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Increased Plasma Immunoreactive 6-Keto-Prostaglandin $F_{1\alpha}$ Levels in Newborns with Idiopathic Respiratory Distress Syndrome

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Summary

Serial plasma concentrations of immunoreactive 6-keto-prostaglandin $F_{1\alpha}$ (6-keto-$PGF_{1\alpha}$), the stable hydration product of prostacyclin (PGI_2), were measured with radioimmunoassay during the first month of life in 25 preterm infants with idiopathic respiratory distress syndrome (IRDS) and 38 preterm controls with normal heart and lung function. The levels of 6-keto-$PGF_{1\alpha}$ (521 ± 81 pg/ml, mean ± S.E.) in the infants with IRDS were higher ($P < 0.05$) than those in the controls (335 ± 42 pg/ml) on the first day of life, but thereafter no difference was seen. The highest first day 6-keto-$PGF_{1\alpha}$ level (1448 pg/ml) was found in the infant who died because of severe IRDS at the age of 19 h. The plasma 6-keto-$PGF_{1\alpha}$ concentrations in the distressed infants correlated positively with the alveolar-arterial oxygen gradient and the need of additional oxygen, but negatively with the arterial pH. In addition, an inverse correlation between the first day concentrations of 6-keto-$PGF_{1\alpha}$ and the lowest arterial oxygen tension in infants needing assisted ventilation was found.

The mode of delivery (Cesarean section *versus* vaginal delivery) the gestational age, birth weight, sex or Apgar scores of the infants were not related to the 6-keto-$PGF_{1\alpha}$ levels on the first day of life. Neither did maternal pre-eclampsia, diabetes mellitus, or antenatal glucocorticoid treatment have any effect on the 6-keto-$PGF_{1\alpha}$ concentrations in the newborns.

Our data suggest that a surge of the vasodilatory and antiaggregatory PGI_2 is released during the early stage of IRDS, possibly in an attempt to increase the pulmonary perfusion. Our results give further indirect evidence that hypoxia stimulates the PGI_2 production.

Speculation

High plasma immunoreactive 6-keto-$PGF_{1\alpha}$ levels during the early phase of IRDS suggest an increased generation of the vasodilatory and antiaggregatory PGI_2 in this syndrome. This may be an attempt to overcome the increased pulmonary vasoconstriction in IRDS. When the PGI_2 formation rapidly declines after the first day of life, a relative PGI_2 deficiency may ensue.

Idiopathic respiratory distress syndrome (IRDS) is a clinical manifestation of lung immaturity in the newborn infants characterized by atelectasis, decreased lung compliance and right-to-left shunting (7). Although the primary or secondary deficiency of the surfactant synthesis is the best known feature in the pathogenesis of IRDS (4, 11), epidemiologic data imply that it is not the only pathogenetic factor (8). There is evidence that pulmonary vasoconstriction with subsequent hypoperfusion could be the central issue in IRDS (4).

Prostacyclin (PGI_2), a potent vasodilatory and antiaggregatory hormone produced by the vascular walls (1, 18, 19), is the major product of prostaglandin (PG) biosynthesis in the fetal and neonatal pulmonary arteries *in vitro* (24, 27). In healthy newborns the plasma concentrations of immunoreactive 6-keto-prostaglandin $F_{1\alpha}$ (6-keto-$PGF_{1\alpha}$), the stable hydration product of PGI_2 (10), are high which suggests increased PGI_2 generation during the first 4 days of life (13). In order to evaluate the role of PGI_2 in IRDS, we have measured the plasma 6-keto-$PGF_{1\alpha}$ concentrations in infants with IRDS.

SUBJECTS AND METHODS

Subjects. Sixty-three preterm infants were studied with the approval of the local Committee of Ethics (Table 1). Twenty-five infants had IRDS, the diagnosis of which was based on the clinical evaluation (early postnatal onset of tachypnea, intercostal retractions, expiratory grunting and cyanosis), need of additional oxygen during the first 48 h of life with or without assisted ventilation, and diffuse reticulogranular pattern on the chest x-ray. Seventeen infants needed ventilatory assistance with inspired oxygen of 60–100% and eight infants were treated with continuous positive airway pressure and additional oxygen of 50–60%. One infant died at the age of 19 h, and hyaline membranes were seen at the microscopic examination of the lungs. Thirty-eight preterm infants with comparable gestational ages and no evidence of heart or lung diseases served as controls. No subjects received drugs known to interfere with the PG synthesis.

