

## Transsinusoidal fluid dynamics in canine liver during venous hypertension.

G A Laine, J T Hall, S H Laine and J Granger

*Circ Res.* 1979;45:317-323

doi: 10.1161/01.RES.45.3.317

*Circulation Research* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Copyright © 1979 American Heart Association, Inc. All rights reserved.

Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://circres.ahajournals.org/content/45/3/317.citation>

**Permissions:** Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation Research* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the [Permissions and Rights Question and Answer](#) document.

**Reprints:** Information about reprints can be found online at:  
<http://www.lww.com/reprints>

**Subscriptions:** Information about subscribing to *Circulation Research* is online at:  
<http://circres.ahajournals.org/subscriptions/>

## Transsinusoidal Fluid Dynamics in Canine Liver during Venous Hypertension

GLEN A. LAINE, JEFF T. HALL, SUSAN H. LAINE, AND HARRIS J. GRANGER

**SUMMARY** We studied arterial pressure, portal pressure, inferior vena caval pressure, hepatic interstitial pressure (implanted capsule technique), prenodal lymph flow, and the protein concentration in plasma and lymph in the anesthetized dog under normal conditions and during graded venous hypertension resulting from inferior vena caval occlusion. Under control conditions, portal, interstitial, and inferior vena caval pressures were 7.0, 5.8, and 2.0 mm Hg, respectively, and the lymph-plasma protein concentration ratio was 0.95. During acute venous hypertension, 64% of the inferior vena caval pressure increase was transmitted to the hepatic interstitium, and lymph flow increased 63% for every 1 mm Hg increment in interstitial pressure. The lymph-plasma protein concentration ratio did not change significantly during venous hypertension, indicating that: (1) the reflection coefficient of the sinusoidal wall for the major plasma proteins is close to zero, and (2) protein transport across the microvascular wall is due mainly to bulk flow. Using portal, interstitial, and inferior vena caval pressures as limits for possible values of sinusoidal pressure, our data suggest that (1) control sinusoidal pressure was between 5.8 and 7.0 mm Hg, and (2) approximately 90% of the increase in inferior vena caval pressure was transmitted to the sinusoids. The results indicate that changes in interstitial pressure, lymph flow, and surface transudation rate are major compensatory mechanisms operating in the liver to limit interstitial engorgement during venous hypertension. *Circ Res* 45:317-323, 1979

THE LIVER, with its extensive vasculature and leaky sinusoids, plays a central role in the control of blood volume and cardiovascular fluid dynamics. More specifically, the high compliance of the hepatic vessels allows the liver to serve as a blood reservoir for maintenance of adequate cardiovascular filling during hemorrhage (Lautt and Greenway, 1976). In addition, in certain clinical conditions such as congestive heart failure, the free communication of the liver interstitium with the potential space of the peritoneal cavity provides a convenient route for spillage of excess plasma out of the circulation via the hepatic sinusoids (Greenway and Lautt, 1970).

In general, transsinusoidal fluid flux should be governed by the same hydrostatic and oncotic forces that determine fluid movement across the capillary wall of other tissues (Starling, 1896). Unfortunately, the magnitude of each sinusoidal and

extravascular force in the normal liver has not been delineated clearly. Furthermore, the interactions of these forces in pathological states, such as cirrhosis and congestive heart failure, are not well understood. The major aim of this paper is to quantify the Starling forces governing transsinusoidal fluid balance under normal conditions and during venous hypertension. In addition, our study focuses on the behavior of the hepatic lymphatics and the permeability characteristics of the blood-lymph barrier in the liver at normal and elevated sinusoidal pressures. Finally, the interactions of Starling forces, lymphatic flow, and sinusoidal permeability in the prevention and genesis of ascites are discussed.

### Methods

#### Animal Preparation

Fifteen mongrel dogs with body weights exceeding 17 kg were anesthetized with sodium pentobarbital (30 mg/kg). Additional sodium pentobarbital was given (5 mg/kg) throughout the experiment whenever the corneal reflex returned. The dogs were intubated and ventilated using a Harvard respirator set to deliver room air at a volume of 25 ml/kg and a rate of 12 breaths/min.

The dogs were placed in the supine position, and the left femoral vein and artery were exposed in the inguinal region. A catheter was inserted into the

From the Department of Medical Physiology, College of Medicine, Texas A & M University, College Station, Texas.

Supported by Grant HL 21498 from the National Heart, Lung, and Blood Institute.

Dr. Granger is the recipient of Research Career Development Award K04 HL 00409 from the National Heart, Lung, and Blood Institute.

Address for reprints: Glen A. Laine, Ph.D., Department of Medical Physiology, College of Medicine, Texas A & M University, College Station, Texas 77843.

