The effects of graded administration of positive end expiratory pressure on the fluid filtration rate in isolated rabbit lungs, using normal lungs, hydrostatic oedema lungs and oleic acid induced oedema*

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Abstract. The influence of positive end expiratory pressure (PEEP) on the fluid filtration rate (FFR) in the pulmonary circulation has been the subject of considerable investigation but data are conflicting. We studied twenty-nine isolated rabbit lung preparations, FFR was sensed by a force transducer. Autologous blood was used to prime the perfusion circuit. Hydrostatic oedema was achieved by increasing the left atrial pressure to 16 mmHg. In order to bring about increased membrane permeability oleic acid was injected through the pulmonary artery. Increasing and decreasing levels of PEEP at 0, 5, 10 and 15 cm H2O were each used for ten minutes in each of three experimental models. The FFR, pH, mean pulmonary arterial pressure (MPAP), mean left atrial pressure (MLAP), PaO2, PaCO2 and oncotic pressure were measured in each experiment. There was a significant correlation between PEEP and FFR (+0.94) in non-oedema lungs. With no PEEP the FFR was 0 g/min and with 15 cm of PEEP it increased to 0.07 g/min, on removing the PEEP the FFR returned to 0 g/min. In the hydrostatic lung oedema model the correlation was also significant but negative (r = −0.94). With no PEEP the FFR was 0.33 g/min, with PEEP of 15 cm H2O it decreased to 0.08 g/min. No correlation between PEEP and FFR was found in the oleic acid preparation. In the normal lung PEEP increases capillary hydrostatic pressure and total lung vascular area and decreases interstitial pressure. It is by these mechanisms that PEEP causes an increase in FFR. In the hydrostatic oedema model PEEP decreases FFR by increasing the interstitial pressure and by decreasing the total lung vascular area. In the oleic acid preparation the coefficient of filtration is so large that small changes in pressure or vascular area do not modify the FFR. We suggest that PEEP may be beneficial by decreasing FFR in hydrostatic lung oedema, but it may increase the FFR in the normal lung, while having no effect in oleic acid lung injury.

Key words: Fluid filtration rate – Positive end expiratory pressure – Lung oedema

Positive end expiratory pressure (PEEP) is commonly used in mechanically ventilated patients. In most patients PEEP increases the oxygen saturation [1], the functional residual capacity [2] and also reduces atelectasis [3, 4]. It has also been suggested that an elevation of airway pressure or the use of PEEP prevents or retards the transudation of fluid from the vascular space into the interstitium of the lung and to the alveolar space. Changes in extravascular fluid volume depend on a variety of factors, described by Starling in 1896 [5] and characterized by Pappenheimer in 1940 in a mathematical model [6]. Similar mechanisms appear to govern the fluid filtration rate (FFR) in the lung, although there are additional factors imposed by the presence of lymphatics and the respiratory variation in pleural and alveolar pressures. From the Pappenheimer equation there appear to be three major ways of producing lung oedema: (1) an increase in intravascular hydrostatic pressure (Cardiogenic Oedema); (2) a decrease in intravascular oncotic pressure; (3) an alteration of the filtration coefficient (Kf) that occurs after endothelial and epithelial cell injury.

Although many studies have been carried out looking at the effects of PEEP on FFR there remains considerable controversy. Several groups have studied the effects of PEEP on pulmonary oedema, and most, [7, 8, 9, 10, 11], although not all [12, 13, 14, 15], report that PEEP increases rather than decreases lung water in isolated lung preparations. These widely differing results can only be explained by different experimental conditions. We have studied the effects of PEEP on FFR using the same experimental preparation in normal lungs (NL), lungs with hydrostatic oedema (HLO), and oleic acid induced lung oedema (OA).
Materials and methods

Twenty-nine rabbits with a mean body weight of 3.1 ± 0.2 kg (mean ± S.D.) were anesthetized with intraperitoneal sodium pentobarbital 30 to 40 mg/kg body weight. A tracheostomy was performed and the lungs ventilated mechanically at a constant tidal volume.

The peak inflation pressure was approximately 15 cm H₂O. A medi-an sternotomy was performed and 2 ml of heparin (1000 IU/ml) was injected via a cannula placed in the right ventricle. Two minutes later the animal was exsanguinated through the same cannula. Approximately 120 ml of blood was obtained and the volume was increased to 200 ml by using 5% Dextran solution and 0.9% NaCl solution. The proportion of Dextran/NaCl solution was adjusted to produce an oncotic pressure of 22 cm H₂O. This blood was used to prime the perfusion circuit. The heart and lungs were removed with minimal handling of the lungs. A silastic perfusion cannula was inserted into the pulmonary artery via an incision in the right ventricle and a second cannula was inserted into the left atrium via the left ventricle. These cannulae had both end and side holes and were fixed in place by a ligature tied round both ventricles.

