Interaction of Capillary and Tissue Forces in the Cat Small Intestine

NICHOLAS A. MORTILLARO, PH.D., AND AUBREY E. TAYLOR, PH.D.

SUMMARY We measured steady state capillary hydrostatic pressure ($P_C$), plasma and lymph protein concentrations, lymph and blood flow, and capillary filtration coefficients in an in situ loop of cat small intestine at venous outflow pressures ($P_v$) of 0, 5, 10, 15, 20, 25, and 30 mm Hg. The data were used to calculate colloidal osmotic pressure of lymph and plasma, interstitial fluid pressure ($P_T$), pre- and postcapillary resistances, and a tissue pressure-volume curve of the intestinal interstitium. When $P_v$ was elevated from 0 to 30 mm Hg, lymph protein concentration decreased from 3.8 to 1.7 g/100 ml (representing a change in colloid osmotic pressure of 4.2 mm Hg), lymph flow increased 7-fold (or an equivalent imbalance in Starling forces of 4.3 mm Hg), and the calculated $P_T$ increased from -1.7 to +5.3. Because lymph flow draining the loop decreased during the determination of $P_C$, at venous pressures between 15 and 30 mm Hg, the corresponding calculated $P_T$ may be in error by 1-2 mm Hg. The tissue pressure-volume relationship calculated from the data indicates that the intestinal interstitial volume expands nonlinearly and this expansion is characterized by two distinctly different compliant components: (1) tissue compliance is low at $P_v$ between 0 and 15 mm Hg (0.4 ml/mm Hg), and (2) at $P_v$ greater than 15 mm Hg the tissue compliance is relatively high (4 ml/mm Hg). We found that when $P_v$ was elevated from 0 to 15 mm Hg, increases in $P_T$ are the major tissue adjustments that oppose the increased filtration pressures. Furthermore, at $P_v$ of 20-30 mm Hg, tissue protein concentration decreases, lymph flow relative to the filtration coefficient ($\Delta P_{\text{m,op}}$) increases, and, to a much lesser extent, $P_T$ increases. Finally, the combination of these changes in tissue force at high filtration pressures represent a maximum tissue edema “safety factor” of 10 mm Hg; further increases in filtration pressures result in large volume movements into the intestinal lumen.

STARYLING PROPOSED, in 1896, that the rate and direction of fluid exchange across the capillary membrane was a function of the capillary hydrostatic pressure ($P_C$) and the plasma colloidal osmotic pressure ($\pi_{PL}$). $P_C$ determined filtration and $\pi_{PL}$ was responsible for absorption. Starling's concept was later extended to include the hydrostatic pressure ($P_C$) and colloidal osmotic pressure ($\pi_T$) of the interstitium, the pressure head driving the lymph (effective capillary filtration pressure ($\Delta P_{\text{m,op}}$)), and the physical properties of the capillary membrane. Under normal conditions these forces are in a steady state with a small net filtration resulting in a low resting lymph flow. When this steady state is disturbed, an increase in net filtration or absorption is observed, and over a period of time the capillary bed and tissue spaces attain a new steady state in which the tissue is not gaining or losing weight. This new steady state is achieved by the readjustment of the Starling forces in a direction to oppose the increases in filtration or absorption forces.

Pappenheimer and Soto-Rivera indirectly measured the tissue forces, tissue colloidal osmotic pressure, and tissue fluid pressure in an isolated hindlimb preparation. They found that the isogravimetric pressure, which is equal to the sum of the other Starling forces, $\pi_{PL}$, $\pi_T$, and $P_C$, was equal to $\pi_{PL} - 2$ (mm Hg); this finding indicates that $P_C$ and $\pi_T$ were very small in their preparation. Any major increase in capillary pressure would result in continuous filtration into the interstitium without any apparent adjustment of Starling forces to oppose filtration. In fact, these authors used the...
continuous filtration phase of weight gain curves to characterize the filtration properties of the capillary membrane.

Johnson and Hanson measured the isogravimetric capillary pressure in an isolated intestinal preparation and found that it was approximately equal to \( \pi_{RL} - 7.4 \text{ (mm Hg)} \), at a normal venous outflow pressure. The relatively low intestinal isogravimetric capillary pressure was interpreted by the authors to reflect a normally high interstitial colloid osmotic pressure, but recent developments indicate that a negative interstitial fluid pressure also might explain their findings. Also, in the absence of lymphatic drainage, tissue colloid osmotic pressure could become elevated because of protein leakage into the interstitium, and this would result in a small isogravimetric pressure.

Because of the large difference between isogravimetric capillary hydrostatic pressure and \( \pi_{PL} \), intestinal preparations will attain isogravimetric states at several venous outflow pressures, e.g., 0, 5, 10, and 18 mm Hg. Using an indirect method, concluded that interstitial fluid pressure changes constitute the major tissue force adjustment that opposes the increased capillary hydrostatic pressure caused by elevating venous pressures. However, Johnson suggested that interstitial proteins were decreased as a result of dilution of tissue proteins by a protein-poor capillary filtrate, and this resulted in a reduced interstitial colloid osmotic pressure. The proposal that reduced tissue colloid osmotic pressure was the major compensatory change in the tissues was further strengthened by the observation that interstitial fluid pressure, measured by inserting a needle directly into the tissues, remained essentially unchanged over a wide range of capillary hydrostatic pressures. One major difficulty in attempting to resolve this controversy is that in the isogravimetric studies mentioned above there was no lymph flow draining the preparations; this could markedly effect the experimental results.

