason
- Previous tracheal intubation
- Hemodynamic instability before the indication of tracheal intubation
- Refuse of the parents to enroll the neonate in the study protocol

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Location: Brazil, Minas Gerais; Dept. of Neonatology of Julia Kubitschek Hospital

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Sponsors and Collaborators: Federal University of Minas Gerais.

Principal Investigator: Yerkes P Silva, PhD; Federal University of Minas Gerais.

More Information

Responsible Party: Federal University of Minas Gerais (Yerkes Pereira e Silva)
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First Received: November 20, 2008
Last Updated: November 24, 2008
ClinicalTrials.gov Identifier: NCT00797160
Health Authority: Brazil: National Committee of Ethics in Research

Exploratory Applications of Surfactant Therapy

By Steven M. Donn, MD, FAAP

Introduction

Surfactant replacement therapy is an established practice in the developed world for the treatment of Respiratory Distress Syndrome (RDS), the primary disorder of the preterm lung. Affected infants lack the ability to produce sufficient surfactant to maintain alveolar inflation and appropriate gas exchange. Repletion with exogenously administered surfactant has been demonstrated in more than 40 randomized, controlled trials to improve mortality and morbidity, whether it is given as a prophylactic, treatment, or rescue therapy [1].

Pulmonary surfactant is a multicomponent complex of phospholipids, neutral lipids, and associated proteins. It is normally synthesized and secreted by the Type II pneumocytes within the alveolar epithelium. It reduces the collapsing forces (surface tension) within the alveoli and confers stability and maintains the alveolar surface free of liquid, thus facilitating pulmonary gas exchange [2].

While RDS may be thought of as a "congenital" surfactant deficiency, other neonatal (and pediatric) lung disorders may have an "acquired" surfactant deficiency as part of the pathophysiology. Numerous factors, including protein, oxygen free radicals, and inflammatory mediators may play a role in surfactant inhibition or inactivation [3-5]. Pulmonary ischemia may damage the alveolar lining and cause the loss of Type II pneumocytes, leading to decreased surfactant production [6].

Two rather common disorders of newborns, Meconium Aspiration Syndrome (MAS), and bronchopulmonary dysplasia (BPD), also known as chronic lung disease (CLD), are characterized by surfactant inactivation. It makes intuitive sense that surfactant repletion for these two disorders might improve the outcomes of affected infants. Both disorders have indeed been subjected to randomized controlled trials of surfactant replacement therapy with encouraging results.

Meconium Aspiration Syndrome

There are 25,000-35,000 annual cases of MAS in the United States. Thirty to fifty percent of affected infants require mechanical ventilation. Pneumothorax is seen in 15-20% of cases, and mortality rates range from 4-7%. The pathophysiology is complex, but several factors probably play roles in creating surfactant insufficiency. The constituents of meconium, especially bile salts and fatty acids, may directly inactivate surfactant. Inflammatory mediators, such as cytokines and eicosanoids, are also present. Protein leaks into the alveolar spaces and pulmonary edema are frequently seen. Pulmonary ischemia may be present, and treatment with high concentrations of inspired oxygen may generate free radicals [7]. Thus, exogenous surfactant repletion makes good sense, at least on a theoretical basis. Two approaches have been attempted: repletion and lung lavage.

Repletion involves therapeutic dosing of exogenous surfactant. The goal is to overcome the inhibitory or inactivating effects by giving enough surfactant. In 1999, Lotze et al reported the results of a multicenter study of surfactant replacement in term infants with severe respiratory failure, who were randomized to receive four doses of either surfactant or sham air before extracorporeal membrane oxygenation (ECMO) and four additional doses if ECMO was required. Although not all of the enrolled infants had MAS, the use of surfactant was shown to reduce the need for ECMO [8].

