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Endogenous Dilator Prostaglandins in Congenital Heart Disease

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SUMMARY. **Maintaining patency of the ductus arteriosus pending surgical intervention can be critical to the survival of the neonate with ductal dependent congenital heart disease. Spontaneously delayed ductal closure has been observed clinically and experimentally in newborns with critical pulmonic stenosis. Infants with ductal dependent congenital heart lesions were therefore studied to ascertain whether there was an endogenous increase in dilator prostaglandins prolonging ductal patency.**

Six neonates with cyanotic lesions (group 1) and six with left ventricular obstructive lesions (group 2) were studied. Circulating PGE_2 was not increased in either group. The levels of plasma 6 keto $PGF_{1\alpha}$, a stable hydrolysis product of prostacyclin, were found to be elevated, but only in the cyanotic group (3143 ± 1844 vs 404 ± 250 pg/ml; $p < 0.05$; normal <500 pg/ml). As expected, Pao_2's were also different (36 ± 15 vs 72 ± 34 mmHg; $p < 0.05$).

It is speculated, therefore, that increased synthesis and/or release of prostacyclin, possibly mediated by the hypoxia of the cyanotic ductal dependent lesion, contributes to persistent patency of the ductus arteriosus.

KEY WORDS: **Prostacyclin — PGE_2 — Neonates — Patent ductus arteriosus (PDA) — 6 Keto $PGF_{1\alpha}$**

Neonates with ductal dependent congenital heart lesions are routinely treated with prostaglandin infusions in attempt to maintain ductal patency [21]. In such cases, the ductus arteriosus facilitates oxygenation, and maintenance of ductal patency may be critical for survival pending lifesaving surgical correction.

The ductus arteriosus is known to be exquisitely sensitive to the mediation of prostaglandins, potent vasoactive substances found naturally in many body tissues. It has been observed [12, 16] that, in addition to the therapeutic effect of exogenous infusions of dilator prostaglandins, there is an endogenous elevation of these vasoactive mediators associated with the persistent ductal patency of the premature neonate. Thus, it was hypothesized that an endogenous elevation of dilator prostaglandins might also be present in the term neonate with ductal dependent cyanotic congenital heart disease.

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Materials and Methods

Clinical Methods

Neonates admitted, within the first week of life, to the Intensive Care Nursery of Wyler Children's Hospital of the University of Chicago Medical Center with a diagnosis of congenital heart disease were candidates for study. Infants were entered regardless of birth weight or gestational age, and were excluded only if they were started on PGE_1 infusion prior to admission. Once parental consent was obtained, a 1.5-cc blood sample was drawn for the measurement of the plasma prostanoid levels. Samples were taken from indwelling arterial lines to avoid hemolysis. Cardiac diagnosis was confirmed by cardiac catheterization in all infants, and the babies were retrospectively classified into two groups as described by Luken and Yeh [21]:

Group 1—those with cyanotic lesions (predominantly secondary to right to left shunting); and
Group 2—those with left ventricular obstructive lesions.

Routine clinical and hemodynamic data, including vital signs, ventilator requirements, and the existence of other diagnostic entities, were serially monitored and recorded in all infants.

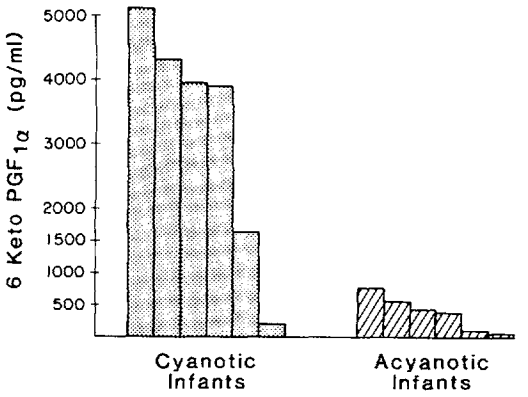

Fig. 1. Plasma 6 keto $PGF_{1\alpha}$ levels (pg/ml) of individual cyanotic and acyanotic (left ventricular obstructive group) infants with congenital heart disease.

plastic lungs, and thus had hypoxemia of a different etiology (pulmonary vs cardiac). It is possible that other unknown factors contributed to this particular infant's somewhat atypical picture.

There was a correlation observed (Fig. 2) between the decrease in Pao_2 and the increase in plasma 6 keto $PGF_{1\alpha}$ levels, with the most severe degrees of hypoxia being associated with the greatest elevations of the vasodilator metabolite (6 keto $PGF_{1\alpha} = 104228/Po_2 - 782$; $r = -0.74$).

Discussion

During the normal transition from intrauterine to extrauterine life, several cardiopulmonary adaptations must occur. Included among these is ductal constriction. Although a critical component of fetal circulation, the ductus arteriosus quickly becomes maladaptive in normal postnatal life. However, in neonates with ductal dependent congenital heart lesions, the ductus remains an important source of blood mixing, and maintaining its patency can be crucial to the survival of such infants.