In an attempt to settle this controversy, the following experiments were designed either to measure or calculate, in an in situ intestinal preparation with intact lymph flow, the relative interaction of the forces involved in the Starling equilibrium at the capillary-tissue interfaces that resulted from sustained increases in venous outflow pressure. We have measured simultaneously for each intestinal preparation: isovolumetric capillary hydrostatic pressure, plasma and lymph protein concentration, both lymph and blood flow, arterial and venous outflow pressure, the capillary filtration coefficient, and changes in tissue fluid volume as venous outflow pressures were elevated from 0 to 5, 10, 15, 20, or 30 mm Hg. It should be emphasized that intestinal preparations used yield information only in terms of changes in the overall intestinal parameters measured or calculated (average or functional tissue and capillary parameters) and do not allow interpretations of the direction or magnitude (or both) of changes in the Starling forces of each individual tissue compartment of the intestine such as mucosa, muscularis, etc.

**Methods**

**SURGICAL PROCEDURE**

Female cats weighing 2–3 kg were anesthetized with sodium pentobarbital, intraperitoneally (ip), 30 mg/kg; supplementary doses were given intravenously (iv) as required. Each cat was partially fasted (as explained under Determination of Lymph Flow) for a period of 24 hours prior to the experiment. A tracheal cannula was inserted. The greater omentum, spleen, stomach, large intestine, and most of the small intestine were surgically extirpated through a midline abdominal incision. A loop of ileum weighing 10–30 g and with intact innervation and lymphatic drainage was isolated and autoperfused by the intact mesenteric artery. The cat's body temperature was monitored with a glass thermometer inserted orally and maintained at 37°C by a heating pad placed beneath the cat. In addition, an overhead heating lamp also was used to maintain a constant body temperature. All exposed tissue was moistened with saline-soaked gauze and covered with a plastic sheet. Atropine, 1 mg/kg, and heparin, 200 USP/kg, were administered iv.

**DETERMINATION OF BLOOD FLOW**

A large cannula was inserted into the superior mesenteric vein and the venous outflow was passed through a silicone (Dow Corning 200), fluid-filled drop chamber onto which was mounted a photoelectric cell (Fig. 1). The signal from the cell was used to drive an impulse flowmeter. After passage through the drop chamber, blood was returned to the cat by a cannula inserted into the right external jugular vein. Heparinized blood from a donor cat killed just before the transfusion was used to fill all tubing of the extra-corpooreal blood flow circuit. Also, additional blood was added to the system in order to maintain the cat's arterial pressure, which at times was susceptible to changes resulting from blood losses during the course of the experimental procedure.

![Diagram illustrating the experimental arrangement used to continuously measure intestinal blood and lymph flows, changes in intestinal volume, systemic arterial pressure, and intestinal venous outflow pressure.](http://circres.ahajournals.org/)

**Figure 1**
DETERMINATION OF LYMPH FLOW

Visual identification of the lymphatic vessels of the intestine was made possible by feeding the cats a mixture of milk and cream at approximately 6 to 12 hours before surgery. This procedure had the advantage of clearly marking the large downstream lymphatic vessels found in the mesenteric pedicle and thereby facilitating their cannulation. With the aid of a dissecting microscope a cannula was inserted into the large lymphatic vessel emerging from the mesenteric pedicle. Entrance into the vessel was made at a point between the pedicle and the site where the vessel drained into the superior mesenteric lymph node. The determination of lymph flow was made by allowing lymph to flow out through the cannula and into a calibrated pipette (1 ml, full scale). The pipette was positioned horizontally and at the level of the intestinal segment under study. Because the greater part of the small intestine had been removed, we believe that the lymph flow measured in this manner reflects near-total lymph flow from the ileal segment.

DETERMINATION OF ARTERIAL AND VENOUS OUTFLOW PRESSURE

Arterial pressure was obtained from a cannula inserted into a femoral artery and measured by a Statham transducer (P23Ac). Large vein pressure in the intestinal loop was measured through a T-connector inserted into the venous outflow circuit immediately distal to the superior mesenteric vein. The T-connector and associated pressure transducer (Statham P23Bc) were positioned at heart level. The desired large vein pressure of the intestine was set by adjusting the height of the drop chamber.

DETERMINATION OF CHANGES IN INTESTINAL VOLUME

The intact intestinal loop was placed in a triangular Lucite plethysmograph. The mesenteric pedicle was passed through a closely fitting opening at the proximal end of the plethysmograph. The opening was sealed with a plasticized hydrocarbon gel (Plastibase, Squibb), and a cover was placed over the top and firmly attached to the base. A rubber gasket placed between the cover and base ensured that a proper seal was achieved. Extreme care was taken to avoid compression of the mesenteric pedicle because this would disturb the blood and lymph flow draining the enclosed ileal segment. The sealed plethysmograph was connected with a short length of Tygon tubing to a Lucite reservoir of large radius. The reservoir had a large diameter so that no excessive back pressure would build up during elevations of venous pressure (A.H. Goodman, unpublished observations). The reservoir was suspended from a precalibrated force-displacement transducer (Grass, FT 10C); both the reservoir and the plethysmograph were filled with Tyrode's solution and positioned at heart level of the supine cat. In several experiments, when intestinal loops were to be subjected to venous pressures of 25 mm Hg or more, the ends of the intestinal loop were mounted on inlet ports located on each side of the plethysmograph. This procedure allowed secretory fluids to drain out of the intestinal lumen, thereby avoiding the accumulation of such fluid, which could influence the measurement of tissue volume.

