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SEMINARS IN PERINATOLOGY

The Ductus Arteriosus: A Refined Approach!

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Although ongoing patency of the ductus arteriosus is common in small extremely preterm infants, consensus is lacking regarding its clinical significance and treatment strategies. Literature regarding likelihood of spontaneous closure, impact on neonatal morbidity and long-term outcomes, and adverse effects of intervention has led to uncertainty as to the best course of action. Enhancing the determination of hemodynamic significance and refining patient selection for therapeutic intervention will streamline the decision-making process. Targeted neonatal echocardiography performed by the clinician has gained popularity worldwide, and preliminary data show that it has the potential to optimize patient outcomes. We review the arguments for and against medical and surgical therapy, explore how targeted neonatal echocardiography used in conjunction with biomarkers may refine the treatment approach, and consider future directions in the field.

KEYWORDS patent ductus arteriosus

Defining the Problem

Patent ductus arteriosus (PDA) remains one of the most common cardiovascular problems in preterm neonates, occurring in about 1/3 infants <30 weeks' gestation and up to 60% of infants <28 weeks.[1] Treatment is also common, but approaches are highly variable. Indomethacin is used for therapeutic closure of PDA in up to 80% of all diagnosed very low–birth-weight (VLBW) infants. In a recent analysis involving infants <32 weeks' gestation over a period of 13 years, 88% (2192 of 2506) were administered indomethacin for medical closure of a PDA.[2] The goal of PDA treatment is to prevent short-term and long-term sequelae secondary to a high-volume ductal shunt. The intent is to prevent respiratory decompensation, heart failure, intraventricular hemorrhage (IVH), chronic lung disease (CLD), necrotizing enterocolitis (NEC), and death. The clinician is faced with the dilemma of balancing the competing risks of duct-attributable morbidity and the complications of therapeutic intervention. It is unlikely that the optimal time of therapeutic intervention may be predicted by postnatal age, as the determinants of a hemodynamically significant ductal shunt include transductal resistance and physiological modifiers. The assignment of hemodynamic significance to a PDA remains a challenge for neonatal intensivists. The inability to accurately differentiate the pathological ductus arteriosus from the innocent ductus arteriosus may contribute, in part, to the lack of scientific evidence of benefit or causality. The consequential impact is medical uncertainty and ongoing debate as to when treatment should be provided, if ever. The essence of the debate relates to the challenge of defining who needs treatment and, if indicated, when intervention is most effective. The nature of the confusion is thought to relate to limitations and/or delays in appraisal of ductal significance. This article reviews current literature about the rationale for withholding or initiating treatment; addresses the triad of PDA, indomethacin, and NEC; explores refinement of strategy based on disease stratification and newer biochemical markers; addresses the role of targeted neonatal echocardiography (TnECHO); and proposes future directions of research.

The nature of the clinical consequences of a hemodynamically significant ductus arteriosus (HSDA) relate to the volume of the shunt and the ability of the pulmonary and/or systemic circulations to compensate for these changes. The current approach to diagnosis and management is highly variable with conflicting interpretation of the same literature.

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Several authors[3,4] have highlighted that trials of nonsteroidal anti-inflammatory drugs (NSAIDs) have not led to any detectable reduction in neonatal morbidities; hence, treatment may not be indicated. The lack of benefit may relate to the lack of standardization of diagnosis of hemodynamic significance, variability in timing of intervention and specific therapeutic regime, and failure of consideration of comorbidities. The latter is particularly relevant, as the pathogenesis of comorbidities, such as NEC or BPD, likely evolves over many days and weeks with multiple contributors, questioning their suitability as an end point of interest for treatment trials. The most relevant question now is "has the right type of trial been conducted?" Trials to date have focused on the time, method, and duration of intervention but not on the degree or magnitude of hemodynamic significance. The traditional barometer by which ductal significance has been adjudicated is transductal diameter, which may not imply hemodynamic significance in some situations. The question remains whether the physiological benefit to an individual translates into improved long-term outcome and an epidemiologic benefit to society. The reduction in early complications (1-3 postnatal days), such as pulmonary hemorrhage and IVH, after prophylactic indomethacin suggests there may be a subpopulation that benefits from PDA closure.[5,6] However, these trials failed to show long-term beneficial effects.

