

The effect of ventilatory patterns on prostacyclin (PGI₂) synthesis in the lung

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Summary

Prostacyclin (PGI₂) appears to be synthesized in the lungs of man and experimental animals. It has been stated that PGI₂ must be regarded as a local hormone that inhibits platelet adhesion to vessel walls only very close to the site of synthesis.

The wide range of normal values given for PGI₂ may be related to the sensitivity and exclusiveness of the different assay techniques used.

In animals hyperventilation increases PGI₂ synthesis by the lung, but in agreement with other authors we demonstrated that hyperventilation did not influence PGI₂ synthesis in man. We used a radio-immunoassay technique to estimate PGI₂ levels.

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Prostacyclin (PGI₂) is continuously generated from arachidonic acid and prostaglandin endoperoxides, mainly in the vascular endothelium of the lungs.¹ Unlike other prostaglandins it is not metabolized in its passage through the lung.² Because this prostaglandin is the most potent anti-aggregator in the body it appears to offer a homeostatic mechanism for the control of platelet aggregation *in vivo*.^{3,4} Edlund *et al.*,⁵ quoting Steer *et al.*⁶ and Sonnenfeld and Wennmalm,⁷ stated that the lowest blood level required for this function is 30-90 pg/ml. If they are correct, one would expect blood levels of this range to be present under normal conditions.

There is controversy about normal PGI₂ blood levels in man, as well as about how the mode of ventilation influences these values. In 12 patients being prepared for total hip replacement under general anaesthesia, we measured PGI₂ and blood gases before anaesthesia and again after 50 ± 4 (mean ± SE) minutes of stable anaesthesia (prior to the onset of surgery). The arterial carbon dioxide tension (Paco₂) was markedly lower during anaesthesia than in the awake state (*P* < 0,001). Our aim was to determine the effect of Paco₂ change on PGI₂ synthesis and to compare our results with those in the current literature.

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Patients and methods

Patients

Twelve patients, 6 males and 6 females with a mean age of 69 years (range 55 - 82), were scheduled for Charnley total hip replacements. No anti-prostaglandin medication was allowed during the week preceding the operation.

Premedication consisted of pethidine and promethazine in doses appropriate to the patients' physical status. Under local anaesthesia an intravenous line was established, a central venous pressure line was inserted via a basilic vein and a 20 GA catheter inserted into a radial artery.

The patients breathed oxygen for 4 minutes and were then anaesthetized with thiopentone (± 2 mg/kg) followed by alcuronium (0,25 mg/kg) or pancuronium (0,1 mg/kg). They were ventilated with a fractional inspiratory oxygen concentration (Fio₂) of 0,4. The trachea was sprayed with xylocaine 4% and a No. 8 cuffed endotracheal tube was inserted. Anaesthesia was maintained with a nitrous oxide and oxygen mixture, the Fio₂ being 0,4. Ethrane (< 1%) and fentanyl (0,2-0,3 mg) in divided doses were added. Ventilation was performed with a Bird Mk II and Ventiva, maintaining the end-expiratory CO₂ at ± 4,5 vols %. Curarization was reversed with neostigmine and atropine.

Monitors

Arterial pressure was continuously monitored by an AE 840 pressure transducer and a Simonsen and Weel oscilloscope with digital display. Central venous pressure was monitored with a water manometer. Expiratory CO₂ was monitored using a Godart infant capnograph. Paco₂ and pH were checked with a Gas Check AVL apparatus at the same times that PGI₂ values were determined. ECG, oesophageal temperature and Fio₂ were also monitored continuously.

During the trial period all parameters were at accepted normal values.

Sampling

Stock solutions were prepared as follows: EDTA 10 g/dl and theophylline 540 mg/dl were dissolved in distilled water and pH was adjusted to 7,0; 120 mg aspirin was added to 1 ml methyl alcohol.

On the day of operation 40 µl aspirin solution was added to 200 µl theophylline-EDTA solution in polypropylene collecting tubes. A 5 ml blood sample was collected in the tube and mixed. The tube was put into crushed ice and immediately transported to the laboratory, where it was centrifuged at 4°C and 1 500 g for 10 minutes. The top of the serum layer was removed. The latter procedure was repeated and the serum stored in capped polypropylene tubes at -20°C until assayed.

