Editorial

Perinatal vascular development

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See article by Boels et al. [3] (pages 140–150) in this issue.

During transition to the extraterine environment, the newborn infant must accomplish complex cardiorespiratory adjustments. Dramatic changes in pulmonary and systemic vascular resistance must occur within minutes, followed by more gradual changes over the succeeding days. A host of mediators of vascular tone are involved in these processes and these have been the focus of extensive study. Differential responses from different vascular beds contribute to these circulatory changes; a variety of exogenous and endogenous factors affect the responsiveness of vascular beds to vasoactive mediators. When these critical circulatory changes are not accomplished successfully, the life-threatening disorder known as persistent pulmonary hypertension of the newborn may result [1]. In older subjects, pulmonary hypertension associated with the acute respiratory distress syndrome, congenital heart disease with left-to-right shunt, and primary pulmonary hypertension remain baffling challenges for the clinician. At the same time, excessive vasodilatation mediated by increased endogenous production of nitric oxide has been implicated in the pathogenesis of septic shock [2]. Thus, modulation of vascular tone is a critical homeostatic mechanism whose failure can lead to life-threatening derangements; it is a subject well worth of the extensive research attention it has received.

Boels et al. describe a developmental assessment of the mechanisms of bradykinin-induced relaxations in pulmonary arteries in this issue of Cardiovascular Research [3]. This represents an important contribution, because improved understanding of the mechanisms of pulmonary vascular bed reactivity and the developmentally determined characteristics are vitally important to developing potential strategies for the treatment of pulmonary vascular disorders. Physiology of the pulmonary vascular bed and influences of vasodilators, such as bradykinin, acetylcholine and substance P, change dramatically in the piglet pulmonary artery model used in this study. In the fetus, bradykinin-mediated relaxation is completely dependent on the local release of nitric oxide. In the immediate postnatal period, bradykinin relaxation evolves to depend on prostaglandin synthesis, in addition to nitric oxide synthesis. This is in contrast to other endothelium-dependent vasodilators including acetylcholine and substance P. In the adult endothelium, bradykinin-dependent relaxation becomes almost completely independent of nitric oxide.

Persistent pulmonary hypertension causes significant morbidity and mortality in the newborn infant. Current treatment consists of respiratory support with mechanical ventilation, including conventional and high frequency modalities, blood pressure maintenance, including the use of inotrophic agents and volume expansion, vasodilators and extracorporeal membrane oxygenation (ECMO). Clearly, these therapies themselves can have significant complications. The use of inhaled nitric oxide (iNO) as a selective pulmonary vasodilator has recently become widely available. Its effectiveness is well documented in several randomized clinical trials [4,5]. iNO, along with adjuvant therapies such as high frequency ventilation has clearly reduced the need for ECMO, but not all infants respond well to the drug. In some instances, the failure to respond may be related to inadequate aeration of the lungs or other factors. However, it is evident from a variety of clinical studies that infants with certain conditions, such as sepsis or congenital diaphragmatic hernia, respond less well to iNO even when the drug is administered optimally [6]. Furthermore, the therapeutic benefit of iNO appears to be much less dramatic in older children and adults with only modest improvement in oxygenation without improvement in survival [7]. Boels et al. [3] demonstrate that the size and location (large vs. small arteries) of the blood vessels markedly influence the effects of vasodilating agents including bradykinin, acetylcholine and substance P. In addition, the mechanisms of contraction and relaxation...
change dramatically with maturation. These findings may offer valuable insights into the observed differences in responsiveness to iNO.

Research aimed at elucidating the NO-dependent and NO-independent vasodilator mechanisms and their ontogeny may help us develop a better understanding of the possible treatment strategies that may eventually further reduce the mortality and morbidity associated with pulmonary hypertension. It should be remembered, however, that the applicability of the findings reported by Boels et al. [3] to the human infant is yet to be confirmed, in view of the likelihood of inter-species differences in response to bradykinin, such as those known to exist between the ovine and porcine animal models. At the very least, however, these investigations provide important groundwork for additional studies for the physiology of transition of the pulmonary circulation and may ultimately lead to adjuvant therapies directed at pulmonary vascular bed relaxation via bradykinin-mediated mechanisms.

References