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Research Article

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Mechanism of Inhibition of Proximal Tubule Fluid Reabsorption after Exposure of the Rat Kidney to the Physical Effects of Expansion of Extracellular Fluid Volume

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ABSTRACT The natriuresis and concomitant decline in absolute proximal reabsorption (APR) that occur in rats in response to saline loading are blunted markedly when renal perfusion pressure is reduced immediately before, but not after, the volume load. To ascertain the mechanism responsible for these differences between early clamp (EC) vs. late clamp (LC), intracapillary and interstitial determinants of peritubular capillary uptake of APR were measured in seven LC and seven EC Munich-Wistar rats before and after isotonic saline loading (8% body wt). With volume expansion in LC animals, we observed a marked decline in APR (averaging 11±1 nl/min), associated with large increases in urinary sodium excretion rate, which averaged 8±2 μeq/min. In EC, the changes in urinary sodium excretion rate (+1±0 μeq/min) and APR (−3±1 nl/min) with volume expansion were smaller in magnitude. Since peritubular capillary reabsorption coefficient and mean peritubular transcapillary hydraulic pressure difference did not change with saline loading in LC, the marked fall in APR was attributed primarily to a measured large decline in mean peritubular transcapillary oncotic pressure difference ($\overline{\Delta\Pi}$). Despite an equivalent mean fall in $\overline{\Delta\Pi}$ with volume expansion in EC, near-constancy of APR was found to be associated with a simultaneous and equivalent decline in mean peritubular transcapillary hydraulic pressure difference (a consequence of decreased mean peritubular capillary hydraulic pressure), which effectively offset the fall in $\overline{\Delta\Pi}$. These results demonstrate the importance of hydraulic pressure patterns of the peritubular capillaries in modulating APR and are consistent with the view that Starling forces across the postglomerular microcirculation play a fundamental role in determining APR.

INTRODUCTION

Almost 20 yr ago, Wardener and his colleagues (1) demonstrated in dogs that saline-induced natriuresis persisted even when renal perfusion pressure was decreased sufficiently to reduce glomerular filtration rate (GFR). More recently, Fitzgibbons et al. (2) noted that whereas natriuresis persisted in saline-loaded rats despite reduction in renal perfusion pressure (late clamp), this natriuretic response to volume expansion was markedly blunted when renal perfusion pressure was reduced before the administration of the saline load (early clamp). This finding has since been confirmed by others (3–6). Osgood et al. (4) showed that this difference in sodium excretion rate was also accompanied by a difference in absolute proximal reabsorption rate (APR). A marked fall in APR occurred with saline loading in the late clamp group, but APR remained essentially constant with early clamping, despite a comparable degree of volume expansion. In view of these observations, the authors of these various studies have suggested that intrarenal, rather than plasma compositional or circulating humoral, factors were primarily responsible for these differing reabsorptive responses to early vs. late clamping. Moreover, insofar as systemic protein concentration (4) and filtration fraction (2) were affected equally by early and late clamping, these studies might also be taken as evidence against a role for postglomerular oncotic pressure as a major determinant of these differing sodium reabsorptive responses. Without an evalua-

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tion of the remaining transcapillary Starling forces, however, a meaningful assessment of the role of peritubular physical factors under these conditions is not possible. We therefore undertook to measure each of the intracapillary and interstitial determinants of peritubular transcapillary fluid exchange to assess more critically whether peritubular physical factors are capable of accounting for the differing responses of APR and whole kidney sodium excretion rate ($U_{Na}V$) to early vs. late clamp in rats subjected to saline loading.

GLOSSARY OF SYMBOLS

A/G	Albumin-to-globulin concentration ratio.
APR	Absolute proximal reabsorption rate, *nl/min*.
C	Protein concentration, *g/dl*.
EABF	Efferent arteriolar blood flow rate, *nl/min*.
EC	Early clamp, i.e., employment of aortic clamp before volume expansion with isotonic saline.
FE_{Na}	Fractional excretion of sodium (sodium clearance/inulin clearance) × 100, %.
GBF	Glomerular blood flow rate, *nl/min*.
GFR	Whole kidney glomerular filtration rate, *ml/min*.
Hct	Blood hematocrit in femoral artery, *vol%*.
K_r	Peritubular capillary reabsorption coefficient, *nl/(s·mm Hg)*.
LC	Late clamp, i.e., employment of aortic clamp after volume expansion with isotonic saline.
P	Hydraulic pressure, *mm Hg*.
P_{GC}	Hydraulic pressure in single glomerular capillaries, *mm Hg*.
P_r	Local net peritubular transcapillary reabsorptive pressure, *mm Hg*.
ΔP	Peritubular transcapillary hydraulic pressure difference, $P_C - P_I$, *mm Hg*.
Π	Oncotic pressure, *mm Hg*.
$\Delta\Pi$	Peritubular transcapillary oncotic pressure difference, $\Pi_C - \Pi_I$, *mm Hg*.
Q	Plasma flow rate, *nl/min*.
R	Resistance to blood flow, *dyn-s-cm*$^{-5}$.
RAP	Mean left renal arterial pressure, *mm Hg*.
SNFF	Single nephron filtration fraction.
SNGFR	Single nephron glomerular filtration rate, *nl/min*.
$(TF/P)_{in}$	Late proximal tubule fluid-to-plasma inulin concentration ratio.
$U_{Na}V$	Whole kidney excretion rate of sodium, *μeq/min*.
V_{TF}	Tubule fluid flow rate, *nl/min*.