Spontaneously delayed closure of the ductus arteriosus has been observed in newborn infants with critical pulmonic stenosis [23] and in lambs with experimental pulmonic stenosis [2]. It has been speculated that the decreased blood flow in utero which is associated with these lesions might result in decreased ductal smooth muscle development and subsequently decreased contractile potential [7].

It has also been speculated that these ductus are relatively insensitive to oxygen. However, the mechanism for this decreased contractile responsiveness to oxygen has not been elaborated. Since some synergistic interaction exists between the dilating prostaglandin, PGE_2, and oxygen in mediating ductal closure [8], it is postulated that prostaglandins may be somehow involved in the delayed closure in such neonates.

Both PGE_2 and prostacyclin (PGI_2) are associated with ductal patency, although controversy remains as to which is more significant clinically [6, 9]. Mahoney et al. [22] studied fetal lambs with experimental pulmonic stenosis and found no increase in either production of or sensitivity to the vasodilator prostaglandin PGE_2. However, prostacyclin is also able to produce ductal vasodilation [6, 9] albeit not as extensively in vitro as PGE_2 [5]. Our previous, as well as current, observations indicate that, in fact, prostacyclin may be more directly related to in vivo ductal patency in the human neonate [16, 17] than is PGE_2.

Furthermore, hypoxia is able to induce prostacyclin synthesis in neonatal lungs [13], presumably in attempt to counteract hypoxic pulmonary vasoconstriction, and in isolated rat and canine arterial segments [3]. It is possible therefore that, in infants with cyanotic congenital heart disease, there is a hypoxia-mediated release of prostacyclin which then acts to prolong ductal patency just when ductal integrity is so critical to survival.

There is some dispute in the literature concerning the validity of measuring plasma prostacyclin levels. Because prostacyclin is not rapidly metabolized in the lungs, some investigators [15, 18] have suggested that it can function as a circulating hormone. Others [4, 21, 23], however, have questioned its potential to act as a circulating hormone because of the extremely low levels detectable in adult plasma. All of these observations, however, have been made in nonstressed adults. Elevated, and clearly measurable, levels of plasma prostacyclin metabolites are, however, well documented in both the human neonate [14, 19, 20] and in newborn animals [24], particularly under conditions of stress.

It might be observed that there appear to be large standard deviations in measured 6 keto $PGF_{1\alpha}$ levels within our cyanotic group, again raising questions as to the validity of these measurements. However, if these levels are examined more closely (Fig. 1), it appears that this is largely due to the one infant whose levels remained within the normal range. With small numbers, one value that is separated from the cluster can greatly increase the observed standard deviation.

Although verified evidence of ductal patency did appear to be correlated with elevation of 6 keto $PGF_{1\alpha}$ levels, few pathophysiologic conclusions can be drawn. Since all of the infants were subsequently treated with PGE_1 infusions, this correlation may

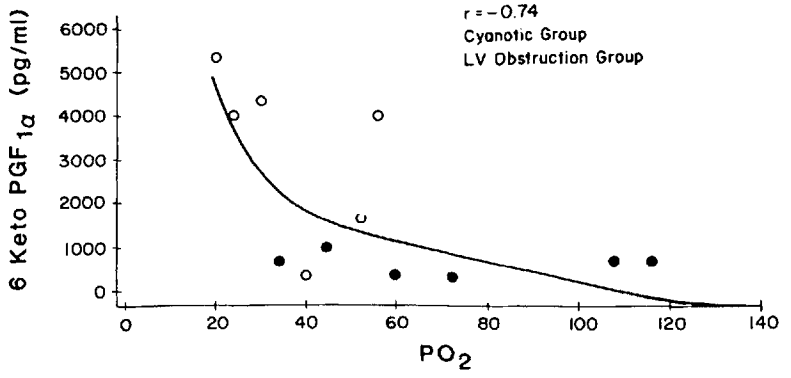

Fig. 2. Relationship between 6 keto $PGF_{1\alpha}$ levels (pg/ml) and Po_2 (mmHg) in infants with congenital heart disease ($r = -0.74$): (○) cyanotic infants and (●) represent infants with left ventricular obstructive lesions.

reflect either a direct effect of the circulating prostacyclin on the ductus, an interaction between the endogenous prostacyclin and the exogenous PGE_1, or a selective effect of PGE_1 on the hypoxic ductal tissue.

In summary, current data are consistent with the following conclusions: (a) neonates with certain types of ductal dependent congenital heart disease may have naturally delayed ductal closure, (b) this delay may be in part prostacyclin mediated, and (c) hypoxia may play a role in this natural delay in ductal closure either directly, or via stimulation of prostacyclin synthesis, or through some end organ synergism with dilator prostaglandins.

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