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LACK OF RELEASE OF PROSTAGLANDINS FROM ISOLATED PERFUSED LUNGS DURING PULMONARY HYPERTENSION AND OEDEMA

ELIZABETH SCOTT, J. VAAGE & T. WIBERG[1]

Institute of Physiology, University of Oslo, Oslo, Norway

1 The effects on pulmonary prostaglandin synthesis of pulmonary hypertension and oedema have been studied.

2 Seventeen isolated lungs of rabbit, cat and guinea-pig were perfused with plasma, whole blood or Krebs Ringer solution in a recirculating system.

3 The venous effluent from the lungs superfused (10 ml/min) a series of smooth muscle tissues sensitive to prostaglandins and thromboxane A_2; these were: rat stomach strip, rat colon, chick rectum and rabbit aorta.

4 Left atrial pressure was increased by between 10 and 30 mmHg for periods of 3 to 59 minutes. Gross alveolar oedema eventually developed in all experiments.

5 Neither pulmonary hypertension nor subsequent oedema caused release of prostaglandins into the venous effluent.

Introduction

It has been established that lungs have considerable capacity to synthesize prostaglandins and release them into the pulmonary circulation on a variety of chemical and physical stimuli (Piper & Vane, 1971; Bakhle & Vane, 1974). Cellular distortion has been suggested by Piper & Vane (1971) to be a common factor in stimulation of prostaglandin synthesis.

Preliminary reports have appeared suggesting that oedema induced by prolonged perfusion in isolated lungs (Said & Yoshida, 1974) or by elevation of outflow pressure (Chijimatsu, Hara & Said, 1976) caused release of prostaglandin-like substances (PGLS) into the venous effluent. Piper & Vane (1971) suggested that the release of prostaglandins after injection of particles might be a consequence of higher perfusion pressure and leakage of fluid. Stretching of the lungs has also been claimed to cause release of prostaglandins, when induced either by airway distension in isolated lungs (Berry, Edmonds & Wyllie, 1971) or in intact dogs (Said, Kitamura & Vreim, 1972).

If pulmonary hypertension and/or oedema stimulate prostaglandin synthesis in lung tissue this may have important physiological and pathophysiological consequences on lung function (Mathé, 1977; Rose & Kot, 1977). When released into the bloodstream prostaglandins may also affect the systemic circulation (Malik & McGiff, 1976).

The purpose of the present work was: (1) to study whether PGLS were released from isolated, perfused lungs secondary to raising outflow pressure; (2) to evaluate whether such a release was induced by the increase in vascular hydrostatic pressure or by oedema development, and (3) to evaluate possible species differences, since several species have been used when investigating stimuli for prostaglandin synthesis. A preliminary account of this work was given to the British Pharmacological Society (Scott, Vaage & Wiberg, 1977).

Methods

Anaesthesia

Seven rabbits weighing 3.0 to 4.0 kg were anaesthetized by intravenous injections of sodium pentobarbitone (Nembutal) 30 to 40 mg/kg, diluted 1:3 with isotonic saline. Six cats (2.0 to 2.5 kg) and 3 guinea-pigs (320 to 800 g) received 30 to 40 mg/kg Nembutal intraperitoneally.

[1] Present address: Hormone and Isotope Laboratory, Aker Hospital, Oslo 5, Norway.

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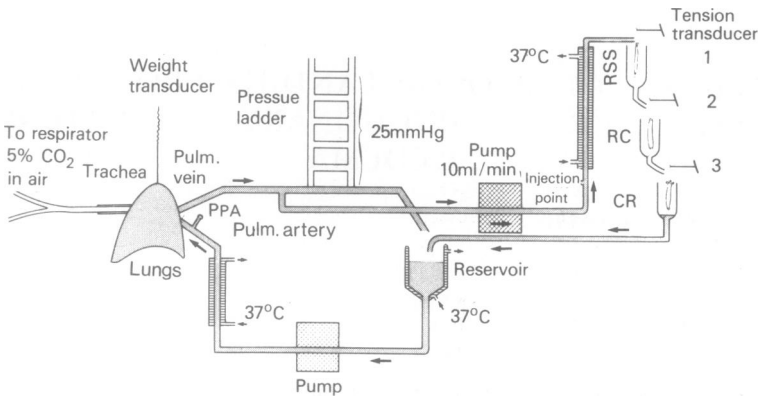

