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Enhancing the Care of Preterm Infants Undergoing Surgical Ligation of a Patent Ductus Arteriosus

By Afif F. EL-Khuffash, MD, Amish Jain, MD,
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Summary

There is limited consensus on the diagnosis and management of a patent ductus arteriosus (PDA) in preterm neonates. PDA remains one of the most common cardiovascular abnormalities in preterm neonates occurring in about a third of infants below 30 weeks gestation and up to 60% of infants less than 28 weeks. Shunting from the systemic to the pulmonary circulations, often-times referred to as ductal steal, results in systemic hypoperfusion and pulmonary overcirculation with end-organ morbidity. Infants are usually referred for surgical ligation following failure of successful treatment or in the presence of contraindications. The decisions relating to selection for and the timing of referral for surgical ligation remain controversial. In addition, the inherent short- and long-term risks associated with PDA ligation are becoming increasingly recognized. As a result, there is a current shift in opinion and a reluctance to refer infants for the procedure. This article describes the physiological changes occurring before, during, and after PDA ligation; we explore the relationship of these changes to short- and long-term clinical observations in the ligation population. A suggested management approach and future research directions are also discussed.

Introduction

The diagnosis and management of a patent ductus arteriosus (PDA) in preterm neonates poses a major challenge. It is the most common cardiovascular abnormality of prematurity occurring in

about a third of infants below 30 weeks gestation and up to 60% of infants less than 28 weeks.¹ The presence of a PDA is associated with morbidities including: feeding intolerance, necrotizing enterocolitis (NEC), severe intra-ventricular haemorrhage (IVH), metabolic acidosis, renal failure, increased ventilator dependence, bronchopulmonary dysplasia (BPD) and pulmonary haemorrhage.^{2,3} In addition, a persistent ductus arteriosus failing medical treatment is associated with a four-fold increase in mortality.⁴ In a retrospective analysis of 301 infants, mortality rates were higher in infants with a persistent PDA compared to controls (70% vs. 11%). The main cause of death in the PDA population was multi-organ failure. This association remains significant following adjustment for gestation, birth weight, disease severity and co-morbidities including IVH, NEC, and sepsis.⁵ It was also noted that infants with moderate to large PDAs had a higher mortality than those with restrictive ducts. However, in spite of these associations, some still advocate leaving the PDA untreated, arguing that it is an innocent bystander. This approach to management is a result of the failure of randomized studies of prophylactic and early PDA treatment to demonstrate a reduction in the above mentioned morbidities or an improvement in neurodevelopmental outcome.⁵⁻⁸ All of these studies however, treated the PDA as an all-or-none phenomenon, with no consideration of the impact a PDA has on pulmonary or systemic blood flow. This over-simplification of the PDA may explain the negative results of these trials. The PDA in the early life of a premature infant should be regarded as a continuum from being physiologic, and potentially beneficial, to being pathological (when pulmonary vascular resistance drops), leading to systemic hypoperfusion and pulmonary congestion.

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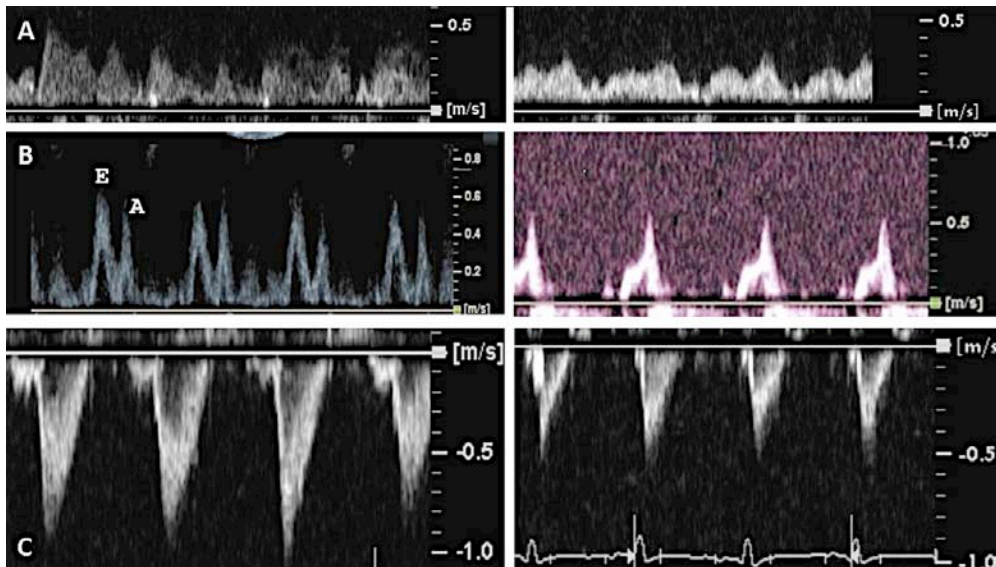


Figure 1. Two-dimensional echocardiography images demonstrating reduction in pulmonary venous peak velocity (Panel A), ratio of passive (E wave) to active (A wave) transmitral flow (Panel B), and left ventricular output (Panel C) after surgical ligation of the ductus arteriosus.