In summary, the inability to accurately differentiate the pathological/symptomatic PDA from the innocent ductus arteriosus may contribute, in part, to the lack of scientific evidence of benefit or causality. Mere patency may not be enough to assign pathological significance. The lack of evidence supporting causality,[7,8] failure of medical treatment in some cases,[9] the inherent risks of medical or surgical treatment options,[10,11] and a high spontaneous closure rate has added to the equipoise. The quest to resolve this medical conundrum is likely to require revisitation of all evidence to date, reconsideration of what constitutes hemodynamic significance, and enhanced selection of candidates for therapeutic intervention in prospective randomized controlled trials (RCTs).

Arguments Against Treatment

The use of indomethacin to induce medical closure of ductus arteriosus was first described in 1976,[12,13] and since then, it has been the first line of therapy to assist with ductal closure. The arguments against treatment include adverse consequences of NSAIDs and surgical intervention, relatively high incidence of spontaneous closure, failure of prophylactic indomethacin to improve neurodevelopmental outcome, and lack of substantial evidence of benefit of treatment of PDA from RCTs. Systemic side effects of NSAIDs are well recognized, as they constrict not only the ductus arteriosus but also the arteries that supply blood to the heart, brain, kidneys, and gut. Indomethacin exposure has been implicated as one of the risk factors for neonatal gut injury in VLBW infants.[13-16] Sharma et al recently published a detailed analysis addressing the association between NEC, isolated intestinal perforation (IIP), and indomethacin. Any postnatal indomethacin exposure increased the odds of IIP (odds ratio [OR]: 4.17, confidence interval [CI]: 1.24-14.08, $P = 0.02$) but decreased the odds of NEC (OR: 0.65, CI: 0.43-0.97, $P = 0.04$). The prevalence of NEC for indomethacin-exposed infants was 9.9% (CI: 7.71-12.38) compared with a prevalence of 14.6% (CI: 10.89-18.88) among unexposed infants. Hence, the relative risk of NEC among infants exposed to indomethacin compared with unexposed infants was 0.67 (CI: 0.48-0.96). Thus, any exposure to indomethacin was associated with decreased prevalence of NEC. There was a negative association between the timing of indomethacin exposure and the odds of developing IIP (OR: 0.30, CI: 0.11-0.83, $P = 0.02$). Compared with NEC, IIP occurred at an earlier age ($P < 0.05$) and was more common ($P < 0.05$) among infants who received early indomethacin (first dose at <12 hours of age) to prevent IVH than among infants who were treated with late indomethacin for closure of a PDA.[17]

Recently, our group demonstrated a transient decrease in coronary flow when indomethacin was given to premature neonates for medical closure of a symptomatic PDA.[18] Support for the biological relevance of these findings comes from evidence of ST segment depression on the electrocardiograph and elevated plasma troponin of premature infants with HSDA, although the latter did fall after PDA closure.[19] Transient, but reversible alterations in cerebral perfusion[20] during indomethacin administration have been shown. Finally, although renal impairment during medical treatment is entirely reversible, changes in renal artery flow may occur.[21,22] These changes, although biologically important, do not provide a compelling case for complete avoidance of medical intervention. Although prophylactic use of NSAIDs reduces the incidence of PDA, spontaneous closure by day 3-7 occurs in more than 44% of the neonates born at a GA of <32 weeks.[23] Van Overmeire reported a spontaneous closure rate of 80% by 7 days in moderately sick infants of 26-31 weeks' gestation.[24] For each week above 23 weeks, odds of spontaneous closure increase by 1.5.[25] In the placebo arm of the prophylactic NSAID trials, about 50% of the very preterm infants closed their ductus spontaneously or never developed evidence of a hemodynamically significant PDA.[26-28] These data suggest there are, at least, some patients who are unnecessarily exposed to the adverse effects of therapeutic intervention. Clinical trials to date have failed to demonstrate a meaningful long-term advantage of therapeutic intervention for the ductus arteriosus.[4,29] This lack of a perceived benefit from ductal closure is highly relevant and warrants careful consideration. It may represent a real lack of therapeutic benefit. On the other hand, it may relate to variability in diagnosis and therapeutic strategies or the multifactorial nature of the outcome studied. For example, the evidence for failure of NSAIDs to decrease the rate of CLD in extremely low-birth-weight (ELBW) infants is widely proposed as one argument against intervention. The pathogenesis of CLD, however, is highly multifactorial, and the current definition of disease does not take account of the heterogeneity in disease severity and clinical impact. It is therefore highly unlikely that any single therapeutic strategy will prove to be the "magic bullet."

