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## Echocardiographic Markers of a Haemodynamically Significant Ductus Arteriosus

By Arvind Sehgal, MD and  
Patrick J. McNamara, MD

Patent Ductus Arteriosus (PDA) is a common neonatal problem, with rates of 40–55% in babies born less than 29 weeks' gestation; but the relationship between the ductus arteriosus and acute physiological change that either acutely or chronically leads to organ damage and neonatal morbidity is unclear [1,2]. Put simply is the PDA an "innocent bystander" or is it pathological to the extent that early detection and intervention is warranted to prevent neonatal morbidity? The traditional assumption that "patency" implies "problematic" is an oversimplification. Physiologically, it is plausible that a major systemic to pulmonary (left-to-right) shunt can lead to cardiorespiratory instability and morbidity in extremely low birth weight (ELBW) infants. The nature of the instability is secondary to pulmonary overcirculation / edema, which in turn may lead to reduced lung compliance and/or leakage of plasma proteins causing the need for increased ventilation (eg, chronic lung disease); and/or systemic hypoperfusion (eg, necrotising enterocolitis (NEC), acute renal impairment or low cardiac output state) [3]. The lack of evidence supporting causality [4,5] failure of medical treatment in some cases, and the inherent risks of medical [6,7] or surgical treatment options [8] has led some investigators to question whether intervention is necessary. The traditional definition of a PDA, which forms the basis of clinical trials

conducted to date, does not take into account physiological variability or the magnitude of clinical effects attributable to a ductal shunt. This approach may account, in part, for the failure to demonstrate any beneficial effects of therapy. A more logical approach is to consider a hemodynamically significant ductus arteriosus (HSDA); a physiologic continuum with a heterogeneity of clinical influence dependant on the volume of the transductal shunt and the ability of the immature myocardium to adapt. Therefore, the assignment of a diagnosis of HSDA requires careful consideration of the degree of clinical compromise and the magnitude of the hemodynamic disturbance on functional echocardiography (fECHO) evaluation.

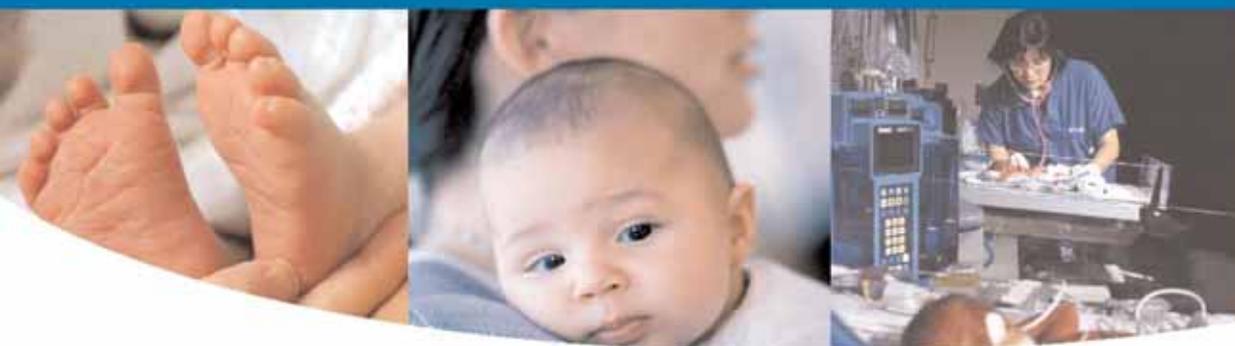
In most centers, the attending physician will use clinical signs and transductal diameter alone to make a diagnosis of significant PDA. This definition is unacceptable, as it does not consider the magnitude of the transductal shunt or the degree of hemodynamic disturbance. A more comprehensive approach would be to combine clinical markers of illness severity with echo-derived markers of hemodynamic disturbance. We have previously proposed a "PDA staging" system that recognises the heterogeneity in clinical and echocardiography significance, similar in outline to the classifications used in NEC or hypoxic-ischaemic encephalopathy (HIE) [9]. This classification recognises that HSDA is a clinical continuum in which the spectrum of disease ranges from mild to severe de-

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**Table 1. Comparison of Echocardiographic Markers of HSDA where LVO = left ventricular output, SVC = superior vena cava, LVSTI = left ventricular stroke volume index, IVRT = isovolumic relaxation time, PWD = pulse wave Doppler, CWD = continuous wave Doppler, PA = pulmonary artery. (empty boxes implies data not available)**