Rationale for Therapeutic Intervention

Prolonged exposure to the effect of left to right transductal shunting leads to increased pulmonary blood flow, and as a consequence, increased pulmonary venous return to the left atrium. The inability of the left ventricle to accommodate the increased blood volume may lead to a rise in LA pressure, and as a result, pulmonary venous congestion. This explains the association of pulmonary haemorrhage with a significant PDA. The left ventricle begins to dilate leading to excessive stretching of the muscle fibres, eventually resulting in reduced contractility. Increased LA pressure may also promote increased left to right shunting across the atrial septum. The results of this are two-fold: an increase in pulmonary blood flow and a reduction in left ventricular output; therein, in turn, effective systemic blood flow. Echocardiography may be used to characterize the magnitude of the shunt volume indirectly through its effects on the pulmonary and systemic circulation (Figures 1, 2). In addition, infants with a significant PDA have lower regional cerebral oxygen saturation, and higher fractional cerebral oxygen tissue extraction when compared to controls when assessed using near-infrared spectroscopy (NIRS). This implies a reduction in cerebral blood flow in the presence of a significant PD.⁹ Prolonged exposure to left to right shunting may also compromise coronary perfusion.¹⁰ Cardiac Troponin T

(cTnT), a cardio-specific marker of myocardial ischemia / damage, rises significantly in infants with a PDA, and subsequently falls dramatically following successful closure.¹¹ Higher cTnT values associated with a PDA were also associated with increased morbidity and mortality, along with worse neurodevelopmental outcome at 2 years of age.^{2,12}

Timing of treatment remains controversial as there is no clear long-term benefit to either prophylactic or early treatment.¹³ Pharmacological closure is only successful in up to 80% of infants treated,¹⁴ with up to 50% in infants less than 25 weeks gestation and less than 750 grams failing to respond to medical therapy.¹⁵ A third of these infants may also relapse following medical closure.¹⁶ Surgical ligation of a PDA is influenced by availability and ease of access to a paediatric cardiothoracic centre. In addition, in some centres surgery may be considered the first-line treatment in infants with NEC, IVH, pulmonary haemorrhage, thrombocytopenia, and severe oliguria. Currently there is no evidence in the literature supporting surgical over medical treatment as a first-line approach.¹⁷ A Cochrane review included one eligible study of prophylactic surgical ligation that enrolled 84 preterm infants. The prophylactic group had ductal ligation performed within 24 hours of life following a pre-specified protocol, while the control group received standard care without indomethacin.

Prophylactic surgical ligation of the PDA resulted in a significant reduction of severe stage NEC, [RR 0.25, 95% CI (0.08, 0.83), p value 0.02, NNT 5], but without any survival advantage. The reduction in NEC probably resulted from the timing of PDA treatment rather than the modality, but the findings are somewhat controversial due to the high incidence of NEC in the control group. In general surgical intervention is contemplated if medical treatment fails. It is possible that delays between attempted medical treatment and surgical ligation may contribute to complications.⁴

Intra operative and Immediate Post-operative Consequences of PDA Ligation

Physiology of the Preterm Myocardium

The preterm myocardium is not conditioned to handle substantial changes in preload or afterload. The biological process leading to contraction of the preterm heart muscle is inefficient and relies on L-type calcium channels as a source of calcium contraction, rather than intrinsic calcium stores.¹⁸ Furthermore, the immature myocytes have a higher surface area to volume ratio to compensate for the lack of the T-tubule system necessary for effective calcium entry into the cell. Therefore, the myocardium of preterm infants is poorly tolerant of increased afterload compared to older children.¹⁹ This is supported by animal and preterm human data showing that velocity of circumferential fibre shortening, a load-dependent measure of contractility, is inversely proportional to end-systolic wall stress.^{20,21} Furthermore, the immature myocardium contains a higher proportion of non-contractile collagen, lower elastin concentrations, and an inefficient process of calcium extrusion from the myocytes. This leads to impaired relaxation and ventricular filling during diastole contributing to diastolic dysfunction.

There is increasing evidence describing a Post ligation Cardiac Syndrome (PLCS) occurring in up to 50% of infants undergoing ligation.²² PLCS is characterised clinically by a fall in systolic blood pressure (usually < 3rd centile expected for age) requiring one or more cardiotropic agents, and increasing ventilator requirements, necessitating an increase in mean airway pressure and FiO₂ by at least 20%. This usually becomes apparent 6 to 12 hours post surgery.^{23,24} These clinical changes coincide with the physiological sequelae described above, and provide clinical validation to the effect of altering load conditions on myocardial



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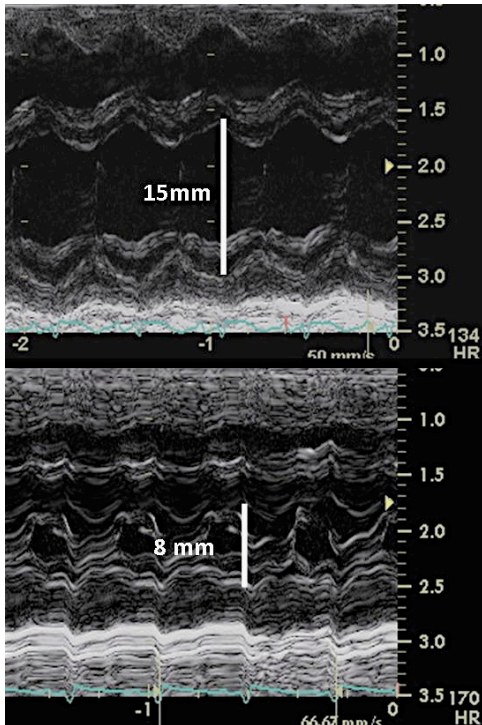


Figure 2. M-mode echocardiography images demonstrating changes in left ventricular cavity size before (Upper Panel) and after (Lower Panel).

function. One paper reported a significantly higher mortality in infants with PLCS compared to controls (33% vs. 11%).²²

