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Renal Lymph Flow and Composition During Acetazolamide and Furosemide Diuresis

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Abstract:

Several lines of research suggest that renal lymph is formed totally, or in part, as a filtrate of postglomerular blood. Even so, renal interstitial fluid dynamics is necessarily dominated by the rapid transfer of large volumes of reabsorbate from tubular lumen to peritubular capillary. To determine the effects of tubular reabsorption on lymph formation, renal lymph flow and composition were studied before and during alterations in tubular reabsorption produced by diuresis. A 25% reduction in whole kidney fluid reabsorption rate did not alter renal lymph flow or lymph protein concentration. A concomitant decrease in plasma protein concentration, however, suggests that any deficit in lymph flow resulting from decreased reabsorbate content may have been obscured by an increase in vascular filtration. An increase in renal lymph PAH and creatinine concentrations relative to those of arterial and renal venous blood plasma supports this conclusion. It appears that renal lymph flow may be determined by both vascular filtration and tubular reabsorption.

There is little doubt that renal lymph formation is related to renal function and hemodynamics. Renal lymph flow is directly proportional to both renal blood flow (1,2) and renal small vein pressure (3). These effects are, for the most part, mediated by changes in the balance of Starling forces in the postglomerular microcirculation. Changes in renal vein pressure are notably without effect until venous pressure is elevated to the level of preexisting interstitial and small vein pressure (4,5) after which intratubular pressure, interstitial fluid pressure, and peritubular capillary pressure rise together (5,6). Thus, increases in peritubular capillary and venular hydrostatic pressures appear to be balanced by similar increases in renal interstitial fluid pressure. The increased renal interstitial fluid pressure provides a driving force for increased renal lymph flow during elevated venous pressure (3) and maintains a relatively constant peritubular capillary transmural hydrostatic pressure to assure adequate uptake of tubular reabsorbate. This latter effect would account for the findings of some workers that show a relatively constant renal lymph composition over a wide range of renal vein pressures (7,8). It is likely that maintenance of renal interstitial fluid pressure is, in part, due to continuous delivery of tubular reabsorbate to the peritubular fluid. The experiments of the present study were designed to determine the changes in renal lymph flow and composition that follow a decreased delivery of tubular reabsorbate to the renal interstitium and peritubular capillary network during unaltered renal vein pressure.

METHODS

The left kidney was exposed in mongrel dogs (n=5) anesthetized with sodium pentobarbital (30 mg/kg). Catheters were secured in the ureter, femoral artery, vena cava *via* the femoral vein and renal vein *via* the gonadal vein. A polyethylene catheter was tied into a hilar renal lymphatic vessel for lymph collections. Arterial and venous

pressures were constantly monitored using resistance bridge transducers and a Grass polygraph. Timed collections of urine and renal lymph were made in calibrated containers with midpoint collections of arterial and renal vein blood. Each animal received a priming dose of PAH and creatinine followed by a sustaining infusion (2 ml/min) of 0.9% saline containing sufficient PAH and creatinine to maintain adequate plasma levels of these substances. In each experiment, a single control sample of renal lymph and urine was collected for no more than 90 min., with blood collections equally spaced by intervals no greater than 30 min. After collecting control samples, each animal was given acetazolamide (10 mg/kg) and furosemide (0.5 mg/kg). No attempt was made to differentiate between the effects of acetazolamide and furosemide diuresis, since our primary objective was to produce a large decrease in tubular reabsorption, regardless of mechanism. Following a 15 min. equilibration period, a final collection of lymph, plasma and urine was made. Urinary fluid loss was replaced by Ringer's solution and additional diuretic was administered, as needed, to maintain the diuresis. Lymph, plasma and urine samples were analyzed for creatinine by the Jaffe reaction and for PAH by the method of Smith, *et al* (9). Lymph and plasma protein concentrations were obtained using a biuret reaction. Renal blood flow was obtained using the Fick principle applied to PAH data and hematocrit.

