Physiology of the ductus arteriosus in the fetus and newborn

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Most previous studies of the physiology of the ductus arteriosus concentrated on the factors responsible for post-natal constriction of the ductus smooth muscle with resultant closure. Only recently has it become evident that the ductus arteriosus is not only actively constricted after birth but that during normal fetal life, is actively maintained in a dilated state by factors responsible for relaxation of the smooth muscle. Post-natal closure therefore reflects not only an increase in forces acting to constrict the ductus arteriosus but also a diminution in those forces responsible for active dilatation.

Early studies demonstrated that an increase in O_2 concentration to which the ductus arteriosus was exposed led to constriction of the ductus arteriosus(11). This phenomenon was considered the major factor responsible for post-natal closure of the ductus. Subsequent studies demonstrated that there was a developmental pattern in the response to oxygen and that the ductus arteriosus of immature animals did not constrict to the same degree when exposed to O_2(12), a factor held responsible for persistent patency of the ductus arteriosus in infants born prematurely.

The exact mechanism by which O_2 induced constriction was not clear. Since O_2 dilated pulmonary vascular smooth muscle whereas it constricted ductus arteriosus smooth muscle it was thought likely that an intermediary vasoactive substance released by the action of O_2 was involved. Many vasoactive substances such as acetylcholine and bradykinin constrict the ductus and several studies therefore investigated their potential role in the physiological response to O_2(1,9,13). Atropine inhibits the O_2 response and therefore acetylcholine was considered as a possible mediator; bradykinin constricts the ductus arteriosus to a slight degree and also is released in significant quantities at the time of birth(8) suggesting a possible role for endogenous bradykinin in post-natal closure of the ductus arteriosus. Since stimulation of smooth muscle contraction by prostaglandins had been shown to require the presence of O_2, COCEANI and OLLEY(7) investigated the role of prostaglandins in post-natal responses of the ductus arteriosus to O_2. In fact, they showed that exogenous prostaglandins E_1 and E_2 dilated rather than constricted isolated ductus arteriosus strips obtained from close to term fetal lambs. This led us to investigate the possibility that prostaglandins may play an active role in maintaining the ductus arteriosus in a dilated

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state during normal fetal life. We administered inhibitors of prostaglandin synthesis to chronically catheterized fetal lambs in utero and were able to clearly demonstrate that the ductus arteriosus constricted significantly after administration of these agents(10). The effect of these inhibitors of prostaglandin synthesis were overcome by infusion of prostaglandin E_1 confirming that the effects were related to specific inhibition of prostaglandin synthesis. These studies led us to completely rethink the role of the ductus arteriosus during fetal life. Previously, the ductus arteriosus had been considered a passive conduit which allowed blood flow to be diverted away from the lungs towards the placenta. It now was apparent that this vascular structure was under active control during fetal life and that prostaglandins and perhaps other substances were involved.

The exact sites of origin of the prostaglandins responsible for maintaining the ductus arteriosus in a dilated state in vivo are not completely understood. PACE-ASCIAK and RANGARAJ(4) have shown clearly that the ductus arteriosus itself produces PGE_2 and even larger quantities of PGI_2. In normal adults, prostaglandins are detectable only in very low concentrations in plasma and are not thought to act as circulating hormones because of the rapid clearance by catabolism in the lungs. The fetus, however, has high circulating concentrations of prostaglandins and particularly PGE_2(2). This probably relates to the low fetal pulmonary blood flow and consequent minimal prostaglandin catabolism by the lungs of the fetus as well as to the fact that the placenta produces prostaglandins. It is likely therefore that PGE_2 plays a hormonal role in the fetus and that it is involved in circulatory control and particularly in maintaining the ductus arteriosus in a dilated state.

At birth, the placental source of production is removed and the increase in pulmonary blood flow from about 40 ml/kg body weight/min in the fetus to about 400 ml/kg body weight/min in the neonate allows effective removal of most if not all circulating PGE_2 thus enabling the ductus arteriosus to constrict. It thus appears that physiologic patency or closure of the ductus arteriosus represents a balance between the constricting effects of O_2 and perhaps certain vasoactive substances such as bradykinin and the relaxing effects of several prostaglandins.

The reasons for the diminished response to O_2 of the immature ductus arteriosus were of great interest to us particularly in view of the high incidence of persistent patency of the ductus arteriosus in premature infants.