Received February 2, 1979; accepted for publication April 18, 1979.

left femoral vein and advanced to a point in the inferior vena cava approximately at the level of the liver. The left femoral artery was cannulated to a distance of 6 inches. All blood vessel cannulations were carried out using polyethylene tubing (P.E. 260). The right femoral vein was exposed in the right inguinal region and cannulated with a water-filled Fogarty occlusion catheter (28 mm maximum inflated diameter) that was advanced to a point in the inferior vena cava at or near the level of the liver. The left and right common carotid arteries were exposed and cannulated to a distance of 4 inches. Care was taken not to traumatize the vagus nerves.

The dogs were placed on their left sides, and an incision was made into the chest cavity between the 9th and 10th ribs. Finochietto rib spreaders then were used to obtain a large opening in the chest. At this point, the inferior vena cava is palpable at the level of the diaphragm, and both catheters within the inferior vena cava can be placed properly. The Fogarty occlusion catheter was situated just above the diaphragm, and the left femoral vein catheter was placed below the diaphragm.

The abdominal cavity was entered through the diaphragm, exposing the caudate process of the caudate lobe of the liver. The hepatorenal ligament was cut and the caudate lobe was reflected. This operation exposed the portal vein at its entry into the hilus of the liver. A prenodal lymphatic leaving the liver and traveling down the portal vein was located. This lymphatic was cannulated with polyethylene tubing (P.E. 50) at a point above all lymphatic bifurcations. A hooked needle catheter (22 gauge) was inserted into the portal vein at the liver hilus. The dogs then were given sodium heparin (Organen), 300 U/kg of body weight, intravenously. At the conclusion of each experiment, the dogs were killed with 10 ml of a saturated solution of potassium chloride injected intravenously.

In seven of the dogs, porous polyethylene capsules (10 mm  $\times$  3 mm) were implanted chronically in the left lateral lobe of the liver. Chronic surgical procedures were carried out under the same anesthesia as the acute preparations. A midline abdominal incision was made into the abdominal cavity using sterile technique. Three polyethylene capsules were inserted into the left lateral lobe of the liver at various points. Each capsule was held in place in the liver parenchyma by a single tie of 4-0 chromic suture. The abdomen was closed to the level of the skin, leaving the capsule catheters (P.E. 60) protruding between two sutures. At this point, a small pouch was formed just below the skin; the catheters were coiled and placed into the pouch. The skin then was closed and the dogs were given antibiotics (Bicillin, 1 million U/day) for 4 days. At the end of 3-4 weeks of recuperation, the capsule catheters could easily be exteriorized from their pouches. These dogs then were ready for use in the acute preparation.

At the termination of several experiments, the positions of the polyethylene capsules within the liver were determined. The tissue containing the capsules then was removed, sectioned, and prepared with hematoxylin and eosin stain for microscopic examination. When viewed microscopically, the polyethylene capsules were found to be encased in 25-100  $\mu$ m of loose connective tissue with no visible signs of inflammation.

### Physiological Measurements

Statham (P23Db) pressure transducers in conjunction with Grass model 7P1 preamplifiers, model 7DA driver amplifiers, and a model 7D chart recorder were used to record all pressures. For each transducer, zero reference pressure was the point at which the pressure measurements would be made. Arterial pressure was controlled at or near 120 mm Hg with a blood reservoir connected to both common carotid artery catheters. Arterial pressure was monitored through the left femoral artery catheter. Pressure in the inferior vena cava was monitored from the left femoral vein catheter placed just below the diaphragm. Portal pressure was obtained from the hooked needle catheter. In a series of dogs, interstitial pressure was recorded from the exteriorized catheters connected to the polyethylene capsules previously implanted in the liver. The criteria established to determine whether or not the capsules were patent and acceptable for use were as follows: (1) at least two out of the three implanted capsules must have been free of blood and patent, (2) the time course for return to control interstitial pressure, following small aspirations of fluid from the capsule catheters, must have been equivalent for two of the capsules, and (3) the absolute interstitial pressures recorded by two capsules in the same dog could not vary by more than 1.5 mm Hg. The capsule pressures recorded from two dogs were not used because of failure to comply with these criteria for patency.

Lymph flow rate and lymph samples were obtained simultaneously and automatically by interfacing a Grass PTTL photoelectric drop counter-tachograph with an automatic fraction collector (LKB 2112 RediRac). Caution was taken to collect lymph samples without applying a positive or negative hydrostatic pressure head to the lymphatic catheter. Protein concentrations in the lymph and plasma were measured with a refractometer (American Optical 10400A TS meter). Lymph samples were obtained from the fraction collector, and plasma samples were obtained by centrifugation of venous blood.