The New England Nuclear 6-keto-prostaglandin F_{1α} (3H) RIA Kit was used for the radioimmunoassay (RIA) of 6-keto-PGI₂. Assays were carried out directly on the stored plasma without prior extraction or chromatography.

Radial arterial blood samples were taken in the prescribed tubes before onset of anaesthesia and again before the onset of surgery. Blood gases were measured simultaneously.

Results

The results of PGI₂ and PaCO₂ estimations are presented in Table I. The mean PaCO₂ was 5,9 ± 0,2 kPa before anaesthesia and 4,7 ± 0,1 kPa during anaesthesia. A paired Student's *t* test demonstrated a significant difference (*P* < 0,001).

TABLE I. PaCO₂ AND PGI₂ LEVELS IN PATIENTS BEFORE ANAESTHESIA AND 50 ± 4 (MEAN ± SE) MINUTES AFTER STABLE ANAESTHESIA HAD COMMENCED

Patient No.	Before anaesthesia		During anaesthesia	
	PaCO ₂ (kPa)	PGI ₂ (pg/ml)	PaCO ₂ (kPa)	PGI ₂ (pg/ml)
1	5,1	32	3,7	190
2	5,2	190	5,1	290
3	5,6	135	4,7	135
4	7,4	50	4,8	50
5	6,8	330	5,1	280
6	5,6	50	5,3	50
7	6,4	23	4,8	30
8	5,6	286	4,7	320
9	4,9	135	4,4	280
10	6,5	251	4,7	234
11	5,7	229	4,9	206
12	5,9	240	5,1	106
Mean ± SE	5,9 ± 0,2	163 ± 34	4,7 ± 0,1	183 ± 31

The mean PGI₂ value was 163 ± 34 pg/ml before anaesthesia and 183 ± 31 pg/ml during anaesthesia. These values were not significantly different (paired Student's *t* test).

Discussion

In anaesthetized cats and rabbits it has been demonstrated^{1,8} that PGI₂ is continuously generated by the lungs. The systemic arterial level is always higher than the venous level, which substantiates this finding.⁸ Gryglewski *et al.*¹ have demonstrated that vigorous hyperventilation of anaesthetized cats increases PGI₂ release from the lungs. In isolated rat lungs Korbut *et al.*⁹ demonstrated that doubling the ventilation resulted in an increase of two and a half times the normal release of PGI₂. There is evidence that in animals the lung synthesizes PGI₂ and that hyperventilation increases this release.¹

In patients undergoing cardiac catheterization Hensby *et al.*¹⁰ observed higher levels (207 ± 33 pg/ml) in systemic arterial than in pulmonary arterial blood (131 ± 13 pg/ml) indicating PGI₂ synthesis in the lung. This was confirmed by Edlund *et al.*,⁵ who found no PGI₂ in venous blood and low levels in arterial blood (< 50 pg/ml).

There is a wide range of 'normal' arterial blood values for PGI₂ in awake patients, from < 50 to 207 pg/ml.^{5,10} In our 12 patients the range was 23-330 pg/ml, which compares favourably with the results mentioned above. PGI₂ values have been assayed by RIA⁵ or gas chromatograph-mass spectrometer¹⁰ techniques. Blair *et al.*¹¹ stated that until assay techniques are standardized and become more specific, PGI₂ results will vary widely.

In animals hyperventilation increases PGI₂ synthesis¹ but in man the evidence is not conclusive. Christ-Hazelhof and

Nugteren¹² hyperventilated awake patients with a CO₂-rich oxygen mixture to the extent of 75 l/min for 5 minutes. They then measured PGI₂, as PGI₁α, in pulmonary artery and vein samples, but could not detect any PGI₂. They concluded that PGI₂ does not fulfil a role in the vascular system at any distance from the site of synthesis. The healthy human body functions under conditions of optimal utilization of its resources and one would doubt the oversight of such a potent inhibitor of platelet aggregation.