Figure 1 Diagram of the experimental set-up. Ventilated lungs were perfused in a recirculating system. The lungs were suspended from a weight transducer and enclosed in a heated (37°C) plastic box. Pulmonary arterial pressure (P_{PA}) was measured from a side arm of the inflow cannula. Outflow pressure (= left atrial pressure) could be raised by clamping successive steps of a ladder of tubes on the venous side of the lung. A fraction (10 ml/min) of the venous effluent was pumped over the assay tissues: rat stomach strip (RSS), rat colon (RC) and chick rectum (CR). The perfusate was heated to 37°C in the venous reservoir, before entering the lungs, and before superfusing the tissues.

The lung preparation

The surgical procedures and the preparation have been described in detail elsewhere (Hauge, Lunde & Waaler, 1966), and will only be briefly outlined here. After tracheostomy the chest was opened during positive pressure ventilation. The trachea, lungs and the larger intrathoracic vessels were dissected free, and heparin (10 mg to cats and rabbits, 1 to 5 mg to guinea-pigs) was injected into the right ventricle before ligating the inferior vena cava. The time interval between arrest of the animal's circulation and the start of lung perfusion was less than 15 minutes.

A plastic inflow cannula (stainless steel for guinea-pig) was inserted through the wall of the right ventricle into the pulmonary artery. The outflow cannula (glass or stainless steel) was placed in the left atrium.

The preparation was suspended freely in a closed and heated (37°C) Perspex chamber by a thread tied around the heart. Its weight was continuously recorded by a force transducer (Sanborn FTA-100-1) connected to a Hewlett Packard Oscillograph recorder (model 7002a). Weight changes were not recorded in guinea-pig lungs.

Perfusion

The lungs were perfused by a roller pump (model 500-200H. Harvard Apparatus) in a recirculating system with constant volume inflow of 100 to 390 ml/min for cat and rabbit lungs and 20 to 25 ml/min for guinea-pig lungs. Pump rate was set to give a perfusion pressure (P_{PA}) of between 10 and 15 mmHg. P_{PA} was measured from a sidearm of the pulmonary arterial cannula with a Statham P23Db pressure transducer and recorded on an 8-channel Grass polygraph model 7B.

In all experiments the reservoir and the inflow tubing to the lungs were heated (37°C) by water jackets (perfusate temperature was monitored continuously by a thermoprobe in the outflow cannula). Left atrial pressure (P_{LA}) was approximately 1 mmHg in the control situation and could be raised in increments of 5 mmHg by clamping successive steps of a ladder of tubes on the venous side of the lungs (Figure 1).

Perfusates

Perfusion was always begun with Krebs Ringer solution (composition mM: NaCl 118.65, KCl 4.64, CaCl 2.51, KH_2PO_4 1.18, $MgSO_4$ 1.18, $NaHCO_3$ 24.64 and glucose 27.8). When plasma or whole blood was used as perfusate the change from Krebs Ringer was performed within 1 to 2 min of the start of perfusion. Horse plasma was obtained by centrifugation of heparinized (30 iu/ml) whole blood at 1000 *g* for 10 minutes. Plasma was filtered before use. Cat whole blood was obtained by cardiac puncture of anaesthetized cats which had been given intravenous heparin (500 iu/kg). A thousand units of heparin was added to each 100 ml of blood.

Measurements of pH

The pH of the perfusate was measured at intervals throughout each experiment (Acid-Base Analyzer PHM71, Radiometer, Copenhagen, Denmark), and ranged from 7.40 to 7.50.

Ventilation

Rabbit and cat lungs were gently inflated at the start of perfusion, then ventilated at constant tidal volume (20 strokes/min) by a Starling 'Ideal' Pump (Palmer Ltd.). Tidal volume was regulated to give a peak inspiration pressure of between 7 and 10 cmH_2O at the start of each experiment. End expiratory pressure (EEP) was kept at 1 cmH_2O by a water seal. Tracheal pressure (which equals transpulmonary pressure, P_{TP}) was monitored by a differential pressure transducer (Hewlett Packard, Model 170). The ventilation gas was 5% CO_2 in air. Guinea-pig lungs were not ventilated and the perfusate (Krebs Ringer solution) was gassed with 95% O_2 and 5% CO_2.

