Original Article

The Hemodynamic Effects of Neonatal Patent Ductus Arteriosus Shunting on Superior Mesenteric Artery Blood Flow

Mayra Freeman-Ladd, MD

Jonathan B. Cohen, MD

Jane D. Carver, PhD

James C. Huhta, MD

OBJECTIVE:

To determine if the ratio of the pulsatility index (PI) of the left pulmonary artery to the PI of the descending aorta, the R_p/R_s index, correlates with the degree of ductal steal from the intestine in neonates with a patent ductus arteriosus (PDA).

STUDY DESIGN:

Echocardiograms and Doppler studies of the superior mesenteric artery (SMA) were performed in 41 neonates less than 35 weeks gestational age with a hemodynamically significant PDA (hsPDA).

RESULTS:

There was a significant negative correlation between the R_p/R_s index and the SMA PI after controlling for ductal size ($r = -0.476$, $p < 0.008$).

CONCLUSIONS:

The R_p/R_s index can be used as an indicator of ductal steal on intestinal blood flow. The R_p/R_s index may be a useful adjunct to existing and new techniques for improving early assessment and treatment of hsPDA, and for evaluating the effects of hsPDA on systemic organs.

Journal of Perinatology (2005) **25**, 459–462. doi:10.1038/sj.jp.7211294
Published online 7 April 2005

INTRODUCTION

Patent ductus arteriosus (PDA) impacts blood flow to vital organs in premature infants, a phenomenon known as ductal steal. Ductal steal is associated with cerebral ischemia,¹ intraventricular hemorrhage,^{2,3} a worsening course of respiratory distress

syndrome,^{4–6} pulmonary hemorrhage⁷ and necrotizing enterocolitis (NEC).^{8–10} Many factors determine the severity of ductal shunting, including the pulmonary to systemic resistance ratio and size of the ductus. Since any factor that alters the pulmonary to systemic resistance ratio will tend to alter ductal shunt independent of ductal size, assessment of PDA size alone is not adequate to determine the extent of ductal shunting. Therefore, to assess adequately the hemodynamic significance of ductal shunting in premature infants, the magnitude of the pulmonary to systemic shunt flow ($Q_p:Q_s$), the size of the ductus, and PAP must be evaluated, albeit indirectly.

Presently, there are no established methods or techniques for grading a hemodynamically significant PDA (hsPDA). Clinical signs, such as a continuous murmur, a hyperactive precordium, hypotension, or metabolic acidosis, have a very low sensitivity in the first 3 or 4 days of life.^{11,12} Intracardiac echocardiographic methods, such as the left atrial-to-aortic-root-ratio (LA/Ao), $Q_p:Q_s$ ratio, and measurement of ductal sizes, are used, however, they are not specific for determining clinical importance of a PDA.

The purposes of this study were to (1) to determine if the ratio of the pulsatility index (PI) of the left pulmonary artery (LPA) to the PI of the descending aorta (DAo) (the R_p/R_s index) correlates with the degree of ductal steal from the intestine in neonates with PDA and (2) to determine if the R_p/R_s index can be used as a semiquantitative method to estimate the degree of left to right shunting through the PDA.

METHODS

This was a retrospective study conducted on infants admitted to three local level III neonatal intensive care units. Data collected from echocardiograms and Doppler studies of superior mesenteric artery (SMA) blood flow velocities (BFV) were used to evaluate the effects of ductal patency and shunting on the SMA BFV. Inclusion criteria included gestational age ≤ 35 weeks and a need for echocardiogram. Neonates who had cardiac abnormalities other than a PDA, pulmonary abnormalities other than respiratory distress syndrome or hyaline membrane disease, gastrointestinal or hematological abnormalities, or any major congenital anomalies were excluded. None of the patients were fed during the study period. The Institutional Review Board for the Protection of Human Subjects approved this study at each institution.

The cardiologist at each hospital routinely measures SMA BFV on infants who have echocardiograms performed due to a

Department of Pediatrics (M.F.L., J.D.C., J.C.H.), University of South Florida College of Medicine, Tampa, FL, USA; and Department of Anesthesiology (J.B.C.), University of South Florida College of Medicine, Tampa, FL, USA.

