Cellular Biology of End Organ Injury and Strategies for Prevention of Injury

Jeffrey M. Perlman, MB, ChB

KEYWORDS

• Asphyxia • Interruption of placental blood flow • Hypoxia-ischemia • Brain injury • Renal injury • Hepatic injury • Resuscitation

KEY POINTS

- The interruption of placental blood flow induces circulatory responses to maintain cerebral, cardiac, and adrenal blood flow with reduced renal, hepatic, intestinal, and skin blood flow.
- If placental compromise is prolonged and/or severe, circulatory collapse is likely with resultant hypoxic ischemic cerebral injury and accompanying renal, hepatic and intestinal compromise.
- Secondary or reperfusion injury may exacerbate the extent of the primary insult and is likely secondary to extended reactions from the primary insult, including excess in oxygen free radicals, intracellular calcium accumulation, microvascular endothelial dysfunction and nitric oxide formation.
- Treatment strategies should include the judicious use of supplemental oxygen, avoidance of hypoglycemia and elevated temperature in the delivery room, and the early initiation of therapeutic hypothermia to infants at highest risk for evolving encephalopathy.

INTRODUCTION

The process of labor increases the fetal risk for cerebral and systemic end organ damage as a consequence of interruption of placental blood flow with reduction in oxygen delivery. Fetal adaptive mechanisms in part involve circulatory responses with redistribution of cardiac output, to preserve cerebral perfusion and maintain cellular integrity. When the interruption of blood flow is severe or prolonged, these mechanisms fail, increasing the potential for cerebral and systemic end organ injury. After the restoration of blood flow either in utero or, more commonly, in the delivery room, there is the potential for secondary or reperfusion injury. This article concerns the initial circulatory changes that accompany a reduction in placental blood flow

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Division of Newborn Medicine, Department of Pediatrics, Weill Cornell Medical College, 525 East 68th Street, Suite N-506, New York, NY 10065, USA
E-mail address: Jmp2007@med.cornell.edu

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and oxygen delivery to the fetus, the fetal adaptive responses, the mechanisms that contribute to ongoing end organ injury after resuscitation, the clinical consequences, and potential strategies to reduce ongoing injury.

CIRCULATORY CHANGES ACCOMPANYING INTERRUPTION OF PLACENTAL BLOOD FLOW

The important circulatory responses to interruption of placental blood flow have been well categorized in experimental studies.[1–4] These include (1) redistribution of cardiac output to preserve blood flow to the more vital organs (ie, brain, myocardium, adrenal gland) with reduced flow to less vital organs (ie, kidney, intestine, muscle); (2) redistribution of umbilical venous blood flow including bypassing the liver through the ductus venosus and preferential streaming of umbilical venous blood across the foramen ovale via the left ventricle toward the upper body circulation to maintain oxygen delivery to the heart and brain[5–7]; and (3) loss of cerebral vascular autoregulation resulting in a pressure passive circulation and eventual diminution in cardiac output with resultant hypotension, and ultimately a critical decrease in cerebral perfusion and oxygen delivery (**Fig. 1**).[1–3,8] The mechanisms involved in the redistribution of blood flow include peripheral vasoconstriction, which is triggered by a carotid chemoreflex, and endocrine factors and then maintained or subsequently modified by endocrine and local components.[9,10] The critical relationship between blood pressure and cerebral blood flow (CBF) has been categorized in the experimental model. Thus, with initial arterial hypoxemia, fetal vascular resistance can decrease by at least 50% to maintain CBF with a minimal decrease in oxygen delivery.[11–13] Critical to this state is a normal or elevated mean arterial blood pressure. However, with persistent hypoxemia, and eventual hypotension, cerebral vascular resistance cannot decrease further, resulting in a marked reduction in CBF.[5,14]

The impact on systemic organ blood flow will vary, also determined in part by both the duration and severity of the insult. Experimental studies in fetal lambs demonstrate that partial occlusion of the umbilical cord causes a prompt reduction in urinary output and in glomerular filtration rate.[15] However, the renal response to experimental hypoxia seems to vary according to levels of CO_2 with a sharp reduction in renal blood flow during hypercapnia but not hypocapnia.[16] If the decrease in renal perfusion is marked, necrosis of the tubular epithelium may occur, resulting in the clinical

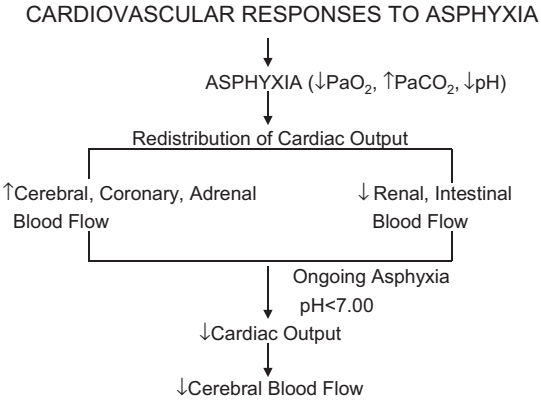

Fig. 1. Cardiovascular responses to interruption of placental blood flow (asphyxia) with preservation of cerebral, coronary and adrenal blood flow at the expense of flow to other organs.