Bioassay

A modification of the blood bathed organ technique of Vane (1969) was used to detect PGLS in the venous effluent (Vaage, Wiberg & Scott 1978b). The lung perfusate was pumped (10 ml/min) to superfuse a series of assay tissues: rat stomach strip (RSS), rat colon (RC) and chick rectum (CR), and returned to the venous reservoir (Figure 1). In 4 experiments a rabbit aorta (RbA) was also included. The time between the perfusate leaving the lungs and reaching the first tissue was 1 to 1.5 minutes. When the RbA was included (2 plasma-perfused and 2 blood-perfused lungs, see Table 1) it was always the first tissue in the cascade since the half-life of 'rabbit aorta contracting substance' (RCS) is short. With this combination of tissues it is possible to detect prostaglandins and various active intermediates in the conversion of arachidonic acid (AA). These tissues are also sensitive to the recently described vasoactive and spasmogenic lung peptides (Said & Mutt, 1977).

Before being used for bioassay, all tissues were bathed for 1 to 2 h in Krebs Ringer solution gassed with 5% CO_2 and 95% O_2 and containing antagonists to acetylcholine, catecholamines (α- and β-adrenoceptors), 5-hydroxytryptamine and histamine (H_1-receptors) to render them more specific to prostaglandins (Piper & Vane, 1969). The solution contained (mg/l): hyoscine hydrobromide 0.15, phenoxybenzamine 0.14, propranolol hydrochloride 2.28, methysergide bimaleate 0.2, mepyramine maleate 0.14 and glucose 5 g/l. In 3 experiments indomethacin (5 mg/l) was added to the solution to prevent prostaglandin generation in the assay tissues themselves (Vane, 1973).

The assay tissues were mounted inside plastic chambers and their isometric tension was continuously measured by semiconductor transducer elements (Vaage *et al.*, 1978b) and recorded on the Grass polygraph. The tissues were superfused for 2 to 3 h with Krebs Ringer solution containing blocking agents before superfusion with lung perfusate was begun. The basal tension of each tissue was 1 to 2 g except for the RbA which was kept at a tension of 3 to 4 g.

Standard solutions of PGE_2 and $PGF_{2\alpha}$ were made up daily in isotonic saline from stock solutions in ethanol, and calibrating doses were infused into the superfusate upstream to the assay tissues to give concentrations of 0.5 to 4 ng/ml over the tissues. RSS and CR were sensitive to as little as 0.5 to 1 ng/ml of PGE_2, while RC and RSS were sensitive to 1 to 2 ng/ml $PGF_{2\alpha}$.

Experimental protocol

Lungs were perfused until a stable weight had been obtained and the tissues had been calibrated. P_{LA} was then raised by clamping the outflow ladder and diverting the venous effluent upwards in steps of 5 mmHg. This manoeuvre caused an initial steep increase in the weight of the preparation followed after about 2 min by a much slower, almost linear, weight increase. The first phase was due to increased pulmonary blood volume and the second to accumulation of fluid in the extravascular space (Lunde & Waaler, 1969; Nicolaysen, Aarseth & Waaler, 1976). When referring to weight increases in this paper we exclude the change in blood volume, only considering the increase in extravascular fluid in the lungs.

When P_{LA} was raised there was a simultaneous increase in P_{PA} and P_{TP}, indicating a reduction in dynamic lung compliance. Compliance usually remained constant and reversible until about 10 g of fluid had been filtered into the extravascular space, then a secondary progressive and irreversible decrease occurred. It has been suggested that this secondary decrease in compliance is caused by alveolar flooding (Hauge, Bø & Waaler, 1975). This has recently been confirmed by histological examinations (Scott, Nicolaysen & Hauge, unpublished observations).

In one experiment P_{LA} was taken back to its control value and then elevated a total of 3 times. However, in the remaining experiments increased P_{LA} was maintained or further elevated until gross pulmonary oedema was present: lungs then became translucent, ventilatory movements decreased and fluid poured from the trachea.

In one experiment AA was given into the pulmonary artery. AA (Sigma) was dissolved in isotonic saline a few minutes before its use. In this experiment the assay tissues were also pretreated with indomethacin as described.

