Oxygen and Perinatal Origins of Adulthood Diseases
Is Oxidative Stress the Unifying Element?
Sandra T. Davidge, Jude S. Morton, Christian F. Rueda-Clausen

In this issue of Hypertension, Yzydorczyk et al1 present a novel approach to investigate how adverse environmental conditions during the early stages of life can lead to cardiovascular complications during adulthood. The authors used a model in which newborn rats were exposed to 80% oxygen from postnatal days 3 to 10. Although the rats used in the study were born at term, the authors suggest that, in some respects, their developmental stage is equivalent to that of a preterm fetus, allowing some aspects, such as kidney, lung, and vascular development, to be related to premature infants. Therefore, the approach taken by Yzydorczyk et al1 also provides additional clinical significance to their findings that may have implications in the care of premature babies in neonatal intensive care units and the use of oxygen therapy.

The ability of organisms to adapt to certain environmental conditions by permanently changing key functional elements is a fascinating concept that has been with us for a long time. One of the events that popularized this “programming” concept was the publishing of an article by Barker and Osmond2 in the early 1980s that demonstrated an association between low birth weight and an increment in standardized mortality rates later in life. During the following decades, other epidemiological studies linked adverse conditions during fetal stages and early childhood with adverse health outcomes later in life, including coronary heart disease, stroke, type 2 diabetes mellitus, and metabolic syndrome.3 Also known as the “fetal origins of adult disease” theory, this association between environment and disease has become a controversial topic studied by many groups. Consequently, a growing body of literature has proposed multiple mechanisms to explain the early stages of programming. However, after 25 years of research, no consensus has been reached regarding the specific pathophysiological mechanisms causing this fascinating phenomenon or the specific time frame (susceptibility window) in which it occurs.

Following the legacy of the work by Barker and Osmond,2 many authors have used various models of intrauterine growth restriction (IUGR) to investigate particular aspects in the early stages of development.4 Human fetuses have several mechanisms to compensate for an acute nutritional restriction,5 whereas they have limited reserves to compensate for oxygen insufficiencies. Low oxygen levels in the fetoplacental circulation, a condition commonly associated with several obstetric complications such as IUGR and preeclampsia, have been found to impact not only the neonate but also the cardiovascular health of the adult offspring. Both adult vascular function6 and structure7 are adversely affected by prenatal oxygen deprivation. In addition, nephron numbers are reduced in IUGR models, potentially via hypoxia-related changes in mitochondrial function leading to increased apoptosis.8

Interestingly, not only oxygen restriction but also exposure to high oxygen levels, such as those commonly used in the treatment of premature infants and modeled by Yzydorczyk et al., has been shown to have both acute and chronic detrimental effects, such as retinopathy of prematurity, respiratory distress syndrome, pulmonary hypertension, and cerebral palsy.9 Together, these data suggest that the level of oxygen exposure, either too little or too high, has a direct bearing on the handling of oxygen within the body. Although oxygen is critical to life, the balance between oxidant and antioxidant pathways determines whether this molecule acts as a friend or foe. An imbalance in oxygen availability or antioxidant levels can lead to increased production of reactive oxygen species (ROS) and subsequent oxidative stress in the tissues.

ROS are produced from many cellular sources, including NO synthase, NADPH oxidase, electron transport, metals, and lipids, to name a few, whereas many cellular signaling pathways have also been linked to oxidant regulatory mechanisms. Of particular interest is that angiotensin II has been demonstrated to be regulated by oxidant status. In their work, Yzydorczyk et al1 showed that, in adult rats exposed to 80% oxygen as neonates, in vitro vascular responses were specifically increased to angiotensin II but not to phenylephrine, an adrenergic agonist, or U46119, a thromboxane analogue. This undesirable effect of postnatal hyperoxia was reversed by the antioxidant Tempol, a superoxide dismutase analogue, suggesting a direct relation to increased oxidative stress in these vessels. This can lead to impaired vasodilation, as shown by decreased endothelial function in their male animals. Yzydorczyk et al1 also demonstrated decreased microvascular density and nephron count. Although not tested by the authors, it is tempting to speculate that ROS may be a common mediating pathway that also lead to reduced nephron number and capillary rarefaction, perhaps secondary to increased apoptosis and impaired angiogenesis, as observed previously in IUGR models.7,8

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From the Departments of Obstetrics and Gynecology/Physiology, University of Alberta; and the Women and Children’s Health Research Institute, Edmonton, Alberta, Canada.
Correspondence to Sandra T. Davidge, 220 HMRC, University of Alberta, Edmonton, Alberta, Canada T6G 2S2. E-mail sandra.davidge@ualberta.ca

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Interestingly, oxidative stress has been shown previously to be increased in IUGR infants, probably because of a decrease in the antioxidant levels leading to increased ROS levels. Despite being the opposite extremes of oxygen availability, there seems to be a common participation of increased oxidative stress in the pathophysiology of chronic diseases mediated by hypoxia and hyperoxia (see the Figure).

Yzydorczyk et al have taken a novel approach to the programming issue by directly inducing generalized oxidative stress in neonatal rats and studying the consequential effects on kidney structure, blood pressure, vascular structure, and function, all of which have been associated with cardiovascular health. This provides the basis for a potential common linkage among prematurity or IUGR, oxidative stress, and common cardiovascular outcomes. The stage at which the oxygen insult occurs, either in utero during hypoxia-induced IUGR or during the premature/neonatal period in the current study by Yzydorczyk et al, also suggests that the time frame in which programming may occur extends to both prenatal and postnatal stages.

In conclusion, the authors have presented an interesting article suggesting that oxygen and antioxidant capacity may be key players in “perinatal programming” of adult disease. A fascinating element of programming is the suggestion that the developing organism can rapidly adapt to adverse conditions to favor survival. However, the long-term consequences of these adaptations could have a significant impact on cardiovascular health later in life. Therefore, understanding the
mechanisms behind this observation may open new avenues in the management of cardiovascular risk factors and chronic diseases.

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