RENEAL LYMPHATIC FUNCTION FOLLOWING VENOUS PRESSURE ELEVATION

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ABSTRACT

The renal lymphatic system plays an important role in removing excess fluid from the kidneys. Unfortunately, the factors influencing lymphatic flow are difficult to measure. We used a simple model to represent renal lymphatics as a single pressure source (P_l) pushing lymph through a single resistance (R_l). In anesthetized dogs, we cannulated renal lymphatics and measured lymph flow rate (Q_l) as we varied pressure (P_o) at the outflow end of the lymphatics. There was no significant change in Q_l as we increased P_o from -5 to 0 cm H_2O. In other words, there was a plateau in the Q_l vs. P_o relationship. At higher P_o's, Q_l decreased linearly with increases in P_o. From this linear relationship, we calculated R_l as (-ΔP_o/ΔQ_l) and we took P_l as the P_o at which Q_l = 0 μl/min. At baseline, R_l = 0.34 ± 0.14 (SD) cm H_2O•min/μl and P_l = 8.2 ± 4.4 cm H_2O. When we increased renal venous pressure (P_v) from baseline (3.5 ± 3.0 cm H_2O), the plateau in the Q_l vs. P_o relationship extended to higher P_o’s, R_l decreased, and P_l increased. Renal interstitial fluid volume and interstitial pressure increased following elevation of P_v. The extension of the Q_l vs. P_o plateau with increasing P_v suggests that renal interstitial pressure may partially collapse intrarenal collecting lymphatics which may compromise lymph flow.

One function of the renal lymphatic vessels is to remove fluid and extravasated plasma protein from the renal interstitium (1-4). Increases in renal lymph flow may be important in maintaining renal function in disease (1-4). Despite the importance of the renal lymphatics, there have been few studies of the physiologic determinants of renal lymph flow. This may be due to the difficulty in measuring the basic factors that affect lymphatic flow. These factors include renal interstitial fluid pressure, the pressure in the initial lymphatics, and the intrinsic contractility of the lymph vessels within the kidney (5-7). However, a model can be used to analyze lymphatic function that does not depend on the direct measurement of any of these factors (8). With this model, the lymphatics of a tissue are represented by an electrical circuit analog consisting of a single pressure source pushing lymph through a single resistance. The values for pressure and resistance are determined from the lymph flow vs. outflow pressure relationship of cannulated lymphatic vessels.

In previous studies, we have used this circuit model to analyze lymphatics from many tissues including lung, liver, and intestine (9-11). In this study, we used the model to investigate renal lymphatics in anesthetized dogs. As in other organs, our results show that increases in renal lymph flow, following augmentation of renal venous
pressure, are attributable to decreases in the effective resistance of the renal lymphatics and increases in lymph driving pressure. Furthermore, increases in pressure at the outflow end of renal lymphatics may significantly decrease renal lymph flow.

**MATERIALS AND METHODS**

All procedures were approved by the University of Texas Animal Welfare Committee and were consistent with the National Institutes of Health “Guide for the Care and Use of Laboratory Animals.” Eleven mixed-breed dogs weighing between 20 and 30 kg were anesthetized with thiopental sodium (25 mg/kg) and intubated. Anesthesia was maintained with 1-2% halothane in room air administered using a Harvard ventilator set at a minute volume necessary to produce PaCO₂ of 40 mmHg.

The left femoral artery and left femoral vein were cannulated with fluid-filled catheters directed into the aorta and the inferior vena cava, respectively. Aortic and inferior vena caval pressures were measured with Statham P23ID transducers and recorded on a Grass polygraph. The right femoral vein was cannulated with a Fogarty balloon-tipped catheter. This was advanced into the inferior vena cava with the balloon positioned between the hepatic and renal veins. The position of the balloon was confirmed by palpation after the abdomen had been opened.