Lavage involved a "washing out" of the lung. The rationale here was to take advantage of the detergent-like properties of surfactant to solubilize the aspirated meconium and to remove it, while instilling active surfactant. Using an investigational synthetic surfactant (lucinactant) comprised of a phospholipid mixture, and a synthetic peptide, which mimics human Surfactant-associated protein B (Surfaxin®, Discovery Laboratories, Warrington, PA), Wiswell et al conducted a randomized, controlled trial on 22 infants with moderately severe MAS and also demonstrated strong trends for reduction in the oxygenation index and fewer days of mechanical ventilation in the surfactant-lavaged patients [9].

"Surfactant replacement therapy is an established practice in the developed world for the treatment of Respiratory Distress Syndrome (RDS), the primary disorder of the preterm lung."

A recent meta-analysis by El Shahed et al examined the results of four randomized trials. Surfactant treatment of MAS showed a statistically significant reduction in the need for ECMO in two trials. One trial reported a reduction in length of stay. The authors concluded that surfactant may reduce the severity of respiratory illness and the number of infants requiring ECMO for this condition [10].

Bronchopulmonary Dysplasia

BPD affects 30-40% of infants with birth weights <1500 grams. It can be severe enough to interfere with normal growth

and development. Although its etiology is multifactorial, there is evidence that a contributing factor is surfactant inadequacy during the recovery phase of RDS [11]. Lung inflammation, protein leak into the alveolar spaces, and oxygen free radicals may be to blame. There is anecdotal evidence that some infants, who were given exogenous surfactant at this stage, showed improvement in lung function, and thus a pilot trial of "late" surfactant dosing was undertaken.

Laughon and colleagues randomized 136 infants to receive either sham air, low dose lucinactant (90 mg/kg phospholipids), or high dose (175 mg/kg phospholipids) between three and 10 days of age if they were ventilator-dependent and required ≥0.30 fraction of inspired oxygen. All patients weighed between 600 and 900 g at birth. They were treated every 48 hrs. up to a maximum of five doses, if they remained ventilated. Infants randomized to the high dose group had a non-statistically significant trend towards a lower incidence of BPD. The estimated treatment effect was 8%. The investigators believe that a larger Phase III trial is warranted to establish whether late treatment with surfactant can be an effective therapy to reduce BPD [12].

Additional Directions

MAS and BPD are not the only neonatal or pediatric lung disorders that might be amenable to surfactant replacement therapy. Many of the same mechanisms of surfactant inactivation - inflammation, protein leak, edema, etc.- are present in a variety of disorders, including: hypoxemic respiratory failure, pulmonary hemorrhage, pneumonia, and congenital diaphragmatic hernia in newborns, and bronchiolitis, Acute Respiratory Distress Syndrome, cystic fibrosis, asthma, and chronic bronchitis in the pediatric population. Exploratory studies are underway in many of these.

Conclusion

Although the safety and efficacy of surfactant replacement therapy for neonatal RDS is well-established, RDS is not the only pulmonary disorder characterized by surfactant deficiency or inadequacy. Other serious conditions, in which there is a functional surfactant deficit, appear to be remediable to surfactant replacement therapy. Evidence supports its use in MAS, and preliminary results for its effect on BPD are exciting, but require further clinical investigation.