Feature quantified	Modality / Position of sample gate	No PDA	Small	Moderate	Large
Transductal diameter (mm)	Two-dimensional, short axis view	0	< 1.5	1.5-3	> 3
Left atrial: aortic ratio	M-mode, long axis view	1.13 ± 0.23	< 1.4:1	1.4 -1.6:1	> 1.6:1
Left ventricular: aortic ratio	M-mode, long axis view	1.86 ± 0.29	-	2.15 ± 0.39	2.27 ± 0.37
Ductal velocity $V_{max}$ (cm/s)	PWD at pulmonary end of duct	0	> 2	1.5-2	< 1.5
Antegrade PA diastolic flow (cm/s)	PWD within main pulmonary artery	0	0-20	> 20	-
Antegrade PA diastolic flow (cm/s)	PWD within left pulmonary artery	0	>30	30-50	> 50
Retrograde diastolic flow (cm/s)	CWD within descending Ao (% of forward flow)	10	< 30	30-50	> 50
Aortic stroke volume (ml/kg)	PWD of LV outflow tract	≤ 2.25	-	-	≥ 2.34
Left ventricular output (ml/kg/min)	PWD of LV outflow tract	190-310	-	-	> 314
LVO / SVC flow ratio	PWD of flow in superior vena cava	2.4 ± 0.3	-	-	4.5 ± 0.6
LVSTI ratio	M-mode of aortic valve	0.34 ± 0.09	-	0.26 ± 0.03	0.24 ± 0.07
E wave / A wave ratio	Transmitral Doppler	< 1	< 1	1-1.5	> 1.5
IVRT (ms)	Between mitral & aortic valves	> 55	46-54	36-45	< 35

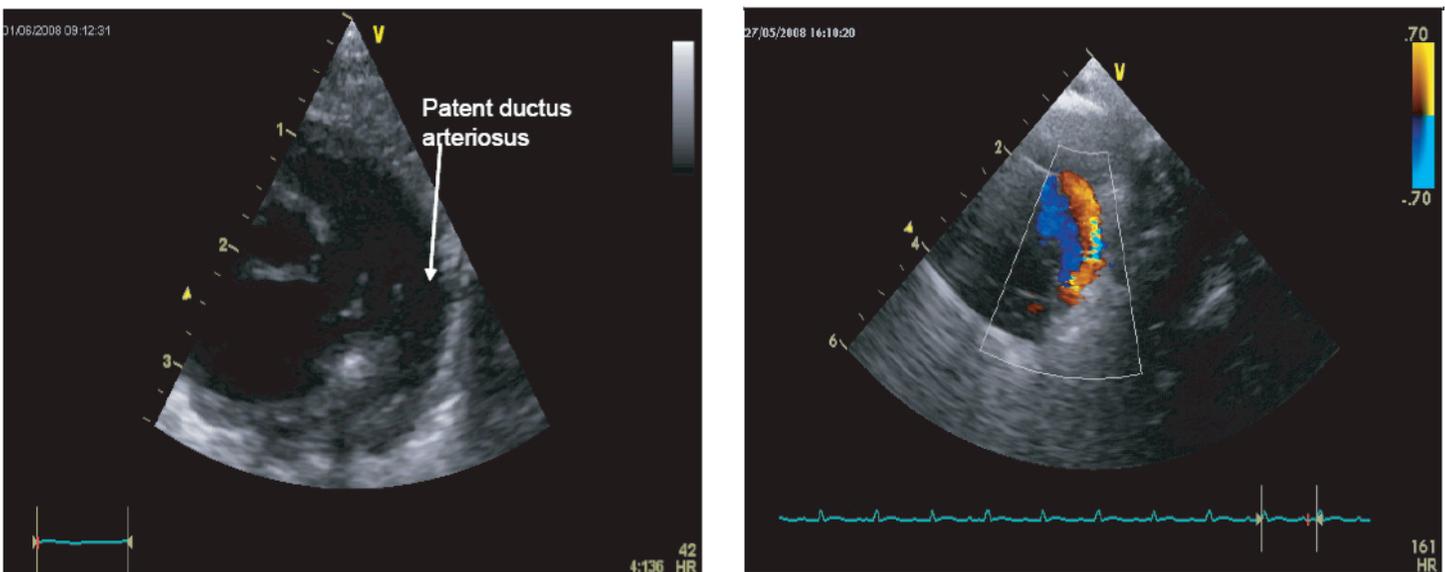


Figure 1. Two dimensional (left panel) and color Doppler (right panel) images of a patent ductus arteriosus (PDA) with left-to-right flow (red jet).

pending on the magnitude of the ductal shunt. The merits of a illness severity staging system has recently been demonstrated in HIE; where a beneficial effect from selective head cooling was only seen in neonates with moderate but not severe HIE [10].

In this review, we discuss the value of echocardiography markers of ductal significance, which may facilitate determining the magnitude of the hemodynamic compromise. These markers include estimates of ductal size, left heart volume loading and systemic blood flow (Table 1).

### 1. Ductal size

The ductus arteriosus is identifiable from a traditional short axis view or suprasternal notch approach where it may be visualised in its entirety (Figure 1). A transductal diameter of >1.5 mm has been proposed as significant on the basis that at this cut-off end-organ hypoperfusion occurs [10-13]. The current definition of an HSDA is problematic and almost exclusively based on size. A definition, based exclusively on transductal diameter, is somewhat limited, as it does not consider clinical factors such as patient size or maturation. In addition, the ductus is not likely to be static and may be influenced by respiratory variation and other biological factors. Operator de-

