# ROLE OF PROSTAGLANDINS IN CONGENITAL HEART DISEASE

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Neonatal heart disease, which would mostly consist of cyanotic congenital heart disease, referred to as the "blue babies" is an enigma to most of the general practitioners as well as to the pediatricians. Only a few of them can be salvaged if they manage to reach centres where specialized care is given to such children. Congenital heart disease (CHD) has become important in recent years because as it is being diagnosed in the neonatal period and early infancy because of the availability of certain specialized diagnostic facilities. The incidence of CHD in the newborns tends to vary a lot and the reported incidence in the western literature varies from 0.65/1000(1) to 11.9/1000(2) and in the Indian studies it varies from 1.45/1000(3) to 4/1000(4). This data is from surveys conducted prior to the availability of echo-cardiography, which is now the most reliable cardiovascular diagnostic facility available.

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Since these children are being increasingly diagnosed and to manage them adequately, medically as well as surgically, one must understand the physiology of neonatal cardiac problems. Neonatal cardiac surgery is still in its in ancy in India, and to set up centres for cardiac surgery for neonates and infants is a very expensive exercise. In the full term and pre-term newborns who are born with cyanotic congenital heart diseases, their life depends on the patency of the ductus arteriosus. Drugs that close or re-open the ductus arteriosus are becoming vital in neonatal cardiology because the presence or absence of ductal patency can have a large impact on newborn physiology, particularly in critically ill infants who may have significant pulmonary compromise on ductal dependent congenital heart lesions.

Indomethacin constricts the ductus(5) and prostaglandin E re-opens it(6). The recognition of the effect of prostaglandins and inhibitors of their synthesis on the ductus arteriosus has been one of the most important developments in the cardiovascular drug therapy in infants and children(7).

## Pharmacological Aspects

Prostaglandins were identified in the human umbilical cord about 20 years ago(8). Prostaglandins are eicosanoids derived from arachidonic acid which are unsaturated, hydroxy fatty acid, 20 carbon compounds(9). They have a cyclopentane ring with 2 side chains containing 1, 2 or 3 double bonds. They are further classified as series E, I and F. PGF causes vasoconstriction whereas PGE and PGI are vasodilators (*Fig.*). Prostaglandins are eliminated by catabolism in the lungs.