Surgical ligation is associated with an increased risk of direct complications, such as left vocal cord paralysis,[30-32] chylothorax,[33] and scoliosis,[34] although the latter is an older study and surgical techniques have improved over the past 20 years. It is likely that these risks, directly related to surgical technique, may vary between centers according to the volume of procedures performed annually. The association of PDA ligation and adverse neurosensory impairment, from a post hoc reanalysis of the trial of prophylactic indomethacin, is very concerning.[35,36] Whether this represents cause-effect or reflects a clinical association confounded by factors such as prematurity, comorbidities, or alternative treatments remains unknown. The association between postoperative cardiovascular instability and PDA ligation has gained recent attention, as it may have impact on short- and long-term outcomes.[37-42] A postligation cardiac syndrome has been described, characterized by systemic hypotension requiring cardiotropic support and respiratory failure. These changes have been shown to relate, at least in part, to impaired myocardial performance secondary to altered cardiac loading conditions.[37,41] It is biologically plausible that sustained exposure to low cardiac output may lead to adverse neurological outcome. Recent neurophysiologic studies show evidence of impaired cerebral electrical activity and cerebral oxygenation during the postoperative period.[43,44] Data from primate studies also shed important light on this issue. Loeliger et al conducted a study to investigate the effect of ligation on short-term brain development.[45] Preterm baboons were ventilated for 14 days, and on day 6, the ductus arteriosus was either ligated or left untreated. Both growth and developmental index scores were decreased in both the unligated and ligated groups compared with gestational-age (GA)–matched controls. Preterm baboons, however, exposed to a PDA for 14 days demonstrated arrested alveolar development, characteristic of the "new" BPD.[5,46] In the context of heterogeneity of both the "problem" studied (PDA) and the "outcome" evaluated (CLD), there is a need for stratification of both when designing studies of both causality and clinical efficacy. Otherwise, the likelihood of appraising the real impact is diluted.

Arguments for Treatment

The main argument forwarded in favor of treatment is the association between presence of a PDA and common neonatal morbidities. To better understand the potential beneficial effect of therapeutic intervention, the evidence should be examined from a physiological, epidemiological, and pharmacological perspective. The likelihood of ***physiological impact*** stems from the magnitude of transductal blood flow, influenced not only by ductal diameter but systemic, pulmonary, and their differential resistance. A number of studies have demonstrated impaired cerebral blood flow in preterm infants with a PDA.[21,22] Specifically, Doppler ultrasonography studies have shown that the negative effect of PDA on cerebral blood flow mainly affects blood flow during diastole, as characterized by a decrease in flow velocity and increase in pulsatility index (PI) or resistance index. These adverse effects of PDA on cerebral hemodynamics are believed, but *not proven*, to have a role in the pathogenesis of IVH.[20]

Increased left-to-right shunting through a PDA can also increase the vulnerability of intestinal mucosa to frank ischemia.[5,46] Studies have consistently shown a reduction in intestinal blood flow in the presence of a PDA with reduced abdominal aorta and superior mesenteric artery (SMA) blood flow assessed by Doppler ultrasonography.[21,47-49] The proposed mechanism is "diastolic steal," whereby blood flows from the mesenteric arteries back into the aorta and through the PDA, creating an intestinal hypoperfusion state, thus compromising the gut diastolic blood flow.[50] The PDA reduces mesenteric blood perfusion by causing a decrease in the arterial perfusion pressure.[51] Because the mucosa has high metabolic activity, it receives about 80% of total intestinal blood flow. This makes it more susceptible to critical reductions in mesenteric and splanchnic blood flow. This may contribute to the development of NEC. The decrease in regional intestinal blood flow occurs despite a net increase in left ventricular output (LVO). Observations in animal experiments support the findings of Doppler studies in humans.[51]