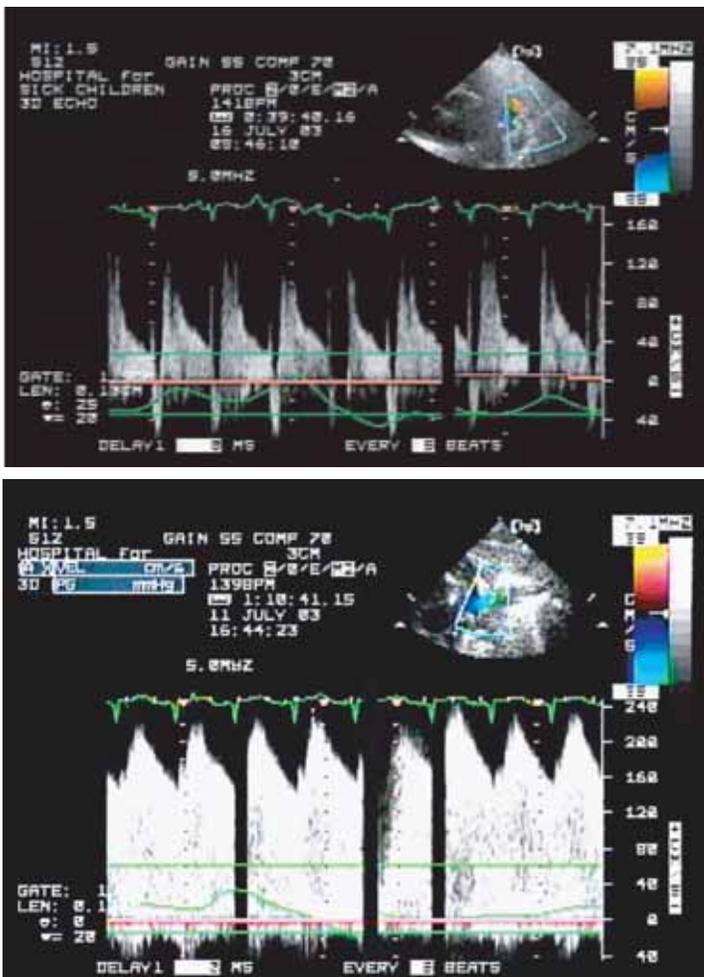


Figure 2. Pulse-wave Doppler interrogation of the ductus arteriosus at the pulmonary end demonstrates pulsatile unrestrictive flow (top panel) in a widely patent vessel and high velocity restrictive flow (lower panel) in a closing vessel.

pendant factors may also influence the accuracy of a diagnosis of HSDA. Errors in the estimation of transductal diameter may result from poor quality two-dimensional (2D) images or excessive color flow Doppler gain. Real-time three-dimensional echocardiography may provide a more accurate estimate of ductal size and the volume of the transductal shunt, although the techniques have not yet been refined for preterm infants [14].

**2. Direction and Pattern of Ductal Flow**

The direction and volume of the transductal shunt is dependant on pulmonary and systemic vascular resistance. Previous stud-

*“Patent ductus arteriosus (PDA) is a common neonatal problem, with rates of 40– 55% in babies born less than 29 weeks’ gestation; but the relationship between the ductus arteriosus and acute physiological change that either acutely or chronically leads to organ damage and neonatal morbidity is unclear [1,2].”*

ies have designated the duct as closing/restrictive or unrestrictive and pulsatile according to pulse wave (PW) Doppler flow patterns (Figure 2), patterns which guide treatment decisions [15]. A large left to right shunt has a pulsatile flow pattern with the highest velocity at end-systole. The peak velocity at the end of diastolic phase is usually very low and occasionally zero. This implies that the relative pulmonary and aortic pressures are equal at end diastole. The ratio of peak systolic: diastolic velocity can be as high as 4:1 [15]. The peak systolic velocity is usually less than 1.5 m/s when the ductus is unrestrictive [9]. As the ductus constricts, flow velocity increases as blood accelerates across a narrower vessel leading to a reduction in the peak systolic: diastolic ratio. Quantification of the transductal flow volume would provide the most accurate estimate of hemodynamic compromise; however, this calculation is not feasible with conventional 2D imaging techniques due to the tortuosity of the duct, variability in transductal diameter across its course and the turbulent rather than laminar nature of flow. The magnitude of the transductal shunt is influenced by both transductal resistance and the ability of the immature myocardium to adapt to increased preload. Calculation of the ratio of right (Qp) to left ventricular (Qs) outputs may provide a surrogate estimate of the degree of transductal flow; however, this measurement may also be influenced large transatrial shunts.

**3. Quantification of Left Heart Volume Loading**

The quantification of left heart size is important, as it is a surrogate of pulmonary overcirculation. The ratio of left atrial to trans-aortic diameter (LA:Ao) derived using m-mode imaging from a long-axis approach is the most well recognised surrogate of ductal significance and was first described by Silverman in 1974 [17]. Other authors have suggested that the rate of ductal misclassification is lowest when the LA: Ao ratio was greater than 1.4 [18]. The ratio of left ventricular to trans-aortic diameter (LV: Ao), where the LV is measured as an end diastolic dimension after obtaining a parasternal long axis view and dropping M-mode cursor across the interventricular septum into the left ventricle at the tips of mitral valve has also been previously proposed as a surrogate marker. Data from a study of 1500 infants without PDA and 415 infants from the PDA group suggests a value of > 2.1 provides the lowest mis-