Results

Continuous bioassay of PGLS was performed on the venous effluent of 17 isolated lungs. Table 1 shows

Table 1 Duration of increased left atrial pressure (P_{LA}) in isolated lungs

Exp. no.	*Species of lung donor*	*Perfusate*	*Duration of P_{LA} elevation (min)* 10 mmHg	15 mmHg	20 mmHg	25 mmHg	30 mmHg	*Total perfusion time (min)*	*Indomethacin into reservoir*	*RbA included*
Group A										
1	Rabbit	Horse plasma	10	10	10			184		
2	Rabbit	Horse plasma	10	18	41			187		
3	Rabbit	Horse plasma		21				173		
4	Rabbit	Horse plasma		10		8		147		
5	Rabbit	Horse plasma		13	15	10		174		
6	Rabbit	Horse plasma	10	23 + 59	39			180	25 μg/ml	×
7	Cat	Horse plasma	7		12			175		
8	Cat	Cat plasma	5	7	38			249		
Group B										
9	Cat	Cat plasma			33	15		191		
10	Cat	Horse plasma			8	14		133		
11	Cat	Cat whole blood				15		301		×
12	Cat	Cat whole blood				50		163		×
13	Guinea-pig	Horse plasma				10	5	105		
14	Guinea-pig	Horse plasma				10		175		
15	Guinea-pig	Krebs Ringer				12		104		
16	Rabbit	Horse plasma				3		105	125 μg/ml	×
17	Rabbit	Horse plasma				3		155		

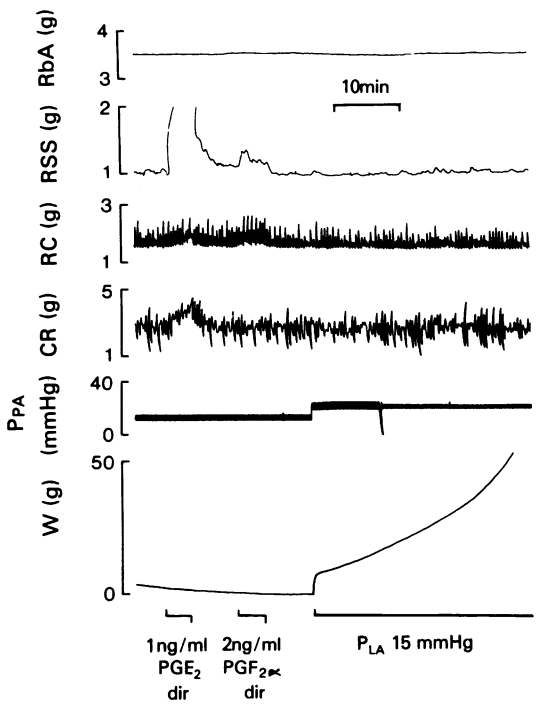

Figure 2 Rabbit lungs perfused with horse plasma. The third of four periods of left atrial pressure (P_{LA}) elevation (15 mmHg) is shown. The tracings show the isometric tensions of the following bioassay tissues, superfused with the venous effluent: rabbit aorta (RbA), rat stomach strip (RSS), rat colon (RC) and chick rectum (CR). Pulmonary arterial pressure (P_{PA}) and the changes in weight of the lung preparation are also shown. The sensitivity of the assay tissues was tested by infusing prostaglandin E_2 (PGE_2) and $PGF_{2\alpha}$ into the superfusate upstream to the assay tissues (dir).

the species of lung donor, type of perfusate, the value of left atrial pressure (P_{LA}) and the length of time P_{LA} was raised. Total perfusion time is also shown. Depending on the magnitude of P_{LA} elevations, the lungs were divided into two groups.

Gradual development of oedema (group A)

In 8 cat and rabbit lungs perfused with plasma or blood, P_{LA} was initially raised to 10 ($n = 5$) or 15 ($n = 3$) mmHg for between 5 to 21 min to induce a slow filtration of fluid from the pulmonary exchange vessels into the interstitium. In 7 lungs raised P_{LA} was maintained, or increased further to a maximum of 25 mmHg, until gross alveolar oedema was observed. Eventually more than 50 g of fluid had accumulated extravascularly. In no experiment could a contraction of the assay tissues be observed during or after oedema development.