DETERMINATION OF CAPILLARY FILTRATION COEFFICIENT

Johnson and Hanson⁵ used the isogravimetric technique to study changes in blood volume in the dog intestine during perturbations in venous outflow pressure and plotted the recorded weight changes against time on a semilogarithmic scale. They found the resulting curve to have two distinct slopes, an initial rapid phase followed by a more prolonged slow phase. The rapid phase was interpreted to be due to venous disention, and the slower, more prolonged phase corresponded to capillary filtration. Wallentin⁶ used an isotope method to determine changes in blood volume and reported similar findings. In our present study we determined the capillary filtration coefficient by measuring the slope of the volume gain during the initial 30 seconds of the slow phase; this gave a value for the initial filtration rate per 100 g of tissue. Dividing this by the changes in capillary hydrostatic pressure yields a value for the capillary filtration coefficient. The change in capillary pressure was calculated from the data obtained during determination of mean hydrostatic capillary pressure (see below).

DETERMINATION OF MEAN HYDROSTATIC CAPILLARY PRESSURE

Mean capillary hydrostatic pressure was determined by the zero-flow isovolumetric method, a modification of the zero-flow isogravimetric method previously used by Johnson and Hanson.⁸ After an isovolumetric state at the desired venous outflow pressure had been established, flow into the intestinal segment was occluded by a clamp placed around the superior mesenteric artery. The drop chamber then was raised to a height at which the organ was neither losing nor gaining volume. The venous outflow pressure, measured at the zero-flow isovolumetric state, was taken as the mean capillary hydrostatic pressure existing immediately prior to the arterial occlusion.

DETERMINATION OF PLASMA AND LYMPH COLLOID PRESSURES

Venous blood and lymph of the intestinal segment were sampled periodically. Protein concentration of both lymph and plasma was read directly from a refractometer (TS meter, American Optical). Values for protein concentration were converted to pressure (mm Hg) according to the cubic equation given by Landis and Pappenheimer.⁹ In a few earlier experiments colloid osmotic pressure was measured with the Prather type osmometer.¹⁰ The calculated values were not statistically different from that measured by the osmometer, and because of the close correlation between the two methods, plasma and lymph colloid osmotic pressure was determined solely by refractometry in all later experiments.

EXPERIMENTAL PROTOCOL

After extracorporeal venous blood and lymph flow had been established the intestinal loop was placed into the plethysmograph and the large vein outflow pressure was set at zero to establish a control measurement of each parameter (Fig. 2). The system was allowed to attain an isovolumetric state and lymph flow was measured by observing the...
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8 OD S O E 060 080 110 .150 .170 200 .210 .220 220 220 220 220 22 23 23 23 24 24 24 24.4 24.4 TT L (mmHg)

FIGURE 2: A: response of the cat intestine to a stepwise elevation in venous outflow pressure ($P_v$), shown here from 0 to 20 mm Hg. Intestinal volume change is biphasic, an initial rapid phase caused by an increase resulting from filtration reaching a new isovolumetric state at about 30 to 35 minutes. Closed circles indicate 5-minute intervals during which lymph flow was measured. At the end of each interval, samples of intestinal venous blood and lymph were taken and colloid osmotic pressure determined. B: results of zero-flow isovolumetric technique used to determine mean capillary hydrostatic pressure. $P_a$ = arterial pressure; $Q_b$ = blood flow.

Results

A summary of all measured and calculated steady state values of intestinal parameters obtained from the present study are given in Table 1. All values given within the text and Table 1 are the mean ± standard error of the mean.

MEAN CAPILLARY HYDROSTATIC PRESSURE ($P_c$)

At a preset venous outflow pressure of 0 mm Hg, the steady state mean capillary hydrostatic pressure, as determined by the zero-flow isovolumetric method, averaged 9.9 ± 0.3 mm Hg. Elevation of venous outflow pressure resulted in an increased capillary pressure, such that a venous outflow pressure of 30 mm Hg yielded a capillary pressure of 30.6 ± 0.4 mm Hg. A straight line estimate of the increase in capillary pressure determined by linear regression analysis yields a linear equation of $P_c = 9.3 + 0.69 P_v$. This finding indicates that 69% of the increment in venous pressure is transmitted to the capillary beds and is in agreement with earlier determinations of intestinal capillary pressure.

BLOOD FLOW ($Q_b$), PRECAPILLARY RESISTANCE ($R_a$), AND POSTCAPILLARY RESISTANCE ($R_v$)

Intestinal blood flow progressively decreased during elevations of venous outflow pressures from 0 up to and
Intestinal Parameters at Different Venous Outflow Pressures ($P_v$)

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Intestinal parameters

Calculated mean resistance values showed a progressive increase in precapillary resistance ($1.9 \times R_L$ at $P_v = 0$ mm Hg), along with a progressive decrease in postcapillary resistance ($0.013 \times R_C$ at $P_v = 0$ mm Hg) as $P_v$ was increased to 30 mm Hg. The overall result was an increase in total resistance of the intestinal vasculature at venous pressure of 30 mm Hg that was approximately 2-fold that measured at a venous pressure of 0 mm Hg. This increase in vascular resistance plus the decrease in pressure head between artery and vein resulted in a progressive decrease in blood flow over the range of venous outflow pressures.  