This ligature was used to suspend the preparation from a force transducer (Grass type FT–03C) which permits the sensing of small changes in the weight of preparations weight to be sensed (Fig. 1). The zero reference point for the vascular pressure recordings was the left atrial level and the transducers were placed at the level of the atrium. All the transducers were repeatedly calibrated by reference to a saline manometer. Since the lungs were suspended vertically, the apices were approximately at atrial level and the diaphragmatic surface was about 8 cm below this point.

Perfusion was commenced within 10 min of exsanguination and the lungs were perfused at a constant flow by means of an osculatory roller pump (Watson-Marlow) at a mean pulmonary artery pressure of 11.25 ± 3.6 (mean ± S.D.) mmHg which resulted in flows of 76 ± 8 (mean ± S.D.) ml/min. Flow was constantly maintained throughout each experiment, the oscillations produced by the pump were minimized by passing the outflow through an air-filled damping chamber, surrounded by a circular water jacket maintained at 37° C using a plastic radiator [16].

Measurements of oncotic pressure (TT) were made using plasma obtained from 1.5 ml samples of blood extracted from the perfusion circuit at the beginning and at the end of each experiment. The oncometer consisted of a differential pressure transducer which sensed the pressure in a small volume of saline sandwiched between the transducer diaphragm and semipermeable membrane. The membrane (Amicon PM10) was central channel in the upper block. The membrane had a typical rejection of 98% for albumin and 90% for dextran. The calibration and performance of the oncometer has been described elsewhere [16].

The lungs were ventilated with a mixture of 5% CO₂ in air, and the PO₂, PCO₂, and pH were measured using a Radiometer BMS 3MK2 Blood Microsystem. The pH of the perfusate was maintained within normal limits by the addition of small aliquots of sodium bicarbonate. The perfusion was usually started within 8 to 10 min of the termination of the exsanguination procedure. The blood reservoir was set at the same height as the left atrium, resulting in a mean left atrial pressure (MLAP) of -0.88 ± 1.3 (mean ± S.D.) mmHg.

After a stabilization period of about 30 min the goal of the force transducer amplifier was adjusted so that a 2 cm deflection was produced when a weight of one gram was added to the hook on which the preparation was hanging.

The FFR was measured using the isogravimetric method described by Lunde and Waaler [18]. With this method it is possible to separate blood volume changes from FFR changes on the lung weight traces. In the former, there is a marked, rapid weight change after a blood volume change, there then follows a more moderate weight change which stabilizes at or maintains a constant slope which corresponds to the FFR.

The data were analyzed by analysis of variance followed by student's "t" test where appropriate. Pearson's coefficient of correlation was also applied where necessary.

Ventilatory protocol

In the three groups of experiments, the heart-lung preparation was allowed to stabilize for 30 min, ventilating it without PEEP and with a gas mixture containing 5% CO₂ in air. Simultaneously the pH was adjusted by adding small amounts of bicarbonate to the reservoir. At this point the preparations were assigned to one of the following three groups.

Group I: Eleven isolated lung preparations were used to test the influence of PEEP in FFR in normal lungs (NL). The MLAP was adjusted to zero (0.66 ± 1.0 mmHg) by changing the height of the reservoir. The MPAP was set at 11.25 ± 3.6 mmHg, giving a flow of 76.0 ± 18.8 ml/min.

Group II: Eleven of the preparations were used in a high hydrostatic pressure (HLO) protocol. The left atrial cannula was partially occluded with a screw clamp to achieve HLO. The MLAP was increased to 15.26 ± 2.6 mmHg with a corresponding increase of MPAP to 18.6 ± 2.40 mmHg with a flow of 76 ml/min.

Group III: Oleic acid induced lung oedema (OA) was produced in 7 lung preparations by injecting 0.08 ml/kg of oleic acid into the pulmonary artery. To ensure a uniform distribution of the injury, the oleic acid was injected slowly over a period of 1 min at a low flow rate and with the outflow reservoir temporarily raised.

The effect of different PEEP levels on FFR were tested in the three groups. For periods of 10 min each, PEEP at 0, 5, 10, 15, 10, 5, 0 cm of H₂O was sequentially applied. We allowed 3 min after each change in PEEP level before measuring FFR, in order to allow vascular and perivascular pressures to stabilize [17, 18, 19]. A complete set of measurements was recorded at each level of PEEP, including PO₂, PCO₂, pH, MPAP, MLAP, PAW, and FFR. The PEEP level was adjusted by placing the respiratory outflow tube under 5, 10 and 15 cm of water.

Fig. 1. Simplified diagram of the preparation. The lungs are suspended from a force displacement transducer fixed to the top of a perspex box. Blood is pumped from the left atrial reservoir through the damping chamber and double trap to the pulmonary artery. Ventilation is achieved through the preparation trachea; p, pressure transducer; t, temperature.