### Experimental Protocol

At the beginning of each experiment, a steady state control recording of arterial pressure, inferior vena caval pressure, portal pressure, and lymph flow rate was obtained. In those dogs having poly-

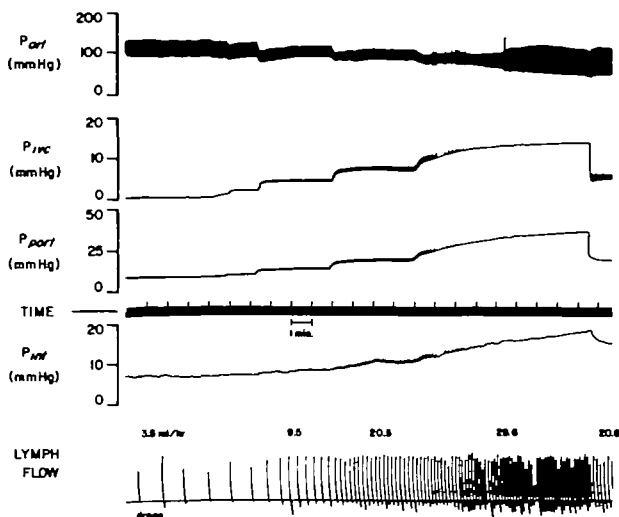


FIGURE 1 Typical response of arterial pressure ( $P_{art}$ ), portal pressure ( $P_{port}$ ), hepatic interstitial pressure ( $P_{int}$ ), and hepatic lymph flow to step increments in inferior vena caval pressure ( $P_{ive}$ ). Note rapidity of interstitial and lymphatic reactions to caval hypertension.

ethylene capsules in their livers, interstitial pressure also was recorded. Protein concentration in both lymph and plasma also were recorded during the control period. The Fogarty occlusion catheter then was inflated with distilled water in incremental steps. Desired step sizes were obtained by observing small increases in inferior vena caval pressure. All pressures and flows were allowed to come to equilibrium at each incremental increase in inferior vena caval pressure during continuous recording. Lymph and plasma protein concentrations also were recorded at several of the incremental pressure steps. When the maximum desired value for inferior vena cava pressure had been obtained, the occlusion catheter was deflated fully and the off transients for all recorded parameters were obtained.

### Data Analysis

All data analysis was carried out on an AMDAHL 470 V/6 computer. Regression lines were generated from data points using the SAS program STEPWISE (Barr et al., 1976), with the exception of lymph flow (x-normal) vs. pressure in the inferior vena cava, which was fitted to a linear regression. An analysis of variance and *F*-test were used to determine if regression lines were significantly different (Neter and Wasserman, 1974).

### Results

Figure 1 shows a typical recording of arterial, inferior vena caval, portal, and liver interstitial pressures, along with a continuous indication of prenodal hepatic lymph flow. Stepwise increments in caval pressure elicited a graded increase in portal pressure and, consequently, sinusoidal pressure rose

in stepwise fashion. In turn, the elevated pressure within the hepatic sinusoids caused an acceleration of transsinusoidal fluid flux and an increased interstitial pressure. The rise in interstitial pressure increased the rate of lymph formation and outflow. The rapidity of the rise of interstitial pressure and lymph flow during a step increase in inferior caval pressure probably reflects the high hydraulic conductance of the sinusoids. Although the duration of each pressure increment was usually 10 minutes or longer, the time required for the variables to reach a new steady state usually was less than 3 minutes, as can be seen in Figure 1. During the entire experiment, the dramatic fall usually observed in arterial pressure was buffered by the arterial reservoir compensator.

A summary of the experimental results is presented in Figure 2. Under control conditions, inferior vena caval pressure ranged between 0 and 3 mm Hg, with an average of  $2.0 \pm 0.78$  mm Hg (mean  $\pm$  SD). Portal pressure averaged  $7.0 \pm 1.88$  mm Hg, and the mean value of interstitial pressure was 5.8

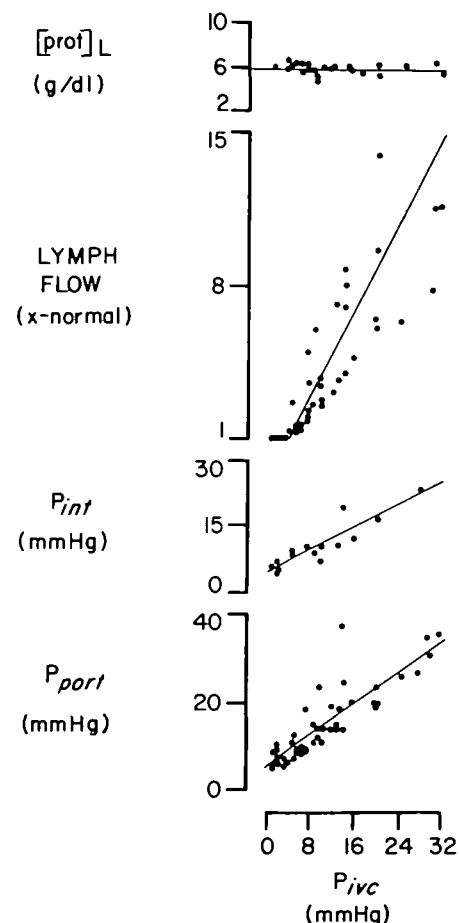


FIGURE 2 Effect of increased  $P_{ive}$  on protein concentration in the hepatic lymph, hepatic lymph flow (x-normal),  $P_{int}$ , and  $P_{port}$ . Regression statistics: lymph flow (x-normal) =  $-0.8 + 0.49 (P_{ive})$ ,  $r = 0.82$ ;  $P_{int} = 4.92 + 0.64 (P_{ive})$ ,  $r = 0.91$ ;  $P_{port} = 5.18 + 0.91 (P_{ive})$ ,  $r = 0.87$ .