CAPILLARY FILTRATION COEFFICIENT ($K_{rc}$)

A decrease in mean capillary filtration coefficient was seen over the entire range of venous outflow pressure elevations. The incremental decrease in capillary filtration coefficient was greatest at low venous outflow pressures, whereas precapillary resistance changes were minimal. In contrast, greater changes in precapillary resistance occurred at high venous outflow pressures, whereas changes in the capillary filtration coefficient were minimal. For example, a change in venous outflow pressure from 5 to 10 mm Hg decreased the capillary filtration coefficient by 0.156 ml/min per mm Hg per 100 g, whereas precapillary resistance increased by 0.3 mm Hg/(ml/min) per 100 g. As venous outflow pressure was increased from 20 to 25 mm Hg the calculated capillary filtration coefficient decreased by only 0.025 ml/min per mm Hg per 100 g, whereas precapillary resistance increased by 1.1 mm Hg/(ml/min) per 100 g.

LYMPH FLOW ($Q_L$)

Mean steady state lymph flow progressively increased over the entire range of venous outflow pressures and appeared to approach a plateau value at the higher venous outflow pressures used in this study (25 and 30 mm Hg). Changes in lymph flow were minimal at the lower venous outflow pressures but a rapid change in lymph flow occurred over the entire range of venous pressures and appeared to approach a plateau value at the higher venous pressures, whereas changes in the capillary filtration coefficient were minimal. For example, a change in venous outflow pressure from 5 to 10 mm Hg decreased the capillary filtration coefficient by 0.156 ml/min per mm Hg per 100 g, whereas precapillary resistance increased by 0.3 mm Hg/(ml/min) per 100 g. As venous outflow pressure was increased from 20 to 25 mm Hg the calculated capillary filtration coefficient decreased by only 0.025 ml/min per mm Hg per 100 g, whereas precapillary resistance increased by 1.1 mm Hg/(ml/min) per 100 g.

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PLASMA ($\pi_{PL}$) AND LYMPH ($\pi_{L}$) COLLOID OSMOTIC PRESSURE

There was a small but steady increase in plasma colloid osmotic pressure over the entire range of venous outflow pressures that reached a maximum change of 3.2 mm Hg at a venous outflow pressure of 30 mm Hg. Lymph colloid osmotic pressure decreased by 6.2 mm Hg over the same venous outflow pressure range, indicating a significant reduction in tissue protein concentration.

INTERSTITIAL FLUID PRESSURE ($P_{I}$) AND TISSUE COMPLIANCE

Mean steady state interstitial fluid pressure was calculated at each different venous pressure level with the following equation, which assumes that the reflection coefficient of the plasma proteins = 1.0:

$$J_{V,c} = K_{F,c}(P_c + \pi_T - \pi_{PL} - P_T)(\text{ml/min per 100 g}) \quad (2)$$

where $J_{V,c}$ is the capillary filtrate. Assuming that the tissue colloid osmotic pressure can be equated to lymph colloid osmotic pressure, that is $\pi_T = \pi_{PL}$; and that during a steady state $J_{V,c} = \dot{Q}_L$. Equation 2 can be rearranged to yield the relationship between $P_T$, the Starling forces, and lymph flow.

$$P_T = (P_c + \pi_{PL} - \dot{Q}_L/K_{F,c}) \quad (mm \ Hg) \quad (3)$$

Calculated tissue pressure is -1.8 mm Hg at zero venous pressure and increases to +1.8 mm Hg at a venous outflow pressure of 10 mm Hg. The $P_T$ calculated at $P_c = 0$ may indicate dehydration of the tissues because of the low capillary pressure; therefore we believe that a value of 1 to +2 mm Hg is more representative of normal interstitial fluid pressure. At higher venous pressures, $P_T$ increases more slowly. This indicates that the compliance of the tissue (see Fig. 4B and Discussion) is not linear.

Discussion

CALCULATION OF EFFECTIVE CAPILLARY FILTRATION PRESSURE

The contribution of the lymphatic system to the regulation of interstitial volume is determined not only by its ability to remove proteins from the tissue spaces but also by how much fluid volume can be removed by the lymphatic system relative to the filtration coefficient of the filtering vessels. Renal physiologists have considered a parameter, similar to the lymph flow factor, to describe glomerular filtration forces and have termed this imbalance in Starling forces across the glomerulus as the effective glomerular pressure. We will use the term effective capillary filtration pressure ($\Delta P_{DROP}$) to discuss the same principle in the intestinal microcirculation—that is, the pressure imbalance in the Starling forces that causes fluid to filter across the exchange vessels and form lymph. If lymph flow is large and the filtration coefficient small, then the effective filtration pressure can be very significant. However, if the filtration coefficient is large (similar to those measured in our preparation at low venous pressures), then lymph flow must be quite large for any significant imbalance in Starling forces to exist across the capillary wall.

The following equation was used to calculate the effective capillary filtration pressure at each venous pressure for a condition of zero volume change in the isolated intestinal preparation:

$$\dot{Q}_L = J_{V,c} = K_{F,c}(-\Delta P_{DROP}). \quad (4)$$

or,

$$\Delta P_{DROP} = \dot{Q}_L/K_{F,c} \quad (5)$$

where $\dot{Q}_L$ is lymph flow and $J_{V,c}$ is capillary filtration which must be formed by pressure filtration. In calculating $\Delta P_{DROP}$ two parameters must be determined accurately: (1) The total lymph flow draining an organ must be measured. We believe that near-total lymph flow was collected in our preparation with no contributions from other beds because the intestinal segment was totally isolated and all remaining intestinal structures had been surgically removed. (2) $K_{F,c}$ must be determined for each lymph flow state. The measurement of $K_{F,c}$ has recently been criticized by Friedman, who contends that the $K_{F,c}$ measured by classic methods overestimates the true capillary filtration coefficient of the bed. Johnson and Hanson and Wallentin have demonstrated that the slow phase of either the weight or volume transient, seen after venous pressure elevation, represents filtration of fluid out of the capillaries into the interstitium. Johnson measured the concentration of plasma proteins in venous blood and related this to observed changes in organ weight, and Wallentin used radioisotopes to separate the vascular and filtration components of the weight gain curves. Both investigators found that, following venous pressure elevation, the rapid phase of the weight gain of an organ represents vascular filling and that the slow phase represents capillary filtration. Friedman has not applied his technique, one that consists of constantly monitoring colloid osmotic pressure of the venous outflow, to an isolated intestinal preparation.

