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


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.

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 Ventiviva, maintaining the end-expiratory CO₂ at ± 4.5 vols. Curarization was reversed with neostigmine and atropine.

Monitors

Arterial 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 1500 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 F₃2 (3H) RIA Kit was used for the radioimmunoassay (RIA) of 6-keto-PGI₁α. Assays were carried out directly on the stored plasma without prior extraction or chromatography.

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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 PG12 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).

The mean PG12 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 that PG12 is continuously generated by the lungs. The systemic arterial level is always higher than the venous level, which substantiates this finding. 6 Gryglewski et al. have demonstrated that vigorous hyperventilation of anaesthetized cats increases PG12 release from the lungs. In isolated rat lungs Korbut et al. demonstrated that doubling the ventilation resulted in an increase of two and a half times the normal release of PG12, which they make from prostaglandin endoperoxides. Blair et al. stated: 'Lungs can certainly regulate their production of PG12. 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.

In animals hyperventilation increases PG12 synthesis 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 PGI2 α in pulmonary artery and vein samples, but could not detect any PG12. 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. 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 PaCO2'. 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. 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.

We thank the technical staff of our departments for skilled assistance and Mrs W. Visser for typing the manuscript.

The research was financed by grants from the Medical Research Council, the Harry Crossley Foundation and Upjohn (Pty) Ltd.

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12. Gryglewski RJ, Bunting S, Moncada S, Fower 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.

TABLE I. PaCO2 AND PG12 LEVELS IN PATIENTS BEFORE ANAESTHESIA AND 50 ±4 (MEAN ± SE) MINUTES AFTER STABLE ANAESTHESIA HAD COMMENCED

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Before anaesthesia</th>
<th>During anaesthesia</th>
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<tbody>
<tr>
<td></td>
<td>PaCO2 (kPa)</td>
<td>PG12 (pg/ml)</td>
</tr>
<tr>
<td>1</td>
<td>5.1</td>
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<td>2</td>
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</tr>
<tr>
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<tr>
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</tr>
<tr>
<td>Mean ± SE</td>
<td>5.9 ± 0.2</td>
<td>163 ± 34</td>
</tr>
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