$\pm 0.87$  mm Hg. The control protein concentrations in plasma and lymph were  $6.0 \pm 0.58$  and  $5.7 \pm 0.57$  g/dl, respectively. At normal caval pressures, lymph flow from the prenodal lymphatic was  $3.5 \pm 1.19$  ml/hour. Portal pressure rose by 0.91 mm Hg for every mm Hg increase in caval pressure. The ratio  $\Delta P_{\text{int}}/\Delta P_{\text{ivc}}$  was 0.64, and lymph flow increased by 49% with every mm Hg increment in caval pressure. Plasma and lymph protein concentrations did not change with graded venous hypertension.

Figure 3 provides an estimate of the sinusoidal pressure at different vena caval pressures. Since sinusoidal pressure must be lower than portal pressure and higher than caval and interstitial pressures, the stipled area delimits the possible values of sinusoidal pressure at each level of caval pressure. At a normal caval pressure of 2 mm Hg, the pressure extant in the hepatic sinusoids is between 5.8 and 7.0 mm Hg. As a first approximation, sinusoidal pressure rises by 0.9 mm Hg for every mm Hg increment in inferior vena caval pressure.

Since interstitial pressure is a major component of the force driving fluid from the interstitium into the terminal lymphatics, the sensitivity of the lymphatics to changes in transcapillary fluid balance is best expressed by plotting lymph flow as a function of interstitial pressure. The direct relationship between hepatic lymph flow and pressure of the liver interstitium is illustrated in Figure 4. Lymph flow increased by 63% with each mm Hg elevation in interstitial pressure. At an interstitial pressure of 24 mm Hg, hepatic flow was 14 times higher than control.

The lymph-plasma protein concentration ratio

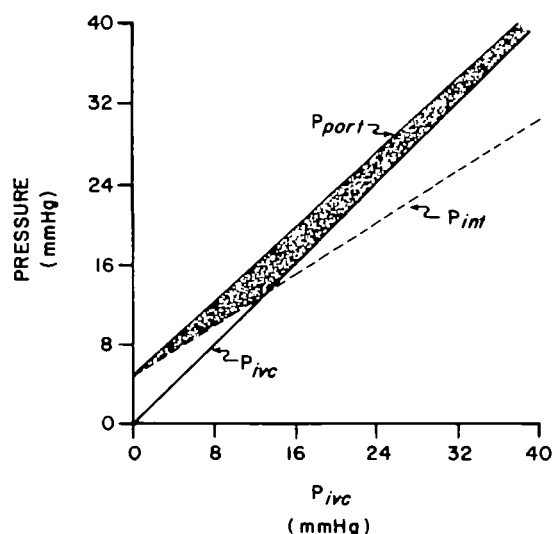


FIGURE 3 Simultaneous plot of  $P_{\text{ivc}}$ ,  $P_{\text{port}}$ , and  $P_{\text{int}}$ . Stipled area delimits the possible values of sinusoidal pressure at each level of caval pressure.  $P_{\text{port}}$  and  $P_{\text{int}}$  relations are obtained from Figure 2.  $P_{\text{ivc}}$  is a line of identity;  $P_{\text{port}}$  and  $P_{\text{int}}$  were found to be significantly different ( $P < 0.025$ ).

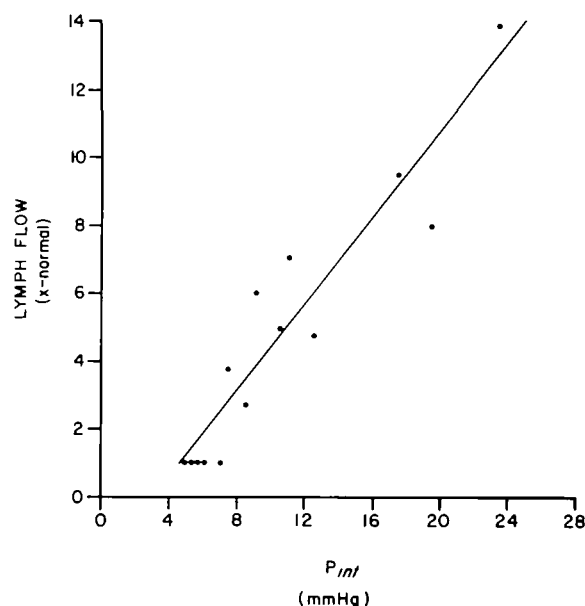


FIGURE 4 Effect of increased  $P_{\text{int}}$  on hepatic lymph flow (x-normal). Note lymph flow does not attain a plateau within the range studied. Regression statistics: lymph flow (x-normal) =  $-1.89 + 0.63 (P_{\text{int}})$ ,  $r = 0.93$ .

