Humoral Transmission of Cardiorespiratory Changes in Experimental Lung Embolism

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Acute pulmonary microembolism causes pulmonary vasoconstriction and closure of the terminal airways. We have given reasons to suppose that these effects are not entirely explicable in terms of mechanical obstruction or neurogenic vasoconstriction and we have postulated that the effects of microembolism may be due, in part, to release of some humoral agent.1-3 The experiments described below were designed to test this hypothesis.

Methods

Material

Fourteen technically satisfactory experiments were carried out on 14 pairs of sheep. Members of each pair will be referred to as recipient (A) and donor (B). The mean weight of the recipients (A) was 33.6 kg and that of the donors (B) was 35.0 kg.

Operative Procedures

The supine animals were anesthetized with 10 to 15 mg/kg iv of pentothal sodium (Thiopen tone) followed by an intravenous drip of 0.20 to 0.25 mg/kg/min pentothal sodium and 0.15 to 0.20 mg/kg/min heparin given in saline. Following anesthesia the trachea was intubated with a cuffed Magill tube. Catheterization of the pulmonary artery was carried out via a femoral vein and the femoral artery was cannulated. A needle was inserted into the intrapleural space and a small (60 to 100 ml) pneumothorax was induced. Rectal temperature was measured with a thermometer.

Pressure Measurements

Femoral arterial, pulmonary arterial, intrapleural, and (whenever a double-lumen catheter was used) pulmonary arterial wedge pressures were measured by Sanborn transducers recorded on two direct-writing multichannel Sanborn oscillographs. Vascular pressures are expressed in mm Hg, intrapleural pressure in cm H2O relative to atmosphere.

Cardiac Output Measurement

The Fick principle was used to calculate cardiac output. Oxygen uptake and ventilation were measured with a twin spirometer (Pulmotest *) while the animal breathed air. Blood samples were taken in the midperiod of ventilation measurements. Oxygen carrying capacity of the arterial blood4 and oxygen saturation of the arterial and mixed venous blood5 were determined spectrophotometrically.

Lung Compliance Measurement

Air flow rate and tidal volume were obtained by using a pneumotachometer and integrator.* Intrapleural pressure, air flow rate, and tidal volume were recorded simultaneously on the oscillograph.

Calculations; Derived Values

Total pulmonary and systemic arterial resistances were calculated by the usual formulas and expressed in dynes-sec-cm−5. Blood flows, resistances, and ventilated volumes were expressed per m2 body surface area (BSA). Lung compliance expressed in ml/cm H2O/kg was obtained by dividing the tidal volume by the simultaneously recorded intrapleural pressure difference between points of zero flow and dividing the result by the body weight of the animal expressed in kg.

Details of these techniques are described in previous publications.6, 7

Technique of Cross Circulation

In each experiment cross circulation between the carotid artery of the donor (B) sheep and the external jugular vein of the recipient (A) sheep was established. The carotid artery of the recipient (A) was connected to the external jugular vein of the donor (B). Tygon tubes (3

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mm in diameter, 45 cm in length *) fitted with T-pieces were used. Magnitude of the cross flow was determined by temporarily clamping the tubes between the T-pieces and jugular veins; by opening the taps on the T-pieces blood was collected for five seconds into measuring cylinders.

CRITERIA OF CROSS CIRCULATION

Initially cross matching of blood between donor and recipient was carried out using standard clinical technique. Since minor incompatibility (not readily detected by routine methods) may already produce pulmonary hypertension and compliance fall in sheep, only those experiments were included in this series in which opening of the anastomotic flow was not followed by pulmonary hypertension or irreversible fall in lung compliance.

Criteria of satisfactory carotid-jugular anastomosis were that the cross flow 1) represented not less than 10% of the cardiac output, 2) was identical in both directions, and 3) did not change significantly throughout the experiment.

EMBOLIZATION OF THE LUNG

This was done in the donor (B) in two ways: 1) using a 33 volume per cent emulsion of barium sulfate (dose: 0.08 ml/kg), and 2) using autologous blood clots. The embolic material was injected rapidly intravenously into the donor (B) animal.

The preparation of autologous blood clots was carried out by allowing 100 ml of blood collected from the donor (B) to clot at room temperature. The material was homogenized using a Waring-Blender mixer and washed with saline 8 to 10 times until contamination with hemoglobin was no longer apparent. The larger clots were removed and the clots injected varied in size between 1 and 3 mm. The material was suspended in a standard volume of saline and an equivalent amount of 1 ml of blood/kg body wt was injected.