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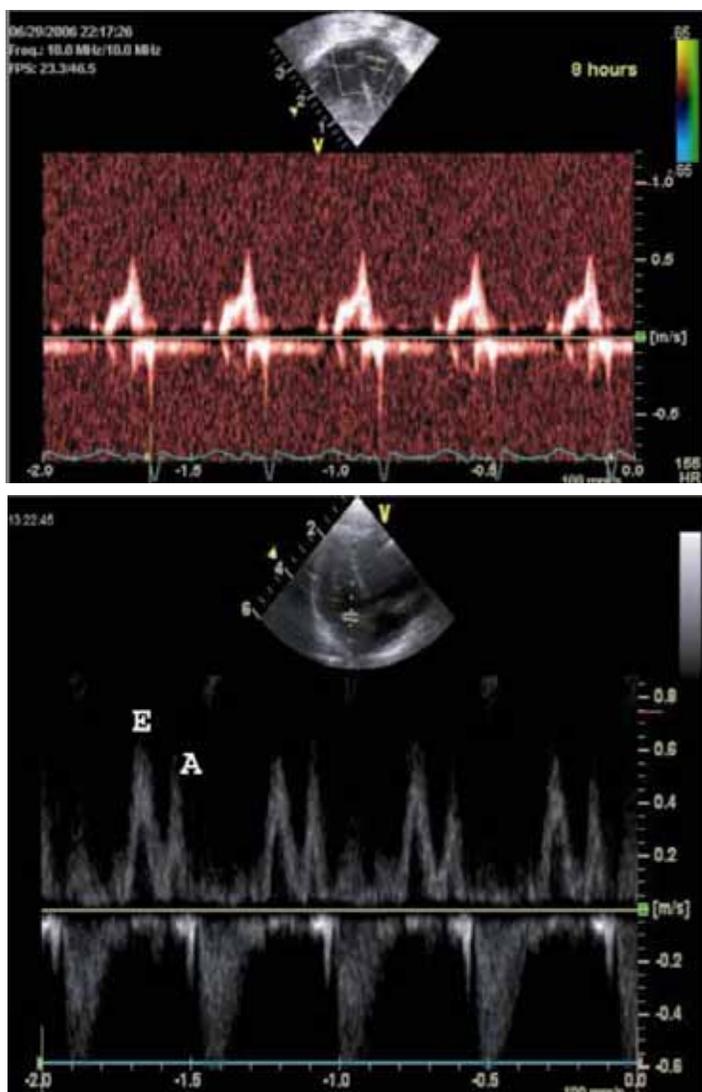


Figure 3. Transmitral flow demonstrates a normal E:A wave ratio  $< 1.0$  (top panel) in the presence of a closed ductus arteriosus, but an E:A wave ratio  $> 1.0$  (lower panel) in the presence of a hemodynamically significant ductus arteriosus.

classification rate [18]. Independently, these markers have poor sensitivity and specificity, which may relate to a number of factors. These include both patient related factors such as patient hydration, left ventricular performance or transatrial shunting and operator dependant factors which may lead to over, or underestimation of these single dimensional measurements. The reliability of left ventricular end - diastolic dimension (LVEDD), or LVEDD: Ao ratio is equally poor [18]. Quantification of pulmonary venous flow may provide the best measure of pulmonary over-

circulation; however, accurate estimation of flow is challenging due to the tortuosity of the veins and variability of flow between veins. We have found transmitral Doppler flow measurements to be a useful marker of left atrial pressure / volume loading. In premature infants transmitral passive flow (E wave) is less than active flow (A wave) due to poor myocardial compliance and impaired diastolic performance [19,20]. The result is an E:A wave ratio of  $< 1.0$ . This differs from the term neonate, where the passive flow phase dominates and the E:A ratio  $> 1.0$ . In neonates with a HSDA, we have identified an increase in passive transmitral flow due to increased left atrial pressure, which leads to pseudonormalization of the E:A ratio  $> 1.0$  resembling the normal term neonatal pattern [19]. The trace reverts to the typical preterm pattern following PDA ligation (Figure 3). The Isovolumic Relaxation Time (IVRT) reflects the time between closures of the mitral valve and opening of the aortic valve and decreases in neonates with a HSDA due to early pressure-related valve closure / opening. The other potential effects of volume loading of the left heart include mitral valve regurgitation and stretching of the interatrial septum leading to increase in the size of the atrial septal defect. These parameters have not subjected to scientific evaluation in any prospective study to date.

#### 4. Doppler Interrogation of the Pulmonary Artery

Flow in the pulmonary artery is typically laminar, exclusively systolic with a  $V_{max} < 1.5$  m/sec. The presence of a HSDA leads to diastolic flow in the main and branches of the pulmonary artery with a turbulent systolic flow pattern. The magnitude of diastolic flow in the left and main pulmonary arteries (Table 1) correlates well with ductal significance [21,22]. The size of the "red" colour jet and the distance it travels depends on the amount of left-to-right flow into the pulmonary artery [16]. A tiny/insignificant shunt causes a narrow jet, which just reaches the pulmonary artery, whereas larger shunts are wider, and may reach the pulmonary valve. This technique has limitations, as high velocity flow through a narrow duct may be high enough to travel deep into the pulmonary artery. It is important to appreciate that the distance travelled by the colour jet relates to its speed as well as the volume. A relatively small duct with high aortopulmonary pressure difference may produce a jet, which reaches a long way into the pulmonary artery. It is important to appreciate that the distance travelled by the colour jet relates to its speed as well as the volume. A relatively small duct with high aortopulmonary pressure difference produces a jet, which reaches a long way into the pulmonary artery.

