Influence of indomethacin on the systemic and pulmonary vascular resistance in man

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Summary

1. Indomethacin, an inhibitor of the cyclo-oxygenase system that converts arachidonic acid into prostaglandins and related substances, was infused intravenously in 12 healthy volunteer subjects.

2. Systemic systolic and diastolic blood pressures and heart rate were recorded in all subjects, and in most of them also the systemic arteriovenous oxygen difference, the total oxygen uptake and the pulmonary arterial and wedge pressures.

3. The infusion of indomethacin was followed by a decreased cardiac output (from 7.3 ± 0.3 to 6.3 ± 0.3 litres/min) and an increased mean systemic blood pressure (from 92 ± 1 to 102 ± 1 mmHg), indicating an elevation of the total systemic vascular resistance (from 98 ± 4 to 124 ± 5 kPa l⁻¹ s⁻¹) by indomethacin. The ventilation and the pulmonary vascular resistance did not change after the infusion of indomethacin.

4. The results suggest that products formed by the cyclo-oxygenase system at rest exert a relaxing effect in certain parts of the systemic vascular bed, thereby lowering the systemic vascular resistance.

Key words: cardiac output, heart rate, stroke volume, right atrial blood pressure, oxygen uptake, prostaglandin synthesis inhibition, pulmonary blood pressure, pulmonary wedge pressure, systemic blood pressure.

Introduction

Prostaglandins are vasoactive in many species (Karim, 1972). In man, infusion of prostaglandin E₁ has been reported to increase heart rate and stroke volume, and decrease both arteriovenous O₂ difference and peripheral resistance (Carlson, Ekelund & Orö, 1969, 1970). In rabbits, infusion of the prostaglandin E₂ precursor, arachidonic acid, causes hypotension, provided that the endogenous synthesis of prostaglandins is not inhibited (Ånggård & Larsson, 1973). Prostaglandins have frequently been proposed to play a role in the regulation of blood pressure (Lee, 1976), in both normotensive and hypertensive subjects. This hypothesis has been supported by the observation that acute administration of indomethacin, an inhibitor of the cyclo-oxygenase that converts arachidonic acid into prostaglandins and prostaglandin-related substances (endoperoxides, thromboxane, prostacyclin) (Vane, 1971), leads to hypertension (Lonigro et al., 1973; Lee, 1976). Such hypertension implies that the peripheral vascular tone is subject to a continuous relaxing influence from endogenous vasodilating prostaglandins or prostaglandin-related substances. In this study we present data to support the role for these endogenous vasodilating substances in the regulation of the systemic vascular resistance in man.

Methods

The study was performed with the permission of the Ethical Committee at the Karolinska Institute. Healthy male volunteer subjects, aged 23–51 years
and weighing 65–89 kg, participated. They were all informed of the nature, possible risks and purpose of the investigation before giving their voluntary consent to participate. A Swan–Ganz catheter (no. 5 or no. 7) was inserted percutaneously into a medial cubital vein and passed under fluoroscopic control to the pulmonary artery. A short Teflon catheter was introduced into a brachial artery. Pressure recording was performed via a pressure transducer (Elema, EMT 35) on a photokymograph (Abem Ultralette). The midthoracic height was used as zero-pressure level. Expired air was collected in Douglas bags and analysed by the Scholander microtechnique. Blood samples from the brachial artery and pulmonary artery were drawn for determination of oxygen content (Holmgren & Pernow, 1959). Pressure recordings were performed with the catheter in the pulmonary wedge position, in the pulmonary and brachial artery, and in the right atrium. The cardiac output was determined by the Fick principle. All pressures, as well as cardiac output, were determined 0–10 min before and immediately after the infusion of indomethacin. In two subjects, blood pressure and cardiac output was also measured 20, 50 and 80 min after the end of the drug infusion.