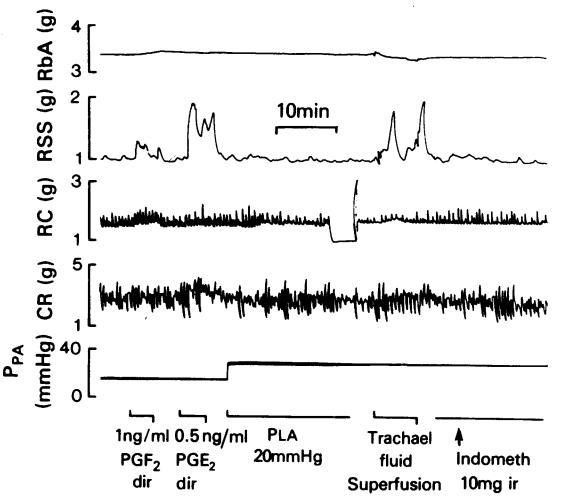

Figure 3 Rabbit lung perfused with horse plasma (same experiment as depicted in Figure 2). The fourth and last period of left atrial pressure (P_{LA}) elevation (20 mmHg) is shown. The tracings show the isometric tension of the following bioassay tissues, superfused with the venous effluent: rabbit aorta (RbA), rat stomach strip (RSS), rat colon (RC), and chick rectum (CR). Pulmonary arterial pressure (P_{PA}) is also shown. The tissues were calibrated by infusion of prostaglandin E_2 (PGE_2) and $PGF_{2\alpha}$ into the superfusate upstream to the assay tissues. Tissue superfusion with venous effluent plasma was temporarily replaced with tracheal fluid for a period of 8 minutes. Indomethacin (Indometh) was given into the reservoir (ir) at the end of the experiment. Due to an electrical disconnection the tracing of the RC was temporarily interrupted.

In one experiment (no. 6, Table 1) P_{LA} was first raised to 10 mmHg for 10 min and then further elevated to 15 mmHg for 23 minutes. When P_{LA} was reduced to control values, pulmonary blood volume normalized and fluid resorbtion started. The pressure could be raised repeatedly but eventually irreversible alveolar flooding developed. A total of 4 P_{LA} elevations were performed. The first part of the third and the fourth are shown in Figures 2 and 3, respectively, where P_{LA} was 15 and 20 mmHg. The end result was fulminant alveolar oedema with fluid pouring out of the trachea to such an extent that ventilation had to be stopped and the perfusate gassed instead. No contractions of the assay tissues were observed during the period of increased P_{LA}. In this experiment tissue superfusion with the venous effluent was temporarily interrupted and immediately replaced by the tracheal fluid. This caused only a short-lasting contraction of the RSS (Figure 3), and a similar short contraction occurred when the venous effluent replaced the tracheal fluid as a superfusate. These contractions may have been due to changes in gas tension or pH in

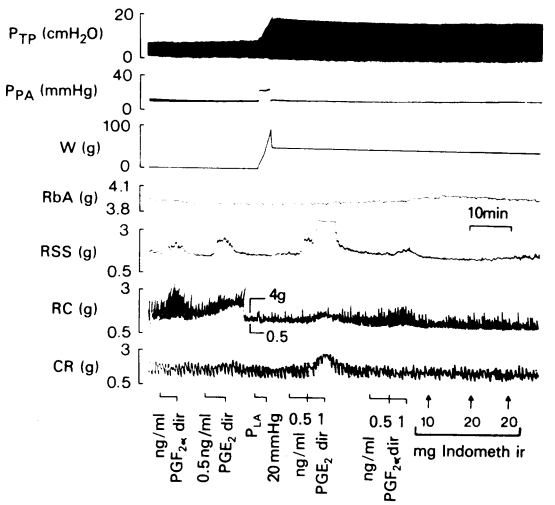

Figure 4 Rabbit lung perfused with horse plasma. The tracings show tracheal pressure (P_{TP}), pulmonary arterial pressure (P_{PA}), changes in weight of the lung preparation (ΔW), and isometric tension of the following bioassay tissues, superfused with venous effluent: rabbit aorta (RbA), rat stomach strip (RSS), rat colon (RC) and chick rectum (CR). The scale of the RC recording was changed electronically during the experiment. Calibrating doses of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) and PGE_2 were infused into the superfusate upstream to the assay tissues (dir). P_{LA} was increased to 20 mmHg for 3 min and then returned to control. Indomethacin (Indometh), given into the reservoir (ir), did not relax the assay tissues.