In five dogs, a left-sided paracostal incision was made and the left kidney was exposed. The prenodal collecting lymph vessel at the hilus of the kidney was identified and cannulated with a 22-gauge catheter (Medicut, Sherwood Medical Industries, St. Louis, MO) in the upstream direction. The
Figure 1B. Measured lymph flow rate from a cannulated renal lymphatic plotted as a function of lymphatic outflow pressure at different renal venous pressures ($P_v$) for a single dog. Note the extension of the plateau with increasing $P_v$.

catheter was fixed in position with a ligature and cyanoacrylate. Following catheterization, dogs were given heparin intravenously at a dose of 100 U/kg body weight. Saline-filled tubing (interior diameter = 1.2 mm) was connected to the catheter. The outflow end of the tubing was connected to a pipette inserted into a clamp attached to a vertical calibrated pole. By raising and lowering the pipette with reference to the site of lymphatic cannulation, we could alter the outflow pressure to the lymph vessel ($P_o$). The flow rate from the cannulated lymphatic ($Q_L$) was measured by timing the flow of lymph past calibrated marks on the pipette. We first measured $Q_L$ with the pipette below the site of cannulation. We then raised the height of the pipette 1-2 cm and remeasured $Q_L$. This procedure was repeated until the pipette was high enough to stop lymph flow ($Q_L = 0 \text{ ml/min}$). At each pipette height, the pressure at the site of lymphatic cannulation was calculated as:

$$P_o = \text{pipette height} + Q_L \times \text{cannula resistance} \ (1).$$

Cannula resistance was determined as previously described (11). $Q_L$ was plotted as a function of $P_o$ and a regression line was determined. The effective lymphatic resistance ($R_L$) was calculated from the regression line as $-\Delta P_o/\Delta Q_L$. The effective driving pressure ($P_{1L}$) producing lymph flow was taken as the $P_o$ at which $Q_L = 0 \text{ ml/min}$. This technique for computing $R_L$ and $P_{1L}$ has been used extensively with lymph vessels in other tissues and has been described in detail by Drake et al (8).

In each experiment the $Q_L$ vs. $P_o$ relationship, obtained by changing pipette height, was first measured at baseline vena caval pressure. The Fogarty balloon was then inflated to raise the pressure within the inferior vena cava and therefore, the renal
veins. Because the renal veins drain directly into the inferior vena cava, we recorded the inferior vena caval pressure as renal venous pressure ($P_v$). Elevated $P_v$ was maintained with a constant pressure device (12). After a new steady-state $Q_L$ had occurred (approximately 30-45 minutes), the $Q_L$ vs. $P_O$ relationship was redetermined. This process was repeated until we had recorded the $Q_L$ vs. $P_O$ relationship for several $P_v$'s. $P_L$ and $R_L$ were calculated at each $P_v$.

In two additional groups of dogs, each containing three animals prepared with a midline laparotomy, two new parameters were measured. In the first group, the cisterna chyli was exposed and cannulated with a 22-gauge catheter. The catheter was connected to fluid-filled tubing and a pressure transducer (Statham P23ID), and the pressure in the cisterna chyli was recorded. In the second group, an index of interstitial pressure within the kidney ($P_{int}$) was obtained by injecting Ringer's solution (0.1 ml) into a subcapsular pocket. A 22-gauge needle, connected with saline-filled tubing to a Statham P23ID pressure transducer, was inserted into the subcapsular pocket. Following an initial spike, $P_{int}$ fell to a steady value in approximately ten minutes. Pressure within the pocket was then recorded as $P_v$ was elevated. In these animals, the volume of interstitial edema fluid was determined using a unitless blood-free wet-to-dry weight ratio technique previously described (13). A right nephrectomy was performed at the beginning of the experiment and each animal was used as its own control for quantitation of renal edema. The left kidney was removed at the conclusion of the $P_v$ elevation protocol for interstitial volume determination.

All data are expressed as mean ± SD in

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Fig. 2. Renal lymphatic resistance plotted as a function of renal venous pressure. Values are mean ± SE.
the text and mean ± SE in the figures. We used the method of least squares to determine regression lines (14). Two-way analysis of variance was used to test statistical signifi-
cance between animals and between different $P_v$'s (15). The wet-to-dry weight ratios were 
compared with a Student's $t$-test. A $p$ value <0.05 was considered significant.