Several pre-operative risk factors for post-operative PLCS have been identified. Teixeira et al compared 29 preterm infants that underwent ligation within the first 4 weeks of postnatal life (early), versus 36 infants undergoing ligation beyond that period (late).²⁴ Twenty-seven percent of infants undergoing early ligation required inotropes for low mean BP compared to 5% in the late group. The presence of NEC or pre-operative shock was also predictive of PLCS. There was a negative correlation between age at ligation and need for cardiotropic support. In a prospective trial, the same group demonstrated that infants weighing less than 1000g were more likely to have post operative LVO less than 170 ml/kg/min, lower shortening fraction, systolic BP less than the third centile, and a higher need for inotropes (30% vs. 4%).²³ Further studies have corroborated these findings. Infants less than 26 weeks gestation, and less than 750 – 1000 grams were more likely to develop PLCS.²⁵⁻²⁷ Echocardiography has also been used to facilitate prediction of PLCS. PDA size prior to ligation has a significant negative correlation with post-operative LVO.²⁸ In addition, there is an inverse correlation between peak velocity across the PDA and ventilator dependence post operatively.²⁶ Jain et al also demonstrated that a LVO less than 200 ml/kg/min at 1 hour post operatively predicted 100% of infants that subsequently de-

veloped PLCS at 6 to 12 hours. All the risk factors for PLCS illustrated above highlight the challenges met by the immature myocardium in the face of the dramatic change in loading conditions.

Intra-operative Cerebral Hemodynamic Changes

PDA ligation has been associated with poor neurodevelopmental outcome; therefore, it is important to understand the intra-operative physiological changes that may impact cerebral function. Intra-cerebral hemodynamic changes, and electrical activity during PDA ligation have been studied using several modalities including NIRS, Doppler assessment of cerebral blood flow, and amplitude integrated electro-encephalography (aEEG). Assessment of tissue oxygenation index (TOI) using NIRS has yielded conflicting results. Zaramella et al examined the effect of PDA clipping on cerebral TOI and cerebral blood flow (CBV) using a combination of NIRS and Doppler assessments at three time points: 35 minutes before ligation, and 14 and 27 minutes post PDA clipping.²⁹ They found a drop in TOI indicating increased tissue oxygen extraction but no change in CBV, measured by NIRS or Doppler, following clipping of the PDA. In contrast, more recent studies using NIRS during the ligation process demonstrated a sudden surge in CBV immediately post clipping, returning to pre-operative baseline within 5 to 10 minutes.^{30,31} One study³¹ showed a transient increase in TOI, supporting the observation of increased CBV, lasting up to 20 minutes post ligation. None of the studies demonstrated a change in heart rate or blood pressure during the monitoring period. There are no studies examining the relationship of changes in CBV and TOI to brain injury or long-term neurological outcomes.

Recent studies have demonstrated changes in cerebral electrical activity following surgical ligation. Leslie et al performed continuous amplitude integrated electroencephalography (aEEG) monitoring in a cohort of 17 preterm infants and demonstrated a fall in the lower border of the aEEG trace and decrease in the proportion of patients with aEEG continuity (from 5/17 to 0/17, $p=0.04$) after PDA ligation. Cerebral background activity recovered to pre-operative levels by 24 hours post surgery. Interestingly, lower band width was associated with PDA diameter and gestation on univariate analysis, although the impact of anesthesia was difficult to assess. Lemmers et al performed combined aEEG and NIRS monitoring in 20 preterm infants before and after PDA ligation.⁹ They demonstrated lower cerebral oxygen saturations and increased fractional oxygen extraction during the induction phase. Some of these infants had cerebral oxygen saturations as low as 35%, approximating levels that lead to functional and morphological brain damage in animal experimental models.³² Cerebral oxygen saturation showed

a steady increase in the 24 hours post ligation, with a concurrent decrease in fractional oxygen extraction to values comparable with infants without a PDA. The changes in aEEG background activity were comparable with those seen by Leslie et al,³³ and were most pronounced at 2 hours post clipping. They did note however that infants with the most pronounced drop in cerebral oxygen saturations had the most significant drop in brain activity. These changes coincided with a fall in blood pressure post induction.

The reported anaesthetic technique used in the studies seems uniform. Infants usually receive opioids (fentanyl or sufentanil) and a muscle relaxant (pancuronium) for induction, followed by an opioid infusion to maintain anaesthesia. Inhalation agents are seldom used.³⁴ It is possible that choice or dose of these agents influences electrical brain activity intra-operatively, although neither study was designed to answer this question. Nevertheless, both studies showed an improvement in aEEG background activity by 24 hours post ligation despite the continuous opioid use. Interestingly, Janvier et al demonstrated that ineffective anaesthesia during ligation is associated with an unstable post-operative respiratory course accompanied by hypotension.³⁴

Post-operative Myocardial Adaptation

Surgical ligation of the ductus arteriosus leads to sudden and dramatic changes in cardiovascular physiology of the preterm infant. These changes include a rise in afterload due to the increase in systemic vascular resistance (SVR), and a dramatic fall in preload, due to the sudden reduction in pulmonary blood flow (Figure 3). There has been a recent interest in characterizing these changes and assessing myocardial function adaptation resulting from these changes using echocardiography.