References

1. Moya F, Maturana A: Animal-derived surfactants versus past and current synthetic surfactants: current status. Clin Perinatol 2007; 34:145=177.
2. Lacaze-Masmonteil T: Surfactant replacement therapy. In Donn SM, Sinha SK (eds.): Manual of Neonatal Respiratory Care, second edition, Philadelphia, Mosby-Elsevier, 2006, pp. 396-401.
3. Andersson S, Kheiter A, Merritt TA: Oxidative inactivation of surfactants. Lung 1999; 177:179-189.
4. Moya F, Hoffman D, Zhao B, et al: Platelet activating factor in surfactant preparations. Lancet 1993; 341:858-860.
5. Thibeault DW, Maabry SM, Ekekezie II, Truog WE: Lung elastic tissue maturation and perturbations during the evolution of chronic lung disease. J Perinatol 2004; 24:663-666.
6. Banagale RC, Donn SM: Asphyxia neonatorum. J Fam Prac 1986; 22:539-546.
7. Wiswell TE: Meconium aspiration syndrome. In Donn SM, Sinha SK (eds.) : Manual of Neonatal Respiratory Care, second edition, Philadelphia, Mosby-Elsevier, 2006, pp. 325-330.
8. Lotze A, Mitchell BR, Bulas DI, et al: Multicenter study of surfactant (beractant) use in the treatment of term infants with severe respiratory failure. Survanta in Term Infants Study Group. J Pediatr 1998; 132:40-47.
9. Wiswell TE, Knight GR, Finer NN, Donn SM, et al: A multicenter, randomized controlled trial comparing Surfaxin (lucinactant) lavage with standard care for the treatment of meconium aspiration syndrome. Pediatrics 2002; 109:1081-1087.
10. El Shahed A, Dargaville P, Ohlsson A, Soll RF: Surfactant for meconium aspiration syndrome in full term/near term infants. Cochrane Database of Systematic Reviews 2007. CD002054 DOI: 10.1002/14651858.
11. Genen L, Davis JM: Chronic lung disease: etiology and pathogenesis. In Donn SM, Sinha SK (eds.): Manual of Neonatal Respiratory Care, second edition, Philadelphia, Mosby-Elsevier, 2006, pp. 358-363.
12. Laughon M, Bose C, Moya F, Aschner J, Donn SM, et al: A pilot randomized, controlled trial of later treatment with a peptide-containing, synthetic surfactant for the prevention of bronchopulmonary dysplasia. Pediatrics 2009; 123:89-96.

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Welcome To Holland

This brief essay by Emily Perl Kingsley, was sent to us by the parent of child with Down Syndrome. We would like to share it with our readers, because it poignantly expresses feelings of many parents who have children with chronic cardiac and neonatal health problems.

I am often asked to describe the experience of raising a child with a disability - to try to help people who have not shared that unique experience to understand it, to imagine how it would feel. It's like this.....

When you're going to have a baby, it's like planning a fabulous vacation trip - to Italy. You buy a bunch of guide books and make your wonderful plans. The Coliseum. The Michelangelo. David. The gondolas in Venice. You may learn some handy phrases in Italian. It's all very exciting.

After months of eager anticipation, the day finally arrives. You pack your bags and off you go. Several hours later, the plane lands. The stewardess comes in and says, "Welcome to Holland."

"Holland?!?" you say. "What do you mean Holland?? I signed up for Italy! I'm supposed to be in Italy. All my life I've dreamed of going to Italy."

But there's been a change in the flight plan. They've landed in Holland and there you must stay.

The important thing is that they haven't taken you to a horrible, disgusting, filthy place, full of pestilence, famine and disease. It's just a different place.

So you must go out and buy new guide books. And you must learn a whole new language. And you will meet a whole new group of people you would never have met.

It's just a different place. It's slower-paced than Italy, less flashy than Italy. But after you've been there for a while and you catch your breath, you look around.... and you begin to notice that Holland has windmills....and Holland has tulips. Holland even has Rembrandts.

But everyone you know is busy coming and going from Italy... and they're all bragging about what a wonderful time they had there. And for the rest of your life, you will say "Yes, that's where I was supposed to go. That's what I had planned."

"I am often asked to describe the experience of raising a child with a disability - to try to help people who have not shared that unique experience to understand it, to imagine how it would feel. It's like this....."

And the pain of that will never, ever, ever, ever go away... because the loss of that dream is a very, very significant loss.

But... if you spend your life mourning the fact that you didn't get to Italy, you may never be free to enjoy the very special, the very lovely things ... about Holland.

NT

Emily Perl Kingsley

E-mail: EPK@neonate.biz

Do you or your colleagues have interesting research results, observations, human interest stories, reports of meetings, etc. that you would like to share with the neonatology community?