Indomethacin (Merck, Sharp and Dohme), 70 μmol (25 mg), was dissolved in 5 ml of ethanol and diluted to 2.3 mmol/l with phosphate buffer (0.1 mmol/l), pH 7.5, and infused at a rate of 4.7–6.4 μmol (1.7–2.3 mg)/min via the Swan–Ganz catheter, to a total dose of 0.91 ± 0.02 μmol (0.32 ± 0.01 mg)/kg body weight. Systemic blood pressure was recorded continuously during the infusion. In some experiments, solvent only (5 ml of ethanol in 25 ml of phosphate buffer, 0–1 mmol/l) was infused.

Values are given as mean ± SE. Standard statistical methods were employed, with the paired t-test.

Results

Before the infusion of indomethacin the circulation was normokinetic in all subjects and the systemic and pulmonary systolic and diastolic blood pressures were well within the normal limits.

Within 2–3 min after the start of the infusion of indomethacin at a rate of 4.7–6.4 μmol (1.7–2.3 mg)/min, the systemic systolic and diastolic blood pressures increased, reaching a maximal value within 10 min. After the end of the infusion of indomethacin the blood pressure slowly returned towards the basal value, but the diastolic pressure remained raised by about 8% in the two subjects in whom the arterial blood pressure was followed 80 min after the infusion had been stopped. Immediately after the end of the indomethacin infusion, the mean systemic blood pressure was 102 ± 1 mmHg, significantly higher (P < 0.001) than before the infusion (92 ± 1 mmHg) (Fig. 1). The increase in blood pressure after indomethacin was due to a rise in both systemic (from 123 ± 2 to 129 ± 3 mmHg) and diastolic (from 72 ± 1 to 82 ± 2 mmHg) blood pressure (Fig. 1).

The cardiac output fell significantly (P < 0.01), from 7.3 ± 0.3 before to 6.3 ± 0.3 litres/min immediately after, the infusion of indomethacin. The fall was due to a reduction in heart rate, from 67 ± 3 to 59 ± 2 beats/min (Fig. 2). The systemic vascular resistance, estimated from the mean arterial — right atrial blood pressure difference and the cardiac output, increased significantly (P < 0.01) after indomethacin, from 98 ± 4 before to 124 ± 5 kPa l⁻¹ s immediately after the infusion (Fig. 1). In the two subjects in whom the post-infusion period of haemodynamic measurements was prolonged the vascular resistance 80 min after the infusion of drug was still elevated by 9% compared with before the infusion.

The pulmonary systolic, diastolic and wedge pressures were not significantly affected by the infusion of indomethacin (Fig. 1 and Fig. 2). The pulmonary vascular resistance, estimated from the mean pulmonary arterial — wedge pressure difference and the cardiac output, changed insignificantly after the infusion (Fig. 1). The mean oxygen uptake of the subjects was 330 ml/min before indomethacin, exceeding their estimated basal oxygen consumption by 28% (range 2–50%), but this was unaffected by indomethacin. The respiratory frequency (13.4 ± 0.7/min before and 14.8 ± 1.3/min after the drug infusion), the tidal volume (0.70 ± 0.08 litre before and 0.67 ± 0.04 litre after the drug infusion) and the arterial oxygen saturation (97.9 ± 0.4% before and 97.9 ± 0.3% after the drug infusion) were also unchanged. No side-effects of the drug were observed. In the control experiments, where solvent was infused alone, the mean systemic blood pressure was 92 ± 2 mmHg before and 93 ± 3 mmHg after the infusion, and the cardiac output was 7.3 ± 0.5 litres/min before and 7.2 ± 0.7 litres/min after the infusion. There was thus no evidence that the solvent possessed any circulatory effects.
Indomethacin and vascular tone

FIG. 1. Blood pressure and vascular resistance in the systemic and pulmonary circulation in man before (B) and after (A) infusion of 70 μmol (25 mg) of indomethacin. The smaller symbols indicate the individual observations, and the larger symbols indicate mean values ± SE of these observations. Significance of differences from the corresponding figure before indomethacin (Student's t-test): *P < 0.05; **P < 0.01; ***P < 0.001.