Sampling and methods. Blood samples (1–2 ml) were taken from the distressed and control infants mostly on three occasions, either at the age of 1, 2, 3–4, 6–8, 12–14 days or 1 month. They were collected either from a peripheral vein or from aortal blood via an umbilical catheter. The site of sampling has no effect on the 6-keto-$PGF_{1\alpha}$ concentrations (13). Blood was drawn into ice-cold heparanized tubes containing acetylsalicylic acid at the final concentration of 20 μmole/liter. Plasma was separated immediately by centrifugation at 4°C and stored frozen (−20°C) until assayed for 6-keto-$PGF_{1\alpha}$ with a specific radioimmunoassay, as described elsewhere (28). Briefly, plasma was acidified to pH 3 with hydrochloride acid and extracted four times with ethyl acetate. The combined organic phases were evaporated to dryness under a nitrogen stream and two different parts of the residue dissolved in ethanol, both in duplicate, were taken for the saturation analysis using specific antibodies raised in rabbits against 6-keto-$PGF_{1\alpha}$-bovine serum albumin conjugate and a tritiated tracer (New England Nuclear Corporation, Boston, Mass., U.S.A.). The specificity of the antibody was tested against 22 other PGs or related compounds, and only 6-keto-PGE_1 caused a crossreaction of 1.8% at the 50% displacement level, whereas the cross-reactivity of all the others was less than 0.1%. The recovery of added 6-keto-$PGF_{1\alpha}$ (50–200 pg/ml) into plasma was between 84–104% (n = 15), and the coefficients of intra-assay and interassay variations were between 6.8–8.5% and 9.3–14.2%, respectively. The plasma 6-keto-$PGF_{1\alpha}$ measurement as an index of PGI_2 production was further validated by demonstrating a linear relationship (r = 0.958, $P < 0.001$, $n = 24$) between infused PGI_2 doses (1–8 ng/kg/min) and the rises in 6-keto-$PGF_{1\alpha}$ levels in plasma of healthy

Table 1. *The clinical characteristics of 63 preterm infants with and without idiopathic respiratory distress syndrome (IRDS)*

	Gestational age[1]	Birth weight[1]	Apgar scores[1] 1 min	Apgar scores[1] 5 min	Cesarean section	Maternal diabetes
IRDS ($n = 25$)	33.6 (26–36)	2264 (1100–3900)	7.0 (2–9)	7.8 (5–10)	14	5
Controls ($n = 38$)	33.7 (27–36)	2176 (880–4000)	7.0 (1–9)	8.5 (5–10)	10	2

[1] The results are expressed as mean (range).

Table 2. *The plasma concentrations of 6-keto-PGF$_{1\alpha}$ in preterm infants with and without idiopathic respiratory distress syndrome (IRDS)*

	Infants with IRDS ($n = 25$)		Controls ($n = 38$)		
Age	No. of specimens	6-keto-PGF$_{1\alpha}$ (pg/ml) (mean ± S.E.)	No. of specimens	6-keto-PGF$_{1\alpha}$ (pg/ml) (mean ± S.E.)	S.D.
Day 1	17	521 ± 81	15	335 ± 42	$P < 0.05$
Day 2	7	303 ± 50	10	295 ± 55	NS
Days 3–4	14	245 ± 38	7	185 ± 15	NS
Days 6–8	12	219 ± 25	13	169 ± 19	NS
Days 12–20	11	177 ± 14	12	157 ± 22	NS

adults. The plasma 6-keto-PGF$_{1a}$ concentrations in adults (aged 21–72 years) were 85 ± 7 pg/ml (mean ± S.E., $n = 21$) (13). Blood samples for arterial blood gas measurements were obtained from the descending aorta through an umbilical arterial catheter into heparinized syringes and analyzed within 15 min for pH and the partial pressures of oxygen (Pa_{O_2}) and carbon dioxide (Pa_{CO_2}) using routine laboratory methods. The alveolar-arterial oxygen gradient ($AaDO_2$) was calculated from a standard formula (12).

Results were analyzed with the Mann Whitney Rank Sum Test and the Spearman Rank correlation.

RESULTS

Plasma 6-keto-PGF$_{1\alpha}$ was higher ($P < 0.05$) in the infants with IRDS than in the controls on the first day of life, but thereafter no difference was seen (Table 2). The highest concentration (1448 pg/ml) was found in the infant who died because of severe respiratory distress at the age of 19 h. The first day concentrations of 6-keto-PGF$_{1\alpha}$ correlated negatively ($r = -0.762$, $P < 0.025$, $n = 8$) with the lowest Pa_{O_2} measured during the first week of life in the distressed infants needing assisted ventilation.