was 0.95 under control conditions and was unchanged at the higher lymph flow rates induced by caval hypertension. Because lymph protein content was not reduced at elevated transsinusoidal filtration rates (Fig. 1), the lymphatic protein flow increased in direct proportion to the rise in lymph flow.

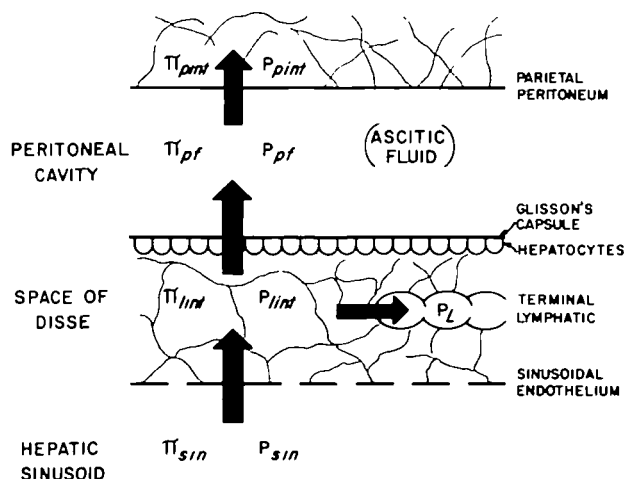


FIGURE 5 Pressures and flows which mediate the fluid dynamics in the hepatoperitoneal system:  $\pi_{\text{pmt}}$  and  $P_{\text{pmt}}$  are osmotic and tissue pressures in the parietal peritoneal interstitium, respectively.  $\pi_{\text{pf}}$  and  $P_{\text{pf}}$  are osmotic and hydrostatic pressures in the peritoneal cavity, respectively.  $\pi_{\text{int}}$  and  $P_{\text{int}}$  are osmotic and tissue pressures in the hepatic interstitium, respectively.  $P_L$  is the hydrostatic pressure in the hepatic lymphatics.  $\pi_{\text{sin}}$  and  $P_{\text{sin}}$  are osmotic and hydrostatic pressures in the hepatic sinusoid, respectively.



## Discussion

In the intact animal, the fluid traversing the hepatic sinusoids may exit the liver interstitium via two routes—the hepatic lymphatics and the liver surface (Fig. 5). The reabsorption of surface transudate from the peritoneal cavity is dependent, in turn, on peritoneal fluid pressure (Zink and Greenway, 1977) and on forces operating in the capillaries, interstitium, and lymphatics of the peritoneal wall (Raybuck et al., 1960). In the present study, we have quantified the forces governing transsinusoidal fluid movement in the anesthetized dog with the abdominal cavity exposed to ambient pressure. Thus, the linkage between liver fluid balance and peritoneal forces is “clamped,” and the major determinants of sinusoidal fluid flux are generated within the liver itself.

### Transsinusoidal Flows and Forces at Normal Caval Pressure

The volume flow ( $J_{v,\text{sin}}$ ) traversing the porous surface of the hepatic sinusoids is given by

$$J_{v,\text{sin}} = K_f \cdot [(P_{\text{sin}} - P_{\text{int}}) - \sigma_p (\pi_{\text{sin}} - \pi_{\text{int}})], \quad (1)$$

where  $\sigma_p(\pi_{\text{sin}} - \pi_{\text{int}})$  is the effective transsinusoidal oncotic pressure differential,  $\sigma_p$  is the osmotic reflection coefficient for protein, and  $K_f$  is the capillary filtration coefficient. Several lines of evidence point to the absence of an effective osmotic component at the sinusoidal membrane. Although postnodal cannulations of hepatic lymphatics have yielded values for the lymph-plasma protein concentration ratio of less than 0.90, it has been shown that this lower protein ratio in postnodal lymph may be a result of lymphatic protein dilution occurring as hepatic lymph passes through the lymph nodes (Quin and Shannon, 1977). To circumvent this problem, we focused our attention on prenodal lymph. In our study, the protein content of lymph was 95% of the plasma value. Consequently, the maximum osmotic potential difference is 1–2 mm Hg if the membrane has a  $\sigma_p \approx 1$ . The hepatic interstitial fluid and thus hepatic lymph may, to some extent, be diluted by a low protein filtrate from the peribiliary capillaries deriving from the hepatic arterial tree. This contamination of hepatic lymph with peribiliary capillary filtrate may lead to an incorrect inference that the sinusoids themselves hinder the movement of albumin and  $\gamma$ -globulin. Thus, even the small transsinusoidal protein differential observed in our study may result from forces operating at sites other than the sinusoids. Finally, the reflection coefficient for the major plasma proteins at the sinusoidal wall is close to zero. The latter conclusion is supported by the lack of sieving during venous hypertension. In other words, if the protein reflection coefficient was finite, the lymph-plasma protein ratio would have decreased with increases in transsinusoidal volume flow. Since both  $\sigma_p$  and  $\pi_{\text{sin}} - \pi_{\text{int}}$  approach zero, the effective trans-

