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Pathophysiology of newborn hypotension outside the transitional period

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Abstract Hypotension is a common diagnosis in neonatal intensive care units. Although there are epidemiological data for normative blood pressure values in preterm and term infants, the ranges of normal blood pressure where adequate organ perfusion is ensured for different gestational and postnatal ages remain unclear. An understanding of the developmentally regulated differences in the physiology and pathophysiology of the neonatal cardiovascular system in comparison to that of mature subjects is important to formulate an appropriate treatment strategy in neonates with circulatory compromise. This article reviews the current understanding of pathophysiology of hypotension and shock in the neonate beyond the transitional period, focusing on hypovolemia, myocardial dysfunction, abnormal peripheral vasoregulation, and relative or absolute adrenal insufficiency with potentially associated down regulation of adrenergic receptors.

1. Normal blood pressure

Although the exact gestational- and postnatal-age dependent autoregulatory blood pressure range has not been defined for the neonatal patient population [1], findings of recent studies on organ blood flow and its autoregulation have provided some novel information in this area [2]. However, several theoretical and clinical aspects of developmental cardiovascular pathophysiology relevant to neonatal shock remain unclear [3]. One area where the available information certainly needs further investigation is the relationship between blood pressure and vital organ perfusion in the very low birth weight (VLBW) neonate during the first 24 postnatal hours and the impact of this relationship on neurodevelopmental outcome. This topic is addressed in detail in chapters written by Kluckow et al. and Osborn et al. in this issue.

The major determinants of blood pressure (BP) in the newborn period and early infancy are weight and gestational and chronological age for which normative values have been published [4]. The increase in blood pressure with advancing gestational and postnatal age is clearly developmentally regulated. Since blood pressure is the product of an

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interaction between cardiac output (CO) and systemic vascular resistance (SVR), the observed elevation in blood pressure could possibly be the result of an increase in cardiac output, systemic vascular resistance or both. Under normal physiologic conditions, in the absence of a patent ductus arteriosus (PDA) and past the immediate newborn period, cardiac output (mL/kg/min) is similar in both term and preterm infants. In addition, cardiac output remains essentially unchanged throughout infancy. Therefore, the increase in BP with advancing gestational and postnatal age is primarily the result of increase in SVR. The developmental changes leading to the increase in the SVR are not known. However, maturation of vascular smooth muscle, changes in the expression of vascular angiotensin II receptor subtypes and maturation of the central autonomic and peripheral nervous system play a significant role in increasing vascular tone and therefore SVR. As for the angiotensin II receptors, there are two major receptor subtypes. The AT_1R is expressed in mature tissues and the umbilical artery and mediates smooth muscle contraction and plays a role in fluid and electrolyte regulation, while the AT_2R is expressed in fetal and newborn tissue with unknown function. The developmentally regulated transition from AT_2R to AT_1R appears to begin at 2 weeks of life and is complete by 3 month of postnatal age [5].

2. Definition and phases of neonatal shock

Shock is a state of cellular energy failure caused by the inability of tissue oxygen delivery to satisfy tissue oxygen demand. Shock presents in phases of advancing severity characterized by specific pathological alterations in cardiovascular, renal and neuroendocrine function [1,6]. In the initial compensated phase, vital organ (brain, heart and adrenal glands) perfusion and blood pressure are maintained by neuroendocrine compensatory mechanisms via redistribution of blood flow from the non-vital (kidneys, intestine, liver, muscle, skin, etc.) organs. This phase may be clinically best recognized by a decrease in urine output and changes in peripheral perfusion on the clinical exam. However, urine output may be affected by processes other than the hemodynamic alterations in compensated shock and our ability to accurately evaluate changes in tissue perfusion in the neonate is limited at best. With progression of the condition, shock enters its uncompensated phase. In this phase, neuroendocrine compensatory mechanisms cannot further maintain vital organ perfusion, and systemic hypotension and generalized tissue ischemia develop. In the neonate, shock is most frequently recognized in its uncompensated phase by the presence of hypotension, oliguria and evolving lactic acidosis. Even then, because of the lack of universally accepted gestational and postnatal age-dependent definition for low blood pressure, the recognition of shock may be further delayed until evidence of organ hypoperfusion emerges. If treatment at this time is delayed or is ineffective, shock enters its final irreversible phase resulting in irreparable cellular damage, multiorgan failure and death.

3. Definition and clinical relevance of neonatal hypotension

Although there is some prospectively collected information on the relationship between blood pressure and organ blood flow in the transitional period especially in the VLBW patient population, very little data exist for the post-transitional neonatal period (from the 2nd to the 28th postnatal days). Except for the VLBW neonate during the first 24 postnatal hours, the general assumption is that the laws of cardiovascular physiology as we know from studies on mature animals and humans govern the relationship between blood pressure and organ blood flow in the rest of the neonatal patient population with a narrow organ blood flow autoregulatory blood pressure range. However, there is very little prospectively collected information available that this is indeed the case [6]. In addition, we manage neonatal shock without substantive direct information on the impact of the treatment on neonatal morbidity and mortality and assume that effective treatment of neonatal hypotension improves neurological outcome and survival in both preterm and term neonates. This assumption is based on lines of indirect evidence such as the association between systemic hypotension and short- and long-term neurological sequelae and is discussed elsewhere in more detail [1].

4. Pathophysiology of hypotension

4.1. Hypovolemia

Although in the pediatric patient population absolute hypovolemia is the most frequent primary cause of hypotension, in neonates, abnormal peripheral vasoregulation with or without myocar-