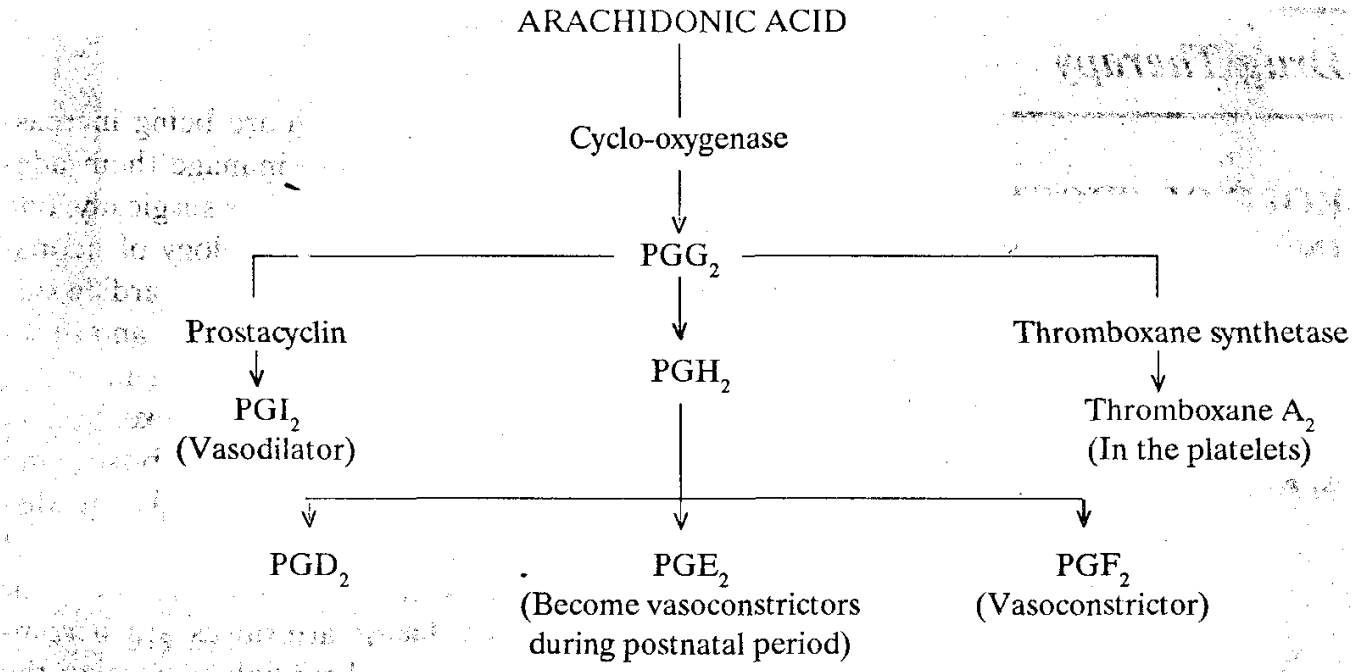


*Fig. Summary of different prostaglandins.*

Prostaglandins $I_2$ and $E_2$ are vasodilators in several vascular tissues. Large amounts of PGE are produced by the placenta. $PGE_2$ is two to three times more potent vasodilator of ductus arteriousus(10,11). This marked sensitivity of ductus arteriosus to $PGE_2$ makes it the most important prostaglandin in the regulation of patency of the vessel. Thus, PGE is used to increase pulmonary blood flow and oxygenation of blood in infants with congenital heart disease, especially in those with restricted pulmonary or systemic blood flow.

**Therapeutic Uses**

During embryonal life, prostaglandins play an important role in maintaining the patency of ductus arteriosus. In infants, several congenital heart diseases are dependent on the patency of ductus arteriosus for maintaining their circulation(7). The various envisaged therapeutic uses include:

1. In transposition of great vessels with intact atrial or ventricular septa or small atrial or ventricular septal defects, patency of ductus arteriosus for mixing of systemic and pulmonary circulations is essential for life. Several workers(12-15) observed a significant increase in $PaO_2$ following PGE infusion in cases with transposition. Prostaglandin E infusion is an effective initial therapy when cardiac catheterization is not available or a balloon atrial septostomy is not feasible. Reports are available of its use in treating severe hypoxemia even after atrial septostomy(1,3,15).

2. In severe right sided obstructions like pulmonary atresia or severe pulmonic stenosis with intact ventricular septum or in tricuspid atresia, again pulmonary circulation depends on ductus arteriosus. Freed(16) found favorable response to intravenous infusions and oral administration of PGE in large series of patients with these conditions. The arterial oxygen tension increased and the ductus remained patent.

3. In aortic arch anomalies, blood flow to the inferior part of the body again

depends on right to left shunting through the ductus arteriosus from the pulmonary artery to descending aorta distal to the interruption. Administration of PGE is beneficial and may be life saving(17).

In infants with coarctation of aorta, flow across ductus leads to increase in blood pressure in descending aorta and decrease of blood pressure in ascending aorta. This hemodynamic improvement results in improved renal function and correction of acidosis(16).

**Factors Determining the Response of Ductus Arteriosus**

The various important factors determining the response are:

(a) *Age:* In infants less than 4 days, the ductus responds more favorably than in older infants(16). However, infants at 3 weeks of age have also responded favorably(18). Hence, a ductus may reopen soon after functional closure or a week after closure too. Therefore, age is not an absolute determinant for the response to PGE.

