

## Lung injury edema in dogs. Influence of sympathetic ablation.

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### Research Article

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# Lung Injury Edema in Dogs

## INFLUENCE OF SYMPATHETIC ABLATION

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**ABSTRACT** Increased vascular permeability characterizes lung injury pulmonary edema and renders fluid balance in the injured lung especially sensitive to changes in hydrostatic pressure. Pulmonary edema is often associated with increased sympathetic nervous system activity which can lead to pulmonary venoconstriction. This postcapillary venoconstriction could raise microvascular pressure and might therefore increase edema in the injured lung. We produced lung injury edema in dogs with oleic acid and directly measured small (<2 mm) pulmonary vein pressure. We found that the small pulmonary vein pressure was increased from  $9.8 \pm 0.5$  mmHg to  $12.6 \pm 0.5$  mmHg ( $n = 10$ ) by oleic acid injury edema. The increase was not due to a rise in left atrial pressure since the small pulmonary vein-left atrial pressure gradient also increased. To test if this increase in the postcapillary pressure gradient was sympathetically mediated, we either unilaterally ablated the stellate ganglion or produced unilateral alpha adrenergic blockade with phenoxybenzamine before giving oleic acid. Both of these "antisympathetic" interventions prevented the increase in pulmonary vein pressure caused by oleic acid edema in the protected lung but not in the intact contralateral lung. These interventions produced a  $30 \pm 6.8\%$  reduction in the amount of edema caused by oleic acid. Restoring the increase in small vein pressure by inflating a balloon in the left atrium of dogs with bilateral stellate ganglion ablations abolished the reduction in edema produced by antisympathetic treatment. However, the decrease in edema was not significantly correlated with the reduction in pulmonary vein pressure. Thus, the mechanism of the effects of these antisympathetic interventions remains unclear. We conclude that lung injury edema causes sympathetically mediated pul-

monary venoconstriction and that antisympathetic interventions significantly reduce lung injury edema and microvascular pressure.

## INTRODUCTION

Pulmonary edema due to lung injury is characterized by increased vascular permeability (1-3). This increased permeability not only promotes edema formation by reducing the oncotic gradient that normally acts to keep fluid within the vascular compartment (1-5), but also causes a dramatic increase in the rate of transvascular fluid flux in response to increased hydrostatic pressure gradients (2-8). Thus, edema can be caused by much smaller increases in microvascular pressure in an injured lung than in a normal lung with intact permeability (1, 2, 6-9).

Pulmonary edema is associated with increased sympathetic nervous system activity (10-14). Increased sympathetic activity can lead to systemic and pulmonary vasoconstriction (10, 12, 15, 16). In particular, pulmonary veins have been shown to constrict in response to sympathetic nervous system stimulation (17-20) and to circulating catecholamines (17, 20-23). If pulmonary venoconstriction occurred in the setting of lung injury edema, the resulting increase in microvascular pressure, even if small, might significantly contribute to edema formation, since fluid balance in the injured lung is especially sensitive to changes in microvascular pressure. Previous studies have shown significant reductions in lymph flow (6, 7, 24) or extravascular lung water (25, 26) even with small reductions in microvascular pressure in a setting of lung injury edema.

Therefore, we carried out a series of studies designed to test the hypothesis that lung injury edema leads to sympathetically mediated pulmonary venoconstriction that increases microvascular pressure and contributes significantly to edema formation.

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## METHODS

### Protocol

In chloralose-anesthetized (50 mg/kg loading dose followed by 0.5 mg/kg per h infusion) mongrel dogs (weight,  $24.1 \pm 1.8$  kg), we measured pulmonary artery and systemic pressure, heart rate, and green-dye dilution cardiac output by inserting catheters via the femoral artery and internal jugular vein. Tidal volume and respiratory rate on a ventilator (Harvard Apparatus Co., Inc., S. Natick, MA) with 3 cm positive end-expirator pressure added were used to adjust initial arterial blood gases to pH 7.30 and  $PCO_2$  30 (Corning Radiometer model 165/2, Corning Medical and Scientific, Corning Glass Works, Medfield, MA) on room air, and were not changed thereafter. In addition, catheters were placed directly in the left atrium and a small pulmonary vein of each lung (see description below) via a left thoracotomy, after which the chest was closed and a chest tube to water seal was left in place. Shunt measurements were made periodically by ventilating the animal with 100% oxygen for 20 min and then measuring the oxygen content (Lex-O<sub>2</sub>-Con, Lexington Instruments Corp., Waltham, MA) of pulmonary and femoral arterial blood samples. Pressures were measured with Statham P23DB transducers (Statham Medical Instruments, Hato Rey, Puerto Rico) zeroed to the level of the respective catheter tip by fluoroscopy. The small pulmonary vein pressures were measured on a Statham Medical Instruments P23AA transducer calibrated with a slanted water manometer. All pressure results were recorded at 15-min intervals and mean values over 20 heartbeats calculated on-line by a digital computer (No. 1200, Data General Corp., Lexington, MA). Green-dye dilution cardiac outputs (Waters Associates [Millipore Corp., Milford, MA] densitometer B-402A) were also calculated on-line by computer. All pressure recordings were monitored by an oscillograph.

After stable base-line measurements of pulmonary artery, left atrial, bilateral small pulmonary vein, and systemic pressures, and of cardiac output, shunt, and arterial blood gases over 1 h, each animal was given 0.05 ml/kg oleic acid (Sigma Chemical Co., St. Louis, MO) intravenously. Control dogs were given saline instead. We found that oleic acid tended to preferentially produce lesions in the lower lobes, presumably owing to streaming and/or gravitational effects causing localized oleic acid deposition. To produce a more homogeneous injury, we rotated the dog from supine to right and left lateral decubitus positions and gave one-third of the total oleic acid dose in each position. By gross examination this appeared to produce a more homogeneous injury than did a single injection.

Measurements were made over 4 h and at the end of that time the animals were killed by rapid exsanguination. The lungs were excised and extravascular lung water corrected for residual blood volume was determined (see description below).

