Pulmonary Capillary Permeability in the Post-Traumatic Pulmonary Insufficiency Syndrome:

Comparison of Isogravimetric Capillary Pressures

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THE *post-traumatic lung syndrome* has become a distinct entity as more patients are resuscitated from traumatic shock.[11] As a result, the syndrome has interested both clinical and basic investigators. Shock and large transfusions of blood and crystalloid solutions have been described in most cases of this syndrome of pulmonary insufficiency. Histologically, it is characterized by interstitial and alveolar edema and inflammation.

The mechanism whereby the lung reacts to form edema while the extremities and visceral organs do not is unknown. Various hemodynamic and humoral theses have been advanced but the pathophysiology remains unclear. In the course of studying the effect of drugs on the capillary membrane of shocked dogs, we have noted the pulmonary capillaries have a greater permeability than capillaries of the extremities or visceral organs.

Methods

Pappenheimer and Soto-Rivera[9] described a method to measure the isogravimetric capillary permeability of an isolated forelimb. This has also been studied by Soloman.[12] Johnson[6] used the technic to study the small intestine and Harrison[4] and Gaar[3] and associates studied the lung.

Forelimb Preparation. Ten adult mongrel dogs of either sex weighing between 22.4 and 28.6 Kg. were anesthesized to the level of the corneal reflex with sodium pentobarbital. One forelimb was surgically isolated from each dog according to the method of Pappenheimer and Soto-Rivera using double ligatures and electrocautery. All cutaneous bleeding was stopped and the opening of the severed bone was sealed with bone wax. All nerves were severed and the brachial artery and vein dissected free for several centimeters. All other veins were ligated. After intravenous heparinization (5 mg./Kg.) the brachial artery to the forelimb was cannulated with polyethylene tubing which extended through a Sigmamotor pump, connected at its proximal end with the femoral artery of the donor dog. The vein of the isolated forelimb was cannulated with polyethylene tubing leading to a reservoir placed in a constant temperature water bath. Blood was returned to the femoral vein of the donor dog from the reservoir by another Sigmamotor pump. The perfused forelimb was placed in a holder attached to a Wheatstone bridge weighing balance. Brachial artery and brachial vein pressures were monitored at the orifices of the vessels by means of needle-tipped catheters attached to Statham pres-

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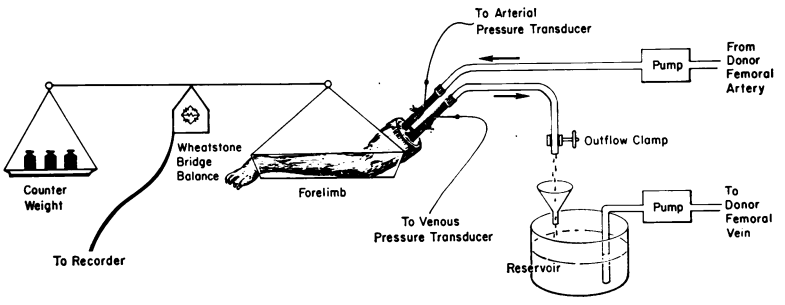

FIG. 1. Diagram of isogravimetric forelimb preparation. When arterial inflow is decreased, venous pressure is increased by tightening the outflow clamp to produce an isogravimetric state.

sure transducers (Fig. 1). All pressures and changes in leg weight from the weighing balance were recorded on a Sanborn four channel recorder. Forelimb blood flows were measured with cylinder and stopwatch and the initial flow rates adjusted to the highest values at which the leg remained in the isogravimetric state. Following a period of equilibration, a series of points was taken in which venous pressures were varied over a wide range by adjusting a screw clamp on the end of the venous line. Each set of values was established during a period of about three to five minutes during which the foreleg weight remained constant. To obtain the various points the arterial inflow was varied and brachial vein pressures adjusted so that limb weight remained constant. Isogravimetric venous pressures were thus obtained at various blood flow values to the foreleg.

A graph was then constructed with venous pressure (mm. Hg) as the ordinate and flow (cc./min.) the abscissa. A straight line function with a negative slope was obtained and the crossing of the ordinate represents the venous pressure at zero flow. The extrapolated venous pressure at zero flow (Fig. 2) is an internal check on the final point taken at zero flow. In obtaining the final point, at equilibrium, a closed system exists across the artery, capillary and vein. The pressures in these three areas become equal as the arterial pressure decreases and the venous pressure increases. This final pressure in the closed system or at zero flow is the isogravimetric capillary pressure (P_{Ci}) which may be defined as the highest capillary pressure in which edema formation (weight gain) does not occur; that is, there is no net outward leak from the capillary.