Submit a brief summary of your proposed article to: Article@Neonate.biz

The final manuscript may be between 400-4,000 words, contain pictures, graphs, charts and tables.

Medical News, Products and Information

Personal Health Records -- A More Efficient Way to Manage Health Information

The days of scrambling to recall or find immunization dates or medication names and doses may be numbered. An electronic personal health record is likely to replace those handwritten notes and scattered papers.

The January 2009 issue of Mayo Clinic *Women's HealthSource* discusses this new way to manage personal health information, most often on the Internet.

A basic personal health record includes the patient's name and date of birth, emergency contacts, names and contact information for care providers, insurance information, a list of past illnesses and surgical procedures, current medications and dates they were prescribed, allergies, results and dates of recent tests or doctor visits, immunization records, family history of illnesses or hereditary conditions, and other health information such as a living will or advanced directives.

Personal health records offer many potential benefits, including quick access to information that could be a lifesaver in an emergency situation. But the technology is still evolving, and many challenges are yet to be worked out.

Among those challenges are where the records will be stored and how they will be accessed and updated. Many of today's personal health records are connected to existing electronic medical records from a single health care provider or insurer. The health care provider may be able to upload data from devices that measure heart rate, blood pressure, blood glucose or peak airway flow. Increasingly, medical providers are offering patients password-protected access to test results and other data in the individual's medical record. One drawback is that providers from other health care organizations may not be able to access this type of personal health record.

Other personal health records are designed to stand alone, giving the patient more control and responsibility over what's included. This approach may allow multiple parties to access and update the information. For example, the patient can record exercise and diet progress, a pharmacist can input prescription information, and a doctor can add test results.

However, various providers might not use the same information format, perhaps hindering efforts to keep health records up-to-date and well organized. The patient has the responsibility to ensure that the information is current and accurate.

Privacy is another concern. Health information stored on a stand-alone Web site may not be as secure as data stored by a health care system, which must comply with privacy rules mandated by the federal government's Health Insurance Portability and Accountability Act (HIPAA).

Patients interested in learning more about a personal health record should start by investigating what's available through primary health care providers or insurers. If no template is available, patients can request electronic or written records to start a stand-alone personal record.

Mayo Clinic Women's *HealthSource* is published monthly to help women enjoy healthier, more productive lives. Revenue from subscriptions is used to support medical research at Mayo Clinic. To subscribe, please call 800-876-8633, extension 9751, or visit www.bookstore.mayoclinic.com.

Drug Therapy for Premature Infants Destroys Brain Cells in Mice

Newswise — A class of drugs that are used in premature infants to treat chronic lung damage can cause damage in the brain. New research at Washington University School of Medicine in St. Louis suggests the drugs may cause cognitive and motor-control problems even when they are given before birth.

The researchers have identified the cells damaged by the drugs, called glucocorticoids, as well as the time window during which brain injury can occur. They say it may be possible to avoid damage to brain cells and still aid the development of premature lungs if synthetic forms of the drugs can be replaced with hormones made naturally in the body.

The researchers reported their findings today at *Neuroscience 2008,* the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Studying the effects of the drugs in mice, the investigators found that the synthetic glucocorticoids dexamethasone and betamethasone, commonly prescribed to spur the development of premature lungs, cause damage in the brain's cerebellum, the structure that controls movement, as well as other functions.

Brain cells in the mice died following glucocorticoid treatment when the drugs were given between four and 10 days after birth. The corresponding window in human infants would be approximately 20 weeks of gestation to six weeks following birth. That's also the time span in which these drugs are given to pregnant women at risk for preterm birth or to prematurely born infants who are having problems breathing.

"The cells that are damaged are called neural progenitor cells, which are responsible for producing new neurons," says first author Kevin K. Noguchi, PhD, a scientist in the Department of Psychiatry. "So you can imagine that if you kill the cells responsible for producing new neurons, you can cause severe neurodevelopmental deficits."