During the active phase of the IRDS, the 6-keto-PGF$_{1\alpha}$ levels correlated positively with the simultaneous $AaDO_2$ ($r = 0.640$, $P < 0.005$, $n = 22$) and inspired oxygen concentrations needed to maintain adequate oxygenation ($r = 0.710$, $P < 0.001$, $n = 22$), but negatively with the arterial pH ($r = -0.366$, $P < 0.05$, $n = 22$).

The mode of delivery (Cesarean section *versus* vaginal delivery), gestational age, birth weight, sex or Apgar scores of the infants did not affect on the 6-keto-PGF$_{1\alpha}$ concentrations on the first day of life. Neither did maternal pre-eclampsia, diabetes mellitus, or antenatal glucocorticoid treatment (Decadron) have any effect on the 6-keto-PGF$_{1\alpha}$ levels in the newborns.

DISCUSSION

In the past few years, much interest has been focused on the possible role of vasoactive prostaglandins, particularly prostacyclin, in the regulation of the fetal and neonatal circulation (5, 27). Because the exogenous administration of PGI_2 effectively decreases the pulmonary vascular resistance in the lambs (15), goats (3) and also in human (14), a decreased synthesis of PGI_2 is supposed to be important in the pathogenesis of pulmonary vasoconstriction (5), which, on the other hand, complicates severe IRDS (2, 4). In view of these considerations, an increased PGI_2 generation during the early phase of IRDS, as suggested from our results, was an unexpected finding.

It is impossible to deduce the mechanisms leading to the increased PGI_2 formation in IRDS on the basis of the data available, but at least the following explanations are possible: (1) the PGI_2 rise might reflect the overall increase in prostaglandin biosynthesis in IRDS, as suggested by the elevated circulating levels of prostaglandin E and F in this syndrome (9, 17), or (2) hypoxia, invariably seen in the infants with IRDS, stimulates PGI_2 synthesis in the distressed infants like in experimental animals (22) or healthy adults (16). The inverse correlation between the plasma 6-keto-PGF$_{1\alpha}$ levels and Pa_{O_2} support the explanation (2). The correlations between the other parameters indicating the severity of hypoxia (need of additional oxygen, arterial pH and $AaDo_2$) (12, 26) and the plasma concentrations of 6-keto-PGF$_{1\alpha}$ are also in accordance with this assumption.

With regard to the known circulatory and other effects of PGI_2 (6), the increased PGI_2 per se, seen in the early phase of IRDS, is very unlikely responsible for the development of the disease, although it may contribute to the systemic hypotension (23, 25) and the impaired platelet aggregation in the distressed infants (21). In this connection, thromboxane A_2 (TxA_2), a biologic antagonist of PGI_2, is of special interest, because a considerable body of evidence suggests that a balance between PGI_2 and TxA_2 rather than either agent alone may regulate the platelet function and vascular tone (20). Because no data exist on TxA_2 production in IRDS, we consider the increased formation of the vasodilatory and antiaggregatory PGI_2 a phenomen of its own. The physiologic significance of PGI_2 rise may be to increase the diminished pulmonary perfusion in IRDS. When the PGI_2 generation declines after the first day of life in distressed infants, a relative PGI_2 deficiency may result and contribute to the pathophysiology of IRDS.

REFERENCES AND NOTES

1. Bunting, S., Gryglewski, R., Moncada, S., and Vane, J. R.: Arterial walls generate from prostaglandin endoperoxides a substance (prostaglandin X) which relaxes strips of mesenteric and coeliac arteries and inhibits platelet aggregation. Prostaglandins, *12:* 897 (1976).
2. Cabal, L. and Hodgman, J.E.: Neonatal monitoring: arterial and venous pressure. In: D. W. Thibeault, G. A. Gregory: Neonatal Pulmonary Care. Ed. 1, pp. 190–206 (Addison-Wesley Publishing Company, Menlo Park, California, 1979).
3. Cassin, S., Winikor, I., and Tod, M. L.: Prostacyclin and fetal vascular resistance. Physiologist, *21:* 17 (1978).
4. Chu, J., Clements, J. A., Cotton, E. K., Klaus, M. H., Sweet, A. Y., and Tooley, W. H.: Neonatal pulmonary ischemia. Pediatrics (Suppl.), *40:* 709 (1967).
5. Coceani, F., Olley, P. M., and Lock, J. E.: Prostaglandins, ductus arteriosus, pulmonary circulation: current concepts and clinical potential. Eur. J. Clin. Pharmacol., *18:* 75 (1980).
6. Dusting, G. J., Moncada, S., and Vane, J. R.: Prostaglandins, their intermediates and precursors; cardiovascular actions and regulatory roles in normal and abnormal circulatory systems. Prog. Cardiovasc. Dis., *21:* 405 (1979).
7. Farrell, P. M. and Avery, M. E.: Hyaline membrane disease. Am. Rev. Resp. Dis., *111:* 657 (1975).

