Pediatrics and Neonatology (2016) **57**, 7—18

Available online at www.sciencedirect.com

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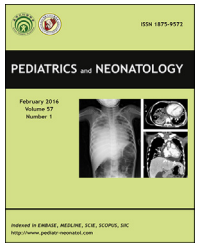

INVITED REVIEW ARTICLE

Transitional Hemodynamics in Preterm Neonates: Clinical Relevance

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Received Jul 1, 2015; accepted Jul 3, 2015
Available online 29 August 2015

Key Words
Preterm neonate;
fetal circulation;
developmental hemodynamics;
neonatal hypotension;
persistent ductus arteriosus

Background: Each newborn enters this world facing tremendous respiratory, hemodynamic and neuroendocrine challenges while going through drastic physiological changes during the process of adaption from fetal to postnatal life. Even though the vast majority of term infants transition smoothly without apparent consequences, this task becomes increasingly arduous for the extremely preterm infant.
Methods & results: This article reviews the physiology and pathophysiology of cardiovascular adaptation of the very preterm neonate. In particular it describes the physiology of fetal circulation, summarizes the hemodynamic changes occurring during preterm births and discusses the impact of the most frequently seen clinical scenarios that place additional burden on the premature infant during immediate transition. Finally an emphasis is placed on discussing common clinical dilemmas and practical aspects of developmental hemodynamics such as neonatal hypotension and patent ductus arteriosus; clinical presentations the neonatologist encounters on a daily basis.
Conclusion: The review provides a physiology-based view on the hemodynamics of the immediate postnatal transitional period.

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http://dx.doi.org/10.1016/j.pedneo.2015.07.002

1. Introduction

"It is not the strongest or the most intelligent that survive, but who can best manage change." — Charles Darwin

Perhaps the most significant and drastic human adaptation to change occurs during the first few breaths of postnatal life, as the fetus transitions from intrauterine to extrauterine environment with major rerouting of fetal hemodynamics. At term, successful postnatal transition is accomplished by a decrease in pulmonary vascular resistance following lung expansion, an increase in systemic vascular resistance as a result of removal of the placenta, and the subsequent closure of fetal vascular channels. Vascular rerouting, exposure to higher oxygen tension, and neuroendocrine surge all contribute to the significant redistribution of systemic and organ blood flows to meet the metabolic and functional demands of extrauterine life.

In the preterm infant, normal physiologic transition is affected by several factors, including but not limited to immaturity of organ systems, maternal conditions and medications, timing of cord clamping, and resuscitation maneuvers. Understanding of this complex process is critical in the care of preterm newborns, especially in the neonatal intensive care setting. The purpose of this article is to review fetal cardiovascular physiology and the hemodynamic changes during transition following preterm birth and their clinical relevance.

2. Fetal to postnatal transition of the circulation

2.1. Fetal-placental unit

The placenta is the principal site of gas and metabolic exchange for the fetus. On the fetal side, blood enters and exits the placenta by way of the umbilical artery and umbilical vein, respectively. Within the placenta, chorionic villi are bathed in mixed arterio-venous maternal blood with a pO_2 around 55 mmHg[1] and gas exchange occurs as blood moves across the vessels within the fetal villus tree.

Overall, absolute placental-umbilical blood flow increases with gestational age, but it exhibits a moderate decrease when normalized for fetal weight. It remains in the range of 110—125 mL/kg/min in the third trimester of pregnancy to meet the metabolic demands of the growing fetus.[2] This constitutes about 30% of the overall fetal biventricular cardiac output.

The fetoplacental unit holds a blood volume of approximately 110 mL per fetal weight in kg. The mean blood volume of the term infant is estimated to be ~80 mL/kg following immediate cord clamping.[3] Based on studies that used either weight-based estimation or dilutional method, an additional 20—35 mL/kg of blood is transferred from placenta to the term infant as a result of placental transfusion when clamping of the umbilical cord is delayed for up to 5 minutes.[4] The volume of placental transfusion is time-dependent; up to 50% of the volume is transferred within 1 minute,[3] and most of the transfusion is complete by 3 minutes. In preterm infants, delay in clamping of the umbilical cord results in increased blood volume as well.[5]

2.2. Fetal circulation

The distinct feature of the fetal circulation is that it is routed for parallel flow under physiologic conditions. Both ventricles work together to provide systemic blood flow resulting in a systemic cardiac output that is nearly double of the left ventricular output in postnatal life. Indeed, in human fetuses during the second half of pregnancy, fetal biventricular output estimated with Doppler ultrasound remains fairly constant in the range of 470—503 mL/kg/min,[6] similar to a combined cardiac output of approximately 450 mL/kg/min as measured with the microsphere method in fetal lambs.[7] Existence and patency of the fetal channels are key for establishing the parallel circulatory pattern. After receiving relatively less saturated blood from the caval veins with a superior vena cava (SVC) dominance, up to 90% of the right ventricular output is shunted through the ductus arteriosus (DA) to the descending aorta in the animal model. Thus, the majority of the right ventricular output bypasses the unaerated lungs and provides blood flow to the lower body and placenta. In human fetuses, however, pulmonary blood flow was reported to be significantly higher as estimated with Doppler ultrasound.[6] Furthermore, an increase in pulmonary blood flow was observed after 20 weeks' gestation, approximating 22—25% of the combined cardiac output during the third trimester. The left ventricle receives relatively oxygen-rich blood, directed from the umbilical vein by the ductus venosus (DV) via the inferior vena cava and foramen ovale (FO). This configuration allows for preferential streaming of blood with the highest oxygen saturation reaching the left side of the heart, thus, prioritizing oxygen delivery to coronary arteries and cerebral circulation. After 20 weeks' gestation, the right ventricle becomes the predominant pump and is responsible for approximately 60% of the combined cardiac output.[6,8] A somewhat decreased blood flow to the left atrium secondary to decrease in DV shunt flow and a more restrictive FO in later gestation have been suggested as important contributing factors to the right ventricular predominance.[9] Figure 1 depicts the fetal circulation and the blood flow changes from 20 weeks, 30 weeks, to 40 weeks of gestation, respectively.

The patency of the DA is primarily maintained by nitric oxide and prostaglandins synthesized within ductal tissue in the low intrauterine oxygen environment. Premature closure of the DA, either spontaneous or drug-induced, has been documented in case reports and case series, and this can result in right heart congestion, persistent pulmonary hypertension postnatally, or fetal demise.[10] The role of the DV as a critical fetal channel is less obvious. Relatively oxygen-rich blood from the placenta returns to the heart by either passing through the liver, or being shunted directly to the IVC via the DV. During midgestation, ~30% of the umbilical venous blood is shunted through the DV, and it decreases to only 20% between 30 weeks and 40 weeks of gestation. *In utero* closure of DV in the human fetus has varying fetal impact, ranging from normal fetal growth to fetal demise, while experimental obstruction of DV in fetal