That's exactly what the researchers found when they studied adolescent mice that had been treated with glucocorticoids during infancy. A single exposure to glucocorticoid

drugs permanently decreased the number of neurons in the cerebellum of the mouse brain.

In the past, the steroid drugs were given to low-birthweight infants after they were born, but studies determined that exposure to the drugs following birth could lead to cognitive problems and neuromotor deficits, particularly difficulty with balance and coordination. In 2002, the American Academy of Pediatrics recommended post-natal glucocorticoid use be stopped unless used in clinical trials, but the drugs still are given frequently to mothers at risk for preterm birth.

"The cerebellum connects to other brain structures, so when granule cells in the cerebellum are lost, you also have detrimental effects on cognitive function in non-motor regions of the brain," says senior investigator Nuri B. Farber, MD, Associate Professor of Psychiatry. "Other researchers have found I.Q. declines in children who have received these drugs early in life, and our findings may help explain why."

But both Farber and Noguchi say therapy with these drugs may be essential for some children with immature lungs as a lifesaving measure. They believe, however, that it may be possible in the future to use different drugs to help the lungs mature without damaging brain cells.

"We're looking at differences between glucocorticoids that are made naturally in the body and hormones that are manufactured," says Noguchi. "The brain has some natural defenses against exposure to endogenous glucocorticoids but not the synthetic ones. So it may be possible to administer some of those natural hormones, which can help the lungs mature without putting the brain at risk."

It also may be possible to develop other drugs that would assist with lung development without killing cells in the cerebellum. But as they study those possibilities, the investigators say they want parents to know that the observed toxic effects of steroid drugs are not a problem for adults and older children. They estimate that by about three months of age, human infants no longer are at high risk for this damage.

"The toxic effects decline when the cerebellum finally finishes its development," Farber says. "These drugs are used for many different purposes, so there are other reasons why a baby might get prednisone or dexamethasone or another glucocorticoid, but our research in mice suggests once a human infant is a few months old, these drugs have fairly innocuous effects in the brain."

Noguchi, KK, Smith DJ, Swiney BS, Farber NB. Acute exposure to multiple corticosteroids can induce selective apoptotic cell death in the neural progenitor cells of the developing cerebellum of neonatal mice. Abstract, presented Nov. 17, 2008 at *Neuroscience 2008.*

This research was supported by grants from the National Institutes of Health.

Washington University School of Medicine's 2,100 employed and volunteer faculty physicians also are the medical staff of Barnes-Jewish and St. Louis Children's hospitals. The School of Medicine is one of the leading medical research, teaching and patient care institutions in the nation, currently ranked third in the nation by U.S. News & World Report. Through its affiliations with Barnes-Jewish and St. Louis Children's hospitals, the School of Medicine is linked to BJC HealthCare.

Are Pediatricians Getting the Training They Need to Meet Patient Needs?

Newswise — The face of pediatric medicine is changing. Beyond new technology, treatments and vaccines, more children than ever before are requiring care for chronic diseases and more families also are seeking pediatricians who have expertise in specialty areas such as sports medicine and mental health.

But are future pediatricians getting the training they need to meet the demands of the changing world of medicine, as well as the needs of their patients?

Although medical training has been adapted to educate trainees about new diseases and therapies, the fundamentals of the training process in pediatrics have remained relatively unchanged during the past decade.

Four studies led by the Child Health Evaluation and Research (CHEAR) Unit at the University of Michigan C.S. Mott Children's Hospital finds recently trained pediatricians and pediatricians-in-training agreed that a one-size-fits-all approach to education in pediatrics may no longer be the right course of action. The studies are set to appear in the November *Pediatrics* supplement.

Many physicians-in-training who took part in the studies noted a desire for more instruction in mental health, outpatient specialty care, oral health, sports medicine and developmental-behavior health. Few, however, felt they needed additional training in patient safety, patient communication and coordination of care for children with complex illnesses, despite studies that have pointed to the contrary.