### Specific methods

**Small pulmonary vein pressure measurements.** At thoracotomy, a No. 5 National Institutes of Health multiple side-hole catheter (outer diameter, 1.7 mm, USCI Co, Billerica, MA) was positioned fluoroscopically in a small (<2 mm) pulmonary vein of each lower lobe near the costophrenic angle via retrograde passage through the left atrial appendage (27). A length of PE 200 polyethylene tubing was attached to the advancing distal end of the catheter before insertion to act as a "nose." This nose was then wedged as far distally as possible while allowing the side-holes to remain unwedged

and in an area of free flow in the vein. Recording of small vein pressure via the side-holes was begun after the following criteria were met: (a) a free flow of contrast dye (Hypaque 60%, Winthrop Laboratories, New York) injected through the side-holes back to the left atrium (i.e., side-holes not wedged) was observed by fluoroscopy; (b) an undamped pressure tracing was obtained on the oscillograph; (c) the position of the catheter in the distal lower lobe was verified fluoroscopically; (d) the distal diameter of a column of contrast dye produced by injecting via the catheter side-holes was 2 mm or less; and (e) small vein pressure was shown to be independent of left atrial and pulmonary artery pressure by brief (30 s) direct stellate ganglion stimulation (electrostimulator [model 58C; Grass Instrument Co., Quincy, MA]: 20 V, 2 ms, 20 Hz) with shielded electrodes. Thereafter, the position of the catheters, free-flow of injected dye, and adequacy of pressure tracings were rechecked before each measurement of small vein pressure during the experiment.

**Extravascular lung water.** Autologous erythrocytes were tagged *in vitro* with 100  $\mu$ Ci <sup>51</sup>Cr (New England Nuclear, Boston, MA) and injected intravenously 20 min before killing each animal. After death, each lung was clamped at the hilum and rapidly excised. The entire lung was weighed and then homogenized in a blender (Waring Products Div., Dynamics Corp. of America, New Hartford, CT) after adding an equal weight of distilled water. An aliquot of each homogenate was counted for <sup>51</sup>Cr activity in a gamma counter (model 5253, Auto-Gamma Spectrometer, Packard Instrument Co., Inc., United Technologies, Downer's Grove, IL) as was a sample of whole blood drawn from the animal just before death. The remaining homogenate of each lung was dried to constant weight at 55°C in an oven. Extravascular lung water corrected for residual blood content was determined by modification of the method of Pearce et al. (28) and expressed as grams of extravascular lung water per gram bloodless dry lung.

### Statistics

Changes from base line within each group were tested for significance by a paired *t* test. Comparisons between lungs with antisympathetic interventions and their contralateral intact lungs were also tested by a paired *t* test. Comparisons between experimental groups were made by a one-way analysis of variance. Correlations between pressures and lung water were established by linear regression analysis. All values are reported as mean  $\pm$  SE. We accepted  $P < 0.05$  as statistically significant.

### Experimental groups

#### CONTROL ANIMALS ( $n = 5$ )

Control animals received no oleic acid. All animals underwent either unilateral or bilateral stellate ganglion ablation. Since there was no difference in hemodynamic or lung water measurements in animals with unilateral or bilateral ablations, these results were pooled.

#### OLEIC ACID AND "ANTISYMPATHETIC"

#### TREATMENT ( $n = 10$ )

To carefully assess the effect of antisympathetic intervention on animals treated with oleic acid, the intervention (either stellate ganglion ablation or alpha adrenergic blockade) was performed unilaterally. This allowed comparison of groups

of lungs with each animal having one intact lung and one lung in which an antisympathetic intervention had been performed. The following three experimental groups therefore refer to groups of lungs rather than animals.

Two different antisympathetic interventions were performed unilaterally before oleic acid administration. Both interventions were designed to produce a functional rather than a total sympathectomy.

**Stellate ganglion ablation** ( $n = 5$ ). Either the right or the left stellate ganglion of the sympathetic chain was identified at thoracotomy in the posteromedial portion of the thorax at the level of T1 and widely ablated under direct vision with disruption of the sympathetic chain and cardiothoracic nerves. Since there is both contralateral and ipsilateral sympathetic innervation of the lung this probably produced a functional unilateral rather than a complete anatomic sympathectomy.

**Alpha blockade** ( $n = 5$ ). Phenoxybenzamine (SmithKline & French Laboratories, Philadelphia, PA), 0.05 mg/kg, was given by slow infusion directly into either the right or the left pulmonary artery by fluoroscopic direction of the infusion catheter. Localized alpha adrenergic blockade produced by infusion of phenoxybenzamine has been previously used in the systemic circulation (29). Phenoxybenzamine produces alpha blockade by avidly and tightly binding to the alpha receptor by alkylation (30). This may explain its ability to produce a blockade that is most intense at the site of administration. This differential blockade was demonstrated in the present study by prevention of the rise in small pulmonary vein pressure in response to stellate ganglion stimulation (this response has previously been shown to be alpha adrenergically mediated [17]) on the side of the infusion and the preservation of this response in the contralateral lung. Before infusion of the phenoxybenzamine, the small pulmonary vein constriction in response to 2 min of supramaximal ipsilateral stellate ganglion stimulation (20 V, 2 ms duration, 20 Hz) was measured in each lung and expressed as the increase in the small pulmonary vein to left atrial pressure gradient. 1 h after the phenoxybenzamine infusion, blockade was tested by repeating the stellate ganglion stimulation of each lung. Only animals in which there was a 75% inhibition of the small pulmonary vein-left atrial pressure increase in the lung infused with phenoxybenzamine and a <25% decrease in the constrictor response of the contralateral lung were considered to have successful unilateral alpha blockade. Thereafter, adequacy of blockade was periodically tested by briefly (1 min) repeating the stellate ganglion stimulation in the alpha blocked lung. In each case the effect was shown to last for the duration of the experiment.

**Intact** ( $n = 10$ ). The intact contralateral lungs of the animals of the two antisympathetic groups served as the comparison group for the effects of oleic acid.