The lymph concentration index (LCI), which relates lymph concentration to the respective arteriovenous concentration difference, was calculated as the arterial plasma concentration minus the renal lymph concentration divided by the arterial plasma concentration minus the renal venous plasma concentration. Whole-kidney fluid reabsorption rate was calculated as creatinine clearance minus urine flow. Student's t test for paired data was used for statistical comparisons, and linear correlation was used where applicable.

RESULTS

The combined effects of acetazolamide and furosemide resulted in a 20 fold increase in urine flow ($P<0.01$), while creatinine clearance remained unchanged (Table 1). This resulted in a significant reduction ($P<0.01$) in whole kidney fluid reabsorption rate (FRR). While plasma protein concentrations were significantly decreased during the diuresis period, the renal lymph protein concentrations were not (Table 2). In spite of this discrepancy, the renal lymph-to-plasma ratio (L/P) for protein during diuresis (0.51 ± 0.06 S.E.) was not significantly different from that obtained during control (0.49 ± 0.07 S.E.). The arterial plasma minus renal lymph protein concentration difference varied from 1.72 to 3.73 g/dl, but this variation was not related to the renal fluid reabsorption rate when tested by linear correlation ($r=0.32$, $P>0.05$). Blood pressures were unchanged during these experiments, as were renal blood flow and lymph flow (Table 1). No significant correlation was found between blood flow and lymph flow changes ($r=0.41$, $P>0.05$).

Table 1
Renal Function and Lymph Flow

		Control	Diuresis
RBF (ml/min/g)	$\bar{x}$	3.24	3.21
	S.E.	0.35	0.10
Ccr (ml/min)	$\bar{x}$	41.4	39.5
	S.E.	4.2	3.1
FRR† (ml/min)	$\bar{x}$	38.3	29.4*
	S.E.	3.9	2.8
Lymph Flow (μL/min)	$\bar{x}$	25.2	26.8
	S.E.	2.8	2.4

*Significant change ($P<0.01$)
†Whole kidney fluid reabsorption rate

As shown in Table 2, renal lymph concentrations of PAH and creatinine were intermediate to those of arterial and renal

Table 2
Renal Lymph (L), Arterial (AB) and Renal Vein Blood (VB) Concentrations of PAH, Creatinine (Cr) and Protein

		Control			Diuresis		
		AB	L	VB	AB	L	VB
PAH	$\bar{x}$	15.76	7.59	4.56	16.60	8.27	3.66
(μg/ml)	S.E.	1.62	0.62	0.70	1.64	0.87	0.60
Cr	$\bar{x}$	152.6	116.6	105.2	157.0	129.0*	115.9*
(μg/ml)	S.E.	9.1	4.4	4.5	8.5	6.7	6.3
Protein	$\bar{x}$	5.21	2.53	5.13	4.97*	2.50	4.97*
(g/dl)	S.E.	0.18	0.34	0.19	0.18	0.28	0.20

*Significant change ($P<0.05$)

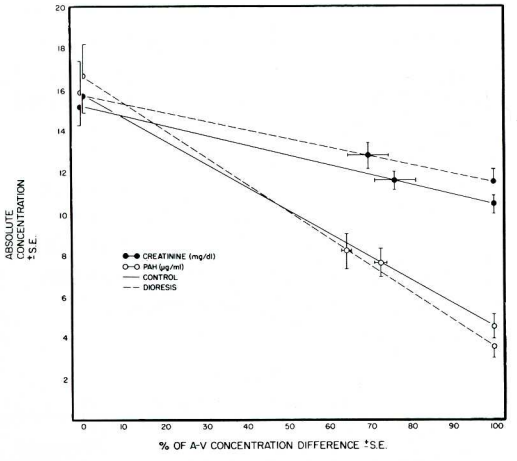

Fig. 1. Absolute concentrations of creatinine (mg/dl) and PAH (μg/ml) in arterial plasma (left margin), renal venous plasma (right margin), and renal lymph (intermediate) are related to total arteriovenous differences as percents (abscissa).