Epidemiological Evidence

Epidemiological evidence suggests, at least, an association between the PDA and neonatal morbidity. Indeed, in VLBW (<1500 g) infants with PDA, epidemiologic data show a 1.9-fold increase in the odds of developing BPD.[52] Although a symptomatic duct has a negative effect on cerebral oxygenation in premature infants, it remains unclear whether these physiological changes place the infant at increased risk of neonatal morbidity and/or poor neurodevelopmental outcomes. The argument for treatment is strengthened by the fact that prophylactic use of indomethacin significantly decreases the incidence of IVH. PDA is also an independent risk factor for the development of NEC in VLBW infants as highlighted in the preceding text. Dollberg et al studied more than 6000 preterm infants and showed that NEC occurred in 9.4% of infants with PDA and in 8.9% of infants where PDA was treated with indomethacin.[53] The occurrence of NEC was significantly associated with PDA in infants who were treated with indomethacin (OR: 1.53) but was *less in those who did not* receive indomethacin therapy (OR: 1.85). Furthermore, treatment with indomethacin did not increase this risk after adjustment for prenatal and neonatal variables associated with excess risk for developing NEC. Finally, recent evidence suggests an association between persistent ductal patency and increased mortality.[54] In a retrospective study of VLBW infants <29 weeks' GA, failure of ductal closure was associated with an increase in mortality after adjustment for the degree of immaturity, initial disease severity, and morbidities such as severe IVH, NEC, and sepsis. The mortality was >8 fold in neonates with a persistent PDA than in those with a closed ductus. The most common cause of death was multiorgan failure. A previous study also reported a 4-fold increase in the mortality of preterm infants with a persistent PDA.[55]

Treatment decisions in neonates with a clinically suspected hemodynamically significant PDA are usually based

on pulmonary symptoms, as these are more clinically recognizable (eg, desaturation episodes, increasing ventilation) compared with the systemic effects of transductal shunt, such as low cardiac output state or absent/reversed diastolic blood flow. To date, the only placebo-controlled trial of therapeutic intervention RCT was the trial by Cassady et al, who randomized patients to surgical ligation on day 7 of life, which demonstrated a lower incidence of NEC in the ligation group.[56] Although the trial showed no difference in the incidence of BPD, when BPD was redefined as oxygen requirement at 36 weeks' postmenstrual age, it was found that the ligation group had a higher rate of BPD.

The interrelations between PDA, pharmacologic treatment with prostaglandin inhibitors, and NEC are highly complex. Despite its proven efficacy, concern about the safety of indomethacin, particularly with respect to neonatal intestinal complications, continues to influence its usage in the neonatal intensive care unit.[16,57,58] Several large RCTs of prophylactic indomethacin failed to identify any effect of indomethacin on NEC.[15,59] In addition, a recently published multicenter RCT on long-term effects of indomethacin prophylaxis showed that the incidence of NEC was strikingly similar between treated and untreated infants.[26] Other studies have reported contradicting results.[60,61] An increased risk of NEC and localized intestinal perforation has been attributed to treatment of PDA with indomethacin.[61] It has been suggested that in situations when the PDA does not close early, the combined constrictor effect of indomethacin therapy with negative fluid balance and diuretic therapy may explain the development of intestinal ischemia and dysfunction.[62] However, several published meta-analyses clearly show that both prophylactic and symptomatic indomethacin therapies do not increase the risk for NEC compared with no treatment or with surgical ligation.[29,63,64] Treatment of PDA when clinical signs first appear may decrease the incidence of NEC when compared with infants receiving treatment after signs of congestive cardiac failure appear.[63] Hence, early indomethacin treatment for PDA closure may be beneficial to reduce the intestinal hypoperfusion associated with the diastolic steal phenomenon. In summary, although indomethacin independently reduces intestinal blood flow, it appears that its net effect on intestinal blood flow when used to treat a hemodynamically significant PDA is beneficial and reduces the risk of NEC. The ability of indomethacin to modulate inflammatory mediators in the intestine may be another mechanism whereby it reduces the risk of NEC.

Strategies to Rationalize Therapy

Variability in clinical efficacy, lack of meaningful impact on long-term neonatal outcomes, and valid concerns regarding side effects of cyclooxygenase inhibitors have prompted attempts to rationalize the approach to therapeutic intervention. This may be achieved by enhancing the definition of hemodynamic significance through using more comprehensive TnECHO, biochemical markers and a system of disease stratification.