EXPERIMENTAL DESIGN

Control observations were made in two stages. First, measurements were taken with the tubes clamped. Subsequently the clamps were released and cross flow allowed to commence while all pressures were continuously recorded. Five minutes later measurements were taken and cross flows were determined.

Postembolic observations were done five minutes after the cross circulation had been terminated (10 minutes after embolism), following lung inflation.

PROCEDURES IN RECIPIENT (A) AND DONOR (B)

Circulatory parameters (cardiac output, systemic and pulmonary arterial pressures and resistances) were measured simultaneously in both animals. In only three experiments was lung compliance measured in both sheep; in the remaining experiments it was determined only in the recipient (A).

Periodic forced inflation of the lung (with a pressure of 30 mm Hg) was done for two reasons: first, to prevent progressive spontaneous fall in lung compliance which occurs in anesthetized animals and second, to test the reversibility of any compliance fall produced by some other stimulus. For example, opening of the anastomotic flow caused a fall in lung compliance even in animals with identical blood groups. We realized only during the course of these experiments that this was reversible by inflation. From then on (in the blood clot series) we invariably inflated the lung after opening the anastomosis. This accounts for the absence of a compliance fall during this period in the blood clot series in contrast to the small fall observed in the barium sulfate experiments. The lung was also inflated prior to the first control measurement and following the postembolic termination of cross circulation.

Results

BARIUM SULFATE EMBOLISM

Following introduction of barium sulfate emboli into the donor (B) there was in the donor (B) sheep a significant rise in pulmonary artery pressure, virtually no change in cardiac output and systemic arterial pressure, and a marked fall in lung compliance and hyperventilation. These direct effects of barium sulfate embolism were in agreement with previous findings.1

With the cross circulation open significant changes occurred simultaneously in the recipient (A) animal consisting of an immediate rise in pulmonary arterial pressure and intrapleural pressure swing as shown in figure 1. Pulmonary arterial wedge pressure (recorded in two experiments) showed a rise of 3 mm Hg in one and no change in the other. Systemic

*) Oro Company, Monroe, North Carolina.
Simultaneous recording of direct (B) and transmitted (A) effects of pulmonary embolism in two sheep connected via a unilateral carotid-jugular anastomosis. B = donor, A = recipient. At arrow 0.08 ml/kg of a 33 volume per cent barium sulfate emulsion was injected into donor (B). P_{p.a.} = pulmonary artery pressure; P_{f.a.} = femoral artery pressure; Δ P_{pl.} = intrapleural pressure swing. P_{p.a.} in B = right ventricular pressure. Right ventricular pressure rise in B commenced 10 seconds after embolism; pulmonary artery pressure rise in A occurred 12 seconds later.
arterial pressure remained virtually unchanged. At five minutes pulmonary arterial pressure was still significantly elevated and lung compliance was significantly reduced.

After the cross circulation had been interrupted and the lung inflated, lung compliance and pulmonary arterial pressure returned to normal in the recipient (A); only slight improvement occurred in the donor (B).

Simultaneous changes occurring in the donor (B) and in the recipient (A) animals during one representative experiment are shown in Figure 2.

![Figure 2](image_url)

**Figure 2**

Direct (B) and transmitted (A) effects of barium sulfate lung embolism as observed in one representative experiment. Simultaneous changes in donor (B) and recipient (A).
TABLE 1

Humorally Transmitted Effects of Lung Embolism: Changes in Recipient (A) Following Barium Sulfate Injection into Donor (B)

<table>
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</table>

Control (first) = control period, animals unconnected; anast. = anastomotic flow opened; emb. = blood clot embolism in donor (B) sheep; control (last) = anastomotic blood flow closed, lungs inflated.

* Difference from preceding value statistically significant (P < 0.05).
in figure 2. Detailed results are shown in table 1.

**BLOOD CLOT EMBOLISM**

The direct effects of blood clot embolism in the donor (B) were similar to those described for barium sulfate embolization.