#### BILATERAL STELLATE-GANGLION ABLATION AND MECHANICALLY ELEVATED LEFT ATRIAL PRESSURE ( $n = 5$ )

Both stellate ganglia were identified by thoracotomy and widely ablated with interruption of the sympathetic chain and cardiothoracic nerves at that level. After placement of the left atrial and bilateral small pulmonary vein catheters, a Foley catheter (No. 12) was placed in the left atrium. 1 h after administration of oleic acid the left atrial balloon was inflated in order to raise the small pulmonary vein pressure to the same level as that which had been measured after oleic acid in the intact, contralateral lungs of animals with

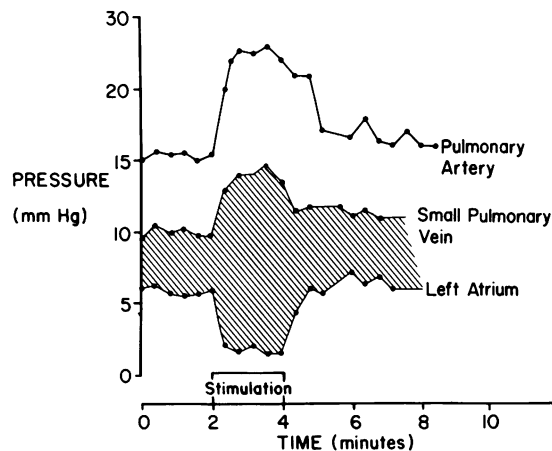


FIGURE 1 Stellate ganglion stimulation causes pulmonary venoconstriction. Results from a representative dog show that direct unilateral stellate ganglion stimulation (20 V, 2 ms, 20 Hz) increases small (<2 mm) pulmonary vein and pulmonary artery pressure. The simultaneous decrease in left atrial pressure is reflected in the PV-LA gradient increase.

unilateral antisympathetic treatment. Balloon inflation was thereafter adjusted to maintain a constant small pulmonary vein pressure.

## RESULTS

In preliminary studies we examined the response of small pulmonary vein pressure to stellate ganglion stimulation (20 V, 2 ms duration, 20 Hz; Fig. 1). There was a rapid increase in both pulmonary artery and small pulmonary vein pressure with a simultaneous decrease in left atrial pressure. This response has been demonstrated by Kadowitz et al. (17).

The increase in small vein pressure was small ( $3.5 \pm 1.8$  mmHg); however, there was a larger increase in the pulmonary vein to left atrial pressure gradient ( $5.6 \pm 2.2$  mmHg), because left atrial pressure decreased. Most of the increase in pulmonary artery pressure appeared to be due to the increase in small vein pressure.

Because small pulmonary vein pressure can change passively with changes in left atrial pressure (i.e., without a change in the small pulmonary vein-left atrial pressure gradient), we calculated the small pulmonary vein-left atrial pressure gradient (PV-LA).<sup>1</sup> This gradient reflects changes in small vein pressure that are independent of changes in left atrial pressure.

Hemodynamic and lung water data are summarized in Tables I and II. Oleic acid administration caused a small but significant increase in the small pulmonary vein pressure (Fig. 2). This increase in small vein pres-

<sup>1</sup> Abbreviation used in this paper: PV-LA, pulmonary vein-left atrial pressure gradient.