Disease Stratification

The traditional definition of a PDA, which forms the basis of clinical trials conducted to date, is limited and somewhat superficial, as it suggests this to be a dichotomous variable rather than a pathophysiological continuum. The physiological and clinical consequences of the ductus arteriosus range from its adaptive role in normal postnatal transition (important role in supporting pulmonary blood flow in the transitioning lung) to a disease state with circulatory instability due to a high-order-of-magnitude left-to-right shunt. The lack of a standardized approach in assigning echocardiographic significance is a major barrier toward better understanding the clinical impact of the ductus arteriosus. A transductal diameter of >1.5 mm has been proposed as significant on the basis that at this cut-off, end-organ hypoperfusion occurs.[65,66] However, multiple factors, such as patient size, gestational and chronologic age, and clinical symptomatology, may account for variability in the decision making. RCTs have failed to consider the magnitude of the ductal shunt in assessing the efficacy of therapeutic intervention on neonatal morbidities. This is highly relevant as ductal hemodynamics are influenced not only by ductal size but also by pulmonary and systemic vascular resistance and by the compensatory ability of the immature myocardium. We have recently proposed a staging system to assess the cumulative effect of an HSDA on myocardial performance and systemic and pulmonary hemodynamics as adjudicated by graded clinical and echocardiographic characteristics.[67] The purpose is to standardize the definition of hemodynamic significance, stratify ductal illness severity in an attempt to provide more streamlined decision making, and facilitate earlier identification of which patients may benefit from therapeutic intervention. The staging system places a greater emphasis on echocardiography markers of hemodynamic significance, rather than on ductal diameter alone. Although it is not possible to directly evaluate the volume of the transductal shunt by using conventional echocardiography methods alone, surrogate markers of pulmonary overcirculation and systemic blood flow provide an indirect estimate of the volume of the shunt. The purpose of these markers is not limited to the estimation of ductal size, but also includes determination of the impact of transductal flow on the systemic and/or pulmonary circulations. A comprehensive appraisal of these echocardiography markers is crucial owing to the individual variability of any one measurement and the influence of confounding physiological or anatomic factors. In addition, a detailed approach to PDA evaluation allows a more systematic and structured approach to evaluation of treatment response.

This approach has not been uniformly adopted, and its impact remains unclear. There is some evidence that staging the ductus arteriosus facilitates identification of neonates at increased risk of respiratory morbidity, although it remains unknown whether this is able to guide therapy.[68] Neonates

classified as having high-risk according to the staging criteria were noted to be more likely to require longer duration of oxygen support and home oxygen therapy and to show a trend toward increased CLD. Since the introduction of a PDA classification system in Toronto, the rates of referral for PDA ligation have reduced by over 50%,[69] which may be attributable to a more comprehensive appraisal of hemodynamic significance and avoidance of intervention in borderline cases.

The use of a staging system in combination with biomarkers, such as B-type natriuretic peptide (BNP), aminoterminal B-type natriuretic peptide (NT-proBNP), and cardiac troponin T (cTnT),[70] may allow the creation of a clinical algorithm for identifying at-risk infants and determining indication, timing, and best mode of therapy. Biomarkers such as CTnT and NTpBNP may be particularly helpful when there is limited access to serial TnECHO. NTproBNP is the inactive by-product of BNP, which is released by the ventricular myocardium in response to volume and pressure loading. NT-pBNP levels rise in the presence of a hemodynamically significant PDA, correlating with echocardiographic markers, and fall following successful treatment.[71] Similarly, cTnT displays a similar pattern with the presence of a PDA and following treatment.[72] In small series of preterm infants, plasma BNP correlated with magnitudes of the ductal shunt (ductal size, La:Ao ratio, diastolic flow velocity of the left pulmonary artery). Plasma NT-proBNP and cTnT levels are higher in preterm infants with a PDA who subsequently develop IVH grade III/IV or risk of death compared with those with a PDA and without complications. The use of these markers in clinical practice is not yet established. They may be of benefit in presymptomatic screening of preterm infants 48 hours of life and in evaluating therapeutic response; these require prospective evaluation.