Address correspondence and reprint requests to Jane Carver, PhD, MS, University of South Florida Pediatrics, 17 Davis Blvd, Suite 200, Tampa, FL 33606, USA.

suspected hsPDA. The echocardiographic studies were performed with the least ultrasound intensity necessary to obtain clinically readable waveforms using echocardiography machines with 5.0 and 7.5 MHz transducers. Both pulsed and continuous wave blood flow and color Doppler images were obtained. A suprasternal or high left parasternal view was used to image the ductus, the LPA and the DAo. A sagittal subcostal view was used to image the SMA. Five waveforms were recorded using color-directed pulsed Doppler of LPA, DAo, and SMA (Figure 1). The size of the ductus was measured in centimeters at its narrowest part on a color Doppler image. The ductal gradient was obtained using continuous wave Doppler and the mean ductal pressure gradient was calculated as described by Lu et al.¹³

The PIs for LPA, DAo, and SMA were calculated as: (maximum velocity–minimum velocity)/mean velocity.¹⁴ Maximum velocity refers to the maximum systolic velocity, and the minimum velocity refers to the end diastolic velocity. If diastolic flow is absent, minimum velocity equals zero. If the diastolic flow is reversed, minimum velocity equals maximum reversed diastolic flow and is recorded as a negative number. Mean velocity is the average velocity under the waveform, which includes both systolic and diastolic flows (Figure 1).

Mean arterial pressure (MAP) at the time of the study was recorded when available. The Doppler-determined PAP was estimated as: MAP minus mean ductal pressure gradient. The PAP/MAP ratio was calculated. The mean PI of three waveforms with the largest systolic flow at the LPA, DAo, and SMA was used for analysis. The R_p/R_s index was calculated as: LPA PI/DAo PI.

Statistical analyses were performed using SPSS (SPSS, version 11.5, SPSS Inc., Chicago, IL). A Pearson's correlation coefficient was used to describe the relationship between the R_p/R_s index and the SMA PI, ductal size, PAP, and the PAP/MAP ratio.

RESULTS

In all, 46 patients were enrolled; five were excluded from data analysis due to poor Doppler sampling of one or more vessels. Table 1 presents subjects demographics. Most of the infants were entered within the first week of life except for two infants studied on days 26 and 29. All of the PDAs demonstrated left to right shunting with no more than mild atrial shunting.

There was a significant negative correlation between the R_p/R_s index and SMA PI ($p < 0.002$, $r = -0.476$) (Figure 2). The correlation remained significant after controlling for ductal size

Table 1 Demographics of the Patients Enrolled in the Study

<i>N</i> = 41	Median	Range
Birth weight (g)	933	510–1921
Gestational age (weeks)	27	24–32
Day of life	1.0	0–29
Ductal size (mm)	2.8	1.4–6.0

Figure 2. Correlation between R_p/R_s index and SMA PI ($r = -0.476$, $p < 0.002$).

Figure 1. Pulsed Doppler of the descending aorta (DAo) and the left pulmonary artery (LPA). Note the reversal of diastolic flow in the DAo (left panel) and the increased diastolic flow from runoff flow from the PDA in the LPA (right panel). cm/s = centimeters per second.

($p = 0.008$). There was no significant correlation between the R_p/R_s index and the ductal size ($p = 0.075$), MAP ($p = 0.402$), PAP ($p = 0.165$), or PAP/MAP ratio ($p = 0.355$).

DISCUSSION

Many techniques have been used to evaluate ductal shunting in infants with PDA. Skelton et al.¹¹ suggested that reliance on clinical signs alone would lead to a mean diagnostic delay of 2 days.¹¹ Electrocardiogram in infants with PDA can demonstrate *S-T* elevations with diastolic overload and left ventricular myocardial ischemia.¹⁵ However, Shipton et al.¹⁶ found that 78% of infants with hsPDA had no ECG changes indicative of left to right shunting.

Intra-cardiac echocardiographic methods include the LA/Ao ratio, $Q_p:Q_s$ and measurement of ductal size. The LA/Ao ratio is based on an increase in the left atrial size due to increased pulmonary venous return as a result of left-to-right shunting. However, Iyer et al. reported that the sensitivity of the ratio was lower if infants were scanned before the second day of life.¹⁷ $Q_p:Q_s$ is estimated by comparing the mitral/tricuspid valve or the aortic/pulmonary valve time-velocity integrals in infants with isolated PDA, the pulmonary blood flow is measured by left ventricular output and systemic blood flow by right ventricular output. However, inter-atrial shunting makes the results invalid.¹⁸

We used the R_p/R_s index to evaluate the effects of ductal shunting on SMA BFV in infants with hsPDA. There was a significant negative correlation between SMA PI and the R_p/R_s index, a relationship that remained significant after controlling for ductal size. We found no correlation between ductal size and the degree of ductal shunting. Our findings are consistent with those of Huhta and colleagues. They performed serial follow-up with 70 echocardiograms in 25 infants and found that a constricted or small ductus may have a large amount of shunting, and a large ductus may have minimal shunting.¹⁹ Their findings and ours indicate that while ductal size is necessary for accurate assessment of ductal shunting, ductal size alone is not adequate.