sinusoidal oncotic pressure difference must be very close to zero. However, the sinusoid may restrict the movement of the larger plasma macromolecules, which are present in small quantity and therefore do not contribute significantly to the oncotic pressure of plasma and lymph.

The above considerations suggest that the major forces governing transcapillary fluid flux in the liver are the hydrostatic pressures extant in the sinusoid and interstitium. The present study suggests that, at normal caval pressure, the hydrostatic pressure in the sinusoids is only slightly lower than portal pressure. Although early estimates of sinusoidal pressure were nearer the hepatic venous pressure (Nakata et al., 1960), our results are consistent with several recent studies (Price et al., 1964; Mitzner, 1974; Sato et al., 1977), indicating that the pressure drop from the portal vein to the hepatic sinusoids is small. To our knowledge, the present study provides the first measurement of hepatic interstitial pressure. Interstitial pressures measured with the implanted capsule range from subatmospheric values for muscle (Granger and Shepherd, 1979), skin (Chen et al., 1976), and lung (Meyer et al., 1968) to positive values for intestine (Mortillaro, 1977), kidney (Ott et al., 1971) and, in our experiments, liver. Thus, positive interstitial pressures have been recorded from tissues characterized by (1) fenestrated or discontinuous capillaries and (2) high transcapillary volume flows. In the canine liver, interstitial pressure averages +5.8 mm Hg. Our measurements also allow an estimation of the possible numerical values for the net filtration pressure in the liver. Since sinusoidal pressure cannot exceed the pressure in the portal vein, the maximum  $P_{\text{sin}} - P_{\text{int}}$  at normal hepatic venous pressure is 7.0 minus 5.8 or 1.2 mm Hg. Therefore, under normal conditions, the actual transsinusoidal pressure difference must lie between a fraction of 1 mm Hg and 1.2 mm Hg.

The filtration coefficient of the sinusoidal membrane can be calculated as the ratio of net transcapillary volume flow to the effective filtration pressure head (i.e.,  $K_f = J_{v,\text{sin}}/(P_{\text{sin}} - P_{\text{int}})$ ). Unfortunately, a precise estimate of the filtration coefficient cannot be obtained from our data since (1) only one component (i.e., lymph flow) of the net transsinusoidal flux was measured, and (2) the exact value of  $P_{\text{sin}} - P_{\text{int}}$  is not known. In three dogs, the intestinal lymphatics, along with the thoracic duct below the cisterna chyli, were ligated. The thoracic duct then was cannulated at the level of the diaphragm, and the resulting lymph flow was considered to be primarily of hepatic origin. Dividing the lymph flow per 100 g of liver (i.e., 0.098 ml/min per 100 g) by the maximum transsinusoidal pressure difference (i.e., 1.2 mm Hg) yields a minimum value of 0.08 ml/min per 100 g per mm Hg. The actual filtration coefficient is probably much larger because (1) surface transudation may be a significant component of net transcapillary flux even at normal caval pressures, and (2) the prevailing value of  $(P_{\text{sin}} - P_{\text{int}})$

may be much smaller than the maximum value of 1.2 mm Hg. Determinations of the hepatic filtration coefficient using plethysmographic techniques yield values near 0.3 ml/min per 100 g per mm Hg in the cat (Greenway and Lauth, 1970).

### Capillary, Interstitial, and Lymphatic Interactions in Caval Hypertension

In many tissues of the body, elevation of capillary pressure causes a rise in interstitial pressure and lymph flow and a reduction in interstitial protein concentration (Guyton et al., 1975; Wiederhielm, 1968). These responses may be viewed as compensatory reactions to elevation of interstitial volume above normal. The compensations, in turn, serve to limit the extent of interstitial fluid accumulation following an increase in capillary pressure (Chen et al., 1976; Krogh et al., 1932; Granger, in press). In the liver, oncotic buffering does not contribute to the "margin of safety" against edema formation, simply because the discontinuous endothelium of the sinusoids does not restrict the passage of the major plasma proteins. Consequently, the major compensatory reactions to sinusoidal hypertension are (1) elevated interstitial pressure and (2) increased outflow of fluid from the interstitial space via the lymphatics and liver surface.