#### 5. The Phenomenon of Ductal Steal

The ductus is a conduit connecting vascular circuits with differential resistance, which leads to blood flow along the path of least resistance. The consequence is significant systemic to pulmonary blood flow during systole and reversal of normal aortic flow during diastole (ductal steal), which also enters the pulmonary artery. The clinical consequence is low diastolic blood pressure. In extremely low birth weight infants, both low systolic and diastolic pressures may occur due to the inability of the immature myocar-

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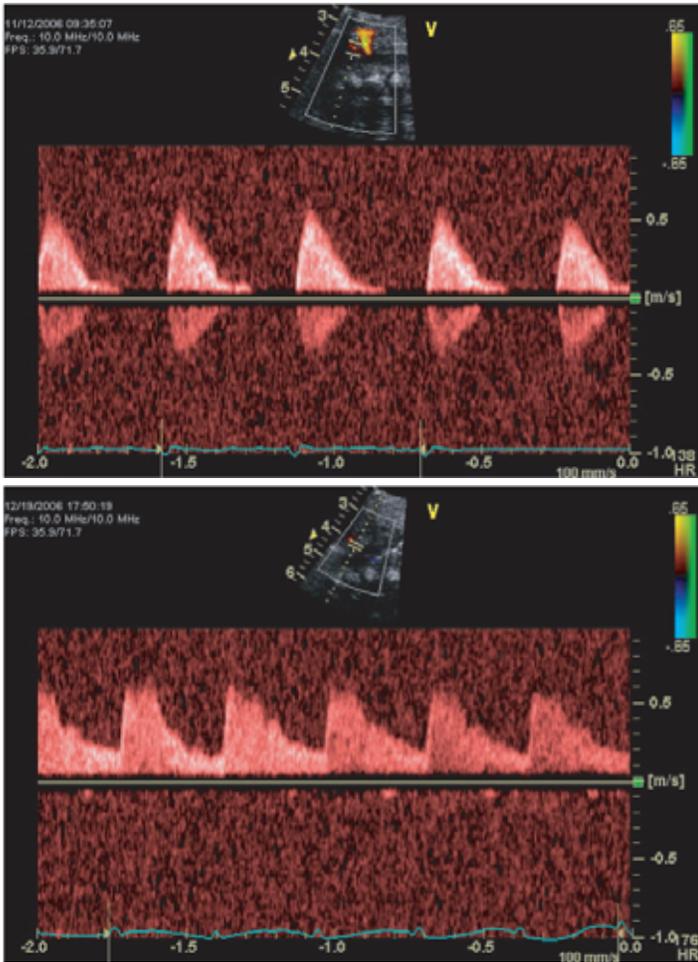


Figure 4. Pulse-wave Doppler interrogation of the superior mesenteric artery demonstrates loss of normal diastolic flow (top panel) in the presence of a hemodynamically significant ductus arteriosus and restoration of diastolic flow (lower panel) following surgical ligation.

dium to increase its stroke volume in an attempt to support cardiac output. The combined effect of low diastolic pressure and ductal steal is regional hypoperfusion of major systemic vessels including the cerebral, splanchnic and renal arteries (Figure 4). Absent or retrograde diastolic cerebral blood flow is said to be present at all times in babies requiring duct ligation, and rare in babies without a duct [23]. Acute renal failure, bowel ischemia and intracranial hypoxic-ischemic injury are morbidities commonly seen in neonates with a HSDA [3,24]. Ductal closure leads to normalization of diastolic flow [19,25]. Serwar et al demonstrated a linear relationship between the ratio of retrograde to antegrade aortic flow and the size of the transductal shunt as determined by radionuclide angiography [26]. Retrograde diastolic flow may account for greater than 50% of forward flow in neonates with a large HSDA (Table 1). Retrograde diastolic flow in the descending aorta also occurs in patients with severe aortic regurgitation or an aortopulmonary window; however, is rarely seen in premature infants. The ratio of the pulsatility index of left pulmonary artery (Rp) to that of descending aorta (Rs) may also predict ductal significance. The pulsatility index is calculated according to the following formula [peak systolic velocity (SysVmax) - peak diastolic velocity (DiasVmax) / SysVmax]. A significant negative correlation was identified between the Rp/Rs index and the pulsatility index

of the superior mesenteric artery, after controlling for ductal size ( $r=-0.476$ ,  $p<0.008$ ). The authors concluded that the Rp/Rs index is useful as an indicator of ductal steal [27].