TABLE I  
Summary of Hemodynamic Data

| Dog No.   | P <sub>PA</sub> |      | P <sub>LA</sub> |      | P <sub>SPV</sub> |      |       |      | P <sub>V-LA</sub> |      |       |      | Q     |       |            |
|---|-----------------|------|-----------------|------|------------------|------|-------|------|-------------------|------|-------|------|-------|-------|------------|
|   | I               | F    | I               | F    | mmHg             |      | mmHg  |      | I                 |      | F     |      | I     | F     |            |
|   |                 |      |                 |      | right            | left | right | left | right             | left | right | left | right | left  | liters/min |
| <b>I. Controls (n = 5)</b>  |                 |      |                 |      |                  |      |       |      |                   |      |       |      |       |       |            |
| 82,080  | 19.6            | 20.4 | 7.2             | 7.9  | 12.6             | 10.7 | 13.0  | 11.0 | 5.4               | 3.5  | 5.1   | 3.1  | 2.80  | 2.01  |            |
| 82,280  | 16.8            | 16.4 | 7.7             | 6.6  | 10.0             | 10.5 | 10.3  | 10.1 | 2.3               | 2.8  | 3.7   | 3.5  | 3.18  | 3.20  |            |
| 92,280  | 20.6            | 24.2 | 6.0             | 8.0  | 9.5              | 11.1 | 11.7  | 13.2 | 3.5               | 5.1  | 3.7   | 5.2  | 2.35  | 2.38  |            |
| 91,680  | 17.2            | 21.1 | 6.2             | 8.0  | 10.7             | 12.3 | 12.0  | 14.0 | 4.5               | 6.1  | 4.0   | 6.0  | 2.16  | 2.13  |            |
| 9,480   | 15.9            | 20.4 | 5.3             | 6.3  | 12.0             | 11.8 | 12.7  | 12.3 | 6.7               | 6.5  | 6.4   | 6.0  | 2.38  | 2.80  |            |
| Mean (±SE)  | 18.0            | 20.5 | 6.5             | 7.4  | 11.1             | 11.1 | 12.0  | 12.0 | 4.6               | 4.6  | 4.7   | 4.7  | 2.57  | 2.50  |            |
|   | ±0.9            | ±1.2 | ±0.4            | ±0.4 | ±0.3             | ±0.3 | ±0.4  | ±0.4 | ±0.5              | ±0.5 | ±0.4  | ±0.4 | ±0.18 | ±0.22 |            |
| <b>II. Oleic acid and unilateral antisymphathetic treatment (n = 10)</b>                                  |                 |      |                 |      |                  |      |       |      |                   |      |       |      |       |       |            |
| 72,280*   | 13.2            | 22.7 | 6.8             | 6.2  | 9.6              | 10.8 | 12.9  | 10.0 | 2.8               | 4.0  | 6.7   | 3.8  | 1.15  | 1.06  |            |
| 73,080*   | 16.8            | 21.0 | 5.8             | 6.1  | 8.2              | 9.0  | 11.4  | 9.2  | 2.4               | 3.2  | 5.3   | 3.1  | 4.15  | 2.73  |            |
| 81,980*   | 17.3            | 24.1 | 5.5             | 6.0  | 10.4             | 8.8  | 12.7  | 10.8 | 4.9               | 4.3  | 6.7   | 4.8  | 2.02  | 2.02  |            |
| 9,980*  | 17.6            | 22.5 | 3.9             | 5.8  | 8.5              | 8.3  | 13.0  | 11.4 | 4.6               | 4.4  | 7.2   | 5.6  | 1.35  | 0.67  |            |
| 91,080*   | 19.4            | 28.3 | 4.8             | 5.3  | 10.5             | 10.6 | 14.3  | 13.8 | 5.7               | 5.8  | 9.0   | 8.5  | 3.10  | 2.50  |            |
| 111,780†  | 18.9            | 22.5 | 8.2             | 5.6  | 11.9             | 12.4 | 13.5  | 11.4 | 3.7               | 4.2  | 7.9   | 5.8  | 1.78  | 1.00  |            |
| 12,580‡   | 18.0            | 22.7 | 7.1             | 6.5  | 11.9             | 13.2 | 14.0  | 10.7 | 4.8               | 6.1  | 7.5   | 4.2  | 2.04  | 1.25  |            |
| 12,980‡   | 14.7            | 18.8 | 5.6             | 4.7  | 8.7              | 9.3  | 9.3   | 8.7  | 3.1               | 3.7  | 4.6   | 4.0  | 1.57  | 0.90  |            |
| 121,180‡  | 13.6            | 16.1 | 2.7             | 4.3  | 7.9              | 8.5  | 12.8  | 10.3 | 5.2               | 5.8  | 8.5   | 6.0  | 1.43  | 1.11  |            |
| 12,781  | 14.9            | 27.8 | 4.1             | 5.0  | 10.0             | 8.9  | 11.7  | 10.5 | 5.9               | 4.8  | 6.7   | 5.5  | 1.92  | 1.48  |            |
| Mean (±SE)  | 16.4            | 22.7 | 5.5             | 5.6  | 9.8              | 10.1 | 12.6  | 10.7 | 4.3               | 4.6  | 7.0   | 5.1  | 2.05  | 1.47  |            |
|   | ±0.7            | ±1.2 | ±0.5            | ±0.2 | 0.5              | ±0.5 | ±0.5  | ±0.4 | ±0.4              | ±0.3 | ±0.4  | ±0.5 | ±0.29 | ±0.22 |            |
| <b>III. Oleic acid and bilateral stellate ganglion ablation and elevated left atrial pressure (n = 5)</b> |                 |      |                 |      |                  |      |       |      |                   |      |       |      |       |       |            |
| 32,381  | 16.7            | 30.9 | 5.7             | 11.8 | 9.4              | 8.4  | 14.5  | 14.4 | 3.7               | 2.7  | 2.7   | 2.6  | 0.77  | 0.53  |            |
| 21,981  | 17.3            | 25.3 | 6.7             | 11.8 | 11.1             | 12.0 | 15.0  | 15.3 | 4.4               | 5.3  | 3.2   | 3.5  | 5.18  | 2.27  |            |
| 22,581  | 14.6            | 26.1 | 8.5             | 11.8 | 10.9             | 13.5 | 15.1  | 17.1 | 2.4               | 5.0  | 3.3   | 5.3  | 3.47  | 2.38  |            |
| 31,181  | 16.8            | 25.5 | 6.5             | 13.5 | 10.5             | 11.0 | 16.3  | 15.7 | 4.0               | 4.5  | 2.8   | 2.2  | 1.87  | 1.51  |            |
| 3,481   | 18.3            | 24.2 | 9.2             | 12.0 | 13.4             | 12.8 | 14.2  | 14.6 | 4.2               | 3.6  | 2.2   | 2.6  | 2.58  | 1.21  |            |
| Mean (±SE)  | 16.7            | 26.4 | 7.3             | 12.2 | 11.3             | 11.3 | 15.2  | 15.2 | 4.0               | 4.0  | 3.0   | 3.0  | 2.77  | 1.58  |            |
|   | ±0.6            | ±1.2 | ±0.7            | ±0.3 | ±0.5             | ±0.5 | ±0.3  | ±0.3 | ±0.3              | ±0.3 | ±0.3  | ±0.3 | ±0.74 | ±0.34 |            |

Initial (I) and final (F) measurements were of: pulmonary artery (P<sub>PA</sub>), left atrial (P<sub>LA</sub>), and small pulmonary vein (P<sub>SPV</sub>) pressures, PV-LA, and cardiac output (Q); measured in both lungs of all animals. P<sub>SPV</sub> and PV-LA are reported as right and left lung values in animals where both lungs received the same experimental treatment and all values pooled to calculate group means (Groups I and III). Where lungs received different experimental treatment (Group II) P<sub>SPV</sub> and PV-LA are reported for intact and treated groups of lungs and mean values of each group shown.

\* Stellate ganglion ablation.

‡ Alpha adrenergic blockade.

