

TITLE: VASOREACTIVITY IN ISOLATED PERFUSED HUMAN LUNGS
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Abnormal pulmonary vasoreactivity may both cause and result from pulmonary hypertension (phtn). Our heart and lung transplant program provided an opportunity to study vasoreactivity in isolated lungs from patients with and without phtn.

Methods: Single lungs were obtained at the time of transplantation from heart donors (normal group, n=7) or from heart-lung or single lung recipients with pulmonary hypertension (phtn group, n=5). Following removal of the lung, the pulmonary artery, bronchus, and pulmonary veins (or atrial cuff) were cannulated. Lungs were perfused with Krebs-Henseleit buffer with 3% albumin (37° C, pH 7.35-7.45) at a flow rate of 1 l/min or a maximum pulmonary artery pressure of 50-60 mmHg. Pulmonary venous pressure was maintained at zero. Lungs were ventilated with air - 5% CO₂ at a tidal volume of 300 ml, rate 8, and 2.5 cm H₂O PEEP. Following stabilization, pulmonary vasoreactivity was studied using acetylcholine (ACH; n = 6 nl, 5 phtn), PGE₁ (n = 6 nl, 3 phtn), PGF_{2α} (n = 4 nl, 3 phtn) and the thromboxane A₂-mimetic U46619 (n = 7 nl, 4 phtn). Each agent was administered every 5 min in logarithmically increasing doses until maximum effect was obtained. Subsequent drugs were studied only if pulmonary vascular resistance (PVR) returned to baseline following discontinuation of the drug. Dose-response curves were analyzed by the 4-parameter logistic equation. Statistical analysis used Student's t-test for paired and unpaired

data.

Results: ACH decreased PVR 23 ± 3% in normal lungs but increased PVR 13 ± 4% in phtn lungs. (Table) All lungs in each group had the same directional response and the effects were significantly different in the two groups. PGF_{2α} increased PVR 70 ± 18% in the normal lungs and 102 ± 20% in the phtn lungs. PGE₁ decreased PVR 19 ± 3% in the normal lungs and 14 ± 3% in the phtn lungs. U46619 markedly increased PVR in all lungs in both groups. There were no differences between the two groups in either the % increase in PVR or the ED₅₀ for these drugs.

Discussion: When perfused *in vitro*, lungs from patients with phtn had markedly increased PVR compared to normal lungs but had similar responses to PGF_{2α}, PGE₁, and U46619, suggesting that phtn is not associated with a global abnormality in pulmonary vasoreactivity. ACH produced vasodilation in normal lungs, presumably due to release of endothelial-derived relaxing factor (EDRF)¹. In contrast, ACH produced vasoconstriction in phtn lungs, presumably due to a cholinergic effect unopposed by any EDRF release. Endothelial dysfunction may be either a cause or a result of phtn and, by resulting in decreased EDRF release, may generate and sustain phtn.

Reference:

1. Cherry PD, Gillis GN, J Pharmacol Exp Ther 241:516-520, 1987

| | Normal lungs | | Phtn lungs | |
|-------------------|--------------|-----------|------------|--------------|
| | Baseline | Final | Baseline | Final |
| ACH | 9 ± 1 | 7 ± 1* | 95 ± 26 | 106 ± 28* |
| PGF _{2α} | 9 ± 1 | 15 ± 1* | 73 ± 18 | 154 ± 51* |
| PGE ₁ | 7 ± 1 | 6 ± 1* | 79 ± 19 | 69 ± 18* |
| U46619 | 8 ± 1 | 132 ± 90* | 67 ± 10 | 3902 ± 3220* |

*P < 0.05 vs. corresponding baseline value

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TITLE: MECHANISM OF THROMBOXANE-INDUCED PULMONARY EDEMA
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Introduction: Thromboxane A₂ may be a mediator of pulmonary hypertension and edema in sepsis, endotoxemia, complement activation, neutrophil activation, microembolization, and after protamine administration. It is not known whether thromboxane-induced pulmonary edema is due to increased capillary pressure or to increased capillary permeability. We therefore studied the effects of the thromboxane A₂-mimetic U46619 in the isolated perfused rabbit lung, a model which allows measurement of both pulmonary capillary pressure and permeability.

Methods: 6 male New Zealand White rabbits were anesthetized with ketamine 65 mg/kg i.m. followed by pentobarbital 15-25 mg/kg i.v. After heparin administration, tracheostomy, and sternotomy, the pulmonary artery and left atrium were cannulated. The heart-lung block was excised and suspended from a counterbalanced force displacement transducer. Lungs were perfused at 150 ml/min with Krebs-Henseleit buffer (pH 7.40, 37° C) with 3% BSA. The initial 200 ml of perfusate were discarded and perfusate was then recirculated. Pulmonary artery (Ppa) and left atrial (Pla) pressures and lung weight were continuously recorded. Pla was altered by changing the height of the reservoir. Pulmonary capillary pressure was estimated by the double-occlusion pressure (Pdo)¹ measured as the average of inflow and outflow pressures 3 sec after simultaneous inflow and outflow occlusion. After an initial 30 min of perfusion at Pla of 2 mmHg, Pdo was measured. Perfusion was then discontinued so that Ppa and Pla were equal and Pla was adjusted to the highest pressure

(isogravimetric pressure = Pisog) at which the lung did not gain weight. Pla was then increased by 7 mmHg over Pisog and the weight gain from 3 to 10 min was used to determine Kf, the fluid filtration coefficient². Flow was resumed at 150 ml/min and U46619 was infused into the PA cannula to raise Ppa to 25-30 mmHg. Pdo, Pisog, and Kf were measured 60 min later. Statistical analysis used Student's t-test for paired data.

Results: There was no gain in lung weight during perfusion at Pla of 2 mmHg prior to U46619. U46619 increased pulmonary vascular resistance four-fold. Weight gain during U46619 infusion at Pla of 2 mmHg was 0.11 ± 0.03 gm/min. U46619 did not affect either Kf or Pisog (Table). In contrast, Pdo was significantly increased by U46619 and exceeded Pisog in all lungs.

Discussion: Previous studies have suggested that pulmonary capillary pressure increases during thromboxane-induced pulmonary edema^{3,4}. In the current study, pulmonary capillary pressure (Pdo) was significantly increased by U46619 while Kf remained unchanged. Pisog and Pdo were approximately equal before U46619. During U46619, Pdo increased above the unchanged Pisog and edema occurred. Since flow was constant, this increase in Pdo likely represents an increase in pulmonary venous resistance. We conclude that U46619 causes pulmonary edema formation by increasing pulmonary capillary pressure without altering pulmonary capillary membrane permeability.

References: J Appl Physiol 54:846-851, 1983 2) Am J Physiol 234:H266-H274, 1972 3) J Appl Physiol 66:929-935, 1989 4) J Appl Physiol 67:846-855, 1989

| | BASILINE | U46619 |
|--|---------------|---------------|
| Pdo (mmHg) | 3.8 ± 0.8 | 6.2 ± 0.3* |
| Pisog (mmHg) | 3.2 ± 0.6 | 3.6 ± 0.3 |
| Kf (ml·min ⁻¹ ·mmHg ⁻¹ ·g lung ⁻¹) | 0.014 ± 0.011 | 0.019 ± 0.003 |

*P < 0.05 vs. baseline