**6. Left Ventricular Output (LVO)**

Cardiac output is determined by calculating flow across the left ventricular outflow tract. This involves PW Doppler interrogation of the left ventricular outflow tract from a five chamber apical view to determine the aortic velocity time integral (stroke distance) and estimating the aortic root diameter from a long-axis view. As the magnitude of the left-to-right transductal shunt increases, stroke volume increases both to support systemic blood flow and in response to increased left heart end-diastolic dimensions and the Frank Starling relationship. The cumulative effect is an increase in LVO, which may be as much as 60%. In a study by Walther et al, an aortic velocity time integral measurement of greater than 12 cm has been shown to have comparable specificity to an LA: Ao ratio > 1.4 in neonates < 32 weeks gestation a HSDA. Infants with a symptomatic PDA had a greater left ventricular stroke volume (> 2.34 ml/kg Vs < 2.25 ml/kg) and LV output (> 314 ml/kg/min Vs 190-310 ml/kg/min respectively) when compared to infants with a closed duct [28]. These effects are less likely in extremely low birth weight infants due to myocardial immaturity or in the concomitant presence of left ventricular dysfunction. The typical clinical manifestation is refractory hypotension with lactic acidosis. The ductus arteriosus should be re-evaluated when there is restoration of normal myocardial performance after commencement of cardiotropic support.

**7. Left Ventricular Systolic Time Intervals (LVSTI)**

Left ventricular systolic time intervals are a surrogate of left ventricular performance and correlate well with other measures of myocardial function [29]. Left pre-ejection period (LPEP) is the time from start of QRS complex on ECG to opening of the aortic valve on a long axis m-mode view. Left ventricular ejection time (LVET) is measured either from the same long axis m-mode view or from an aortic pulse-wave Doppler trace from the 5-chamber view. The normal value for LPEP in this population is  $45 \pm 5$  milliseconds (ms) and for LVET is  $177 \pm 16$  ms. LVSTI is calculated as the LPEP/LVET ratio. The potential effects of a HSDA include a reduction in LPEP and an increased in LVET leading to an overall

	Normal Infants	Infants with PDA	p values
Left atrial: Aortic ratio	1.13 ± 0.23	1.46 ± 0.36	< 0.001
Left ventricular: Aortic ratio	1.86 ± 0.29	2.15 ± 0.39	< 0.001
LVSTI ratio	0.34 ± 0.09	0.26 ± 0.1	< 0.001
% Δ D	31.2 ± 7.2	33.6 ± 8.7	NS
mVCFc	1.8 ± 0.49	1.85 ± 0.61	NS

*LVSTI = left ventricular stroke volume index, mVCFc = mean rate corrected velocity of circumferential fiber shortening (index of myocardial contractility), % ΔD = percentage change in left ventricular internal dimension*

decline in LVSTI [30]. Studies of LVSTI in preterms with a suspected HSDA (Table 2) have shown values  $\leq 0.27$  to be associated with the least misclassification rate [18]. Other investigators have demonstrated an LVSTI  $\leq 0.3$  as strongly suggestive of a clinically significant PDA; no infants with a clinically significant left to right ductal shunt had a ratio of  $< 0.3$  [30]. LVSTI may be an unreliable marker of HSDA in neonates with impaired myocardial performance, which characteristically leads to lengthening of LPEP and shortening of LVET.

**8. Novel Surrogate Markers**

Hajjar and colleagues have proposed the left ventricular output to superior vena caval (LVO/SVC) flow ratio as an additional criterion for evaluating the magni-

tude of the ductal shunt [31]. They demonstrated that the flow of ductal shunt is directly proportional to LVO/SVC ratio and may be derived according the following calculation: transductal flow =  $0.37 \times$  total systemic blood flow [(LVO/SVC)  $-2.7$ ]. The LVO/SVC ratio may be a more reliable estimation of the ductal flow, as it is unaffected by transatrial flow, unlike other markers. Although a precise threshold for this ratio is not known, the authors chose a ratio of  $\geq 4$  to define a HSDA and concluded that the LA: Ao ratio, ductal diameter, mean flow velocity of LPA and end diastolic velocity of the LPA correlated significantly with the LVO/SVC ratio. Our group has recently proposed a HSDA staging system (Table 3) based on clinical and echocardiography markers in an attempt to provide an overall appraisal of the magnitude of the impact

of the shunt [9]. In isolation, these markers are poorly predictive; however, in combination, they provide a more holistic appraisal of the ductus, which may facilitate differentiating a HSDA from the innocent bystander ductus. These markers have facilitated triaging and prioritizing neonates for surgical ligation at our centre by providing a valuable insight into physiological changes attributable to the ductus arteriosus [9]. In addition, they are useful in monitoring response to therapeutic intervention particularly in the immediate postoperative period in the form of Post Ligation Cardiac Syndrome (hemodynamic instability and impaired myocardial performance). The incorporation of ductal staging into trials of therapeutic intervention may assist with the identification of patients who have a beneficial outcome.