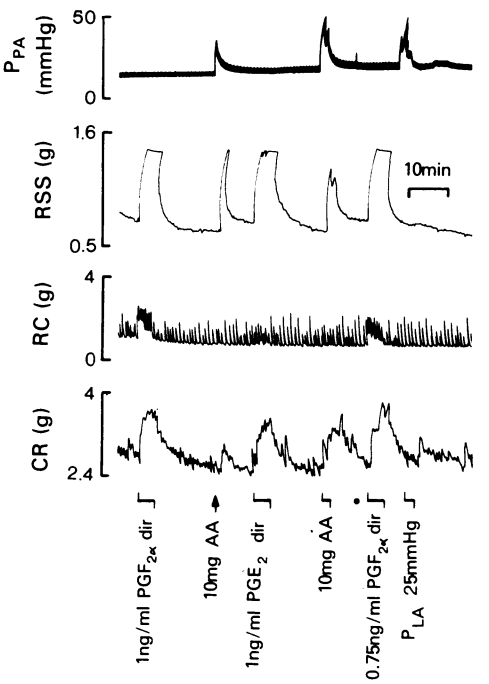

Figure 5 Rabbit lung perfused with horse plasma. The tracings show pulmonary arterial pressure (P_{PA}) and isometric tension of the following bioassay tissues, superfused with venous effluent: rat stomach strip (RSS), rat colon (RC) and chick rectum (CR). The tissues were calibrated with prostaglandin E_2 (PGE_2) and $PGF_{2\alpha}$. Arachidonic acid (AA) was twice given into the pulmonary artery; one injection (arrow), and one infusion over 2 minutes. The black point indicates that the lungs were hyperinflated. Left atrial pressure (P_{LA}) was elevated to 25 mmHg for 3 minutes.

the superfusate. Basal tissue tension was the same in tracheal fluid and plasma. When indomethacin was added to the reservoir (25 μg/ml) it did not relax the assay tissues, showing that no prostaglandin synthesis had occurred.

Rapid development of oedema (group B)

In a total of 9 cat, rabbit and guinea-pig lungs perfused with blood, plasma or Krebs Ringer solution, P_{LA} was initially raised to 20 ($n = 2$) or 25 ($n = 7$) mmHg. In one experiment P_{LA} was increased further to 30 mmHg (Table 1). These manoeuvres caused marked pulmonary hypertension and rapid onset of gross alveolar oedema. However, this never caused a contraction of the assay tissues, indicating that no release of PGLS had taken place. Figure 4 shows the results from one such experiment.

In one experiment AA (10 mg) was twice administered directly into the pulmonary artery before P_{LA} was elevated. AA challenge caused marked contractions of the assay tissues as well as a transient increase in P_{PA} (Figure 5).

Discussion

Induction of hydrostatic pulmonary oedema will cause stretching and distortion of several cell types in the lungs. When pulmonary venous pressure is increased there is an initial rise in pulmonary blood volume due to distension and recruitment of vessels. There follows a net outward filtration of fluid from the exchange vessels into the interstitial space (Lunde & Waaler, 1969; Nicolaysen *et al.*, 1976). The extravascular space is distended and, if filtration continues, fluid enters the alveolar space (Staub, Nagano & Pearce, 1967).

Piper & Vane (1971) have postulated that distortion of cell membranes leads to the generation and release of prostaglandins. Thus we reasoned that prostaglandins might be released from the lungs when increased outflow pressure distends blood vessels and/or when pulmonary oedema develops and dis-