"We need to make sure that we are educating physicians in the new millennium in a way that is not only responsible, but also responsive to the changing needs of medicine and our patients and their parents," says lead author of the studies Gary L. Freed, MD, MPH, chief of the Division of General Pediatrics and director of the CHEAR Unit at Mott.

"In order to meet those needs, there must be a balance in the workforce between general pediatricians and specialty pediatricians who focus their careers on a specific disease. But to ensure that happens, we first need to understand what makes people want to go into pediatrics and how they select particular training programs."

To take a closer look at medical training for future pediatricians, the studies asked general pediatric residents, pediatric fellows, and recently trained general and subspecialty pediatricians about their decisions to choose certain residency or fellowship programs and career paths in pediatric subspecialties.

The studies show:

- Location matters. The majority of pediatric residents, fellows and sub-specialists say they selected their residency or fellowship program based on its location.
- Structured hours/lifestyle and interest in a specific disease/patient population were the two most important factors in physicians' decisions to pursue a particular career path in pediatrics.
- Fifty-four percent of recently trained pediatric sub-specialists say they would have shortened either their pediatric residency or fellowship training, if given the opportunity.
- Half of the respondents made the decision to pursue subspecialty training in the first or second year of residency, while 36% decided prior to residency training.
- Fifty-two percent of pediatric fellows would have selected a two-year fellowship without research training, if it were offered.

Training and decision-making related to a physician's career choice in pediatrics was last assessed in 1995 as part of the Future of Pediatric Education II (FOPE) project. Since then, there have been significant changes in the structure of pediatric resident education, medical technology, and the prevalence of the children with chronic illnesses.

The new findings from the four studies provide important insight into the future of the pediatric workforce. As Freed notes, the past decade has seen an increase in more pediatricians pursuing careers in subspecialty areas as opposed to primary care in pediatrics. The findings also point toward the need to adapt medical training in pediatrics to ensure a balanced pediatric workforce in the future.

"We need to take a closer look at how we're educating our physicians and determine the proper balance of that content," says Freed, the Percy and Mary Murphy Professor of Pediatrics and Child Health Delivery at the U-M Medical School. "Do we teach them more about issues related to mental and behavioral health, and do we provide more training in an outpatient setting since pediatric care is increasingly being delivered there? These are all important questions to address to ensure our future pediatricians are prepared to handle those issues."

Already, the American Board of Pediatrics is working with other pediatric organizations across the country to launch a new medical training program. This project will allow medical education sites to experiment with new training structures to adequately prepare future physicians to care for patients and their families as the field of pediatrics evolves.

"The challenge has been, and will continue to be, to ensure excellence of care across a broad spectrum of clinical areas while preserving a measure of flexibility relative to the individual interests and needs of each trainee," says Freed.

For the studies, the researchers used a database of physicians maintained by the American Board of Pediatrics to select groups of general pediatric residents, pediatric fellows, and recently trained general and subspecialty pediatricians to participate in the studies. Each study sent its own questionnaire via mail to a specific group of either trainees or recently trained pediatricians.

All four studies were funded by the American Board of Pediatrics Foundation.

Along with Freed, the studies' co-authors included: from the U-M Division of General Pediatrics and CHEAR Unit: Kelly M. Dunham, MPP and Kara E. Switalski, MPH; M. Douglas Jones Jr., MD, Department of Pediatrics, University of Colorado Health Sciences Center; and from the American Board of Pediatrics Linda Althouse, PhD, and Gail A. McGuinness, MD.