RESULTS

Data from a total of 11 dogs are 
presented. At baseline $P_v$ ($P_v = 3.5 ± 3.0$ cm 
H$_2$O), we found little change in $Q_L$ as we 
increased $P_o$ from -5 to 0 cm H$_2$O (Fig. IA). 

In three dogs, this plateau in the $Q_L$ vs. $P_o$ relationship extended to higher $P_o$'s as we 
increased $P_v$ (Fig. IB). In two other dogs, the 
plateau did not appear to shift substantially 
with augmented $P_v$ (Fig. IA).

$Q_L$ decreased linearly with increases in

$P_o$ above the plateau region. At baseline $P_v$, 
we calculated $R_L = 0.34 ± 0.14$ cm 
H$_2$O•min/μl and $P_L = 8.2 ± 4.4$ cm H$_2$O from 
the linear $Q_L$ vs. $P_o$ relationships. When we 
increased $P_v$, the $Q_L$ vs. $P_o$ relationship 
became steeper and shifted to the right (Figs. 
1A and 1B). Accordingly, the calculated $R_L$'s 
decreased (Fig. 2) and the $P_L$'s increased (Fig. 
3). These changes in $R_L$ and $P_L$ with 
elevations in $P_v$ were significant, but we 
found no significant between-animal 
differences in the data. As found in other 
studies (9,16), the absolute value for $Q_L$ 
varied considerably between animals.

Renal $P_{in}$ varied directly with changes in 
$P_v$. The blood-free wet-to-dry weight ratio 
increased significantly from $4.20 ± 0.26$ at 
baseline to $4.90 ± 0.20$ following two hours of 
$P_v$ elevation. We could not detect a change in 
$P_{in}$ associated with this edema formation as 
determined by the $P_{in}$ vs. time relationship. A
Fig. 4. Equivalent circuit diagram of a cannulated renal lymph vessel. \( P_L \) = effective lymph driving pressure; \( R_L \) = effective resistance of lymphatic vessels; \( Q_L \) = lymph flow rate; \( P_O \) = pressure at the site of lymph cannulation (calculated as \( P_O = Q_L \times \text{cannula resistance} + \text{height of the pipette above the cannulation site} \)).

Line with a constant slope was found indicating that increases in \( P_{int} \) were directly attributable to venous engorgement secondary to increased \( P_v \). Control cisterna chyli pressure was 3.2 ± 1.5 cm H₂O.

**DISCUSSION**

Our results show that, as in other tissues, increases in \( P_O \) to renal lymphatics cause \( Q_L \) to decrease. However for \( P_O \)'s lower than a critical level, there was a plateau in the \( Q_L \) vs. \( P_O \) relationship. Although this plateau occurs in the \( Q_L \) vs. \( P_O \) relationships of other organs (9,16), it was more prominent in the renal lymphatics of this study (Figs. 1A and 1B). Furthermore in some experiments, the \( P_O \) at which \( Q_L \) began to decrease, increased when we elevated \( P_v \). In other words, the plateau extended farther to the right (Fig. 1B) with augmented \( P_v \). We have not found this phenomenon in lymphatics from any other organs.

We have previously proposed that the plateau of the \( Q_L \) vs. \( P_O \) relationship is attributable to the “Starling resistor” phenomenon (9). That is, if the pressure within a flaccid lymphatic vessel is less than the
external pressure, the vessel will collapse. \( Q_l \) through collapsed lymphatics will not vary with changes in \( P_o \) if this pressure is less than the external pressure acting on the lymphatics. For instance in our previous lung experiments (9), that part of the lymphatic vasculature outside the lung parenchyma was exposed to an external pressure equal to atmospheric pressure, and the plateau was evident for \( P_o = 0 \) cm H\(_2\)O. In the experiments of this study, the plateau often extended well above \( P_o = 0 \) cm H\(_2\)O. We believe this results from the relatively high renal tissue pressure surrounding the intrarenal portion of the lymphatics. This tissue pressure collapses the intrarenal portion of the collecting lymphatics so that, for \( P_o \)'s less than \( P_{int} \), there should be little change in \( Q_l \) with alterations in \( P_o \). This is in contrast to the effects of increasing \( P_{int} \) on the initial intrarenal lymphatics which are tethered via anchoring filaments to the interstitium. The equivalent circuit model for the kidney is illustrated in Fig. 4. At \( P_o < P_{int} \), the intrarenal portions of the collecting lymphatics would be collapsed and \( Q_l = (P_L - P_{int})/R_L \). However when \( P_o > P_{int} \), \( Q_l = (P_L - P_o)/R_L \). When we increased \( P_v \) in this study, we observed that the kidney became more tense, \( P_{int} \) increased, and renal edema developed. Consequently, the intrarenal collecting lymphatics may have remained collapsed at higher \( P_o \)'s. This could explain the extension of the plateau with increasing \( P_v \)'s shown in Fig. 1B.