Small Intestine Preparation. Another ten adult mongrel dogs of either sex weighing between 22.8 and 31.2 Kg. were anesthesized as in the previous group. Laparotomy was performed and a 20 cm. length of distal ileum was isolated using double ligatures and electrocautery. All small bleeding points were carefully controlled. The main artery and vein leading to the bowel segment were left intact and after intravenous heparinization (5 mg./Kg.) these vessels were cannulated with polyethylene tubing. The artery was connected at its proximal end through a Sigmamotor pump with the femoral artery of the donor dog (Fig. 3). The vein of the isolated gut segment led to a reservoir in a constant temperature water bath. Blood returned to the femoral vein of the donor dog from the reservoir by another Sigmamotor pump. The perfused gut was placed in a plastic

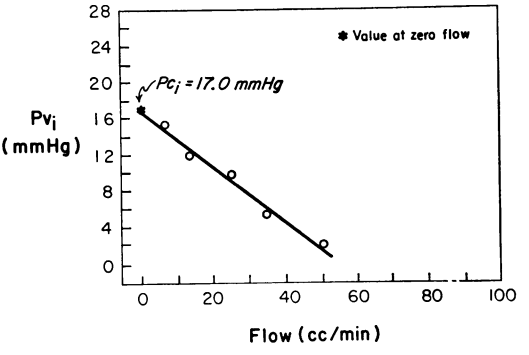

FIG. 2. Single forelimb experiment showing relationship between isogravimetric venous pressure (P_{Vi}) and leg blood flow.

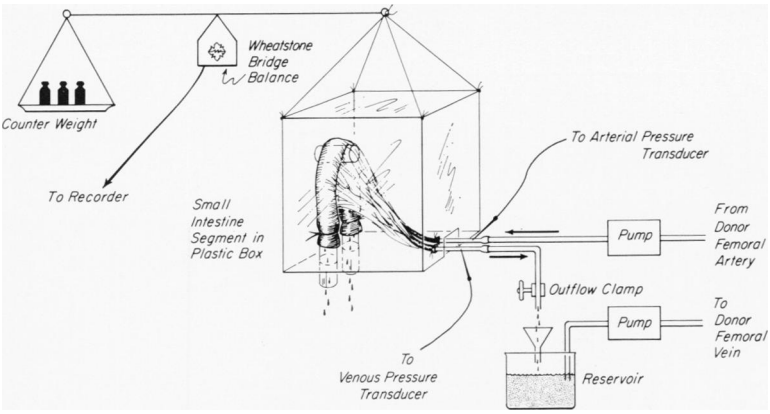

FIG. 3. Diagram of isogravimetric small intestine preparation. Intestinal secretions drain from the lumen through tubes out of the plastic box. Arterial inflow and venous pressure are altered as with the forelimb.

box to avoid drying. Intestinal secretions were led through the bottom of the plastic box via large plastic tubes placed in the ends of the bowel to avoid collection of fluid. The plastic box with the perfused gut segment was attached to a Wheatstone bridge weighing balance. Arterial and venous pressures were monitored at the orifices of the vessels by means of needle tipped catheters attached to Statham pressure transducers. All measurements were obtained as with the forelimb studies (Fig. 4).

Lung Preparation. Thoracotomy was performed on another ten adult mongrel dogs of either sex weighing 24.2 to 29.9 Kg. after anesthesia with sodium pentobarbital. After heparinization (5 mg./Kg.) the lower lobe of the left lung was excised and polyethylene cannulas were inserted into the pulmonary artery and vein and bronchus. The lobe was covered with a plastic bag to prevent drying and supported from a Wheatstone bridge weighing balance (Fig. 5). Pulmonary artery and vein pressures were monitored at the orifices of the vessels by means of needle-tipped catheters attached to Statham pressure transducers with the reference point being the level of the pulmonary vein. Blood flowed into the pulmonary artery from the femoral vein of the donor dog and into a reservoir from the pulmonary vein. The reservoir blood was directed into the inferior vena cava. Ventilation of the lobe was by respiration with ambient air at 4 cc./Gm. lung at 15 cycles per minute. Pulmonary arterial and venous pH, P_{O_2} and P_{CO_2} were measured in some preparations. Flow and venous pressures were determined as for the forelimb and small intestine (Fig. 6).

Results

The mean isogravimetric capillary pressures for the forelimb, small intestine and lung are listed in Table 1. Although the mean values for the isogravimetric capillary pressure (P_{Ci}) of the forelimb and small intestine are quite similar, being 16.0 and 15.4 mm. Hg, respectively, the mean lung P_{Ci} is markedly lower at 7.6 mm. Hg.