With the cross circulation open the simultaneous changes in the recipient (A) sheep were less marked and less abrupt than in the barium sulfate group. There was only a small increase in pulmonary arterial pressure and the rise in the intrapleural pressure swing, though similar in magnitude, was somewhat more gradual. At five minutes the only significant changes in the recipient were a fall in lung compliance and hyperventilation; the average rise in pulmonary arterial pressure was not significant.

 Interruption of the cross circulation and inflation of the lung resulted in a decrease in ventilation in four out of five experiments and a rise in lung compliance in all animals. At the same time there was only a slight improvement in the donor (B).

Details of these results are shown in table 2.

**Discussion**

The experiments demonstrate that blood from a donor subjected to barium sulfate embolism of the lung produced in a recipient animal rise in pulmonary arterial pressure and a fall in lung compliance. Blood from donors subjected to blood clot embolism produced smaller and more variable changes in the pulmonary circulation and a similar fall in lung compliance.

The effect on the recipient is probably the result of some blood-borne agent since it has been shown previously that barium sulfate is completely retained by the lung; the size of the injected blood clots would automatically exclude passage through the lung capillaries.

The interpretation of the changes in the pulmonary circulation is rendered difficult in the present preparation in view of the fact that flow from the cross circulation amounted to 10 to 15% of the cardiac output. Under these conditions 350 to 650 ml of blood were transferred from the donor to the recipient and vice versa. During steady conditions the application of the Fick principle to the estimate of cardiac output is valid but under conditions in which the anastomotic flow changes problems of application of the Fick principle would arise. In these experiments there was no major change in the systemic arterial pressure, cross flow, oxygen uptake, and arteriovenous oxygen difference five minutes after lung embolism in the donor. It also appears unlikely that there were significant transient changes during the embolization procedure. Whilst some reservation must be entertained regarding the interpretation of the cardiac output values it is likely that the application of the Fick principle is valid in the present experiments. It is probable that the rise in pulmonary arterial pressure in the recipient following barium sulfate lung embolism in the donor was produced by pulmonary vasoconstriction mediated by a blood-borne agent.

The equivocal nature of the pulmonary arterial pressure rise in the recipient following blood clot lung embolism in the donor is consistent with findings reported by Dexter et al. They observed an inverse relationship between the functional components of lung embolism-induced pulmonary hypertension and the particle size of the embolic material. However, their technique was different from ours in one important aspect. In order to simulate the suddenness of clinical lung embolism we injected the embolic material rapidly within 5 to 10 seconds; they preferred gradual “saturation” of the pulmonary vascular bed by injecting their material over an average period of 15 minutes. In our experience speed of administration considerably affects the severity of the response.

The degree of transmitted pulmonary hypertension was trivial in these experiments. However, these changes were produced by only that quantity of the postulated humoral agent which was carried by about 10% of the directly affected animal’s cardiac output. The much greater effect on the pulmonary circulation of the donor is probably due to the
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direct obstruction by the embolic material which is added to the effect of this humoral agent.

It is probable that the terminal airway closure was produced by the constriction of strategically situated muscle rings.\textsuperscript{1} 6, 8, 23 This was responsible for the transmitted fall in lung compliance which was identical after both types of lung embolism. This in turn seems sufficient to account for the increase in ventilation observed in these experiments.

The release of a humoral agent as a contributing factor in the mechanism of lung embolism-induced cardiorespiratory distress has been repeatedly suggested in the past\textsuperscript{12--24} but no definitive experiments exist to identify the active principle. The present experiments show, however, that release of the postulated humoral agent is an evanescent phenomenon, occurring only in the first few seconds after embolism; reopening of the cross circulation some time after the embolic episode never produced transmitted changes. In addition, the transmitted changes were short-lived and readily reversible, thus suggesting that the active material may be rapidly inactivated. These characteristics seem to be consistent with the virtual absence of functional changes in experiments\textsuperscript{11} where pulmonary vascular occlusion is gradual instead of rapid as in the present experiments.

Summary

Pairs of sheep were connected via a unilateral carotid-jugular anastomosis in fourteen experiments. With the cross circulation open, pulmonary embolism induced in the donor sheep produced a rise in pulmonary arterial pressure, a fall in lung compliance, and an increase in ventilation in the recipient animal. The transmitted effects were more pronounced with barium sulfate lung embolism than with blood clot lung embolism.

These observations are consistent with the assumption that in acute experimental lung embolism a humoral agent is being released causing constriction of the lung vessels and airways.

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