There is no reason why his technique, if applied to an intestinal preparation, should yield results different from that of Johnson, since both approaches are very similar. Table 2 shows computed values for $\Delta P_{DROP}$ for various filtration coefficients. When the filtration coefficient is assumed to remain high, as shown in the first row of Table 2, then the imbalance in Starling forces can only be small. The last row in Table 2 shows calculated values for $\Delta P_{DROP}$ for a
small filtration coefficient that is actually equal to that calculated at a venous outflow pressure of 30 mm Hg (this would more closely represent the argument of overestimating \( K_{FC} \)). \( \Delta P_{DROP} \) is larger at the lower venous outflow pressures and becomes a significant force at \( P_v = 15 \) mm Hg. The diagonal arrangement of the boldface values represents data obtained from this study for which the calculated filtration coefficient decreased with increasing \( P_v \). An overestimation of \( K_{FC} \) causes a smaller calculated \( \Delta P_{DROP} \), and if the true value for \( K_{FC} \) were smaller, as argued by Friedman, this would only increase the magnitude of \( \Delta P_{DROP} \) at lower venous outflow pressures. In contrast, if \( K_{FC} \) were overestimated at all levels of \( P_v \), then lymph flow could be a much more important factor than indicated by our study. Even with the smallest \( K_{FC} \), \( \Delta P_{DROP} \) would not become large until venous outflow pressures are elevated to levels that substantially increase lymph flow.

The changes in the calculated \( \Delta P_{DROP} \) at higher venous outflow pressures demonstrates the importance of the myogenic reflex (Bayliss effect) in protecting the small intestine against sudden increases of venous outflow pressures. If the filtration coefficient remained high at increased venous pressures, then the lymphatics could not provide any significant safety factor and the intestine would become edematous even at the lower venous pressures. In fact, because decreases in \( K_{FC} \) occur at increased venous pressures, then \( \Delta P_{DROP} \) would increase even if lymph flow remained constant. The present data do not allow an evaluation of the problems associated with measuring \( K_{FC} \). However, we believe that published data strongly support Johnson's and Wallentin's concept that the measured \( K_{FC} \) does reflect the filtration coefficient of the perfused vascular bed of the small intestine with the following exceptions: Small errors might be associated with the calculation because filtration could occur during the early vascular filling phase also, or alternatively, vascular filling due to stress relaxation could occur during that portion of the weight gain curve at which \( K_{FC} \) values were measured. The maximum \( \Delta P_{DROP} \) measured in our preparation was only 4 mm Hg and occurred at a venous pressure of 30 mm Hg.

**CALCULATION OF FORCE IMBALANCE FOR EACH ISOVOLUMETRIC STATE**

Table 1 demonstrates for each isovolumetric state, that \( P_{C.i} \neq \pi_h \); therefore, a net imbalance of forces always exists across the capillary wall. This imbalance in force must be due to alterations in \( \pi_h \) or \( P_v \), or in both, since \( \Delta P_{DROP} \) is only 4 mm Hg at the highest venous pressures used in this study. Table 1 shows calculations of \( P_v \) using Equation 3. The calculated value of \( P_v \) is negative at \( P_v \) below about 7 mm Hg and increases to positive values at higher \( P_v \). This computation of \( P_v \) for our experimental preparation is complicated by two questions: (1) What happens to lymph flow during the isogravimetric measuring procedure? (2) Does lymph actually reflect tissue fluid protein concentrations?

Reference to Table 1 and Table 2 shows that the problems associated with measuring \( P_{C.i} \) cannot be significant at values of \( P_v \leq 15 \) mm Hg relative to lymph flow changes because \( \Delta P_{DROP} \leq 1 \) mm Hg. However, at values of \( P_v \) greater than 15, because \( \Delta P_{DROP} \) increases from about 1 to 4 mm Hg, if lymph flow changes during the isogravimetric determination of \( P_{C.i} \), then the calculated \( P_v \) will be in error.

For the data in Table 1, \( P_{C.i} \) was determined assuming that lymph flow was not altered by the experimental procedure. Because this could constitute a problem when determining \( P_{C.i} \), another series of intestinal preparations was investigated and lymph flow was determined during the 10-minute interval after clamping the arterial inflow and elevating \( P_v \). Figure 3 demonstrates the effect on measured lymph flow of determining \( P_{C.i} \) by zero-flow procedures. At \( P_v = 30 \) mm Hg, lymph flow decreased to about ½ the steady state values during the zero-flow procedure, and a similar result was observed at \( P_v = 25 \) mm Hg. However, at \( P_v = 20 \) mm Hg, lymph flow fell very dramatically during the first minute and approached a value of zero after 3 minutes. At \( P_v = 15 \), lymph flow would sometimes decrease to zero immediately after the determination of \( P_{C.i} \). Similar results were obtained at the same venous pressures in seven other intestinal preparations. Why lymph flow decreases or ceases during the measurement of \( P_{C.i} \) is unclear at the present time; perhaps arterial pulsations are necessary for...
maximum lymph propulsion. Whatever the reason, the error is not great and amounts maximally to only 2 mm Hg at \( P_V \) = 20, 25, and 30 mm Hg. Since \( \Delta P_{DROP} \) is small at \( P_V \) < 20 mm Hg, then even with cessation of lymph flow, a calculation of force balance in this pressure range is not in serious error. However, for any preparation with intact lymph flow, the determination of \( P_{C} \) constitutes a problem, especially if \( \Delta P_{DROP} \) is large.