The homeostatic significance of the close interaction between interstitial pressure and the outflow rate at lymphatic and surface sites can best be understood using Equation 1 as a framework. Since  $\sigma_p$  and  $\Delta\pi$  are close to zero and the rate of outflow ( $J_{v,out}$ ) is equal to  $J_{v,lin}$  in the steady state, then

$$J_{v,out} = J_{v,lin} = K_f(P_{sin} - P_{int}). \quad (2)$$

Solving for  $P_{int}$ , we obtain

$$P_{int} = P_{sin} - (J_{v,out}/K_f). \quad (3)$$

Thus, for a given increment in sinusoidal pressure, the rise in interstitial pressure can be minimized by either an acceleration of outflow rate or a myogenic (Mellander and Johansson, 1968) reduction in the filtration coefficient of the liver capillary bed. Since changes in interstitial pressure reflect alterations in interstitial volume, minimization of the extent of transmission of sinusoidal pressure to the interstitium can be viewed as a "safety factor" against hepatic edema formation. For changes in inferior caval pressure in the range of 0 to 24 mm Hg, at least 60% of the rise in sinusoidal pressure is transmitted to the liver interstitium (Table 1). The remaining fraction of the sinusoidal pressure increment is dissipated at the sinusoidal barrier, as reflected in the rise in the net transsinusoidal pressure difference ( $P_{sin} - P_{int}$ ). Since we measured increases in lymph flow and observed increased rates of surface transudation with elevated caval pressure, we know that  $J_{v,out}$  rose and hence aided in limiting the rise in interstitial pressure. We do not know if  $K_f$  was reduced by a myogenic response to elevated intravascular pressures.

TABLE 1 *Transmission of Sinusoidal Pressure to the Interstitium during Venous Hypertension*

$P_{v,c}^*$ (mm Hg)	$P_{sin}^*$ (mm Hg)	$P_{int}^*$ (mm Hg)	$P_{sin} - P_{int}$ (mm Hg)	$\Delta P_{int}/\Delta P_{sin}$
2	5.8 - 7.0	5.8	$\leq 1.2$	
8	10 - 12	10.0	$\leq 2$	0.84 - 1
16	16 - 20	15.2	0.8 - 4.8	0.65 - 0.87
24	24 - 27	20.3	3.7 - 6.7	0.64 - 0.73

\* Values obtained from Figure 3.

In the above discussion, changes in interstitial pressure were viewed as resulting exclusively from alterations in interstitial volume subsequent to an increase in transsinusoidal fluid flux. However, during venous hypertension, an alternate mechanism is available for transmission of intravascular disturbances to the interstitium. As venous pressure is elevated, the venules and veins expand and compress the interstitium. Consequently, interstitial pressure is elevated before transsinusoidal fluid filtration is increased significantly. We examined this phenomenon in several tissues (Granger, Chen, and Laine, unpublished observations) and found that venous bulging can account for as much as 50% of the interstitial pressure elevation in hindpaw, gastrocnemius, and kidney subjected to venous hypertension. A common characteristic of these three tissues is the presence of an external shell of stiff connective tissue. In muscle, hindpaw, and kidney, interstitial pressure exhibits a rapid rising phase and a slow rising phase when venous pressure is elevated in stepwise fashion. The rapid phase is synchronized with pooling of blood in the veins, and the slow phase presumably reflects transcapillary fluid transfer. The extent to which venous bulging accounts for the elevations of interstitial pressure in liver is difficult to assess, since the two-phase response was not observed. We suspect that, due to the expandability of Glisson's capsule, the interstitial pressure elevations observed in our study reflect primarily translocation of fluid from the sinusoids to the interstitium.

### The Hepatoperitoneal Fluid System and Body Fluid Balance in the Intact Animal

In the intact animal, under normal as well as pathological conditions, hepatic interstitial fluid continuously traverses the liver surface. The driving force for this transudative flux probably is the hydrostatic pressure differential between the liver interstitium and the peritoneal cavity. In turn, the peritoneal pressure provides the impetus for absorption of peritoneal fluid via the capillaries and lymphatics of the peritoneal lining (Zink and Greenway, 1977). Peritoneal pressure at any instant is determined by the compliance of the peritoneal cavity and the volume of fluid located within it. In a recent study (Barnes et al., 1978) from our laboratory, the compliance of the canine peritoneal cavity was estimated at 9.5 ml/mm Hg per kg body