The equivalent circuit model, when applied to the kidney, predicts that \( R_L \) represents the effective hydraulic resistance and \( P_I \) approximates the driving pressure of the renal lymphatics (9,16). The decrease in \( R_L \) (Fig. 2) and the increase in \( P_L \) (Fig. 3) associated with increases in \( P_v \) are consistent with the \( R_L \) and \( P_L \) changes in lymph vessels of other tissues (9-11). Because anesthesia inhibits lymphatic contractions, we believe that the increase in \( P_L \) may be attributable to an increase in interstitial fluid pressure at the entrance to the lymphatic vessels (16). The decrease in \( R_L \) may be associated with lymphatic distention or recruitment of previously collapsed lymphatic vessels (9).

We do not believe that lymph shunting contributed to variations in flow from the cannulated lymphatic. Previously, we showed that lymphatic to lymphatic shunting may not significantly contribute to removal of interstitial fluid (17). Furthermore, when we isolated the lymphatic to be cannulated at the renal hilus, a single collecting prenodal lymphatic vessel resulting from the anastomosis of several smaller lymphatic vessels was frequently found. We selectively cannulated this larger collecting lymphatic. Although the kidney has two lymphatic drainages, hilar and capsular (18), we contend that the measured \( Q_L \) accurately represents the lymph flow arising from the renal hilus.

As shown in Figs. 1A and 1B, \( Q_L \) from the cannulated lymphatic vessels varied with \( P_o \). Flow from a cannulated lymphatic vessel should equal flow in uncannulated vessels only when \( P_o \) equals the pressure normally opposing lymphatic flow. Renal lymphatics drain into the cisterna chyli. Thus, \( P_o \) to uncannulated renal lymphatics should approximately equal the pressure within the cisterna chyli. For each experiment, we estimated uncannulated renal lymph flow from the \( Q_L \) vs. \( P_o \) relationships with \( P_o = \) cisterna chyli pressure that we measured (3.2 ± 1.5 cm H\(_2\)O). The resulting \( Q_L \)'s are plotted vs. \( P_v \) in Fig. 5. It illustrates our estimate of the relationship between \( Q_L \) in uncannulated renal lymph vessels and \( P_v \).*

*In previous studies, we used calculated \( R_L \)'s and \( P_L \)'s to estimate \( Q_L \) in uncannulated lymphatic vessels from various tissues (9-11). However, in some experiments of the present study, the \( Q_L \) vs. \( P_o \) plateau region included \( P_o \) equal to cisterna chyli pressure. Because \( R_L \) and \( P_L \) were calculated from \( Q_L \) vs. \( P_o \) data at \( P_o \)'s above the plateau, we could not use \( P_L \) and \( R_L \) to estimate \( Q_L \) that would have occurred in lymphatics with \( P_o = \) cisterna chyli pressure.
We conclude that for renal lymphatics, as in lymphatics from other tissues, \( Q_L \) varies inversely with \( P_O \). Increases in renal \( Q_L \) resulting from \( P_V \) elevation are attributable to increases in \( P_L \) driving lymph from the kidneys and decreases in \( R_L \) of the renal lymphatic vessels. In contrast to previous studies, there was an extension of the \( Q_L \) vs. \( P_O \) plateau associated with high renal tissue pressure. Extension of this plateau suggests that compensatory increases in \( Q_L \) may be compromised by increases in renal interstitial pressure because the intrarenal portions of the collecting lymphatics may partially collapse.

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REFERENCES


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