Impact of TnECHO

An enhanced approach to diagnosis and monitoring will require more comprehensive and frequent echocardiography. In many centers, this approach may be limited by issues such as accessibility and temporal delays in the acquisition of information. In many parts of the world, it is now incumbent on neonatologists to acquire the necessary skills and training to perform TnECHO.[73-75] Although the usefulness of echocardiography as a research tool to understand neonatal hemodynamic is well established,[76,77] its impact on PDA management is less well understood. There are emerging data that short-term outcomes may be improved. O'Rourke et al[78] evaluated the effect of serial echocardiography performed by a neonatologist and early targeted medical PDA treatment compared with historical controls. Serial echocardiography facilitated earlier identification and treatment of an HSDA before evolution of clinical signs. The clinical impact was a reduction in severe intraventricular hemorrhage and number of ventilator days. Several groups have demonstrated usefulness of point-of-care echocardiograms in the setting of post-surgical ligation hemodynamic instability.[37,40] The introduction of a standardized TnECHO-guided care program led to decreased postoperative cardiorespiratory instability compared with historical controls.[79]

Echocardiography Evaluation of the Ductus Arteriosus

The discordance between the appearances of clinical vs echocardiographic signs is well appreciated. The common practice is to intervene and assess outcome based on ductal size and the clinical consequences of excessive pulmonary blood flow (for example, increased ventilatory requirements and CLD). Our approach represents a paradigm shift from reliance on transductal diameter alone to paying more attention to echocardiography surrogate markers of the volume and impact of the shunt volume. Although transductal diameter appears to be the most predictive of all markers, its value is questionable for several reasons. First, ductal size may vary with oxygen saturation, surfactant treatment, or intravenous furosemide.[80-82] Second, although the vessel is widely patent, the determinant of the volume of transductal flow is the pressure differential across the length of the ductus, which may be negligible in the presence of elevated pulmonary vascular resistance. Finally, a two-dimensional estimate at a single point may not be best reflective of the architecture of the ductus across its length and in three dimensions. Although there may be restriction in size at the pulmonary end following medical therapy to a level considered "nonsignificant" ($<$1.7 mm), this may not be sufficient to restrict transductal flow and its hemodynamic consequences. Individually, each marker is subject to measurement error, interobserver variability, and inaccuracy secondary to confounding physiological factors. For example, increased pressure and/or volume loading of the left heart secondary to increased pulmonary venous return with consequential elevation in LVO reflects a high-volume transductal shunt. In the presence of a large atrial septal defect, or stretched patent foramen ovale due to the increased size of the left atrium, a high-volume left-to-right transatrial shunt leads to decompression of the left heart and normalization of LVO, decreasing the sensitivity of these markers. A large left-to-right transatrial shunt is therefore a marker, in itself, of a high-volume shunt; if not measured, the significance of the ductus arteriosus may not be appreciated. It must not be assumed that increased LVO implies adequate systemic blood flow. Hajjar et al[83] demonstrated that the flow of ductal shunt is directly proportional to LVO/superior vena caval (SVC) flow ratio and this ratio may be a more reliable estimation of the ductal flow, as it is unaffected by transatrial flow, unlike other markers. The authors chose a ratio of $\geq$4 to define an HSDA and concluded that the left atrial to aortic ratio, ductal diameter, mean flow velocity of left pulmonary artery (LPA), and end-diastolic velocity of the LPA correlated significantly with the LVO/SVC ratio. The left atrial to aortic ratio, used to assess volume overloading, although relatively easy, may not be accurate:[84] Firstly, left atrial volume is dependent on the hydration status of the neonate and may be normal in the presence of volume depletion. Secondly, the measurement is prone to intra- and interobserver variability.