weight in the pressure range of 0–25 mm Hg. The direct hydraulic linkage of this high compliance cavity with the liver interstitium provides an effective fluid venting system for the circulation. Thus, in heart failure, a rise in caval pressure of a few mm Hg can induce a significant increase in hepatic interstitial pressure and liver surface transudation rate. Hence, ascites formation ensues. As fluid accumulates in the peritoneal space, peritoneal pressure rises. The rise in peritoneal pressure, in turn, impedes further fluid accumulation by (1) reducing the pressure gradient driving surface transudation and (2) increasing the rate of reabsorption by the peritoneal capillaries and lymphatics. Thus, during venous hypertension, the pressures and volumes of the hepatic interstitium and the peritoneal cavity are elevated in the steady state. Indeed, in one dog with a chronically distended abdomen and confirmed ascites, the hepatic interstitial pressure was 18 mm Hg. Edema of parenchymatous tissues is often associated with organ dysfunction (Granger, *in press*). From a functional standpoint, when fluid seeps from the circulation into the liver stroma, venting the parenchyma is more effective and less detrimental to body homeostasis than the accumulation of excess fluid in the hepatic interstitium. The pervasive lymphatic network in the liver and the potential space of the hepatoperitoneal system subserve such a venting function and thereby play an important role in overall regulation of body fluid balance.

### Acknowledgments

We are indebted to Vicki Black for her technical assistance and to Donna Crenan and Mildred Kuder for typing the manuscript.

### References

- Barnes GE, Giam P, Molstad LS, Granger HJ (1978) Effect of elevated intraabdominal pressure on cardiovascular dynamics (abstr). *Fed Proc* 37: 778
- Barr AJ, Goodnight JH, Sall JP, Helwig JT (1976) A user's guide to SAS-76. Raleigh, N.C., SAS Institute Inc., pp 251–256
- Chen HI, Granger HJ, Taylor AE (1976) Interaction of capillary, interstitial and lymphatic forces in the canine hindpaw. *Circ Res* 39: 245–254
- Granger HJ, Shepherd AP (1979) Dynamics and control of the microcirculation. In *Advances in Biomedical Engineering*, vol 7, edited by JHU Brown. New York, Academic Press, pp 1–63
- Granger HJ (*in press*) Role of the interstitial matrix and lymphatic pump in regulation of transcapillary fluid balance. *Microvas Res*
- Greenway CV, Lautt WW (1970) Effects of hepatic venous pressure on transsinusoidal fluid transfer in the liver of the anesthetized cat. *Circ Res* 26: 697–703
- Guyton AC, Taylor AE, Granger HJ (1975) *Circulatory Physiology II. Dynamics and Control of the Body Fluids*. Philadelphia, W. B. Saunders, pp 149–165
- Krogh A, Landis EM, Turner AH (1932) The movement of fluid through the human capillary wall in relation to venous pressure and to the colloid osmotic pressure of the blood. *J Clin Invest* 11: 63–95
- Lautt WW, Greenway CV (1976) Hepatic venous compliance and role of liver as a blood reservoir. *Am J Physiol* 231: 292–295
- Mellander S, Johnsson B (1968) Control of resistance, exchange and capacitance functions in the peripheral circulation. *Pharmacol Rev* 20: 117–196
- Meyer BJ, Meyer A, Guyton AC (1968) Interstitial fluid pressure. V. Negative pressure in the lungs. *Circ Res* 22: 263–271
- Mitzner W (1974) Hepatic outflow resistance, sinusoid pressure, and the vascular waterfall. *Am J Physiol* 227: 513–519
- Mortillaro NA (1977) Intestinal interstitial pressure and its relationship to interstitial volume (abstr). *Physiologist* 20: 66
- Nakata K, Leong GF, Brauer RW (1960) Direct measurement of blood pressures in minute vessels of the liver. *Am J Physiol* 199: 1181–1188
- Neter J, Wasserman W (1974) *Applied Linear Statistical Models*. Homewood, Ill., Irwin, pp 160–165
- Ott CE, Navar LG, Guyton AC (1971) Pressures in static and dynamic states from capsules implanted in the kidney. *Am J Physiol* 221: 394–400
- Ott CE, Cuche JL, Knox FG (1975) Measurement of renal interstitial fluid pressure with polyethylene matrix capsules. *J Appl Physiol* 38: 937–941
- Price JB, McFate PW, Shaw RF (1964) Dynamics of blood flow through the canine liver. *Surgery* 56: 1109–1120
- Quin JW, Shannon AD (1977) The influence of the lymph node on the protein concentration of efferent lymph leaving the node. *J Physiol (Lond)* 264: 307–321
- Raybuck HE, Weatherford T, Allen L (1960) Lymphatics in genesis of ascites in the rat. *Am J Physiol* 198: 1207–1210
- Sato T, Shirataka M, Ikeda N, Grodins FS (1977) Steady-state systems analysis of hepatic hemodynamics in the isolated perfused canine liver. *Am J Physiol* 233: R188–R197
- Starling EH (1896) On the absorption of fluids from the connective tissue spaces. *J Physiol (Lond)* 19: 312–326
- Wiederhielm CA (1968) Dynamics of transcapillary fluid exchange. *J Gen Physiol* 52 (suppl): 29–63
- Zink J, Greenway CV (1977) Intraperitoneal pressure in formation and reabsorption of ascites in cats. *Am J Physiol* 233 (suppl 2): H185–190