(b) *Time:* The time of onset of effect may range from 15 min to as much as 20 hours(16). Therefore, infusion of PGE should be continued till its maximum efficacy is determined(7).

(c) *Cyanotic or acyanotic congenital heart disease:* The response to infusion in cyanotic CHD is seen in younger infants, *i.e,* less than 4 days and as early as 30 min after birth. In contrast, in acyanotic congenital heart disease age was not critical for a positive response and the initiation of response was observed at 1.5 hours (15 min to 4 hours)(16).

**Treatment**

(a) *Initiation of Treatment*

The treatment can be initiated in a critically ill infant suspected of having a ductus dependent congenital cardiac anomaly even before catheterization for confirming the diagnosis(19). This has been based on the good results achieved alongwith relative safety of the drug in clinical studies. However, the problems encountered may be further deterioration of congestive heart failure in certain infants and also the overall mortality due to PGE infusion has not yet been determined.

(b) *Monitoring of Treatment*

During PGE infusion, one must monitor heart rate, systemic arterial blood pressure, rate of respiration, body temperature, central nervous system signs and electrocardiogram(7).

(c) *Dosage and Administration*

Intravenous infusion of PGE should be started at a rate of 0.002 to 0.006 $\mu$g/kg/min and increased upto about 0.05 to 0.06 mg/kg/min(2). Once the patient responds favorably the high dose may be reduced gradually and maintained at lower rates of 0.2 $\mu$g/kg/min(12). It can be given intra-arterial, but has no added advantage.

It can be given orally in a dose of 30-45 $\mu$g/kg/hour at 1 hour interval which can be gradually increased to 6.5 $\mu$g/kg/hour if no response is observed within 2 hours. This may have to be continued for the initial 2-3 weeks(19).

**Side Effects**

When given for short periods and at low doses, PGE is well tolerated by infants. However, side effects do occur occasionally. The most common adverse effects are cardiovascular followed by central nervous system and respiratory as observed by Lewis and associates(21). The various side effects are summarized below:

1. Cardiovascular effects are the most common and include bradycardia or

tachycardia, arrhythmias, hypotension and cutaneous vasodilation and edema. These are more common in infants less than 2 kg with a cyanotic lesion and infusion for more than 48 hours. Heart failure may develop or may worsen during therapy.

2. The central nervous system side effects observed are seizure like activity, irritability, lethargy and elevation of body temperature.

3. Respiratory depression is a common side effect, more in infants less than 2 kg and with cyanotic lesions.

4. Structural changes in the pulmonary circulation were observed as aneurysmal dilatations in the arterial walls which correlated with the duration of infusion. So the treatment should be as short as possible(22,23).

5. Gastrointestinal side-effects were observed as necrotizing enterocolitis in a few patients and diarrhea was seen more commonly in orally treated patients.

6. Hematological effects included hemorrhage, disseminated intravascular coagulation and thrombocytopenia.

7. Other side effects observed were hypocalcemia, hypoglycemia(17) and cortical hyperostosis of the long bones(24).

Prostaglandins are routinely being used to palliate and to mange a number of critical cardiac lesions in the newborn period in many centres in the West. Although, these drugs are not freely available in our country, they have a definite role to play in the management of newborns with cyanotic congenital heart lesions in the near future.