Early studies attempting to demonstrate deterioration in ventricular performance following ductal ligation showed equivocal results. Taylor et al noted a temporal relationship between impaired left ventricular performance and increased systemic vascular resistance, coinciding with changes in arterial pressure in a primate model.³⁵ The first human neonatal study in 1996 by Kimbal et al characterized echocardiography-derived indices of systolic performance, preload and afterload in 14 infants undergoing PDA ligation.³⁶ They demonstrated a rise in blood pressure and systemic vascular resistance following ligation, but failed to demonstrate any change in left ventricular performance. Further examination of the data revealed a trend towards a reduction in both LVO and shortening fraction immediately after ligation, suggesting that the study was limited by a small sample size. More recently, Noori et al studied the effect of PDA ligation on myocardial performance.²⁸ Echocardiography data was obtained 2 hours prior to ligation, 2 hours and 24 hours after ligation in a group of 23

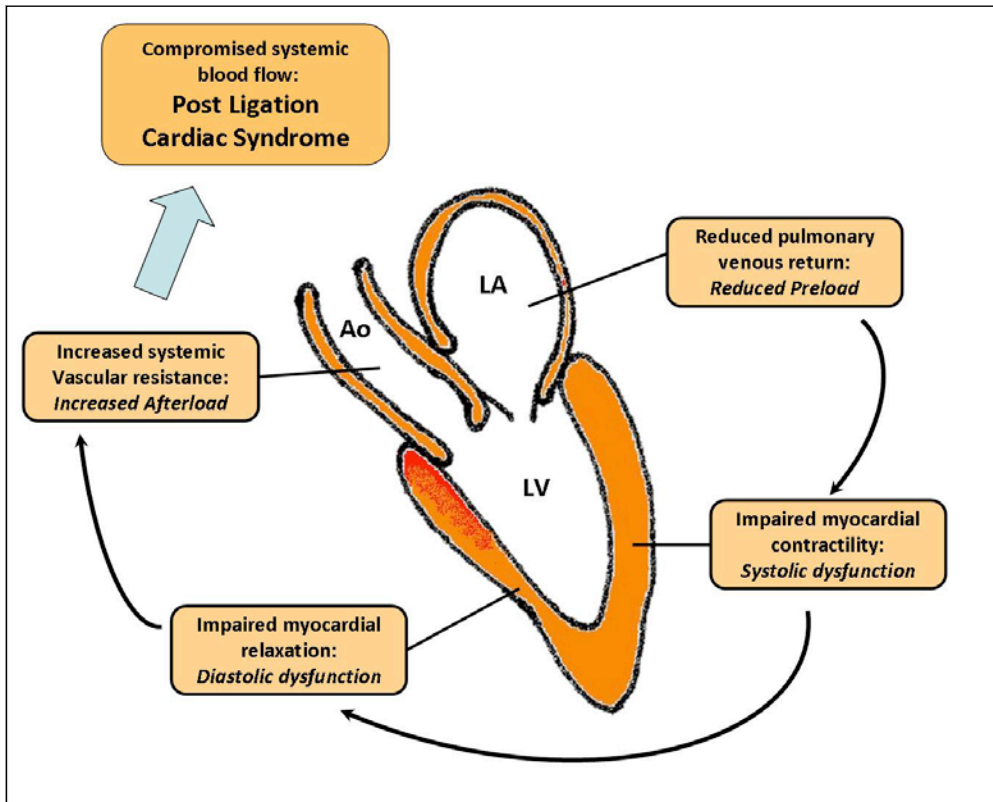


Figure 3. Schematic of cardiovascular physiologic factors contributing to the development of Post-Ligation Cardiac Syndrome.

infants (gestation 26.2 ± 2.2 weeks, birth weight 845 ± 280 grams). They demonstrated a significant increase in SVR, accompanied by a significant drop in LVO, and mitral inflow velocities in the immediate post-operative period. These data support the prior suggested physiological changes that accompany PDA ligation: a reduction in preload and an increase afterload. The group also measured the myocardial performance index (MPI), a global myocardial performance indicator which incorporates both systolic and diastolic function and is less influenced by loading conditions.³⁷ There was deterioration in MPI following ligation, which began to normalise by 24 hours post ligation. Interestingly, there was no difference between the study's time points in the load-dependent measures of systolic function: namely shortening fraction (SF), and the velocity of circumferential fibre shortening (VCFc). This may have resulted from the small sample size, relative insensitivity of these conventional markers of systolic function or the lack of echocardiography evaluation at the time of clinical deterioration. It is worth bearing in mind that the methods used to calculate SVR rely on

the following formula: $(\text{mean arterial pressure} - \text{right atrial pressure}) / \text{LVO}$, therefore, if LVO is significantly compromised due to left heart preload compromise, this formula may overestimate true SVR, although the net rise in diastolic arterial pressure following PDA ligation would suggest otherwise.

Neither of the two described studies assessed myocardial performance at 8 hours post ligation, the time point at which clinical hemodynamic and respiratory deterioration usually become evident in this population. In the largest prospective study to date including 46 infants (gestation 28.5 ± 11.3 , birth weight 1058 ± 272), McNamara et al characterised the effects of PDA ligation on myocardial performance before and after (one, eight, and 24 hours) PDA ligation. The significant decrease in LA: Ao ratio and left ventricular end diastolic diameter (LVEDD) suggest a fall in left heart preload. In addition, impairment in indices LV systolic performance, namely LV shortening fraction and VCFc, was identified eight hours after surgery coinciding with the clinical deterioration. An increase in the slope of the in-

verse relationship between end systolic wall stress and VCFc, suggests the changes in myocardial performance were influenced by LV afterload. The overall reduction in LVO is likely to be a consequence of increased LV exposed afterload and decreased preload, although the relative contribution of each is difficult to evaluate. This study provides the best evidence to suggest that myocardial performance post PDA ligation is adversely affected by the altered loading conditions. Interestingly, infants less than 1000 grams were at greatest risk of compromise, further supporting the idea of the vulnerability of the immature preterm myocardium described above.