**TABLE II**  
*Summary of Pulmonary Vein Pressure and Lung Water Data by Individual Lungs*

| Dog No.   | $P_{SPV}$         |                   |                   |                   | $\Delta(PV-LA)$   |                  | EVLW               |                    | EVLW increase      |                   |
|---|-------------------|-------------------|-------------------|-------------------|-------------------|------------------|--------------------|--------------------|--------------------|-------------------|
|   | Initial           |                   | Final             |                   |                   |                  | g/g bloodless dry  |                    | %                  |                   |
|   | right             | left              | right             | left              | right             | left             | right              | left               | right              | left              |
| <b>I. Control (n = 5)</b>   |                   |                   |                   |                   |                   |                  |                    |                    |                    |                   |
| 82,080  | 12.6              | 10.7              | 13.0              | 11.0              | -0.3              | -0.4             | 3.43               | 2.55               | —                  | —                 |
| 82,280  | 10.0              | 10.5              | 10.3              | 10.1              | 1.4               | 0.7              | 3.58               | 3.55               | —                  | —                 |
| 92,280  | 9.5               | 11.1              | 11.7              | 13.2              | 0.2               | 0.1              | 3.61               | 3.55               | —                  | —                 |
| 91,680  | 10.7              | 12.3              | 12.0              | 14.0              | -0.5              | -0.1             | 3.38               | 3.93               | —                  | —                 |
| 9,480   | 12.0              | 11.8              | 12.7              | 12.3              | -0.3              | -0.5             | 3.30               | 3.47               | —                  | —                 |
| Mean ( $\pm$ SE)  | 11.1<br>$\pm$ 0.3 |                   | 12.0<br>$\pm$ 0.4 |                   | +0.1<br>$\pm$ 0.2 |                  | 3.44<br>$\pm$ 0.11 |                    | —                  |                   |
| <b>II. Oleic acid and unilateral anti-sympathetic treatment (n = 10)</b>                                  |                   |                   |                   |                   |                   |                  |                    |                    |                    |                   |
|   | intact            | treated           | intact            | treated           | intact            | treated          | intact             | treated            | intact             | treated           |
| 72,280*   | 9.6               | 10.8              | 12.9              | 10.0              | 3.9               | -0.2             | 6.25               | 5.55               | 81.3               | 61.3              |
| 73,080*   | 8.2               | 9.0               | 11.4              | 9.2               | 2.9               | -0.1             | 5.82               | 4.65               | 69.2               | 35.2              |
| 81,980*   | 10.4              | 9.8               | 12.7              | 10.8              | 1.8               | 0.5              | 5.55               | 5.27               | 61.3               | 53.2              |
| 9,980*  | 8.5               | 8.3               | 13.0              | 11.4              | 2.6               | 1.2              | 5.98               | 5.38               | 73.8               | 56.4              |
| 91,080*   | 10.5              | 10.6              | 14.3              | 13.8              | 3.3               | 2.7              | 6.64               | 5.43               | 93.0               | 57.8              |
| 111,780†  | 11.9              | 12.4              | 13.5              | 11.4              | 4.2               | 1.6              | 7.37               | 6.31               | 114.2              | 83.4              |
| 12,580†   | 11.9              | 13.2              | 14.0              | 10.7              | 2.7               | -1.9             | 7.62               | 5.55               | 121.5              | 61.3              |
| 12,980†   | 8.7               | 9.3               | 9.3               | 8.7               | 1.5               | 0.3              | 5.16               | 5.29               | 50.0               | 53.8              |
| 121,180†  | 7.9               | 8.5               | 12.8              | 10.3              | 3.3               | 0.2              | 6.24               | 5.34               | 81.4               | 55.2              |
| 12,781†   | 10.0              | 8.9               | 11.7              | 10.5              | 0.8               | 0.7              | 5.98               | 5.29               | 73.8               | 53.8              |
| Mean ( $\pm$ SE)  | 9.8<br>$\pm$ 0.5  | 10.1<br>$\pm$ 0.5 | 12.6<br>$\pm$ 0.5 | 10.7<br>$\pm$ 0.4 | 2.7<br>$\pm$ 0.3  | 0.5<br>$\pm$ 0.4 | 6.26<br>$\pm$ 0.24 | 5.42<br>$\pm$ 0.13 | 82.0<br>$\pm$ 7.0  | 57.5<br>$\pm$ 3.7 |
| <b>III. Oleic acid and bilateral stellate ganglion ablation and elevated left atrial pressure (n = 5)</b> |                   |                   |                   |                   |                   |                  |                    |                    |                    |                   |
|   | right             | left              | right             | left              | right             | left             | right              | left               | right              | left              |
| 32,381  | 9.4               | 8.4               | 14.5              | 14.4              | -1.0              | -0.1             | 7.88               | 7.63               | 129.1              | 121.8             |
| 21,981  | 11.1              | 12.0              | 15.0              | 15.3              | -1.2              | -1.8             | 7.72               | 6.94               | 124.4              | 101.7             |
| 22,581  | 10.9              | 13.5              | 15.1              | 17.1              | 0.9               | 0.3              | 6.44               | 6.94               | 87.2               | 101.7             |
| 31,181  | 10.5              | 11.0              | 16.3              | 15.7              | -1.2              | -2.3             | 7.14               | 7.02               | 101.6              | 104.1             |
| 3,481   | 13.4              | 12.8              | 14.2              | 14.6              | -2.0              | -1.0             | 7.33               | 7.63               | 113.1              | 121.8             |
| Mean ( $\pm$ SE)  | 11.3<br>$\pm$ 0.5 |                   | 15.2<br>$\pm$ 0.3 |                   | -0.9<br>$\pm$ 0.3 |                  | 7.27<br>$\pm$ 0.14 |                    | 111.3<br>$\pm$ 4.1 |                   |

Initial and final measurements of small pulmonary vein ( $P_{SPV}$ ) pressure; changes in small pulmonary vein-left atrial pressure gradient [ $\Delta(PV-LA)$ ] from initial to final measurement; extravascular lung water (EVLW), and percentage increase in EVLW compared with mean control EVLW (EVLW increase) for individual lungs within groups were made. Values are reported as right and left in animals where both lungs received the same experimental treatment and all values are pooled to calculate group means (Groups I and III). Values are reported as intact and treated where lungs were treated differently and mean values of each group of lungs shown (Group II).

\* Stellate ganglion ablation.

† Alpha adrenergic blockade.

sure was not associated with a change in left atrial pressure and the PV-LA gradient therefore increased. In contrast, whereas small vein pressure increased slightly during the experiment in the lungs of control

animals receiving no oleic acid, this was because of an increase in left atrial pressure since there was no increase in the PV-LA gradient. Cardiac output decreased from base line in oleic acid-treated animals, but not in

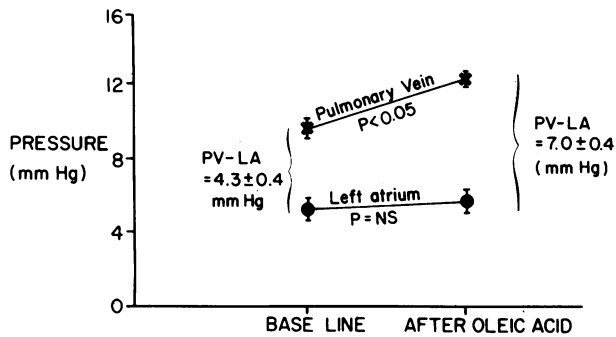


FIGURE 2 Small pulmonary vein pressure increases in lung injury edema. Pulmonary vein pressure increases 4 h after production of lung injury edema with oleic acid ( $n = 10$ ). Left atrial pressure is unchanged.

control animals. Pulmonary artery pressure increased after oleic acid and this increase was greater than could be accounted for by the increase in pulmonary vein pressure.

