Developmental physiology of the cardiovascular system

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The transition from the fetal circulation to isolated extraterine life marks the most dramatic challenge to an individual's cardiovascular system. Even though the fundamental peculiarities of the fetal circulation have been discovered in the 19th century already, many mechanisms playing important roles in the late gestational and perinatal fetal circulation remain poorly understood. This is reflected by the large number of articles dealing with such unsolved problems that have been published recently in the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology. These studies address the maintenance of a high pulmonary vascular resistance and low pulmonary blood flow before birth (12), regulation of vascular tone of the fetal ductus arteriosus (15, 29), specific responses to hypoxia and hypoxemia (1, 9, 10, 30), programming of postnatal cardiovascular development by maternal undernutrition (11), and cardiovascular responses to pharmacological treatment (6, 24, 28).

Particular attention has been paid to time-dependent changes of local vascular tone. Given its constantly evolving structure, the presence of strongly time-dependent functional changes in the fetal circulation does not seem very surprising. Nevertheless, many of these changes have not yet been well described and are only beginning to become unraveled. For example, constriction of fetal ovine cerebral arteries induced by norepinephrine is, in contrast to adult vessels, independent from intracellular Ca^{2+} release, but nearly entirely relies on Ca^{2+} influx from the extracellular space through L-type Ca^{2+} channels (19). Correspondingly, vascular tone in these fetal vessels appears to be tightly regulated by K^{+} channels via changes in membrane potential (18). Fetal cerebral arteries also express much lower levels of the Ca^{2+}-independent isoform protein kinase C-ε, which mediates Ca^{2+}-independent contraction of smooth muscle (20). These observations suggest considerable developmental changes in pharmacomechanical and electromechanical coupling. Similarly, endothelium-dependent responses of isolated resistance arteries greatly vary during the final third of gestation (7). These responses appear to be agonist specific and differ between individual vascular beds. This makes extensions from findings in one vascular bed to another very difficult, but it may also provide clues to hitherto unrecognized physiological functions. An example to support such a reasoning may be the finding that smooth muscle cells from the ovine bladder, which is already functional early in the midtrimester, undergo a more rapid maturation of the contractile protein phenotype than aortic smooth muscle cells (2).

Another focus of recent interest addresses the developmental roles of ANG II and nitric oxide (5, 21, 25). The renin-angiotensin system is activated in both the maternal and fetal circulation. Elevated levels of ANG II are possibly detrimental to an adequate perfusion of critical organs, including the maternal uterus and the fetal kidney. Cox and co-workers (5) showed, by comparing systemic and local intra-arterial infusions of ANG II in sheep, that uterine vascular responses to ANG II are markedly attenuated during pregnancy. In the developing kidney, excessive vasoconstriction induced by ANG II appears to be counterbalanced by nitric oxide. Renal vasodilator effects of nitric oxide are well established in the adult (4, 16, 17, 22, 31). The precise source of the enhanced local release of nitric oxide in the postnatal kidney is not clear yet; however, both renal nitric oxide synthase I and III mRNA and protein are expressed at high levels during the first days after birth (26, 27).

The vast majority (>80%) of the studies described above have been performed in sheep, which may be rightly named the model organism for the study of fetal and perinatal cardiovascular development. Because of a long reproduction time and a lack of genomic information, however, sheep studies are less useful for the deciphering of the developmental function of single genes or complex gene pathways. The most promising model organisms for the study of these latter questions are the mouse and the zebrafish (Danio rerio). The technique of homologous recombination to induce mutations has produced an increasingly growing number of mice carrying targeted gene mutations. Several studies investigating the normal cardiovascular physiology of the mouse have recently appeared in this journal (13, 14, 23). Most notably, Porter and Rivkees...
(23) studied the ontogeny of humoral heart rate regulation in cultured murine embryos from postcoital day (PC) 8 onward. As early as PC 8, immediately after completion of cardiogenesis, heart rate is significantly altered via A1 adenosine-receptor activation and shortly thereafter by adrenergic receptor stimulation. In contrast, responsiveness to acetylcholine develops only after PC 13, even though muscarinic M2-receptor mRNA expression was detected by PC 11. This suggests that coupling of muscarinic M2 receptors to the intracellular signaling cascade is also developmentally regulated. These findings emphasize the importance of local control mechanisms of cardiac function during embryogenesis.

The zebrafish may gain even more importance than the mouse. With regard to developmental studies aiming to uncover genetic pathways important for the genesis of the cardiovascular system, the zebrafish has two advantages: applicability of large-scale mutagenesis screens and its transparency. Thus genetic alterations can be easily induced and easily detected. The power of this experimental system was described in detail in an invited review appearing last month in this journal (3). The usefulness of this model organism to generate insights into the relationship between embryonic cardiovascular structure and function was recently demonstrated by Fritsche and associates (8). Using a video microscopic technique, these authors could demonstrate that before peripheral vessels are functionally innervated they are regulated by an interplay of local factors, including nitric oxide and catecholamines. Future studies will link these physiological processes to genetic pathways.

REFERENCES