Pulmonary Mechanics Following PDA Ligation

The presence of prolonged left to right shunting across the PDA leads to altered pulmonary compliance. In animal model experiments, premature newborn baboons [125 d (67% gestation)], exposed to a moderate-size PDA have impaired pulmonary function and arrested alveolar development and surface area when compared with age-matched fetuses (140 d gestation).³⁸ Several human studies have also demonstrated decreased lung compliance in preterm infants with a PDA compared to controls, but no change in airway resistance. Infants treated with indomethacin also exhibit improved lung compliance following successful medical PDA closure.³⁹⁻⁴¹ More dramatic changes in lung compliance can be observed in preterm infants undergoing PDA ligation. In a group of 16 premature infants, dynamic lung compliance improved significantly, coupled by increases in tidal volume and minute ventilation. It should also be noted that baseline lung compliance prior to PDA ligation was lower than expected values normal for matched controls.⁴² It is therefore prudent to consider these changes following ligation, as maintaining similar ventilator settings in the post-operative period may lead to lung over-distension. This may further compromise vena caval and pulmonary venous flow leading to impairment in ventricular filling and contributing to lower cardiac output.

Short-term Surgical Complications

Several studies have examined the immediate and short-term sequelae of ligation. Surgery related complication include: intra-operative bleeding, pneumothorax, vocal cord paralysis, chylothorax, and phrenic nerve injury. The collective incidence of these complications is usually low.¹⁶ The collaborative trial by Gersony et al showed that babies randomized to

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surgery as primary treatment had a higher incidence of pneumothoraces and retinopathy of prematurity. There was no difference in BPD, IVH, bleeding, sepsis, elevated creatinine, duration of ventilation or duration of stay.⁴³ Nevertheless, PDA ligation is still considered a relatively uncomplicated procedure; as in a large series of 306 ligations, Mikhial et al reported a 2% incidence of intra-operative bleeding, less than 5% incidence of air leaks and no surgically related deaths.⁴⁴ It is also feasible to carry out the procedure in a neonatal intensive care setting which has the advantage of avoiding transport of sick neonates to a tertiary centre and a delay in ligation. In a series of 115 infants operated on in intensive care, there was no surgical morbidity.⁴⁵

Long-Term Complications

The data from the TIPP trial was re-examined to determine whether surgical closure of a PDA is a risk factor for BPD, severe ROP, and neurosensory impairment at 18 months. The clinical course of 426 ELBW infants with a symptomatic PDA, 110 of whom underwent PDA ligation and 316 of whom received medical therapy only with successful PDA closure was reviewed.⁴⁶ Of the 95 infants who survived to 18 months after PDA ligation, 50 (53%) had neurosensory impairment, compared with 84 of the 245 infants (34%) who survived after receiving only medical therapy (adjusted odds ratio, 1.98; 95% CI, 1.18-3.30; $p = 0.009$). Both BPD (adjusted odds ratio, 1.81; 95% CI, 1.09-3.03; $p = 0.02$) and severe ROP (adjusted odds ratio, 2.20; 95% CI, 1.19-4.07; $p = 0.012$) were also more common after surgical PDA closure. Death appeared to be less common in infants who underwent surgical PDA ligation (14 vs. 22%, $p = 0.09$). They concluded that surgical PDA ligation may be associated with increased risks of BPD, severe ROP, and neurosensory impairment in ELBW infants and offered several explanations for this association. First, brain injury secondary to prematurity may have preceded the surgery in some patients; second, infants who underwent surgery may have been sicker with a higher degree of ductal illness severity; third, perioperative or intraoperative events such as hypothermia, cardiorespiratory instability, or exposure to anaesthetic drugs may directly contribute to poor outcome. Anaesthetic drugs that are routinely used during neonatal surgeries have been shown to cause apoptotic neurodegeneration in the developing rat brain.⁴⁷ The latter may be better understood by investigating the

impact of anesthesia on neonatal outcomes after other surgical procedures in premature infants.

A major omission from this analysis was the failure to consider duration of exposure to a hemodynamically significant PDA as a potential contributor, particularly in those patients with end-organ blood flow compromise. It is possible that surgical ligation is a surrogate marker for illness severity. It is also possible that the post-operative hemodynamic instability outlined above, may also contribute to the poor neurodevelopmental outcome, but this has not been studied to date.

In a recent study of 446 infants less than 28 weeks gestation, logistic regression analysis was used to examine the effects of several PDA-related variables (presence of a symptomatic PDA, the number of indomethacin doses used, the ductus response to indomethacin, and the use of surgical ligation) on the incidence of ROP, NEC, BPD, death, and neurodevelopmental impairment.⁴⁸ The infants' immature gestation accounts for most of the predictive effects that the presence of a patent ductus arteriosus and its treatment had on neonatal morbidity. Use of surgical ligation, however, was significantly associated with the development of chronic lung disease and was independent of immature gestation, other patent ductus arteriosus-related variables, or other perinatal and neonatal risk factors known to be associated with chronic lung disease. These findings add to the growing uncertainty about the benefits and risks of surgical ligation during the neonatal period.

Refining Decision-Making

The optimal timing of surgical ligation is still under debate. The competing risks of PDA related morbidity and surgical complications make this decision difficult in many cases. The staging system, based on clinical and echocardiography criteria, proposed by McNamara and Sehgal has streamlined the decision-making process in Toronto with enhanced patient outcomes.⁴⁹ This staging system takes into account clinical characteristics including ventilation, systemic perfusion, along with radiological evidence of pulmonary edema and grades these symptoms in a hierarchical fashion. Similarly, echocardiography criteria to determine myocardial function in addition to markers of pulmonary over circulation and systemic hypoperfusion are also used.³ This composite