Johnson and Richardson recently have calculated the force imbalance for a dog intestinal preparation and also measured tissue pressure by direct needle puncture at different values for \( P_V \). Brace et al. have recently measured needle pressures in normal subcutaneous tissue and obtained average values of \(-4.8 \pm 1.0 \) (SD). After expansion of the tissues by intravenous infusion of large volumes, the needle pressures averaged \(-4.9 \pm 1.0 \) \((n = 10)\), a value which is not different from the control. If the needle was cleared by injecting minute amounts of fluid through it, the measured pressures were similar to those obtained by others who used wicks and implanted capsules (see Guyton et al. for a complete discussion of tissue pressure). The technique of direct needle puncture does not appear to provide tissue pressure values that follow changes in hydration of subcutaneous tissue without modifications such as small fluid infusions. Johnson's measurements of pressure changed slightly as \( P_V \) was increased from 0 to 15 mm Hg, but not to any significant degree; this finding is very similar to the measurements made in subcutaneous tissue by Brace, et al.

Because Johnson and Richardson did not observe any change in tissue pressure, but there was a large imbalance between the Starling forces, they assumed that \( \pi_L \) overestimated \( \pi_T \). This force imbalance also could be due to tissue pressure and does not necessarily reflect a concentrating ability of the lymphatic system. Table 3 presents a comparison of the force imbalance (calculated using \( \Delta F = P_{C} - \pi_{FL} - \pi_L \)) between our data \( (\Delta F_{MT}) \) and that of Johnson and Richardson \( (\Delta F_{JR}) \).

At each value of \( P_V \), the imbalance of forces in each preparation is quite different, since the values of Johnson and Richardson are usually greater. At \( P_V = 20, 25, \) and 30, the force imbalance in our preparation becomes large and is similar to the data of Johnson and Richardson for lower \( P_V \).

## Table 3 Comparison of Force Imbalance Calculation from Johnson and Richardson \( (\Delta F_{JR}) \) and Our Data \( (\Delta F_{MT}) \)

<table>
<thead>
<tr>
<th>( P_V )</th>
<th>( P_{C} ) (JR)</th>
<th>( P_{C} ) (MT)</th>
<th>( \Delta F_{JR} )</th>
<th>( \Delta F_{MT} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>9.8</td>
<td>9.9</td>
<td>+3.6</td>
<td>-1.7</td>
</tr>
<tr>
<td>5</td>
<td>12.8</td>
<td>12.6</td>
<td>+7.2</td>
<td>+0.1</td>
</tr>
<tr>
<td>10</td>
<td>16.1</td>
<td>15.5</td>
<td>+7.5</td>
<td>+2.1</td>
</tr>
<tr>
<td>15</td>
<td>19.1</td>
<td>18.4</td>
<td>+6.0</td>
<td>+4.6</td>
</tr>
<tr>
<td>20</td>
<td>23.1</td>
<td>23.1</td>
<td>+6.6</td>
<td>+6.6</td>
</tr>
<tr>
<td>25</td>
<td>27.3</td>
<td>27.3</td>
<td>+8.6 (7.0)</td>
<td>+8.6 (7.3)</td>
</tr>
<tr>
<td>30</td>
<td>30.6</td>
<td>30.6</td>
<td>+9.6 (7.3)</td>
<td>+9.6 (7.3)</td>
</tr>
</tbody>
</table>

\( JR = Johnson \) and Richardson; \( MT = Mortillaro \) and Taylor (present study); \( P_{C} = venous outflow pressure; P_{C} = capillary hydrostatic pressure \)

\( \Delta F_{MT} \) was calculated assuming that the lymph flow factor was not present during the measurement of \( P_{C} \). Values in parentheses are corrected for lymph flows observed during the determination of the isovolumetric capillary pressure.

ESTIMATION OF \( P_{C} \)

Since it is well known that intestine begins to "secrete" if serosal pressures are elevated to 3-6 mm Hg above mucosal pressure, then we must be overestimating \( P_{C} \) at high \( P_V \) values. Since our preparation "secreted" at \( P_V \) equal to 25 mm Hg, we believe that \( P_{C} \) should be approximately 3-6 mm Hg at this pressure. Because filtration is occurring into the intestine, this fluid plus lymph fluid must be passing across the capillary wall, i.e., the imbalance in Starling forces across the capillary = \( \Delta P_{DROP} = \Delta P_{DROP} + \Delta P_{DROP} \), where \( L \) and \( M \) refer to lymph and mucosa. Since calculated \( P_{C} \) is approximately 7.0 (assuming \( \Delta P_{DROP} = \frac{1}{2} \) maximum calculation) at \( P_V > 20 \) mm Hg, we probably have overestimated \( P_{C} \) at high venous pressures. In fact, it may actually decrease to values below that observed at \( P_V \) = 20 mm Hg because of the movement of fluid into the intestinal lumen.