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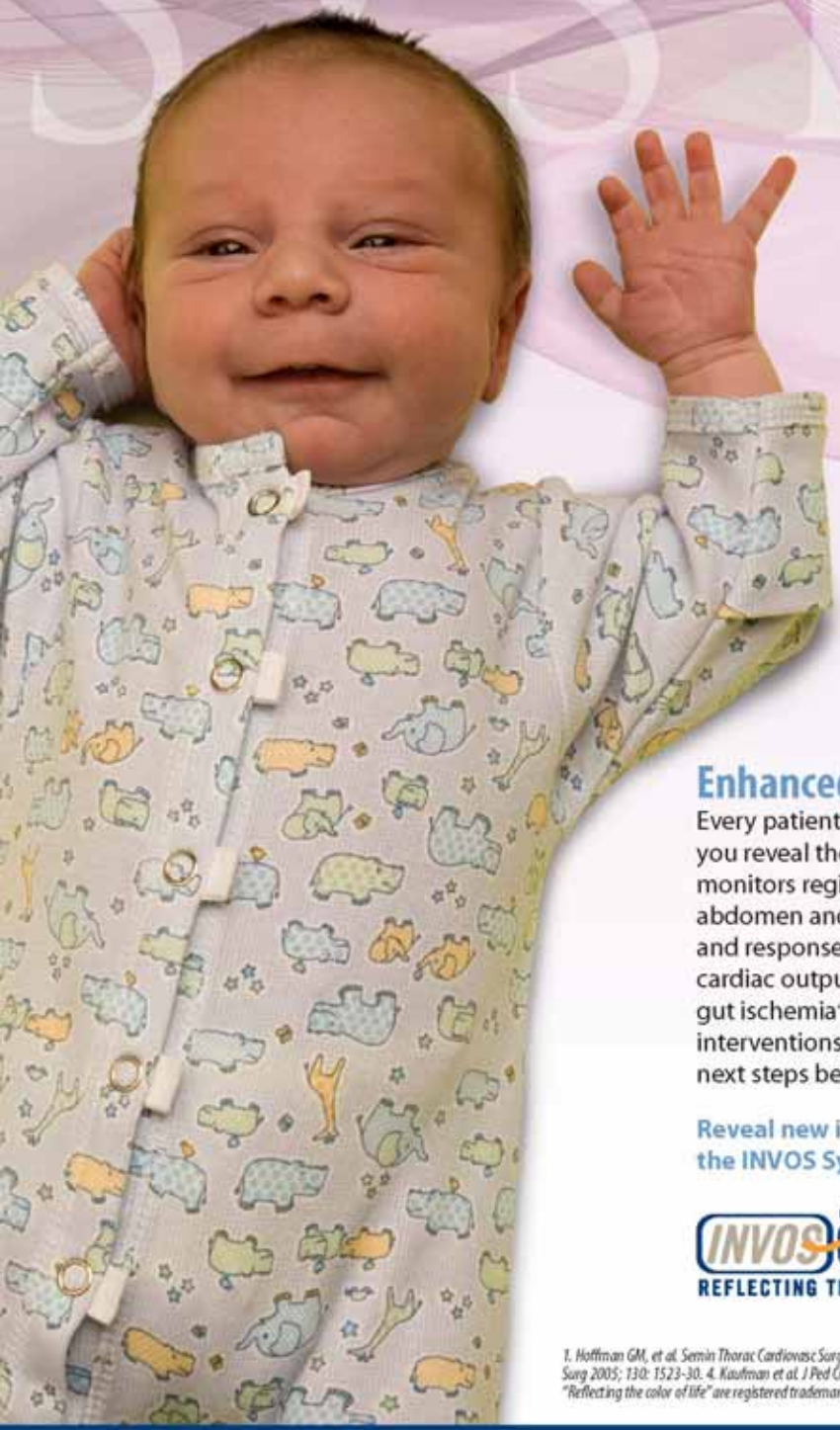

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1. Hoffman GM, et al. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu. 2005; pp 12-21. 2. Hoffman GM, et al. Anesthesiology 2005; 103:A1327 3. Dent CL, et al. J Thorac Cardiovasc Surg 2005; 130: 1523-30. 4. Kaufman et al. J Ped Crit Care Med 2008; 9:62-8. 5. Diaz GA, et al. Eur J Paediatr Neurol 2006; 10:19-21