There are significant advantages to the R_p/R_s index for assessing ductal shunting. It is a semiquantitative, extracardiac method that measures the downstream blood velocity in the pulmonary artery and DAO just distal to the PDA. The results from our study demonstrate that the R_p/R_s index can be used to identify neonates in whom PDA is associated with diastolic steal from the SMA. Since both the numerator (LPA PI) and denominator of the equation (DAO PI) are inversely related in the infant with PDA, the equation is likely to be predictive of small changes in the neonate's hemodynamic status. Sensitivity of the index to systemic changes is particularly advantageous since events that alter the peripheral resistance such as cold stress may be occult. The hemodynamic status of the ductus can change rapidly with time and with altered

pulmonary function after birth. The index is also easy to calculate from the Doppler echo recordings, and it can be used as an adjunct to other methods.

Ductal steal can have significant clinical consequences. Cassels²⁰ first described the ductal steal phenomenon in premature infants with hsPDA over 30 years ago, and it has been described in preterm lambs.²¹ The association between NEC and PDA was first described in 1980.⁹ Van Bel et al.²² reported an inverse relationship between the time average mean velocity of the SMA and vascular resistance, while Shimada et al.²³ reported that higher PI in the abdominal aorta of infants with surfactant-treated RDS and hsPDA decreased to control levels after PDA closure. While none of our study patients developed NEC, we found that large ductal shunting or a low R_p/R_s index resulted in absence or reversal of diastolic flow in the SMA. Since hypoperfusion and hypoxia may contribute to the development of NEC, a semiquantitative method like the R_p/R_s index could be useful in identifying infants with systemic steal from the SMA who are at risk for intestinal hypoperfusion. In addition, the index is sensitive to the diastolic effects of the PDA on systemic circulation.

We found no significant correlation between MAP and the R_p/R_s index. Shimada et al.²⁴ reported that the mean and diastolic blood pressure were significantly lower in extremely low birth weight infants with RDS and hsPDA. Evans et al.²⁵ reported that in infants with birth weights between 1000 and 1500 g, there was no significant difference in systolic blood pressure between infants with or without hsPDA. However, in infants with birth weights less than 1000 g, MAPs were significantly lower in the presence of hsPDA in the first week of life. Since MAPs were only available on half of our study patients, insufficient data may have contributed to the apparent lack of a relationship between MAP and R_p/R_s index.

We also found no significant correlation between PAP and the R_p/R_s index, although correlation might be expected. Infants with severely elevated pulmonary resistance or pressure were excluded from our study. If pulmonary pressure or resistance is elevated, right to left shunting would increase, and pulmonary blood flow would decrease. In infants with RDS who are administered surfactant, pulmonary vascular resistance and PAP decrease as ductal flow velocity increases, while systemic blood pressure does not change.²⁶ This highlights another advantage of the R_p/R_s index: its ability to describe peripheral events even though the proximal hemodynamics of the PDA itself are changing.

Limitations to our study include its retrospective design, and the lack of MAP and PAP data for many of the subjects. The R_p/R_s index is also a semi- and not quantitative measurement, since it measures downstream relative resistance instead of actual blood flow or blood volume. Also, it is not measuring absolute values of resistance because normal values are approximately 1.0, while normal pulmonary to systemic ratios are between 0.1 and 0.3 in normal subjects. In addition, the index only evaluates ductal shunting at the time of study and not continuously over time.

In summary, we have demonstrated that the R_p/R_s index correlates with SMA BFV, and that it can therefore be used as an indicator of ductal shunting. Additional studies are needed to clarify its clinical relevance, and to define normal values with varying degrees of ductal shunting. We conclude that the R_p/R_s index may be a useful adjunct to existing and new techniques for improving early assessment and treatment of hsPDA, and for evaluating the effects hsPDA on systemic organs.

Acknowledgements

We acknowledge the assistance and cardiac technical support from Pamela Humiston, Judy Zaritt, Felicia Jones, James Paul, Susan Levy, Stan Timofeev, Chris Madramootoo, Mike French, Patrick Johanboeke, Greg Peters, Johanna Loaiza, and Kelli Sinclair. We also like to express great appreciation to USF Neonatology Department (Terri Ashmeade, MD, Lewis Barness, MD, Laura Haubner, MD, Robert Nelson, MD and Monisha Saste, MD) for their cooperation, support and editorial review skills.