The increase in the small vein pressure and PV-LA gradient after oleic acid could be prevented by either unilateral stellate ganglion ablation or by unilateral alpha blockade with phenoxybenzamine (Fig. 3). Both of these antisymphathetic interventions also produced a decrease in the amount of edema caused by oleic acid. We defined edema as the increase in extravascular lung water caused by oleic acid. This amounted to a  $30.2 \pm 6.7\%$  decrease with stellate ganglion ablation and a  $29.5 \pm 12.2\%$  decrease with alpha blockade (Fig. 4). The amount of edema correlated with the small pulmonary vein pressure when all oleic acid-treated lungs were compared (Fig. 5). However, there was not a significant relationship between extravascular lung wa-

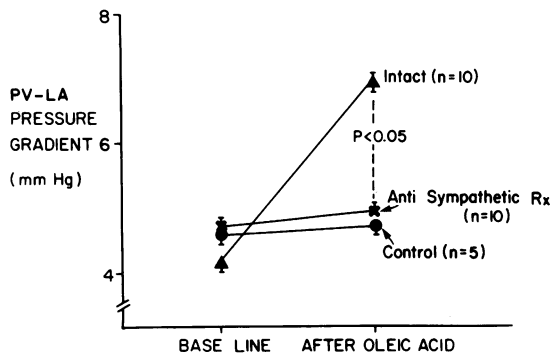


FIGURE 3 Unilateral antisymphathetic treatment prevents the increase in small pulmonary vein pressure caused by lung injury edema. Either unilateral stellate ganglion ablation ( $n = 5$ ) or unilateral alpha adrenergic blockade with phenoxybenzamine ( $n = 5$ ) prevents the increase in pulmonary vein pressure (PV-LA pressure gradient) caused by oleic acid lung injury edema in the intact contralateral lungs ( $n = 10$ ) of the same animals.

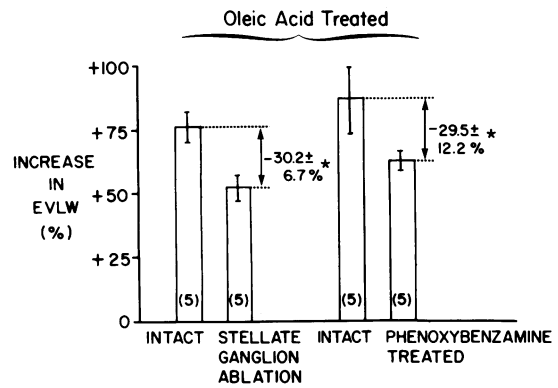


FIGURE 4 Unilateral antisymphathetic treatment decreases lung injury edema. The increase in extravascular lung water (EVLW) caused by oleic acid is reduced by unilateral stellate ganglion ablation ( $n = 5$ ) and by unilateral alpha adrenergic blockade with phenoxybenzamine ( $n = 5$ ) when compared with the EVLW of intact contralateral lungs of the same animals. \*,  $P < 0.05$ .

ter and vein pressure within the antisymphathetic intervention group alone. Control lungs showed no correlation between lung water and small vein pressure.

As noted, the increase in small vein pressure caused by oleic acid was small. To determine whether such a small increase in vein pressure could account for the large increase in lung edema observed, we mechanically raised vein pressure by inflating a left atrial balloon after oleic acid administration and bilateral stellate ganglion ablation. The small vein pressure was increased due to the increase in left atrial pressure with an accompanying slight decrease in the PV-LA gradient. Although the small pulmonary vein pressure was actually higher in this group than in the intact oleic acid-injured lungs, the relationship between vein pres-

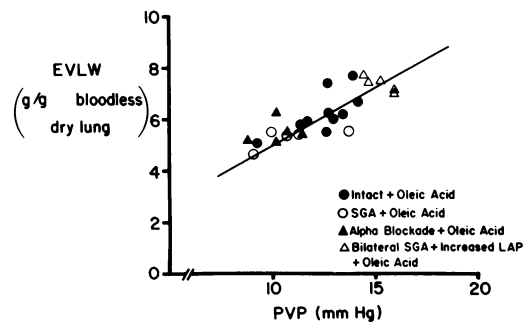


FIGURE 5 Lung water content correlates with small pulmonary vein pressure in lung injury edema. In oleic-acid lung injury, extravascular lung water (EVLW) correlates with pulmonary vein pressure (PVP) when compared among intact lungs ( $n = 10$ ), lungs with stellate ganglion ablation (SGA) ( $n = 5$ ), alpha adrenergic blockade ( $n = 5$ ), or mechanically-increased left atrial pressure (LAP) plus stellate ganglion ablation ( $n = 10$ ).  $P < 0.05$ ,  $r = 0.776$ ,  $n = 30$ .

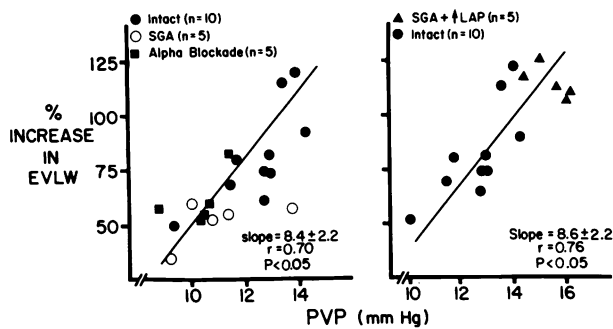


FIGURE 6 The decrease in lung injury edema caused by antisympathetic treatment is abolished by preventing the decrease in pulmonary vein pressure. (Left) Decreasing pulmonary vein pressure (PVP) by antisympathetic treatment reduces oleic acid lung injury edema (extravascular lung water, EVLW). (Right) Mechanically elevating PVP by increasing left atrial pressure (LAP) abolishes the reduction in edema caused by antisympathetic treatment (stellate ganglion ablation). The EVLW-PVP relationship has the same slope in both comparisons.

sure and extravascular lung water in these lungs was comparable to that in the other lungs. In fact, the rate of the increase in lung water with increasing small vein pressure was identical ( $8.6 \pm 2.2\%$  vs.  $8.4 \pm 2.2\%$  excess lung water per millimeter of mercury) as shown in Fig. 6.

