

# Oxygen homeostasis and stress in the ductus arteriosus

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## 9.1 Relevance

Failure of DA closure is a common complication in very preterm infants that can have significant clinical consequences and still presents challenges in terms of diagnosis, assessment and treatment options [1]. It is generally assumed that prolonged patency of the DA (PDA) is associated with several comorbidities, such as necrotizing enterocolitis, intracranial hemorrhage, pulmonary edema/hemorrhage, broncho-pulmonary dysplasia and retinopathy, and has a negative impact on outcome in such infants [1,2]. Nevertheless, there is an ongoing debate about the thresholds and strategies for PDA treatment. Adverse effects of pharmacological and surgical therapies must be weighed against conflicting information on which adverse outcomes can be attributed to PDA and unclear determinations of whether PDA closure alleviates those outcomes. Yet daily rounds in the neonatal intensive care unit frequently include bedside deliberations over management of preterm infants whose PDA is considered problematic [3]. In summary, PDA in preterm infants has been defined as a continuing conundrum –i.e., a question or problem having only a conjectural answer- for the neonatologist [4]. Needless to say, a more profound understanding of the (patho)biology of the DA, and the mechanisms that regulate its vascular tone, could have clinical implications and lead to better management options and better neonatal outcome.

Significant progress in our understanding of the DA physiology and pathophysiology has been achieved with the use of animal models, including the sheep, the rabbit, the mouse, the rat, or primates [1,2]. However, mammalian models are complex because the fetal/placental circulation has to be exposed to intervention only through complex surgery and experimental manipulations affect both the mother and the fetus. Therefore, there is a need for additional models, addressing these limitations [2]. The chicken (*Gallus gallus*) embryo represents an excellent model for investigating developmental physiology of the cardiovascular system [5]. Chicken embryos have a mammalian-like circulation, with an extraembryonic circuit involved in the gas exchange (the chorioallantois), analogous to the placenta and they maintain bilaterally developed DA [6]. As the chicken embryo develops outside the mother, the number of experimental animals is divided by two, and effects of external stresses on cardiovascular development can be studied without interferences of maternal hormonal, metabolic, or hemodynamic alterations.

## 9.2 Innovation

With the present project, we aimed to implement and extend the utilization of the chicken embryo as a model for developmental vascular biology. Although probably more is known about the descriptive embryology, teratology, and experimental embryology of the chicken embryo than of any other model organism, developmental changes in the reactivity of the chicken DA had not been studied until our recent investigation [7]. In fact, the publication of our findings has already attracted the attention of other investigators in the field of DA developmental biology (see reference [2]). The numerous groups of investigators that are currently using expensive, aggressive, and technically complex mammalian-based experimental models to study developmental vascular biology would benefit from a model characterized by its tractability for experimental manipulation, its rich history in developmental biology, and a relatively short incubation time. If the similarities that we have already observed between the chicken and the mammalian and human DA are confirmed, then a new model will be available for translational studies for the human DA and, moreover, for the biology of vascular O<sub>2</sub> sensing in vivo and in vitro. In addition, investigators interested in the effects of prenatal insults in development or in the pathophysiology of human diseases would benefit from a model in which insults (such as hypoxia, malnutrition or exposure to drugs or toxics) are easily performed and are not interfered by maternal influences.

The use of animal subjects is fundamental to the advancement of biomedical research and practice, at least until viable replacements are found. Equally important are the ethical guidelines and welfare protocols that shape the conduct of such research. Animal welfare guidelines and legislation still emphasise Russell and Burch's 'three Rs': reduction (of the number of animals used), refinement (of testing procedures to minimise suffering), and replacement (of animal models with alternatives) [7].

Nevertheless, there are those with the strongly held belief that it is morally indefensible for mankind to subject animals to experimental procedures that cause any degree of discomfort, as an animal is unable to provide informed consent and does not benefit directly or indirectly from the studies. These guidelines and protocols mark the interface between the experimental needs of medical and scientific researchers and the socially acceptable degree of suffering the experimental subjects should endure and/or consent to for research benefits. However, there is a marked distinction between human

phase regulations, which focus on issues of patient recruitment and consent, and the laboratory animal phase that focuses on the `three Rs' of reduction, refinement, and replacement.

In conclusion, this thesis adds to the body of knowledge about DA vasoreactivity, furthering our understanding of it's pathophysiology. This bring us one step closer to developing better treatment strategies for PDA in a vulnerable group of patients - the very preterm and/or growth restricted infants at risk for several associated neonatal comorbidities - and thus contributing towards a better outcome.

## References

1. Clyman, R.I., Mechanisms regulating the ductus arteriosus. *Biol Neonate*, 2006. 89(4): p. 330-5.
2. Sutendra, G. and E.D. Michelakis, The chicken embryo as a model for ductus arteriosus developmental biology: cracking into new territory. *Am J Physiol Regul Integr Comp Physiol*, 2007. 292(1): p. R481-4.
3. Reese J, Laughon MM. The Patent Ductus Arteriosus Problem: Infants Who Still Need Treatment. *J Pediatr*. 2015 Nov;167(5):954-6. doi:10.1016/j.jpeds.2015.08.023. Epub 2015 Aug 24. PubMed PMID: 26316368.
4. Evans N. Preterm patent ductus arteriosus: A continuing conundrum for the neonatologist? *Semin Fetal Neonatal Med*. 2015 Aug;20(4):272-7. doi: 10.1016/j.siny.2015.03.004. Epub 2015 Mar 25. Review. PubMed PMID: 25818393. 3.
5. Ruijtenbeek, K., J.G. De Mey, and C.E. Blanco, The chicken embryo in developmental physiology of the cardiovascular system: a traditional model with new possibilities. *Am J Physiol Regul Integr Comp Physiol*, 2002. 283(2): p. R549-50; author reply R550-1.
6. Agren, P., et al., Ontogeny of chicken ductus arteriosus response to oxygen and vasoconstrictors. *Am J Physiol Regul Integr Comp Physiol*, 2007. 292(1): p. R485-96.
7. Russell WMS, Burch RL 1959. *The Principles of Humane Experimental Technique*. London: Methuen & Co. Ltd. [Reissued: 1992, Universities Federation for Animal Welfare, Herts, England.]