We therefore evaluated the possible mechanisms responsible for this phenomenon. We confirmed our earlier findings that the O_2 response was significantly less in the immature animal and also showed that inhibition of prostaglandin synthesis by indomethacin in the immature ductus arteriosus produced significantly greater constriction than in the mature(3, 6). We further evaluated this difference in response to inhibition of prostaglandin synthesis at different gestational ages. Production of PGE_2/unit mass of ductus was not different at the two gestational ages, however, immature ductus arteriosus did produce greater concentrations of PGI_2 than did rings from animals at term(3, 5). However, since the ductus arteriosus is far more sensitive to the dilating effects of PGE_2 than PGI_2(3, 6), and in fact PGI_2 appears to have very little role despite its active production by the ductus arteriosus, it is unlikely that this increased production in the immature animal is in reality responsible for the gestational differences observed. More important in these gestational differences is the change in sensitivity of the ductus arteriosus to the various prostaglandins. The immature ductus arteriosus is far more sensitive to PGE_1 and PGE_2 than is the ductus arteriosus obtained from more mature animals(3, 6). A further factor possibly responsible for maintenance of persistent patency of the ductus arteriosus in a preterm infant is the fact that the pulmonary catabolism of PGE_2 is less efficient in the immature lung than in the mature lung(4) thereby possibly allowing a somewhat higher circulating concentration of prostaglandins to be present in the immature infant.

In conclusion, post-natal closure of the ductus arteriosus represents a change in the balance between factors actively dilating or constricting the ductus arteriosus. Attenuation or suppression of normal factors that maintain the ductus arteriosus in a dilated state allows the factors which produce constriction to predominate thereby leading to constriction of the smooth muscle with subsequent permanent closure. Immature animals or premature infants have not yet completely developed this normal balance.

Bibliography

BOREUS, L.O., T. MALMFORS, D.M. McMURPHY, and L. OLSON: Demonstration of adrenergic receptor function and innervation in the ductus arteriosus of the human fetus. Acta Physiol. Scand. 77(1969)316-321.

CHALLIS, J.R.G., S.R. DILLEY, J.S. ROBINSON, and G.D. THORBURN: Prostaglandins in the circulation of the fetal lamb. Prostaglandins 11(1976)1041-1052.

CLYMAN, R.I.: Ontogeny of the ductus arteriosus response to prostaglandins and inhibitors of their synthesis. Seminars in Perinatology 4(1980)115-124.

CLYMAN, R.I., F. MAURAY, M.A. HEYMANN, and C. ROMAN: Effect of gestational age on pulmonary metabolism of prostaglandin E_1 & E_2. Prostaglandins 21(1981)505-513.

CLYMAN, R.I., F. MAURAY, M.A. KOERPER, F. WIEMER, M.A. HEYMANN, and A.M. RUDOLPH: Formation of prostacyclin (PGI_2) by the ductus arteriosus of fetal lambs at different stages of gestation. Prostaglandins 16(1978)633-642.

CLYMAN, R.I., F. MAURAY, A.M. RUDOLPH, and M.A. HEYMANN: Age-dependent sensitivity of the lamb ductus arteriosus to indomethacin and prostaglandins. J. Pediatrics 96(1)(1980)94-98.

COCEANI, F. and P.M. OLLEY: The response of the ductus arteriosus to prostaglandins. Can. J. Physiol. Pharmacol. 51(1973)220-225.

HEYMANN, M.A., A.M. RUDOLPH, A.S. NIES, and K.L. MELMON: Bradykinin production associated with oxygenation of the fetal lamb. Circ. Res. 25(1969)521-534.

HEYMANN, M.A. and A.M. RUDOLPH: Control of the ductus arteriosus. Physiol. Rev. 55(1975)62-78.

HEYMANN, M.A. and A.M. RUDOLPH: Effects of acetylsalicylic acid on the ductus arteriosus and circulation in fetal lambs in utero. Circ. Res. 38(1976)418-422.

KOVALCIK, V.: The response of the isolated ductus arteriosus to oxygen and anoxia. J. Physiol. 169(1963)185-197.

McMURPHY, D.M., M.A. HEYMANN, A.M. RUDOLPH and K.L. MELMON: Developmental changes in constriction of the ductus arteriosus: Responses to oxygen and vasoactive substances in the isolated ductus arteriosus of the fetal lamb. Pediatr. Res. 6(1972)231-238.

PACE-ASCIAK, C.R. and G. RANGARAJ: Prostaglandin biosynthesis and catabolism in the lamb ductus arteriosus, aorta and pulmonary artery. Biochim Biophys Acta 529(1978)13-20.

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