approach helps delineate the likely contribution of the ductus arteriosus to the overall clinical state rather than consideration of ductal size alone. In some cases, independent of ductal size, the decision is not to intervene on the basis that the clinical and echocardiography evidence suggests a low volume transductal shunt. Recently Jhaveri et al described a reduction in the incidence of NEC following the introduction of a preoperative stratification system similar to the one described by McNamara.⁵⁰ These data support the need for, and potential benefits of, a more comprehensive clinical and echocardiography assessment of infants undergoing PDA ligation. Both approaches recognize that the hemodynamically significant PDA is not a dichotomous variable, but is a physiologic continuum from biological normality to a pathological disease state with clinical instability and varying effects on bodily organs. We believe surgical ligation should still remain as a treatment option for some infants with a hemodynamically significant PDA, but all patients need comprehensive clinical and echocardiography evaluation to determine the nature of the shunt volume and physiologic consequences. It is prudent to ensure adequate anaesthesia intra-operatively with adequate volume support in anticipation of left-heart preload compromise once the ductus arteriosus is ligated. Targeted neonatal echocardiography (TnECHO) should be used to assess post operative myocardial function. Vasopressors e.g. dopamine, epinephrine should be avoided in the face of increased afterload, and consideration should be given to agents that reduce afterload e.g. dobutamine, milrinone and improve contractility. Volume replacement should be considered in view of the reduced preload. After the decision to ligate the ductus is made, the approach in our center is as follows: a cortisol response stress test is performed to assess the infants stress response and potentially guide post-operative hemodynamic instability. We perform echocardiography assessment one hour post operative to assess left ventricular output. Based on the cohort study mentioned above,⁵¹ infants with a LVO less than 200 mls/kg/min are at a high risk of developing PLCS and therefore receive milrinone in an attempt to reduce afterload and improve diastolic dysfunction. A bolus of normal saline is also given to counteract the effect of reduced preload and prevent any fall in diastolic pressure. Further volume replacement is given if there is evidence of volume depletion especially if there is fluid loss from intra-thoracic drains. Serial blood pressure



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monitoring is performed to ensure that systolic and diastolic pressures do not fall below the third centiles for any given gestation. Intractable blood pressures should be managed with volume, inotropes and steroids replacement if the preoperative stimulation test yielded suboptimal results. Weaning the mean airway pressure should also be considered following ligation as the compliance of the lungs invariably improves.

Conclusion

Infants undergoing PDA ligation face several challenges that may contribute to worst neurodevelopmental outcome. The surgical act of ligation of the ductus arteriosus per se is unlikely to contribute to brain injury, but the processes occurring around the event may have more of an impact. Chronic left to right shunting prior to ligation, intra-operative compromise to cerebral oxygen saturation, and post operative hemodynamic instability may all contribute to brain injury. Further research into characterisation of myocardial function before and after surgery is needed, along with assessment of therapies aiming to improve preload and afterload compromise. The impact of such therapies on neurodevelopment outcome should also be examined.

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Medical News, Products and Information

FDA Clears Expanded Compatibility for INOMAX Drug-Delivery Systems

Ikaria, Inc., a critical care company focused on developing and commercializing innovative therapies for critically ill patients in the hospital and ICU settings, today announced that the Center for Devices and Radiological Health (CDRH) branch of the US Food and Drug Administration (FDA) has granted 510(k) clearance for compatibility of its INOMAX drug-delivery systems with six additional respiratory care devices. The INOMAX DS and the INOMAX DSIR are now compatible with more than 50 makes of ventilators, anesthesia systems and other respiratory care devices.

The INOMAX DS and INOMAX DSIR are proprietary drug-delivery systems that deliver INOMAX[®] (nitric oxide) for inhalation, the only drug approved by the FDA to treat hypoxic respiratory failure (HRF) associated with pulmonary hypertension in term and near-term infants greater than 34 weeks gestational age. HRF is a serious condition in which blood vessels in the lungs constrict, making it difficult to oxygenate blood. INOMAX selectively relaxes pulmonary blood vessels, improves oxygenation and treats HRF in this fragile newborn population.

The FDA's clearance of compatibility with these respiratory care devices makes Ikaria's INOMAX drug-delivery systems fully compatible with most invasive mechanical ventilation methods and non-invasive respiratory strategies used in neonatal intensive care units (NICUs), including continuous positive airway pressure (CPAP) and nasal cannulae. This represents Ikaria's commitment to meet the needs of its customers by allowing clinicians the flexibility to safely deliver INOMAX to critically ill patients using many ventilation strategies.

The INOMAX drug-delivery systems are now compatible with the following additional respiratory care devices: Newport e360; Impact Instrumentation EMV+[®] Ventilator; Teleflex Comfort Flo[™] Humidification System and Nasal Cannula; Dräger Babylog[®] VN500; Dräger Evita Infinity[®] V500, and; Vapotherm Precision Flow[™]. For a complete list of ventilators, anesthesia systems and other respiratory care devices with which INOMAX drug-delivery systems are compatible, please visit www.inomax.com.

The INOMAX DS and INOMAX DSIR drug-delivery systems are part of a comprehensive offering known as the INOMAX therapy package. In addition, to use of Ikaria's proprietary, FDA-cleared drug-delivery systems, the INOMAX therapy package includes INOMAX (nitric oxide) for inhalation, distribution, emergency delivery, technical and clinical assistance, quality maintenance, on-site hospital training, 24/7/

365 customer service, and all related disposable items.

INOMAX[®] is a vasodilator, which, in conjunction with ventilator support and other appropriate agents, is indicated for the treatment of term and near-term (>34 weeks gestation) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, where it improves oxygenation and reduces the need for extracorporeal membrane oxygenation.

INOMAX should not be used in the treatment of neonates known to be dependent on right-to-left shunting of blood. Abrupt discontinuation of INOMAX may lead to a worsening condition. Methemoglobinemia is a dose-dependent side effect of inhaled nitric oxide therapy. Nitrogen dioxide (NO₂) forms rapidly in gas mixtures containing nitric oxide and oxygen, and therefore may cause airway inflammation and damage. Methemoglobin, NO₂, and FiO₂ should be monitored during nitric oxide administration.