Discussion

Fluid overload following intravenous infusions of crystalloids or blood in acutely

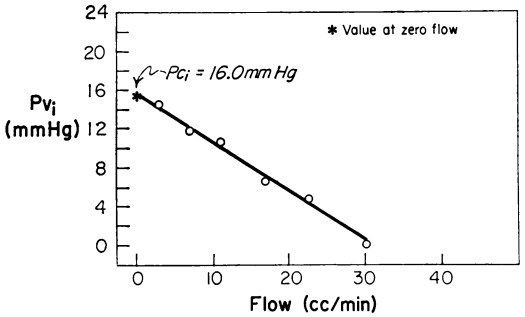

FIG. 4. Single small intestine experiment showing relationship between isogravimetric venous pressure (P_{VI}) and gut segment blood flow.

TABLE 1. *Isogravimetric Capillary Pressures* (P_{Ci})

Organ	P_{Ci} (mm. Hg) Mean ± SE
Forelimb	16.0 ± 0.8
Small Intestine	15.4 ± 2.4
Lung	7.6 ± 0.6

ill or shocked patients commonly precedes the onset of the *post-traumatic pulmonary insufficiency syndrome.* Cook and Webb,[2] with a hemorrhagic shock model, found an increased pulmonary artery pressure and increased pulmonary resistance associated with an increased relative volume of blood in the lungs after bleeding. They concluded pulmonary venous constriction was a response to hemorrhage resulting in pulmonary congestion. Veith and coworkers [14] concluded pulmonary arteriolar constriction was the response to hypotension, foreign blood and cardiopulmonary bypass. Nahas *et al.*[8] believe the graft versus host reaction may also play a part in the pulmonary reaction following cardiopulmonary bypass. Mobilization of fat has also been suggested as a cause for the pulmonary insufficiency and Pomerantz [10] has demonstrated the deleterious effects of oleic acid on a perfused lung preparation to support this theory.

Oxygen toxicity has been implicated in the post-traumatic pulmonary insufficiency syndrome and most patients suffering this deficiency have been inspiring high percentages of oxygen by mask or via tracheal intubation. Decreased dehydrogenase activity [5] and surface tension alterations [7] can occur with increased oxygen tensions. Caldwell [1] has shown a decrease in both vital capacity and diffusing capacity in human subjects breathing 100% oxygen for just a few hours.

Although bacterial infection almost always plays a role in the final stages of the syndrome, it is probably not the initiating factor, unless aspiration was an initial event.

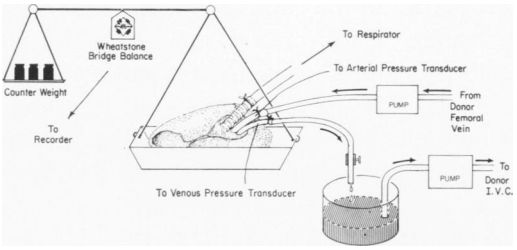

FIG. 5. Diagram of isogravimetric lung preparation. The lower lobe is ventilated throughout the experiment. Pulmonary artery inflow is from femoral vein of donor dog. Arterial inflow and venous pressure are altered as with the forelimb and small intestine.

In this study, we found that the pulmonary vascular bed has a greater permeability across its capillary membrane than other organs as shown by measurements of the isogravimetric capillary pressure (P_{Ci}). The P_{Ci} may be defined as the highest pressure at which edema formation does not occur and was examined using isolated organ systems. This experiment is, of course, subject to the disadvantages of a denervated preparation. Nonetheless, the three organs were examined in similar fashion and the results of the P_{Ci}'s agree with those obtained by other workers.[4, 6, 12]

Starling [13] described the factors influencing transcapillary fluid exchange: 1) the difference in hydrostatic pressure across the capillary membrane; 2) the difference in the protein osmotic pressure in the intravascular and interstitial space; and 3) the

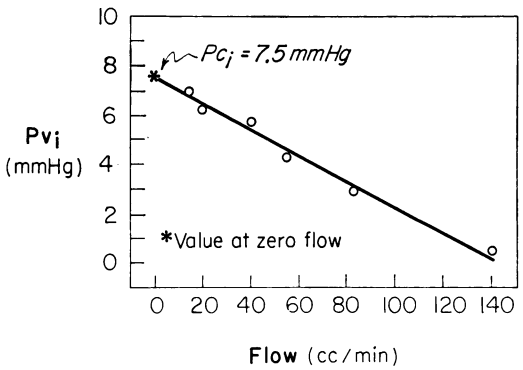

FIG. 6. Single lung (lower lobe) experiment showing relationship between isogravimetric venous pressure (P_{Vi}) and lobe blood flow.

properties of the capillary membrane which influence fluid transfer. Since the hydrostatic pressure across the pulmonary capillary bed in this experimental procedure could not be elevated as high as for the other organs studied, one can conclude the "effective osmotic pressure" (consisting of factors 2 and 3 of Starling's law) is lower in the lung.