8. Farrell, P. M. and Kotas, R. V.: The prevention of hyaline membrane disease: new concepts and approaches to therapy. Adv. Pediatr., *23:* 213 (1976).
9. Friedman, Z. and Demers, L. M.: Essential fatty acids, prostaglandins, and respiratory distress syndrome of the newborn. Pediatrics, *61:* 341 (1978).
10. Johnson, R. A., Morton, D. R., Kinner, J. H., Gorman, R. R., McGuire, R. R., and Sun, F. F.: The chemical structure of prostaglandin X (prostacyclin). Prostaglandins, *12:* 915 (1976).
11. Kotas, R. V.: Surface tension forces and liquid balance in the lung. In: D. W. Thibeault, G. A. Gregory: Neonatal Pulmonary Care. Ed. 1, pp. 35–53 (Addison-Wesley Publishing Company, Menlo Park, California, 1979).
12. Krauss, A. N.: Ventilation-perfusion relationship in neonates. In: D. W. Thibeault, G. A. Gregory: Neonatal Pulmonary Care. Ed. 1, pp. 54–69 (Addison-Wesley Publishing Company, Menlo Park, California, 1979).
13. Kääpä, P., Viinikka, L., and Ylikorkala O.: Plasma prostacyclin from birth to adolescence. Arch. Dis. Child. (in press).
14. Lock, J. E., Olley, P. M., Coceani, F., Swyer, P. R., and Rowe, R. D.: Use of prostacyclin in persistent fetal circulation. Lancet, *1:* 1343 (1979).
15. Lock, J. E., Olley, P. M., and Coceani, F.: Direct pulmonary vascular responses to prostaglandins in the conscious newborn lamb. Am. J. Physiol., *238:* H631 (1980).
16. Masotti, G., Galanti, G., Poggesi, L., Abbate, R., and Neri Serneri, G. G.: Differential inhibition of prostacyclin production and platelet aggregation by aspirin. Lancet, *2:* 1213 (1979).
17. Mitchell, M. D., Lucas, A., Whitfield, M., Etches, P., Brunt, J. D., and Turnbull, A. C.: Selective elevation of circulating prostaglandin concentrations in hyaline membrane disease in preterm infants. Prostaglandins Med., *1:* 207 (1978).
18. Moncada, S., Gryglewski, R., Bunting, S., and Vane, J. R.: An enzyme isolated from arteries transforms prostaglandin endoperoxides to an unstable substance that inhibits aggregation. Nature, *263:* 663 (1976).
19. Moncada, S., Korbut, R., Bunting, S., and Vane, J. R.: Prostacyclin is a circulating hormone. Nature, *273:* 767 (1976).
20. Moncada, S. and Vane, J. R.: Arachidonic acid metabolites and the interactions between platelets and blood-vessel walls. N. Engl. J. Med., *300:* 1142 (1979).
21. Mull, M. M. and Hathaway, W. E.: Altered platelet function in newborns. Pediatr. Res., *4:* 229 (1970).
22. Needleman, P. and Kaley, G.: Cardiac and coronary prostaglandin: synthesis and function. N. Engl. J. Med., *298:* 1122 (1978).
23. Neligan, G. A. and Smith, C. A.: The blood pressure of newborn infants in asphyxial states and in hyaline membrane disease. Pediatrics, *26:* 735 (1960).
24. Pace-Asciak, C. R. and Rangaraj, G.: Prostaglandin biosynthesis and catabolism in the lamb ductus arteriosus, aorta and pulmonary artery. Biochim. Biophys. Acta., *529:* 13 (1978).
25. Rudolph, A. M., Auld, P. A., Golinko, R. J., and Paul, M. H.: Pulmonary vascular adjustment in the neonatal period. Pediatrics, *28:* 28 (1961).
26. Rudolph, A. M. and Yuan, S.: Response of the pulmonary vasculature to hypoxia and H^+ ion concentration changes. J. Clin. Invest., *45:* 399 (1966).
27. Terragno, N. A. and Terragno, A.: Prostaglandin metabolism in the fetal and maternal vasculature. Fed. Proc., *38:* 75 (1979).
28. Ylikorkala, O., Kaila, J., and Viinikka, L.: Prostacyclin and thromboxane in diabetes. Brit. Med. J., *283:* 1148 (1981).
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