vein blood plasma. No significant changes in PAH concentrations were observed, but both lymph and renal vein plasma concentrations of creatinine were increased during diuresis. As suggested by the data of Table 2, the arterial plasma minus renal lymph concentration differences were significantly correlated ($P<0.01$) to the arteriovenous concentration differences for both PAH and creatinine ($r=0.94$ and $r=0.84$ for PAH and creatinine, respectively). The pertinent relationships are shown graphically in Figure 1. The significant change in mean lymph creatinine concentration shown in Table 2 is now seen to result from an upward shift in arterial and venous plasma concentrations, while the relationship of the arterial plasma — lymph creatinine concentration difference to the overall arteriovenous difference remains unchanged ($P>0.05$). The arterial plasma — lymph PAH concentration, however was shifted toward the arterial plasma concentration ($P<0.05$).

DISCUSSION

In a similar study, Stowe and Hook (10) reported that renal lymph flow was often increased during furosemide diuresis. These authors, however, concluded that the lymph flow changes resulted from furosemide induced increases in RBF, rather than from the diuresis itself. Similarly, O'Morchoe, *et al* (11) reported that renal lymph flow decreases found in their study were not correlated with either the dose of furosemide given, or the extent of the ensuing diuresis, but RBF was not measured. In our experiments, both RBF and renal lymph flow were constant throughout each experiment while whole-kidney fluid reabsorption rate was greatly decreased.

Furosemide induced changes in RBF and redistribution of blood flow within the kidney are likely on the basis of available data (12). Even so, variability in the renal

hemodynamic response has been predicted on the basis of differences in experimental design and technique (10). Stowe and Hook (10) also reported that in 4 dogs renal lymph protein concentration was unchanged during furosemide diuresis, but they found that RBF increased in 11 of 16 dogs without specifying in which of the 16 dogs lymph protein was measured. In our study, we have shown that a substantial reduction (about 25%) in whole kidney fluid reabsorption rate does not alter either renal lymph flow or lymph protein concentration when RBF remains constant. It is reasonable to expect a decrement in renal lymph flow that is proportional to the decrease in FRR and relative to the reabsorbate content of the lymph. On the other hand, interpreting these data is seriously complicated by the decrease in plasma protein concentration observed during the diuresis phase of the experiment. This protein concentration difference probably results from plasma dilution by the "sustaining" infusion given over the two to three hours necessary to obtain the renal lymph samples. Calculated by the method of Navar and Navar (13) this plasma protein change would result in an oncotic pressure decrease of approximately 0.75 mmHg. While this pressure decrease was not statistically significant ($p>0.05$), it could account for an increase of approximately 2 μL/min in single lymphatic lymph flow as estimated from previous studies (3,7).

The lack of any lymph flow change in our data suggests that a decrement in lymph reabsorbate content may have been replaced by an increase in vascular filtration. In support of this possibility, it should be noted that the renal lymph protein concentration was unchanged during diuresis, while those of blood plasma were decreased. In addition, the increase in lymph PAH concentration noted in Fig. 1 could be the result of increased vascular filtration and a decrease in PAH-free reabsorbate in the lymph.

A similar change in renal lymph PAH content was observed during a diuresis produced by renal artery infusion of acetylcholine (14). In the latter study, the lymph PAH change was attributed to a presumed increase in outer medullary lymph formation. We know of no data that would preclude this interpretation for our present data as well, especially since the anatomical sites of postglomerular vascular filtration are as yet unknown (8). In any case, the mechanism(s) of renal lymph formation produce a fluid in which creatinine and PAH concentrations are strongly correlated to their respective overall arteriovenous concentration differences. Even so, the intermediate positions of lymph concentrations illustrated in Fig. 1 suggest that the lymph must be formed from blood plasma which has not yet attained the characteristics of renal vein blood plasma, that lymph composition is altered in transit through the renal parenchyma, or both.

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I began to think whether there might be a motion as it were in a circle in the same way as Aristotle says that the air and the rain emulate the circular motion of the superior bodies....And so in all likelihood does it come to pass in the body through the motion of the blood.

William Harvey, De Motu Cordis