Rusznjak et al. have suggested that the protein concentration of lymph is higher than the protein concentration of the interstitium. However, several experimental findings do not support the concept of a protein-concentrating mechanism in the lymphatic system. Taylor et al. reported that samples of fluid obtained from subcutaneously implanted capsules contained protein in concentrations not significantly different from lymph fluid draining the same tissue area. More important, we have observed a very close correlation between the volume of fluid filtered from the vascular compartment into the interstitial spaces and the dilution of interstitial protein as measured in the lymph fluid at the higher venous pressures. Over the range of venous pressures from 5 to 20 mm Hg, the intestinal volume increased 3.6 ml/100 gm while lymph protein concentration decreased from 3.7 to 3.0 gm per cent. If one assumes an interstitial fluid volume for the intestine of 15 ml/100 gm, at a normal portal pressure of 10 mm Hg, the calculated values of absolute fluid volumes at venous pressures of 5 and 20 mm Hg are 14 and 17.6 ml/100 g. Multiplication of the lymphatic protein concentration at 5 mm Hg by 14 ml yields a value of 0.518 g/100 g for total tissue protein. Division of the total protein by the tissue volume at 20 mm Hg venous pressure, 17.6 ml, yields a concentration of 2.9 g/100 ml as compared to the measured value of 3.0 g/100 ml.
would appear that at the high pressure ranges the lymphatics do not concentrate the lymphatic fluid. The values are so different at the lower values for \( P_v \) that it is highly unlikely that a concentrating mechanism exists, because this would only increase the calculated differences in \( \Delta P \).

One may argue that other factors possibly could lead to calculations of tissue pressures in our in situ intestinal preparation that are not related to normal physiological values: (1) If the preparation was in an edematous state due to surgery, etc., then the interstitial fluid pressure would be positive. (2) Absorption of fluid across the serosa from the Tyrode's solution surrounding the intestine in the plethysmograph could cause accumulation of tissue fluid and influence the \( P_T \) calculation. It is difficult to see how negative pressures could be calculated for the low venous pressures if either of these problems had been present in our preparation. If fluid had entered the serosal membrane, then the amount of fluid should be minimal, since the serosal surface area is extremely small relative to the capillary filtration area. (3) When \( P_T \) is calculated using \( r_{PL} \), \( P_{CT} \), and \( \Delta P_{DROP} \), a certain error is introduced because of the combined variances of each measured parameter. This error can be estimated from the data in Table 1, assuming that the standard deviation of the calculated \( P_T \) is equal to

\[
\sqrt{\sigma_1^2 + \sigma_2^2 + \sigma_3^2 + \sigma_4^2},
\]

where \( \sigma \) refers to the variance of each measured parameter used in the calculation of \( P_T \). When this variance calculation was applied to the data in Table 1 used to calculate \( P_T \), all values of calculated tissue pressure were significantly different from the zero venous pressure values (unpaired t-test) with the exception of \( P_v = 5 \text{ mm Hg} \) (0.10 > \( P > 0.05 \)). The majority of the variance in \( P_T \) was due to the variability of \( r_{PL} \), and if the preparations had been less variable with respect to this parameter, then all calculations of \( P_T \) would have been statistically different. (4) \( P_T \) was calculated assuming that the reflection coefficient of the plasma proteins (\( \sigma_C \)) was equal to 1.0. We could estimate the effective osmotic pressure from our data assuming that the reflection coefficient of the plasma proteins (\( \sigma_C \)) of proteins for our preparation is close to 1.0.

**PRESSURE-VOLUME CURVE**

Figure 4B is a pressure-volume curve calculated assuming that \( P_T \) was equal to the imbalance in forces across the capillary (solid curve). The dotted curve was calculated assuming that \( \Delta P_{DROP} \) changed maximally (the corrected imbalance in force) during the determination of \( P_{CT} \). The shape of the pressure-volume curve shown in Figure 4 suggests many similarities between intestinal and subcutaneous tissue relative to the structure and dynamics of the interstitial spaces. Briefly, the interstitial spaces contain mucopolysaccharides, mainly hyaluronic acid, which are cross-linked to collagen fibers and thus form a gel-like network. The state of hydration of the mucopolysaccharides is a determinant of the interstitial fluid pressure. Interstitial fluid pressure was found to be negative as determined by the implanted capsule method and the wick method in subcutaneous, muscle, and lung tissues. When the interstitial fluid pressure is negative, small increases in interstitial volume cause a rapid increase in the interstitial fluid pressure. When the pressure rises to 0 mm Hg (atmospheric), there is an inflection in the pressure-volume curve and large increases in interstitial fluid volume are necessary to increase interstitial fluid pressure only slightly. Granger et al. suggest that the point of inflection is related to the disruption of the mucopolysaccharide-collagen cross-linkages caused by the imbibition of fluid beyond the gel's saturation point. The increased compliance of the tissue gel reduces the effectiveness of further increases in interstitial fluid pressure in counteracting the accumulation of interstitial fluid.