Gas exchange data are summarized in Table III. Initial gas exchange parameters were not different between experimental groups and shunt fraction was at an acceptably low level. All animals had an initial moderate metabolic acidosis which we attributed to prolonged time under anesthesia, mechanical ventilation, and extensive surgery. Although acidosis can affect pulmonary vascular tone, the degree of acidosis was similar in all experimental groups and therefore we doubt it was a source of difference between the groups. Final blood gases showed a decrease in the arterial  $P_{O_2}$  and an increase in shunt fraction in the oleic acid-treated groups, but these changes were not different between the groups.

## DISCUSSION

These studies indicate that lung injury edema produced by oleic acid (26, 31) causes an increase in small pulmonary vein pressure. The pressure increase appears to be sympathetically and alpha adrenergically mediated since it could be prevented by antisympathetic treatment, either by stellate ganglion ablation or by alpha adrenergic blockade with phenoxybenzamine. The increase in vein pressure is small. However, preventing the pressure increase by antisympathetic treatment was associated with a significant decrease in the amount of edema produced by oleic acid injury. Since a graded relationship between vein pressure and edema was not present within the antisympathetic group, a non-pressure-mediated antisympathetic effect on edema is also possible. We prevented the decrease in vein pressure produced by stellate ganglion ablation by mechanically elevating left atrial pressure with a balloon. Preventing the vein pressure from decreasing abolished the decrease in edema caused by stellate ganglion ablation.

Pulmonary edema is associated with increased sympathetic nervous system activity (10–13). The precise stimulus for sympathetic activation is not clear but it could arise within the lung, reflecting activity of irritant or mechanical receptors (32) or could represent a systemic response to acute injury perhaps triggered by hypoxemia or hypotension. The small pulmonary vein pressure appeared to increase approximately 1 h after oleic acid administration but this was not a consistent finding.

Constriction of pulmonary veins to a wide variety of stimuli has been shown by both direct and indirect measurements. Direct measurements of pulmonary vein pressure in vivo have shown constrictor responses to norepinephrine (17), histamine (17, 22), prostaglandin  $F_{2\alpha}$  (17), ice-water immersion (18), aortic chemoreceptor stimulation (19), serotonin (22), acetylcholine (22), and endotoxin (33). In vitro studies of pulmonary veins have demonstrated similar responses (17, 22, 34). Venoc constriction had been demonstrated in response

TABLE III  
Summary of Gas Exchange Data

| Group       | Initial ( $FI_{O_2} = 1.0$ ) |            |           |           | Final ( $FI_{O_2} = 1.0$ ) |            |           |           |
|-------------|------------------------------|------------|-----------|-----------|----------------------------|------------|-----------|-----------|
|             | pH                           | $P_{CO_2}$ | $P_{O_2}$ | Qs/Qt     | pH                         | $P_{CO_2}$ | $P_{O_2}$ | Qs/Qt     |
| I (n = 5)   | 7.28±0.05                    | 28±1       | 422±15    | 0.05±0.01 | 7.33±0.04                  | 33±3       | 390±25    | 0.07±0.01 |
| II (n = 10) | 7.34±0.03                    | 26±1       | 395±22    | 0.05±0.01 | 7.27±0.04                  | 30±3       | 282±61    | 0.08±0.02 |
| III (n = 5) | 7.33±0.03                    | 26±2       | 367±11    | 0.08±0.01 | 7.23±0.04                  | 28±4       | 256±43    | 0.14±0.03 |

Initial and final measurements were made of pH,  $P_{CO_2}$ ,  $P_{O_2}$  ( $FI_{O_2} = 1.0$ ) and shunt (Qs/Qt) for control (Group I), oleic acid and unilateral antisympathetic treatment (Group II), and oleic acid and bilateral stellate ganglion ablation and elevated left atrial pressure (Group III) groups of animals.



to histamine (21), norepinephrine (20, 21), and epinephrine (20) by the outflow occlusion technique measurement of vascular resistance changes. In addition, lymph flow studies have reflected increases in microvascular pressure due to constriction of "downstream vessels"—presumably pulmonary veins, in response to endotoxin (7), norepinephrine (23), serotonin (35), arachidonate (36), cyclic endoperoxides (37), and histamine (38).

Responsiveness of the pulmonary veins to sympathetic stimuli seems well established. Anatomic studies have demonstrated sympathetic innervation of the veins (32). Pulmonary veins have been shown to constrict to a variety of sympathetic stimuli. Kadowitz et al. (17) demonstrated constriction of intralobar pulmonary veins (2–3 mm diam) to stellate ganglion stimulation by direct pressure measurements. The constriction was prevented by alpha adrenergic blockade. Stern and Braun showed increases in directly measured pulmonary vein pressure in response to ice-water immersion (18) and in response to aortic chemoreceptor stimulation (19). Both these responses appeared to be sympathetically mediated. Maron and Dawson (20) and Peterson et al. (39) showed venoconstriction in response to elevated intracranial pressure (20) and Sugg et al. (40) showed increases in small pulmonary vein pressure in a hemorrhagic shock model. In addition, as already mentioned, pulmonary veins respond to circulating catecholamines as well (17, 20–23).

Sensitivity of the injured lung to changes in hydrostatic pressure is shown by the correlation between small vein pressure and extravascular lung water (Fig. 5) and the steep relationship between excess lung water (i.e., edema) and vein pressure (Fig. 6). The sensitivity of the injured lung to hydrostatic pressure changes has been demonstrated previously in sheep treated with *Pseudomonas* (6), endotoxin (7), and intravenous air emboli (8); and in dogs treated with oleic acid (9, 26), alpha naphthyl thiourea (7), or acid aspiration (5). Foy et al. (24) showed decreases in lymph flow in sheep with *Pseudomonas* bacteremia with small vasodilator-induced decreases in microvascular pressure. Ali et al. (25) used furosemide and Prewitt et al. (26) infused nitroprusside to show similar dramatic beneficial effects of small decreases in microvascular pressure on oleic acid edema in dogs.