**Table 3. Proposed Staging System for Determining the Magnitude of the Haemodynamically Significant Ductus Arteriosus (HSDA),** which is based on clinical and echocardiography criteria where OI = oxygenation index, NCPAP = nasal continuous positive airway pressure, MAP = mean airway pressure, BP = blood pressure, NEC = necrotizing enterocolitis, 2D = two dimensional, DA  $V_{max}$  = ductus arteriosus peak velocity, LA: Ao ratio = left atrium to aortic ratio, E/A = early passive to late atrial contractile phase of transmitral filling ratio, IVRT = isovolumic relaxation time. Detailed discussion of the echocardiography parameters is beyond the scope of this review article. *Reproduced with permission from Archives of Disease in Childhood -Fetal & Neonatal Edition 2007: 92:F424-F427, McNamara PJ, Sehgal AS: A rationale approach to the hemodynamically significant ductus arteriosus. The need for disease staging!*

Clinical		Echocardiography	
C1	<i>Asymptomatic</i>	E1	No evidence of ductal flow on 2D or Doppler interrogation
C2	<p><i>Mild</i></p> <ul style="list-style-type: none"> <li>Oxygenation difficulty (OI<math>&lt;6</math>)</li> <li>Occasional (<math>&lt; 6</math>) episodes of oxygen desaturation, bradycardia or apnoea</li> <li>Need for respiratory support (NCPAP) or mechanical ventilation (MAP<math>&lt;8</math>)</li> <li>Feeding intolerance (<math>&gt; 20\%</math> gastric aspirates)</li> <li>Radiologic evidence of increased pulmonary vascularity</li> </ul>	E2	<p><i>Small non-significant Ductus Arteriosus</i></p> <ul style="list-style-type: none"> <li>Transductal diameter <math>&lt; 1.5\text{mm}</math></li> <li>Restrictive continuous transductal flow (DA <math>V_{max} &gt; 2.0 \text{ cm sec}^{-1}</math>)</li> <li>No signs of left heart volume loading (e.g. mitral regurgitant jet <math>&gt; 2.0 \text{ cm sec}^{-1}</math> or LA:Ao ratio <math>&gt; 1.5:1</math>)</li> <li>No signs of left heart pressure loading (e.g. E/A ratio <math>&gt; 1.0</math> or IVRT <math>&gt; 45</math>)</li> <li>Normal end-organ (e.g. superior mesenteric, middle cerebral) arterial diastolic flow</li> </ul>
C3	<p><i>Moderate</i></p> <ul style="list-style-type: none"> <li>Oxygenation difficulty (OI 7-14)</li> <li>Frequent (hourly) episodes of oxygen desaturation, bradycardia or apnoea</li> <li>Increasing ventilation requirements (MAP 9-12)</li> <li>Inability to feed due to marked abdominal distension or emesis</li> <li>Oliguria with mild elevation in plasma creatinine</li> <li>Systemic hypotension (low mean or diastolic BP) requirement a single cardiotropic agent</li> <li>Radiologic evidence of cardiomegaly or pulmonary edema</li> <li>Mild metabolic acidosis (pH 7.1- 7.25 and/or base deficit -7 to -12.0)</li> </ul>	E3	<p><i>Moderate HSDA</i></p> <ul style="list-style-type: none"> <li>Transductal diameter 1.5-3.0 mm</li> <li>Unrestrictive pulsatile transductal flow (DA <math>V_{max} &lt; 2.0 \text{ cm sec}^{-1}</math>)</li> <li>Mild-moderate left heart volume loading (e.g. LA:Ao ratio 1.5 to 2:1)</li> <li>Mild-moderate left heart pressure loading (e.g. E/A ratio <math>&gt; 1.0</math> or IVRT 36-45)</li> <li>Decreased or absent diastolic flow in superior mesenteric, middle cerebral or renal arterial</li> </ul>
C4	<p><i>Severe</i></p> <ul style="list-style-type: none"> <li>Oxygenation difficulty (OI <math>&gt;15</math>)</li> <li>High ventilation requirements (MAP <math>&gt;12</math>) or need for high frequency modes of ventilation</li> <li>Profound or recurrent pulmonary haemorrhage</li> <li>“NEC-like” abdominal distension with tenderness or erythema</li> <li>Acute renal failure</li> <li>Hemodynamic instability requiring <math>&gt; 1</math> cardiotropic agent</li> <li>Moderate-severe metabolic acidosis (pH <math>&lt; 7.1</math>) or base deficit <math>&gt; -12.0</math></li> </ul>	E4	<p><i>Large HSDA</i></p> <ul style="list-style-type: none"> <li>Transductal diameter <math>&gt;3.0 \text{ mm}</math></li> <li>Unrestrictive pulsatile transductal flow</li> <li>Severe left heart volume loading (e.g. LA:Ao ratio <math>&gt;2:1</math>, mitral regurgitant jet <math>&gt; 2.0 \text{ cm sec}^{-1}</math>)</li> <li>Severe left heart pressure loading (e.g. E/A ratio <math>&gt; 1.5</math> or IVRT <math>&lt; 35</math>)</li> <li>Reversal of end-diastolic flow in superior mesenteric, middle cerebral or renal arteries</li> </ul>



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### Conclusion

The lack of a standardised approach in determining hemodynamic significance is a major barrier towards better understanding the clinical impact of the ductus arteriosus, and its contribution to neonatal morbidities. There is a need to refocus our approach to determining hemodynamic significance, and consider a more holistic approach based on clinical and echocardiographic markers. In most centers, ductal staging is not feasible as the echocardiography evaluation performed by pediatric cardiologists is mostly limited to transductal diameter and flow direction or pattern. It is therefore, incumbent on neonatologists to consider acquiring the necessary skills and competence to perform functional echocardiograph evaluations.