FIG. 2. Haemodynamic variables and oxygen uptake in man before (B) and after (A) infusion of 70 μmol (25 mg) of indomethacin. For explanation of symbols see Fig. 1. a–v: Arteriovenous difference.
Discussion

Infusion of indomethacin, but not of solvent, caused a rise in systemic blood pressure which started after infusion of 10–20 μmol (3.6–7.2 mg), and was fully developed after infusion of about 50 μmol. This rise was in parallel with a fall in cardiac output, indicating that the underlying mechanism was an increase in the systemic vascular resistance.

The ventilation and the pulmonary haemodynamics were not affected significantly. This seems to contrast with recent findings in dogs, where indomethacin was reported to increase the pulmonary vascular resistance (Kadowitz, Chapnick, Joiner & Hyman, 1975). However, that study used a technique which cannot be applied in humans and the possibility that discrete changes in pulmonary resistance occurred also in the present investigation cannot be ruled out.

The observed effect of indomethacin in raising the peripheral vascular resistance may arise centrally or peripherally. Although the possibility of a central action cannot be excluded, there is an attractive hypothesis for a peripheral effect. Indomethacin is an inhibitor of the cyclo-oxygenase that converts arachidonic acid into prostaglandins and prostaglandin-related substances like endoperoxides, thromboxane and prostacyclin (Vane, 1971), of which some are potent vasodilators. If production of vasodilating prostaglandins or related substances occurs normally in the walls of the systemic resistance vessels the observed effect of indomethacin may have arisen from withdrawal of these vasodilating substances. There is good reason to assume that the cyclo-oxygenase system really was inhibited: in humans indomethacin in an oral dose of 140 μmol (50 mg) x4 depresses the urinary excretion of the main prostaglandin E metabolite by 77–98% (Hamberg, 1972). Furthermore, intravenous administration of indomethacin results in about twice the plasma concentration obtained when the same dose is given orally (Duggan, Hogans, Kwan & McMahon, 1972), and consequently the 70 μmol (25 mg) that we gave intravenously should have been adequate for inhibition of synthesis. In addition, indomethacin has recently been shown to inhibit synthesis of prostaglandin in man at a plasma drug concentration of 0.28 μmol/l (0.1 μg/ml) (Rane et al., 1977). Assuming a volume of distribution for indomethacin of 50 litres in our subjects, a drug concentration of 0.28 μmol/l would be reached after 2–3 min of infusion. Thus, if the rise in systemic blood pressure after indomethacin was due to cyclo-oxygenase inhibition, this would account for the rapid onset of the effect. However, we cannot exclude the possibility that the observed effect of indomethacin was to some extent independent of inhibition of synthesis of prostaglandin and related substances. Such a non-specific effect by this drug on vasoconstrictor responses has been proposed earlier (Janczewska & Herbaczynska-Cedro, 1974; Manku & Horrobin, 1976).

We did not perform regional flow measurements and so cannot identify the vascular bed or beds affected by indomethacin. It has recently been shown that the blood flow in the resting skeletal muscle in humans is unaffected by indomethacin (Kilbom & Wennmalm, 1976), suggesting that muscular vasoconstriction is not responsible for the observed increase in resistance. The renal blood flow has been reported to fall upon the infusion of indomethacin in dogs (Lonigro, Itskovitz, Crowshaw & McGiff, 1973). Such an effect might also account for our findings, but an isolated fall in renal blood flow cannot by itself explain the observed fall in cardiac output of about 1 litre/min. An increased resistance elicited by the drug in other regions too, e.g. the splanchnic vascular bed, may also have contributed.

Our studies show that the cyclo-oxygenase inhibitor indomethacin increases the systemic vascular resistance in man. This observation may indicate a resistance-regulatory role for endogenously formed prostaglandins or related substances in the systemic vascular bed.

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References

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