For additional information about INOMAX, please visit www.inomax.com.

Ikaria, Inc. is a critical care company focused on developing and commercializing innovative therapies designed to address the significant needs of critically ill patients. The company's lead product is INOMAX[®] (nitric oxide) for inhalation, the only FDA-approved drug for the treatment of hypoxic respiratory failure associated with pulmonary hypertension in term and near-term infants. It is offered through the INOMAX therapy package, an all-inclusive offering of drug product, drug-delivery system, on-site training and 24/7/365 technical assistance and support. The INOMAX therapy package also is marketed in Puerto Rico, Canada, Australia, Mexico and Japan. The company is pursuing a number of new indications with INOMAX. The company also has a number of investigational compounds in development. Ikaria is headquartered in Hampton, NJ, with research facilities in Seattle, WA and Madison, WI, and a manufacturing facility in Port Allen, LA. Please visit www.ikaria.com.

Prenatal Exposure to Certain Antidepressants May Modestly Increase Risk of Autism Spectrum Disorders

Prenatal exposure to Selective Serotonin Reuptake Inhibitors (SSRIs), especially during the first trimester, is associated with a modest increase in the risk of developing an autism spectrum disorder, according to a report published *Online First in the Archives of General Psychiatry*, one of the JAMA/Archives journals.

"The prevalence of Autism Spectrum Disorders (ASDs) has increased over recent years," the

authors write as background information in the article. "Use of antidepressant medications during pregnancy also shows a secular increase in recent decades, prompting concerns that prenatal exposure may contribute to increased risk of ASD."

To evaluate if prenatal exposure to antidepressants, including SSRIs, is associated with an increase in ASD, Lisa A. Croen, PhD, of Kaiser Permanente Northern California, Oakland, and colleagues examined medical records for children drawn from the Childhood Autism Perinatal Study conducted by Kaiser Permanente Medical Care Program in Northern California. The authors included 298 children with ASD (case group) and their mothers, and 1,507 control children and their mothers in the study.

Twenty mothers of children in the case group (6.7%) and 50 mothers of children in the control group (3.3%) had at least one prescription for an antidepressant in the year prior to the birth of the study child. Of the 20 case mothers who were prescribed antidepressants: 13 (65%) were prescribed SSRIs only, two (10%) were prescribed an SSRI in combination with another antidepressant and five (25%) were prescribed one or more non-SSRI antidepressants only. Of the 50 control mothers who were prescribed an antidepressant, 25 (50%) were prescribed SSRIs only, nine (18%) were prescribed an SSRI in combination with another antidepressant and 16 (32%) were prescribed one or more non-SSRI antidepressants only.

After adjusting for maternal and birth factors, mothers of children with ASD were twice as likely to have at least one antidepressant prescription in the year prior to delivery. When compared with women with no antidepressant prescription during the study period, those with a prescription for a SSRI were more than twice as likely to have a child later diagnosed with ASD. This association was not seen for the small group of women who were prescribed a non-SSRI antidepressant only.

Additionally, after adjustment for a history of depression during the year prior to delivery, SSRI exposure during the first trimester remained significantly associated with risk of ASD, as was a history of SSRI exposure at any point during the year prior to delivery. Conversely, no association was seen between risk of ASD and the indication for treatment (mother having a history of depression or any mental health disorder) for the year prior to delivery.

"Although the number of children exposed prenatally to selective serotonin reuptake inhibitors in this population was low, results suggest that exposure, especially during the first trimester, may modestly increase the risk of ASD," the authors conclude. "We recommend that our findings be considered as preliminary

and treated with caution, pending results from further studies designed to address the very complex question of whether prenatal exposure to SSRIs may be etiologically linked to later diagnoses of ASDs in offspring."

Hospital Clinicians Can Now View Up-to-the-Moment ECG Data on iPads, iPhones

GE Healthcare and AirStrip Technologies has announced a secure mobile app empowering clinicians with access to precise, near real-time cardiac information. Data from the GE Healthcare MUSE® Cardiology Information System is now available on iPhones® and iPads,™ via AirStrip Cardiology.™ This enables a continuous flow of electrocardiograph (ECG) data and interactive historical data access, helping mobile clinicians make more informed care decisions. Cedars-Sinai Medical Center in Los Angeles, Texas Health Resources and several other large hospitals and healthcare systems will soon be live with AirStrip Cardiology.

Today, remote physicians commonly view ECG data from static scanned images, which require computer access and easily distort upon zooming. ECGs measure electrical cardiac activities, such as ST elevation, an indication of heart attack risk. Remote ECG measurements are challenging because changes as small as 0.5 millimeters can indicate the presence of a serious or emergency heart condition. AirStrip Cardiology's high resolution can detect such small differences through completely interactive iPad or iPhone views. Unlike traditional remote diagnostics, zooming in on waveforms does not affect visual clarity. With AirStrip Cardiology, clinical information is available from 12- and 15-lead ECGs, supporting high precision levels. Clinicians can view current data and historical tests conducted up to one year ago, in ten-second increments.

A remote cardiologist can now use AirStrip Cardiology to precisely measure ECG waveforms, helping on-site ED clinicians determine, for example, if a patient requires cath lab intervention.

"When I am on call, I need instant access to clinical data to help make informed treatment decisions," said Mark Peterman, MD, an interventional cardiologist on the medical staff at Texas Health Presbyterian Hospital Plano, one of Texas Health Resources' 16 acute-care hospitals. "Traditionally, off-site cardiologists must rely on caregiver descriptions and incomplete information, such as a faxed ECG. Viewing near real-time ECG data from any location, as well as a complete database of prior ECGs, is an incredibly powerful way to increase accuracy of diagnosis."