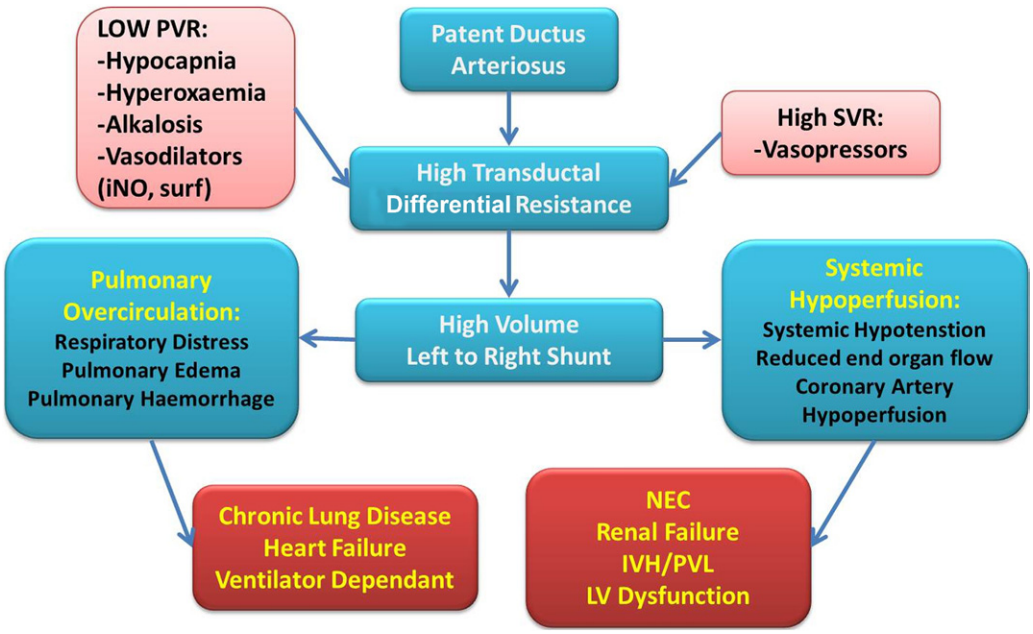

Figure 1 Relationship between hemodynamically significant ductus arteriosus, abnormal blood flow, and neonatal morbidity. PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; iNO, inhaled nitric oxide; surf, surfactant; NEC, necrotizing enterocolitis; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; LV, left ventricular. (Color version of figure is available online.)

Studies describing patterns of left-to-right shunting show that transductal flow increases during diastole, leading to a marked reduction of net flow down the descending aorta (DAo). After PDA closure, the absolute (net) forward flow increased 33%. In preterm infants <31 weeks' gestation, Groves et al observed that when ductal diameter was >1.7 mm, DAo diastolic reversal was associated with 35% decrease in DAo flow volume.[50] The degree of ductal steal can be semiquantitatively assessed by planimetering reversed to forward flow (R/F) to assign a ratio. A strong linear correlation between the ratio of pulmonary to systemic blood flow (Qp/Qs) and R/F (assigned by Doppler) has been demonstrated ($R^2 = 0.82$, $P < 0.01$).[85] The ratio of the PI of the LPA to the PI of the DAo (Rp/Rs index) has been proposed as a semiquantitative, extracardiac index that measures the downstream blood velocity in the pulmonary artery and DAo just distal to the PDA. A recent study has shown that the Rp/Rs index can be used to identify neonates in whom PDA is associated with diastolic steal from the superior mesenteric artery.[86] Abnormal diastolic flow patterns are commonly seen in other vessels, for example, renal and celiac arteries.[83] Although the "ductal steal" phenomenon is present in neonates

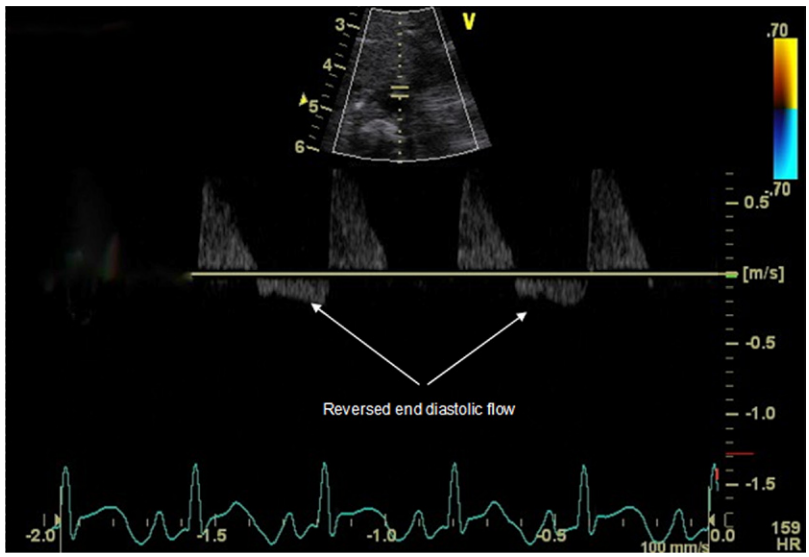

Figure 2 Abnormal flow pattern showing reversed end-diastolic flow in superior mesenteric artery. (Color version of figure is available online.)