References

- Shortland DB, Gibson NA, Levene MI, Archer LN, Evans DH, Shaw DE. Patent ductus arteriosus and cerebral circulation in preterm infants. *Dev Med Child Neurol* 1990;32(5):386–93.
- Martin CG, Snider AR, Katz SM, Peabody JL, Brady JP. Abnormal cerebral blood flow patterns in preterm infants with a large patent ductus arteriosus. *J Pediatr* 1982;101(4):587–93.
- van Bel F, den Ouden L, van de Bor M, Stijnen T, Baan J, Ruys JH. Cerebral blood-flow velocity during the first week of life of preterm infants and neurodevelopment at two years. *Dev Med Child Neurol* 1989;31(3):320–8.
- Bancalari E. Changes in the pathogenesis and prevention of chronic lung disease of prematurity. *Am J Perinatol* 2001;18(1):1–9, Review.
- Neal WA, Bessinger Jr FB, Hunt CE, Lucas Jr RV. Patent ductus arteriosus complicating respiratory distress syndrome. *J Pediatr* 1975;86(1):127–32.
- Cotton RB, Stahlman MT, Kovar I, Catterton WZ. Medical management of small preterm infants with symptomatic patent ductus arteriosus. *J Pediatr* 1978;92(3):467–73.
- Kluckow M, Evans N. Ductal shunting, high pulmonary blood flow, and pulmonary hemorrhage. *J Pediatr* 2000;137(1):68–72.
- Coombs RC, Morgan ME, Durbin GM, Booth IW, McNeish AS. Abnormal gut blood flow velocities in neonates at risk of necrotizing enterocolitis. *J Pediatr Gastroenterol Nutr* 1992;15(1):13–9.
- Ryder RW, Shelton JD, Guinan ME. Necrotizing enterocolitis: a prospective multicenter investigation. *Am J Epidemiol* 1980;112(1):113–23.
- Wong SN, Lo RN, Hui PW. Abnormal renal and splanchnic arterial Doppler pattern in premature babies with symptomatic patent ductus arteriosus. *J Ultrasound Med* 1990;9(3):125–30.
- Skelton R, Evans N, Smythe J. A blinded comparison of clinical and echocardiographic evaluation of the preterm infant for patent ductus arteriosus. *J Paediatr Child Health* 1994;30(5):406–11.
- Davis P, Turner-Gomes S, Cunningham K, Way C, Roberts R, Schmidt B. Precision and accuracy of clinical and radiological signs in premature infants at risk of patent ductus arteriosus. *Arch Pediatr Adolesc Med* 1995;149(10):1136–41.
- Lu CZ, Xu QL, Hu YY. Estimation of systolic pulmonary artery pressure with continuous wave Doppler pressure gradient method: a simultaneous Doppler and catheter correlative study. *Zhonghua Nei Ke Za Zhi* 1990;29(5):290–2, 317–8.
- Gosling RG, Dunbar G, King DH, et al. The quantitative analysis of occlusive peripheral arterial disease by a non-intrusive ultrasonic technique. *Angiology* 1971;22(1):52–5.
- Krovetz IJ, Warden HE. Patent ductus arteriosus. An analysis of 515 surgically proved cases. *Dis Chest* 1962;42:46–57.
- Shipton SE, van der Merwe PL, Nel ED. Diagnosis of haemodynamically significant patent ductus arteriosus in neonates — is the ECG of diagnostic help? *Cardiovasc J S Afr* 2001;12(5):264–7.
- Iyer P, Evans N. Re-evaluation of the left atrial to aortic root ratio as a marker of patent ductus arteriosus. *Arch Dis Child Fetal Neonatal Ed* 1994;70(2):F112–7.
- Evans N, Iyer P. Assessment of ductus arteriosus shunt in preterm infants supported by mechanical ventilation: effect of interatrial shunting. *J Pediatr* 1994;125(5 Part 1):778–85.
- Huhta JC. Patent ductus arteriosus in the preterm neonate. In: Long WA, editor. *Fetal and Neonatal Cardiology*. Philadelphia: WB Saunders Company; 1990. P. 389–400.
- Cassels DE. Hemodynamics. In: Cassels DE, editor. *The Ductus Arteriosus*. Springfield: Charles C Thomas; 1973. P. 143.
- Clyman RI, Mauray F, Heymann MA, Roman C. Cardiovascular effects of patent ductus arteriosus in preterm lambs with respiratory distress. *J Pediatr* 1987;111(4):579–87.
- Van Bel F, Van Zoeren D, Schipper J, Guit GL, Baan J. Effect of indomethacin on superior mesenteric artery blood flow velocity in preterm infants. *J Pediatr* 1990;116(6):965–70.
- Shimada S, Kasai T, Konishi M, Fujiwara T. Effects of patent ductus arteriosus on left ventricular output and organ blood flows in preterm infants with respiratory distress syndrome treated with surfactant. *J Pediatrics* 1994;125:270–7.
- Shimada S, Kasai T, Hoshi A, Murata A, Chida S. Cardiocirculatory effects of patent ductus arteriosus in extremely low-birth-weight infants with respiratory distress syndrome. *Pediatr Int* 2003;45(3):255–62.
- Evans N, Moorcraft J. Effect of patency of the ductus arteriosus on blood pressure in very preterm infants. *Arch Dis Child* 1992;67(10 Spec No): 1169–73.
- Kaapa P, Seppanen M, Kero P, Saraste M. Pulmonary hemodynamics after synthetic surfactant replacement in neonatal respiratory distress syndrome. *J Pediatr* 1993;123(1):115–9.