**REFERENCES**


1. May S, Barahare H. Incidence of congenital heart disease in live births. Teratology 1972, 6: 271-275.
2. Meszaros M, Nary A, Kraszana G, *et al.* Birth prevalence of congenital cardiovascular malformation in Hungary. Acta Pedia Acad Sc Hung 1980, 21: 221-225.
3. Sharma B, Bajpai PC, Sharma NL. Some observations in congenital malformations. Indian J Pediatr 1972, 39: 286-289.
4. Saifullah S, Chandra RK, Pathak IC, Dhall GI. Congenital malformation in newborn–a prospective congenital study. Indian Pediatr 1967, 4: 251-255.
5. Friedman WF, Hirschklan MJ, Printz MP. Pharmacologic closure of patent ductus arteriosus in the premature infant. New Engl J Med 1976, 295: 526.
6. Elliot RB, Starling MB, Mentze JM. Medical manipulation of the ductus arteriosus. Lancet 1975, i: 140-142.
7. Schneewiss A. Prostaglandins. *In:* Drug Therapy in Cardiovascular Diseases. Ed. Schneeweiss A. Philadelphia, Lea and Febiger, 1986, pp 341-351.
8. Kasim SMM. The identification of prostaglandins in human umbilical cord. Br J Pharmacol Chemother 1967, 29: 230-231.
9. Long WA. Developmental pulmonary circulatory Physiology. *In:* Fetal and Neonatal Cardiology. Ed. Long WA. Philadelphia, WB Saunders Co, 1990 pp 76-96.
10. Clyman RJ. Ontogeny of the ductus arteriosus response to prostaglandins and inhibitors of their synthesis. Semin Perinatol 1980, 4: 115-124.
11. Coceani F, Bodack E, White E, *et al.* $PGI_2$ is less relaxant than $PGE_2$ on the lamb ductus arteriosus. Prostaglandins 1978, 15: 551-556.
12. Britzke A, Suppan CH. Use of prostaglandin $E_2$ in management of transposition of great arteries balloon atrial septostomy. Br Heart J 1983, 49: 341-344.
13. Long P, Freed MD, Bierman FZ, Morwood WI, Nadas AS. Use of

prostaglandin $E_1$ in infants with d-transposition of the great arteries and intact ventricular septum. Am J Cardiol 1979, 44: 76-81.

14. Benson LN, Olley PM, Patel RG, Coceani I, Rowe RD. Role of prostaglandin $E_1$ infusion in the management of transposition of the great arteries. Am J Cardiol 1979, 44: 691-696.

15. Driscoll DJ, Kugler JD, Nihill MR, McNamara DG. The use of prostaglandin $E_1$ in a critically ill infant with transposition of the great arteries. Am J Pediatr 1979, 95: 259-261.

16. Freed MD, Heyman MA, Lewis AB, Roehl SL, Kensey RC. Prostaglandin $E_1$ in infants with ductus arteriosus dependent congenital heart disease. Circulation 1981, 64: 899-905.

17. Heymann MA, Berman W, Rudolph AM, Whitman V. Dilatation of the ductus arteriosus by prostaglandin $E_1$ in aortic arch abnormalities. Circulation 1979, 59: 169-172.

18. Coe JY, Radley Smith R, Yacoub M. Management of tricuspid atresia with orally administered prostaglandin $E_2$. J Pediatr 1982, 100: 496-497.

19. Heymann MA. Pharmacologic use of prostaglandin $E_1$ in infants with congenital heart disease. Am Heart J 1981, 101: 837-843.

20. Silove ED, Coe JY, Shiu MF, *et al.* Oral prostaglandin $E_2$ in ductus dependent pulmonary circulation. Circulation 1981, 63: 682-688.

21. Lewis AB, Freed MD, Heymann MA, Roehl SL, Kensey RC. Side-effects of therapy with prostaglandin $E_1$ in infants with critical congenital heart disease. Circulation 1981, 64: 893-898.

22. Haworth SG, Saver U, Bublney UK. Effect of prostaglandin E on pulmonary circulation in pulmonary atresia: A quantitative morphometric study. Br Heart J 1980, 43: 306-314.

23. Haworth SG, Silove ED. Pulmonary arterial structure in pulmonary atresia following prostaglandin $E_2$ administration. Br Heart J 1981, 45: 311-315.

24. Ueda K, Saito A, Nakano H, Aoshima M, Yokoto M, Muraoka RC, Iwaya T. Cortical hyperostosis following long term administration of prostaglandin E in infants with cyanotic congenital heart disease. J Pediatr 1980, 97: 834-836.