In 4 patients Edlund *et al.*⁵ found awake PGI₂ levels of 17 ± 4 pg/ml. These patients were then anaesthetized and ventilated with a minute volume of about 8 litres and 'optimized PCO₂'. After 15 minutes of anaesthesia mean arterial PGI₂ levels rose to 191 ± 21 pg/ml (a tenfold increase on pre-anaesthetic levels). Unfortunately we do not have PaCO₂ levels available to judge the degree of ventilation. In our patients arterial PaCO₂ levels measured simultaneously with those of PGI₂ were significantly lower (*P* < 0,001) when these patients were anaesthetized than when they were awake (Table I); PGI₂ levels ranged from 30 to 320 pg/ml (mean 183 ± 31 pg/ml), and values were almost identical whether the patient was awake or anaesthetized. In view of our patients' mean age (69 ± 2 years), it was not deemed advisable to lower the PaCO₂ further. Our results obtained with moderate hyperventilation and those of Christ-Hazelhof and Nugteren¹² with extreme hyperventilation suggest that hyperventilation does not influence PGI₂ synthesis in man.

In animals, however, there is a definite increase in PGI₂ synthesis with hyperventilation. Gryglewski *et al.*¹ stated: 'Lungs can certainly regulate their production of PGI₂. We have seen in 3 experiments that an artificial vigorous hyperventilation (80 breaths/minute) in anaesthetized cats is followed by an increased release from lungs of a disaggregating principle . . .'. It would appear that the difference in man and animal may be related to the vigorous ventilation animals were subjected to, or due to species variation.

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REFERENCES

- Gryglewski RJ, Korbut R, Ocetkiewicz A. Generation of prostacyclin by lungs *in vivo* and its release into the arterial circulation. *Nature* 1978; **273**: 765-767.
- Armstrong JM, Lattimer N, Moncada S, Vane JR. Comparison of the vasodepressor effects of prostacyclin and 6-oxo-prostaglandin F₂α with those of prostaglandin E₂ in rats and rabbits. *Br J Pharmacol* 1978; **62**: 125-130.
- Moncada S, Gryglewski RJ, Bunting S, Vane JR. An enzyme isolated from arteries transforms prostaglandin endoperoxides to an unstable substance that inhibits platelet aggregation. *Nature* 1976; **263**: 663-665.
- Gryglewski RJ, Bunting S, Moncada S, Flower RJ, Vane JR. Arterial walls are protected against deposition of platelet thrombi by a substance (Prostaglandin X) which they make from prostaglandin endoperoxides. *Prostaglandins* 1976; **12**: 685-713.
- Edlund A, Bomfin W, Kayser L *et al.* Pulmonary formation of prostacyclin in man. *Prostaglandins* 1981; **22**: 323-332.
- Steer ML, Mac Intyre DE, Levine L, Salzman W. Is prostacyclin a physiologically important circulating anti-platelet agent? *Nature* 1980; **283**: 194-195.
- Sonnenfeld T, Wennmalm A. Inhibition by nicotine of the formation of prostacyclin-like activity in rabbit and human vascular tissue. *Br J Pharmacol* 1980; **71**: 609-613.
- Moncada S, Korbut R, Bunting S, Vane JR. Prostacyclin is a circulating hormone. *Nature* 1978; **273**: 767-768.
- Korbut R, Boyd J, Eling T. Respiratory movements alter the generation of prostacyclin and thromboxane A₂ in isolated rat lungs: the influence of arachidonic acid-pathway inhibitors on the ratio between pulmonary PGI₂ and thromboxane A₂. *Prostaglandins* 1981; **21**: 491-503.
- Hensby CN, Barnes PJ, Dollery CT, Dargie H. Production of 6-oxo-PGF₂α by human lung *in vivo*. *Lancet* 1979; **ii**: 1162-1163.
- Blair IA, Barrow SE, Waddell KA, Lewis PJ, Dollery CT. Prostacyclin is not a circulating hormone in man. *Prostaglandins* 1982; **23**: 579-589.
- Christ-Hazelhof E, Nugteren DH. Prostacyclin is not a circulating hormone. *Prostaglandins* 1981; **22**: 739-746.