We measured small pulmonary vein pressure directly. We did not use the pulmonary artery wedge pressure because small postcapillary pressure changes might not be detected by the use of a wedge arterial catheter. The wedged catheter would likely stop flow in the small pulmonary veins downstream to it and therefore preclude the measurement of changes in small vein pressure. Indeed, on several occasions when the pulmonary artery catheter and the small vein catheter were in the same lung segment, wedging of the arterial catheter

reduced the measured small vein pressure to the level of the wedge pressure. The larger the artery that is occluded during the wedge pressure measurement, the less likely it is that the wedge pressure will reflect changes in small vein pressure.

It seems probable that the increases in small vein pressure that we observed reflect increases in venous resistance. Sympathetic nerve stimulation has been shown to increase small vein pressure by increasing resistance when measured in isolated perfused lobes with constant flow (17). In our experiments, cardiac output decreased in the oleic acid-treated animals. Therefore, we expect that any pressure increases reflected true resistance increases. We did not measure blood flow to each lung. Our pressure measurements might have been influenced by redistribution of blood flow between the lungs. However, pulmonary blood flow is typically diverted away from severely edematous lung regions (41, 42) which would tend to lower the pressure gradients, whereas we observed pressure gradient increases in the more edematous lungs. Therefore, it seems unlikely that the increase in small vein pressure we observed in the more edematous lungs was due to an increase in flow. In fact, the pressure increases probably underestimate the actual resistance change in the intact, and therefore, more edematous lungs which probably have less blood flow. Similarly, the resistance change in the antisymphatically treated, less edematous lungs would, if anything, be overestimated.

While antisymphatic treatment appears to prevent the small vein pressure increase, it also appears that blockade need not be complete. Unilateral stellate ganglion ablation is not a total autonomic denervation of the lungs—there is remaining ipsilateral as well as contralateral innervation and our criteria for successful unilateral alpha adrenergic blockade allowed for up to 25% residual response to stellate ganglion stimulation. However, both of these interventions were effective in preventing the increase in pulmonary vein pressure as demonstrated by this study. More complete sympathectomy is also effective as shown by Sugg et al. (40) who prevented hemorrhagic shock induced pulmonary venoconstriction by autotransplantation of one lung and by Kabins et al. (43) who significantly reduced starch-embolism-induced pulmonary edema by bilateral thoracic sympathectomy. Interestingly, unilateral thoracic sympathectomy appeared to have prevented the development of edema in one lung of a patient with the adult respiratory distress syndrome (44).

Our findings suggest that stellate ganglion ablation and alpha blockade decreased edema by lowering microvascular hydrostatic pressure. However, a graded relationship between small pulmonary vein pressure and the amount of edema was not present within the intervention group itself but only for the oleic acid-treated groups as a whole. This lack of a graded re-

lationship may be due to the narrow range of extravascular lung water resulting from antisympathetic treatment. It might also reflect a non-pressure-mediated mechanism by which antisympathetic treatment reduces edema. Unfortunately, due to the nature of the antisympathetic interventions we used, establishing a graded range of pulmonary vein pressure responses was not possible.

Hakim et al. (45) have shown that prolonged stellate ganglion stimulation increases the flow of protein-rich lymph in sheep, suggesting an increase in vascular permeability that can be prevented by alpha adrenergic blockade. Alpha blockade has been shown to prevent histaminergic pulmonary vascular effects (46) and therefore might prevent the edemogenic effects of histamine as well. It is possible that the beneficial effect of antisympathetic treatment was due to one or both of these mechanisms or other non-pressure-mediated effects. The resultant decrease in edema could then produce the observed decrease in pulmonary vein pressure. The experiments in which we mechanically elevated left atrial pressure after stellate ganglion ablation suggest that the hemodynamic effects of the antisympathetic interventions (stellate ganglion ablation and alpha blockade) could account for most of the observed decrease in the edema. We found that raising the vein pressure reversed the beneficial effect of bilateral stellate ganglion ablation.

In conclusion, pulmonary edema due to lung injury with oleic acid caused sympathetic, alpha adrenergically mediated pulmonary venoconstriction in small pulmonary veins. The resulting microvascular hydrostatic pressure increase, although small, significantly contributed to the amount of edema (Fig. 7) due to the enhanced sensitivity of the injured lung to edema formation. Antisymphathetic treatment (either stellate ganglion ablation or alpha adrenergic blockade with phenoxybenzamine) decreased the edema produced by oleic acid. The decrease in edema was associated with the

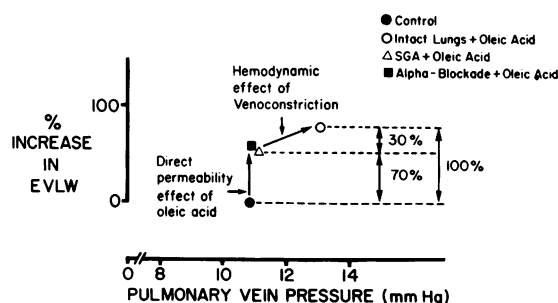


FIGURE 7 The increase in lung water after oleic acid lung injury is determined by both permeability and hemodynamic effects of lung injury. Direct effect of oleic acid on permeability accounts for 70% of the resulting edema (extravascular lung water, EVLW). The remaining 30% is due to the hemodynamic effect of pulmonary venoconstriction.

decrease in small pulmonary vein pressure but a correlation within the antisympathetic intervention group was not present. Vasodilator interventions aimed at decreasing small pulmonary vein pressure might have therapeutic usefulness in patients with lung injury edema. Since pulmonary artery wedge pressures may not fully reflect increases in small vein pressure, reduction of microvascular pressure might be useful in treating pulmonary edema even when wedge pressures are normal or only slightly elevated. These results suggest that adrenergically mediated increases in pulmonary microvascular pressure contribute significantly to the pathogenesis of pulmonary edema due to lung injury and that interventions that decrease this response might have therapeutic utility.

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