"Among physicians, there is incredible demand for enterprise medical information on iPhones and iPads," said Darren Dworkin, CIO at Cedars-Sinai Medical Center. "This new appli-

cation introduces secure cardiology decision making anywhere and anytime. The interactive functionality is more advanced than anything else available today and pushes the path toward a day when all clinical hospital information will be available on a mobile platform."

Based on a GE Healthcare and AirStrip global alliance for in-hospital cardiac diagnostics, U.S. hospitals can now purchase AirStrip Cardiology through GE Healthcare. The technology directly links to the GE Healthcare MUSE Cardiology Information System, a central cardiac repository that facilitates ECG analysis, supporting informed clinical decisions. AirStrip Cardiology is an initial step in the collaboration and an important milestone in advancing GE Healthcare's Clinical Information Logistics vision, which reflects the company's commitment to deliver actionable clinical intelligence at the right time and place, supporting quality of care and patient safety.

"Working with mobile health pioneer AirStrip, GE Healthcare is now bringing its unique cardiology heritage and innovation to the iPad and iPhone," said David Ataide, VP & GM of Patient Care Solutions, GE Healthcare. "To make efficient clinical decisions, caregivers need access to clinical intelligence across and beyond hospital boundaries. Offering highly accurate cardiac data on mobile devices supports our commitment to deliver comprehensive clinical information wherever it is needed."

"Our vision is to eliminate geographic and logistical barriers associated with clinical care," said Cameron Powell, MD, President and Chief Medical Officer, AirStrip. "GE Healthcare's global presence and cardiac innovations will help us expand our powerful mobile apps to cardiologists worldwide."

A native application, AirStrip Cardiology is specifically designed for iPad and iPhone screens, functionality and mobile environments. Instead of clicking through each step with a mouse or keyboard, clinicians can use their fingers and touch to quickly zoom and switch between viewing formats.

In 2010, the FDA cleared the platform behind AirStrip Cardiology. This technology is HIPAA compliant and uses state-of-the-art security protocols and cloud computing to securely transmit information rather than allowing data to reside on the mobile device, thereby enhancing privacy protections. For more information: www.airstriptech.com.

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Global Neonatology Today Monthly Column- The Information Gap and the Millennium Developmental Goals (MDGs)

By Dharmapuri Vidyasagar, MD, FAAP, FCCM

Over the last 12 months this column has attempted to explain the core goals of MDGs. As the target year of 2015 is fast approaching, increasing efforts are being made to insure that implementation of MDGs across the globe are met. Unfortunately, there are several barriers, and implementation varies in different countries.

The success of implementation of the eight Millennium Developmental Goals is dependent mainly on the governments and policy makers. Implementation of programs to achieve MDGs by 2015 also requires sufficient funding. But all these efforts can be successful, only if the public and the consumers are well-informed about the concepts of health and ill-health. Education improves health awareness. Extensive studies indicate education is an important proxy for people to seek health care, and thereby stay healthy. Unfortunately, the data shows that there is a wide gap in health awareness among the lay public, as well as health care givers around the world. A group of individuals led by Dr. Neil Pakenham-Walsh in UK has launched an ambitious global project: Health Information For All by 2015 (HIFA2015). They state, "Every day, tens of thousands of children, women and men die needlessly for want of simple, low-cost interventions – interventions that are often already locally available. A major contributing factor is that the mother, family caregiver or health worker does not have access to the information and knowledge they need, when they need it, to make appropriate decisions and save lives."

Here are some examples of information issues among the lay public and health care personnel around the world.

1. Worldwide, 1.8 million children die every year from dehydration due to diarrhea. Many women in developing countries believe fluid should be withheld rather than replenishing the fluids in babies with diarrhea. In one study, 4 in 10 mothers in India believed that they should withhold fluids if their baby develops diarrhea.
2. Seven in 10 children with malaria treated at home are mismanaged, contributing to 2000 deaths every day in Africa alone. The gaps in knowledge about health problems are not limited to lay public!
3. According to studies, 8 in 10 caregivers in developing countries do not know the two key symptoms of childhood pneumonia – fast and difficult breathing – which indicate the need for urgent treatment. Only 20% of children with pneumonia receive antibiotics

despite wide availability, and 2 million die each year.

4. Three in 4 doctors caring for sick children in district hospitals in Bangladesh, Dominican Republic, Ethiopia, Indonesia, Philippines, Tanzania, and Uganda had poor basic knowledge of leading causes of child death, such as childhood pneumonia, severe malnutrition, and sepsis.
5. Four in 10 family doctors in Pakistan used tranquilizers as their first-line treatment for hypertension.
6. Seven in 10 women giving birth in health facilities in Africa and South Asia were incorrectly managed during the 3rd stage of labour, predisposing them to postpartum hemorrhage. Postpartum hemorrhage kills more than 300 women every day in the developing world.
7. The typical quality doctor in a government primary health centre has a more than 50-50 chance of prescribing a harmful treatment according to a study in India.

It is recognized that it is not the fault of health-care providers or the public, but it is the lack of access to information. It is important that the latest information is made available to all the health care providers around the world.

"As the target year of 2015 is fast approaching, increasing efforts are being made to insure that implementation of MDGs across the globe are met. Unfortunately, there are several barriers, and implementation varies in different countries."

Healthcare providers can only function effectively if their basic professional needs are met. That is the objective of HIFA2015.

We in the developed countries have the obligation to accelerate the diffusion of knowledge to our colleagues across the globe. The year 2015 is fast approaching!

Source: www.HIFA2015.org

"The Clock is Ticking!"

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