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Ductus venosus closure results in transient portal hypertension—Is this the silent trigger for necrotizing enterocolitis?

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Abstract

Introduction: The etiology of necrotizing enterocolitis (NEC) remains elusive and no definite trigger has been identified. There are no studies to date examining the potential role of closure of the ductus venosus (DV), its effect on increasing portal venous pressure (PVP) and its association to mesenteric venous ischemia in the development of NEC. Our aim was to develop an animal model to examine this physiology.

Methods: Fifteen near-term lambs were used. The DV was occluded in experimental animals by a balloon tip catheter, while the sham controls underwent catheterization without DV occlusion. Vital signs and PVP were monitored for 4 h, followed by intestinal biopsy.

Results: The experimental group ($n=5$) demonstrated a significant increase in PVP following DV occlusion (11.87 mm Hg [95% CI: 11.40–12.34]), compared to controls (8.95 mm Hg [95% CI: 8.34–9.56]) ($F=12.16$, $p=0.001$). Histology of the terminal ileum showed vacuolar degeneration, indicative of reversible cellular damage in the experimental group.

Conclusions: We demonstrate that DV closure in the neonatal lamb leads to transient portal hypertension which is associated with cellular damage and inflammatory changes of the intestinal mucosa. Additional studies will be necessary to determine if the transient portal hypertension following DV closure leads to clinically apparent intestinal ischemia and NEC.

Abbreviations: NEC, necrotizing enterocolitis; DV, ductus venosus; PVP, portal venous pressure; DA, ductus arteriosus; CVP, central venous pressure; SaO_2, oxygen saturation; TUNEL, TdT-mediated dUTP nick-end labeling; ANOVA, analysis of variance.

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Necrotizing enterocolitis (NEC) is a cause of significant morbidity and mortality in premature infants with an incidence of 1%–5% among all neonatal intensive care admissions and up to 5%–10% of all very low birth weight (<1500 g) infants [1–3]. While the etiology of the disease remains elusive, enteric feeding, bacterial colonization and ischemic injury to the immature intestine have all been implicated as potential factors in the development of NEC [4–6]. Traditionally, theories implicating ischemia have focused on the arterial side of the circulation with vasoconstriction, hypotension, low flow states, or thrombosis of the intestinal vasculature as the major potential mechanisms of disease [7]. However, NEC rarely begins with an obvious antecedent triggering event that might result in intestinal ischemia.

Mesenteric venous ischemia resulting from venous hypertension is a well-described condition that can lead to intestinal necrosis in adults [8]. Interestingly, this same mechanism of ischemia has been implicated as the cause of intestinal necrosis in newborns after exchange transfusion through an umbilical vein catheter [9]. This observation led us to hypothesize that NEC may result from transient mesenteric venous congestion secondary to closure of the ductus venosus (DV). The DV is a fetal shunt that connects the umbilical vein with the inferior vena cava, allowing a large proportion of well-oxygenated umbilical vein blood to bypass the portal system and reach the central circulation (Fig. 1) [10–12]. It is estimated that 18%–50% of umbilical blood flow is shunted through the DV in the human fetus [13], with the flow decreasing as gestational age progresses [12,14]. With postpartum closure of the umbilical vein, the blood flow and blood pressure in the umbilical vein decrease abruptly, but the DV remains open for a variable amount of time as a porto-systemic shunt. Postnatal closure of the DV is a clinically silent event that usually occurs after the closure of the ductus arteriosus (DA).

Similar to the DA, DV closure has been shown to be delayed in premature neonates [15,16]. However, in contrast to the DA, no specific trigger for DV closure has been reported [17]. In addition, hemodynamic changes in the mesenteric venous circulation following DV closure have not been previously described. This study was designed to determine if DV closure after birth causes a rise in portal vein pressure that is sufficient to cause intestinal ischemic changes. We hypothesize that mesenteric ischemia may result from transient portal and mesenteric venous hypertension caused by DV closure and this may be the silent triggering event for NEC.

1. Materials and methods

This study was approved by the Children's Hospital Boston Institutional Animal Care and Use Committee. Studies were carried out in 15 time-dated pregnant ewes at 140–145 days' gestation (term 145 days). Ewes were

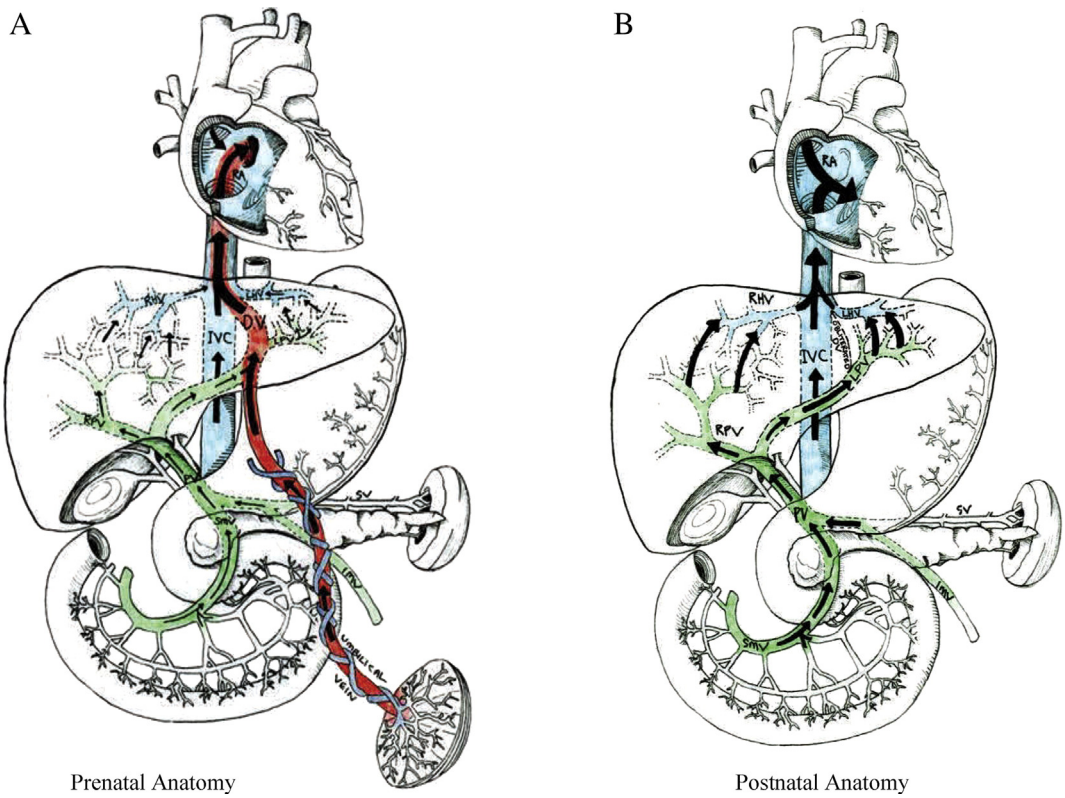

Fig. 1 Vascular anatomy of the Liver, portal circulation and the ductus venosus prenatal (A) and postnatal (B).