In our study, the point of inflection for the intestine does not occur at an interstitial fluid pressure of 0 mm Hg, but instead at approximately 3.5–6 mm Hg. This suggests that a greater number of mucopolysaccharide collagen cross-linkages may exist in the intestine and thus require a greater pressure before disruption occurs. The normal interstitial...
INTERACTION OF TISSUE AND CAPILLARY FORCES

As P_C was increased from 0 to 15 mm Hg, tissue pressure increased from 1.8 to 3.4, tissue colloids decreased from 10.8 to 9.7, and ΔPDROP changed by about 1 mm Hg. The total increase in capillary pressure over this same range was 9 mm Hg and the change of P_CT was 1.6. This yields a net change in filtration force of 7.4 mm Hg which was counterbalanced by a change at 5.2 mm Hg in tissue pressure, 1 mm Hg in tissue colloid osmotic pressure and 1 mm Hg by the increased lymph flow. Even with the possible errors involved in our calculation of P_C, it appears that, in this lower range of capillary pressures, P_C provides the major alteration in the Starling forces that opposes increased filtration pressures.

As P_V was increased from 15 to 30 mm Hg, P_C, increased by 11.7 mm Hg and the calculated tissue pressure changed from 3.4 to 5.3 (Table 1), lymph protein decreased from 9.7 to 4.6 mm Hg, and P_CT increased from 24.0 to 25.6 mm Hg. The change in net filtration pressure was 10.1 mm Hg and P_CT decreased by 5.1 mm Hg, tissue pressure increased by 2 mm Hg, and ΔPDROP increased by 1–3 mm Hg. Over this range, the changes in Starling forces that oppose filtration are equally divided between changes in tissue colloid pressure and increases in tissue pressure plus ΔPDROP.

These findings (summarized in Fig. 5) are in agreement with Wallentin's argument because tissue pressure appears to provide the major force that opposes increases in filtration forces at P_C less than 15 mm Hg. At higher venous pressures, the decrease in tissue colloids provides 50% of the force that tends to oppose filtration, i.e., at high venous pressures, washout of tissue proteins provides the major force opposing filtration forces.

EDEMA SAFETY FACTOR

The edema safety factor has been defined as the changes in Starling forces that oppose increases in filtration forces and thus act as a mechanism to keep the tissues in a more dehydrated state. The tissue edema safety factor should be calculated assuming a normal P_C of 10 mm Hg, since the tissues are dehydrated at lower venous pressures. We have defined the edema safety factor in the P_C range of 10–20 mm Hg, because the compliance of the tissues increases abruptly at P_C = 20 mm Hg, and the tissue factors no longer can prevent large increases in tissue fluid volume beyond this point even for small elevations of P_C. In the P_V range of 10–20 mm Hg, P_CT decreases by 2.3 mm Hg, ΔPDROP increases by 1–2 mm Hg, and tissue pressure increases by 2–3 mm Hg. Thus capillary filtration forces can be altered by only approximately 6 mm Hg above the normal range of capillary pressures before the intestinal tissues begin to swell rapidly. In addition, the tissue forces can change by an additional 4 mm Hg before there is movement of fluid into the intestinal lumen.

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References

SUMMARY The transcapillary escape rate of albumin (TER alb), i.e., the fraction of intravascular mass of albumin that passes to the extravascular space per unit of time, was determined from the disappearance of intravenously injected 125I-labeled human serum albumin during the first 60 minutes after injection in 10 subjects with chronic right heart failure. The investigation was repeated after sodium and water depletion. Before treatment TER alb was significantly elevated (mean 83 ± 1.6%/hour, in comparison to values for normal subjects (mean 5.4 ± 1.1%/hour, P < 0.001). With treatment TER alb decreased significantly (mean 5.9 ± 1.2%/hour, P < 0.001). Right atrial pressure decreased from an average of 10 mm Hg to 6 mm Hg during treatment. A statistically significant, positive correlation was found between TER alb and right atrial pressure (r = 0.77, P < 0.001). Our results best can be explained by increased filtration, mainly through the venous end of the microvasculature, due to the increased venous pressure in heart failure.

THE FINDING of a normal or low protein concentration in edema fluid from subjects with congestive heart failure (CHF) has led to the conclusion that the protein permeability of the capillaries is normal or reduced and thus of no importance in relation to the formation of cardiac edema. However, the use of qualitative, nonkinetic methods to study a dynamic process, viz., the escape of proteins from plasma into the interstitial fluid, is highly questionable. Kinetic methods have yielded conflicting results concerning the microvascular-protein permeability in CHF; some have found a decreased permeability, some a normal permeability, and others have reported a markedly elevated protein permeability. Recently we found the transcapillary escape rate of albumin (TER alb), the fraction of intravascular mass of albumin that passes to the extravascular space per unit of time, to be significantly increased and this change to be accompanied by increases in central venous pressure during acute plasma volume expansion in man. This condition simulates heart failure because intravascular volume is enlarged and filling pressures of the ventricles are elevated. The aim of the present study was to measure the transcapillary escape rate of albumin before and after diuretic treatment of subjects with right heart failure.

Methods

The study comprises 10 patients with chronic heart failure referred for hemodynamic investigation. Clinical data are presented in Table 1. All patients except patient 3 were on maintenance treatment with digitalis. Five (patients 1, 5, 6, 8, and 10) received thiazide diuretics at the time of admission. For two of the patients (nos. 5 and 6) the diuretic therapy was stopped 1 week before the first investigation. Then a potent diuretic (bumetanide, 2 mg daily) was given and the second investigation was carried out after 1 or 2 weeks when the patients no longer were losing weight. All the patients had clinical signs of right-sided failure with liver enlargement and intermittent or constant peripheral edema. Three patients (nos. 1, 3, and 8) had gross edema and ascites at the time of their first examination. No patient but no. 7 had hypertension. None had diabetes mellitus or any major
Interaction of capillary and tissue forces in the cat small intestine.
N A Mortillaro and A E Taylor

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