tends the interstitium. However, the present experiments clearly show that neither increased hydrostatic pressure in the pulmonary circulation nor pulmonary oedema caused detectable release of PGLS, although the assay tissues were sensitive to calibrating doses of as little as 0.5 to 1 ng/ml of PGE_2 and 1 to 2 ng/ml $PGF_{2\alpha}$. Nor did the addition of indomethacin, a prostaglandin synthesis inhibitor, to the perfusate have any effect on tissue tension. Thus, if any prostaglandins were released, it must have been in concentrations below the limit of detection of the bioassay method. The conversion of arachidonic acid (AA) to PGLS in lungs may have occurred, but the prostaglandin endoperoxides formed could have been transformed to thromboxanes and to a lesser extent to PGE_2 and $PGF_{2\alpha}$ (Hamberg & Samuelsson, 1974; Hamberg, Svensson & Samuelsson, 1976). Furthermore, the prostaglandins released could have been inactivated in the pulmonary circulation (Piper, Vane & Wyllie, 1970) and thus would not have appeared in the perfusate as PGE_2 or $PGF_{2\alpha}$. However, several factors indicate that no significant conversion of AA occurred in the present experiments. Prostaglandin metabolites are to some extent active on the bioassay tissues (Crutchley & Piper, 1975). Also, by using a combination of tissues it is possible to detect the presence of prostaglandin endoperoxides and thromboxane A_2 (TxA_2). In fact, the RSS is equally and the RbA is far more sensitive to endoperoxides and TxA_2 than to PGE_2 and $PGF_{2\alpha}$ (Hamberg, Hedqvist, Strandberg, Svensson & Samuelsson, 1975: Bunting, Moncada & Vane, 1976). Although the former are highly unstable, they would be detected despite the delay of 1 to 1.5 min before the venous effluent reached the assay tissues. Rabbit aorta contracting substance (RCS), which is a mixture of TxA_2 and endoperoxides, mainly TxA_2 (Hamberg *et al.*, 1976), has a half-life of 1 to 2 min in Krebs Ringer solution (Palmer, Piper & Vane, 1973). However, this is probably longer in plasma since the half-life of TxA_2 is about 3 min in plasma but only 30 s in artificial media (Granstrøm, Kindahl & Samuelsson, 1976; Smith, Ingerman & Silver, 1977).

Thus it is unlikely that any increased conversion of AA occurred during elevation of P_{LA} since no assay tissue activity was detected. The present findings have recently been supported by radioimmunological determinations of $PGF_{2\alpha}$ and its main pulonary metabolite 15-keto 13, 14-dihydro $PGF_{2\alpha}$ in oedema fluid and perfusate from isolated, perfused rabbit lungs during hydrostatic pulmonary oedema (Scott, Wiberg & Vaage, unpublished findings).

The release of spasmogenic and smooth muscle relaxing peptide has been reported from lungs during oedema (Said & Mutt, 1977; Chijimatso *et al.*, 1976). Since we found no trace of any smooth muscle active substances, this might argue against such a release. However, this is inconclusive since our tissues were not calibrated with these compounds.

Our findings are in contrast to reports that pulmonary oedema in isolated, perfused cat lungs induced by extended perfusion time (Said & Yoshida, 1974) and by raised outflow pressure (Chijimatsu *et al.*, 1976) is followed by release of PGLS. The biological activity in tracheal foam was equivalent to up to 20 ng/ml of $PGF_{2\alpha}$ (Chijimatsu *et al.*, 1976). In our experiments oedema did not cause release of PGLS into the perfusate. One experiment with bioassay of tracheal fluid indicates that the concentration of PGLS in pulmonary extracellul fluid was probably not higher than in the perfusate.

One methodological difference between our experiments and those of Said's group is that these investigators used Krebs Ringer dextran as perfusate (Said & Yoshida, 1974). Recently, we have shown that the presence of dextran in the perfusate releases PGLS from lungs independently of oedema development (Vaage Scott & Wiberg, 1978). Consequently, the release of PGLS reported during oedema development by Said & Yoshida (1974) might be due to perfusate characteristics and not to oedema.

The observation that no PGLS were released in the present experiments was somewhat surprising, considering the large variety of chemical and physical stimuli that have been reported to induce synthesis and release of prostaglandins in the lungs (Piper & Vane, 1971; Bakhle & Vane, 1974). On the basis of the present experiments, we feel that great care should be taken in interpreting the available information in this field. As already stated, perfusion with a dextran-containing solution may by itself affect the prostaglandin synthesis of the lungs. Other investigators have used sensitized lungs (Palmer *et al.*, 1973) which have been shown to synthesize prostaglandins more readily than unsensitized lungs (Mathé, Yen, Sohn & Hedqvist, 1977). Additionally, as tissue trauma is associated with the release of prostaglandins, care must be taken in the initial handling, manipulation and perfusion of the lungs in order to maintain the lungs in a condition as close to physiological as possible before and during application of test stimuli. If not, conflicting results may easily be produced.

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