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***“The lack of a standardised approach in determining hemodynamic significance is a major barrier towards better understanding the clinical impact of the ductus arteriosus, and its contribution to neonatal morbidities.”***

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## Medical News and Information

### Common Treatment To Delay Labor Decreases Preterm Infants' Risk For Cerebral Palsy

Intravenous magnesium sulfate supplementation before preterm delivery cuts the risk for handicapping cerebral palsy, a leading cause of chronic childhood disability, in half, according to research led by University of Alabama at Birmingham (UAB) obstetrician Dwight Rouse, MD, and published in the Aug. 28 issue of *The New England Journal of Medicine*.

Magnesium sulfate is given routinely to prevent seizures in women with preeclampsia and to stop preterm labor. Previous research suggested that fetal exposure to magnesium sulfate before preterm birth might reduce the risk of cerebral palsy.

"The association between magnesium sulfate and a lower incidence of cerebral palsy has biologic plausibility, because magnesium stabilizes blood vessels, protects against damage from oxygen depletion, and protects against injury from swelling and inflammation, all of which threaten the vulnerable preterm brain," Rouse said. "Our study is the largest, most comprehensive effort to evaluate the effect of magnesium sulfate on the incidence of cerebral palsy in preterm infants."

Early preterm birth is a risk factor for cerebral palsy, and the magnitude of the risk rises the earlier a baby is born. During the past 20 to 30 years, the survival of infants born severely preterm has improved dramatically, and while some research suggests that the rate of cerebral palsy among the survivors of early preterm birth has decreased, other research suggests that it has not. Currently, approximately one of every three cases of cerebral palsy is associated with early preterm birth.

This multi-center study, co-funded by the National Institute of Neurological Disorders and Stroke, and conducted by the 20 participating research centers of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal Fetal Medicine Units Network, enrolled 2,241 women between Dec. 1997 and Mar. 2004. The women were randomly assigned to receive either placebo or magnesium sulfate. They all had similar characteristics, including gestational age (24 to 31 weeks) at randomization and risk factors for preterm birth. Eighty-seven percent of the women had experienced preterm membrane rupture.

Those in the treatment group were given six grams of magnesium sulfate intravenously over 20 to 30 minutes, followed by two grams of magnesium sulfate every hour after that —

until either 12 hours had passed, labor subsided or they had given birth. If the women in either group did not deliver within 12 hours, they were treated again if they went into labor by the 34th week of pregnancy.

"Our finding that magnesium sulfate protects against cerebral palsy is consistent with two previous randomized trials, both of which were well done, and which in total enrolled over 1,600 women. Until we can prevent early preterm birth, the best that we obstetricians can do is to improve the prospects for infants who are born very early. I think that our study says that magnesium sulfate can help us do that," Rouse said.

### Newborns Can be Protected from Flu When their Mothers are Vaccinated During Pregnancy

Researchers at the Johns Hopkins Bloomberg School of Public Health observed a 63% reduction in proven influenza illness among infants born to vaccinated mothers, while the number of serious respiratory illnesses to both mothers and infants dropped by 36%. The study is the first to demonstrate that the inactivated influenza vaccine provides protection to both mother and newborn. The findings were presented during the National Vaccine Advisory Committee meeting in Washington, DC, and published in the Oct. 9 issue of the *New England Journal of Medicine*.

The inactivated influenza vaccine (the flu shot) is not licensed for infants younger than six months. The alternative nasal flu vaccine is not available for children under age 2. The flu shot has been recommended for pregnant women in the US since 1997, although approximately 15% of pregnant women are vaccinated each year.

"Even though there is no flu vaccine for these children, our study shows that a newborn's risk of infection can be greatly reduced by vaccinating mom during pregnancy. It's a two-for-one benefit. Pregnant women should be encouraged to be vaccinated for the flu to protect their infants and themselves," said Mark Steinhoff, MD, the study's senior author and Professor in the Bloomberg School's Department of International Health.

The research was supported by the Bill & Melinda Gates Foundation, US Agency for International Development (USAID), the NPVO Research Fund, Wyeth Pharmaceuticals Inc., the Thrasher Research Fund, Aventis Pasteur, ICDDR,B and the Johns Hopkins Bloomberg School of Public Health.

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- ICD-9 00.12 is the procedural code assigned to identify the administration of inhaled nitric oxide
- ICD-9 00.12 provides tracking data for payers that may affect current and future reimbursement levels
- ICD-9 00.12 may reduce claims-processing delays associated with miscellaneous HCPCS<sup>a</sup> or CPT<sup>b</sup> codes
- ICD-9 00.12 may trigger contractual payment mechanisms

<sup>a</sup> HCPCS, Healthcare Common Procedure Coding System.

<sup>b</sup> CPT, current procedural terminology.



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