These data indicate that with alterations in osmotic pressure (as could be brought about by the administration of large fluid volumes) the lung would have a greater propensity to leak fluid into interstitial spaces even without damage to capillary membranes. Alterations in precapillary and postcapillary sphincter tone, as have been described following hypotension, blood transfusion or cardiopulmonary bypass would accentuate this transcapillary fluid movement into the interstitium.

We believe these findings constitute a possible mechanism contributing to the development of interstitial pulmonary edema seen in patients treated with large volumes of parenteral fluid who do not develop edema in other organs. These findings also indicate further caution in the indiscriminate use of fluids in resuscitation.

Summary

We studied the isogravimetric capillary pressure (P_{Ci}) of the forelimb, small intestine, and lung of the dog.

2. The mean P_{Ci}'s of the forelimb and small intestine were 16.0 mm. Hg and 15.4 mm. Hg, respectively, while that of the lung was much lower, 7.6 mm. Hg.

3. The P_{Ci} is defined as the highest pressure at which edema formation does not occur and has an inverse relation to capillary permeability.

4. These data indicate the lung has a greater propensity to leak fluid into the interstitial space than the intestine or forelimb even without damage to its capillary membrane. Decreases in colloid osmotic pressure with administration of large fluid volumes could accentuate transcapillary fluid movement resulting in interstitial pulmonary edema.

References

1. Caldwell, P. R. B., Giammona, S. T. and Lee, W. L., Jr.: Changes in Lung Volume, Diffusing Capacity, and Blood Gases in Men Breathing Oxygen. Ann. N. Y. Acad. Sci., 121:823, 1965.
2. Cook, William A. and Webb, Watts R.: Pulmonary Changes in Hemorrhagic Shock. Surgery, 64:85, 1968.
3. Gaar, K. A., Jr., Taylor, A. E., Owens, L. J. and Guyton, A. C.: Pulmonary Capillary Pressure and Filtration Coefficient in the Isolated Perfused Lung. Amer. J. Physiol., 213:910, 1967.
4. Harrison, L. H., Beller, J. J., Hinshaw, L. B., Coalson, J. J. and Greenfield, L. H.: Effects of Endotoxin on Pulmonary Capillary Permeability, Ultrastructure and Surfactant. Surg. Gynec. Obstet., 129:723, 1969.
5. Jamieson, D. and Van den Brenk, H. A. S.: Pulmonary Damage Due to High Pressure Oxygen Breathing in Rats 2. Changes in Dehydrogenase Activity of Rat Lung. Aust. J. Exp. Biol. Med. Sci., 40:51, 1962.
6. Johnson, Paul C. and Hansen, Kenneth M.: Effect of Arterial Pressure on Arterial and Venous Resistance of Intestine. J. Appl. Physiol., 17:503, 1962.
7. Morgan, T. E., Finley, T. M., Huber, G. L. and Fialkow, H.: The Pulmonary Toxicity of Oxygen. J. Clin. Invest., 44:1737, 1965.
8. Nahas, Roger A., Melrose, Denis G., Sykes, M. Keith and Robinson, Branwen: Postperfusion Lung Syndrome: Role of Homologous Blood. Lancet, 2:251, 1965.
9. Pappenheimer, J. R. and Soto-Rivera, A.: Effective Osmotic Pressure on the Plasma Proteins and Other Quantities Associated with the Capillary Circulation in the Hind Limbs of Cats and Dogs. Amer. J. Physiol., 153:471, 1948.
10. Pomerantz, M. and Eiseman, B.: Experimental Shock Lung Model. J. Trauma, 8:782, 1968.
11. Simmons, Richard L., Heistercamp, Charles A., Collins, John A., Bredenberg, Carl E., Mills, Douglas E. and Martin, Arthur M.: Respiratory Insufficiency in Combat Casualties: IV. Hypoxemia During Convalescence. Ann. Surg., 170:53, 1969.
12. Solomon, L. A. and Hinshaw, L. B.: Effect of Endotoxin on the Isogravimetric Capillary Pressure in the Forelimb. Amer. J. Physiol., 214:443, 1968.
13. Starling, E. H.: On the Absorption of Fluids from Connective Tissue Space. J. Physiol., 19:312, London, 1896.
14. Veith, Frank J., Hagstrom, Jack W. C., Panossian, Alexander, Nehlsen, Sandra L. and Wilson, James W.: Pulmonary Microcirculatory Response to Shock Transfusion and Pump-oxygenation Procedures: A Unified Mechanism Underlying Pulmonary Change. Surgery, 64:95, 1968.