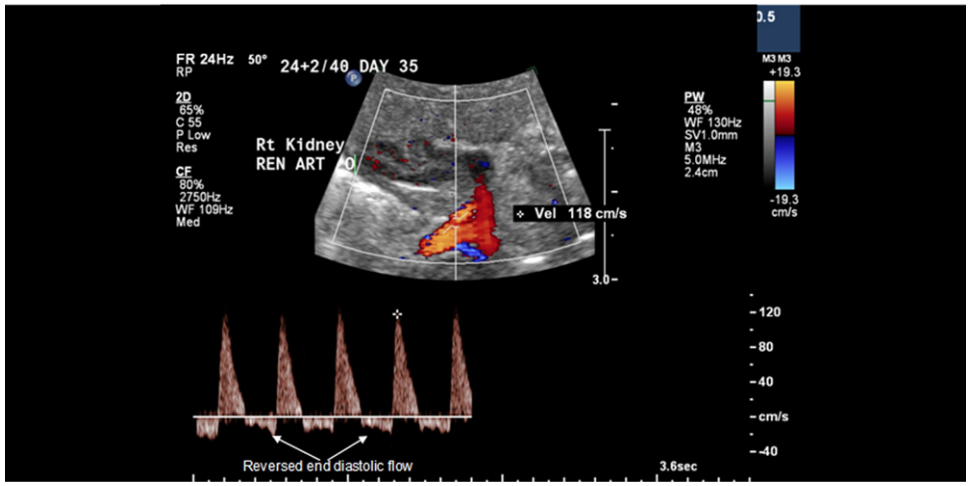

Figure 3 Abnormal flow pattern showing reversed end-diastolic flow in renal artery. (Color version of figure is available online.)

with an HSDA and resolves after ductal closure, the exact relationship to neonatal morbidity has not been well established. Figure 1 depicts the physiological relationship between abnormal flow patterns in systemic arteries and morbidity. Figures 2 and 3 depict abnormal arterial flow using Doppler interrogation of superior mesenteric artery and renal artery. There are, however, anecdotal reports of resolution of end-organ compromise (eg, acute renal failure) following surgical intervention.[87] The use of arterial Doppler patterns to guide decision making is not unique to the management of an HSDA. Umbilical artery flow reversal is a significant predictor of perinatal mortality, bronchopulmonary dysplasia, IVH, and NEC[88] and a common indication to deliver the preterm fetus. Comparable findings of flow alteration exist in adults with the subclavian steal syndrome or patients with the Blalock–Taussig shunt in which the steal phenomenon contributes to changes in cardiovascular physiology, blood flow, and patient well-being.

In summary, although the HSDA is associated with acute cardiorespiratory instability that is oftentimes alleviated with medical therapy, treatment has not been shown to improve long-term outcomes and may expose some patients to unheralded and well-recognized adverse effects. Previous studies have not considered the spectrum of illness severity attributable to an HSDA, which limits accurate appraisal of the impact of treatment. The use of cTnT and NTpBNP in combination with echocardiography assessment should be studied in a trial examining the short-term and longer-term effects of using this diagnostic model in targeted PDA treatment.

Future Directions

There remain many unresolved issues that cloud medical judgment and prohibit reaching a consensus approach to therapeutic intervention. It is our belief that the ductus arteriosus is hemodynamically significant and contributes to pathophysiological disease in a proportion of patients. RCTs performed to date have not satisfactorily addressed the relevant clinical question, as the definition of a HSDA was poorly standardized, not stratified, and somewhat superficial. The point at which hemodynamic instability, attributable to a high-volume ductal shunt, contributes to end-organ compromise needs prospective investigation and clarification. Whether these patients may be identified in the presymptomatic phase by using comprehensive TnECHO is unclear, but again needs prospective evaluation. Once the population of interest has been redefined, the issue of a RCT should be revisited. The role of TnECHO in monitoring treatment response needs future consideration.

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