Superscript

——	Mean value.

Subscript

A	Afferent arteriole.
C	Peritubular capillary.
C^1	Distal-most surface branches of peritubular capillary.
E	Efferent arteriole.
I	Cortical interstitium.
T	Proximal tubule.

METHODS

Experiments were performed in 14 adult male Munich-Wistar rats weighing 251–350 g and allowed free access to standard rat pellet chow and water before study. Rats were anesthetized with Inactin (100 mg/kg, i.p.; Byk Gulden Lomberg Chemische Fabrik GmbH, Konstanz; W. Germany) and prepared for micropuncture as described (7). To restore plasma losses during surgical preparation and micropuncture study (7, 8), each rat received an intravenous infusion of homologous rat plasma (obtained at time of micropuncture by exsanguination of a littermate) at the rate of 10 ml/kg per h for the first 45 min, followed by reduction in infusion rate to 1.5 ml/kg per h for the remainder of each experiment. To widen the subcapsular space for micropuncture measurements of cortical interstitial hydraulic pressure (P_I) (see below) each rat was given an intravenous infusion of a volume of isotonic saline equal to 3% body wt administered in a period of 45 min. The infusion rate was then reduced to 10 ml/kg per h for the remainder of the initial study period, thus maintaining urine flow rate essentially constant. An intravenous infusion of inulin in 0.9% NaCl, given at the rate of 1.2 ml/h, was begun 60 min before micropuncture study, resulting in final plasma inulin concentrations of about 100 mg/dl. Left renal arterial pressure (RAP) was monitored via a catheter placed in the left femoral artery by means of an electronic transducer (model P23Db, Statham Instruments Div., Gould Inc., Oxnard, Calif.) connected to a direct-writing recorder (model 7754A, Hewlett-Packard Co., Palo Alto, Calif.). Late surface convolutions of proximal tubules were located by observing the passage of lissamine green dye, which was injected rapidly (0.05 ml of a 5% solution) into a right jugular vein catheter.

In all experiments the following micropuncture measurements and collections were carried out in random order: exactly timed (1–2 min) samples of fluid were collected from surface late proximal convolutions from each of two or three nephrons for determination of flow rate and inulin concentration and calculation of tubule fluid-to-plasma inulin concentration ratios [$(TF/P)_{in}$], and single nephron glomerular filtration rate (SNGFR) and APR. Coincident with these tubule fluid collections, two or three samples of femoral arterial blood were obtained for determination of systemic arterial hematocrit (Hct) and plasma concentrations of total protein, inulin, and sodium. In addition, two or three samples of urine from the experimental kidney were collected for determination of flow rate, and inulin and sodium concentrations, and for calculation of total kidney GFR, and $U_{Na}V$ and fractional excretion of sodium (FE_{Na}). For these urine collections, indwelling ureteral polyethylene catheters (PE-50 or PE-10) were used.

Hydraulic pressures were measured in single capillaries of surface glomeruli with a continuous recording, servo-null micropipette transducer system (model 3, Instrumentation for Physiology and Medicine, San Diego, Calif.). Micropipettes with outer tip diameters of 2–3 μm and containing 2.0 M NaCl were used. Hydraulic output from the servo-null system was coupled electronically to a second channel of the Hewlett-Packard recorder by means of a pressure transducer. Direct measurements of time-averaged hydraulic pressures in single glomerular capillaries ($\bar{P}_{GC}$), proximal tubules (P_T), efferent arterioles (P_E), and the distal-most surface branches of peritubular capillaries (P_{C^1}) were recorded in each rat. Using the same device, subcapsular space hydraulic pressures were also measured and the values were taken to reflect renal P_I.[1]

[1] Since the mathematical model for peritubular transcapillary fluid exchange recently developed by us and others for rats deals with data from superficial cortical nephrons primarily, subcapsular hydraulic pressure has been exclusively used in assessing local interstitial hydraulic pressure in this area. For these measurements of P_I, micropipettes were inserted just beneath the renal capsule. After

During all study periods, the subcapsular space was sufficiently wide for easy insertion of micropipettes and thus measurement of P_I.

Protein concentration of plasma entering glomerular (C_A) and peritubular capillaries (C_E) was determined by analyzing femoral arterial and surface efferent arteriolar blood plasmas, respectively. These inlet estimates of pre- and postglomerular plasma protein concentration also permit calculation of single nephron filtration fraction (SNFF). Oncotic pressure (Π) was estimated from values of C_A or C_E using Eq. 2. In addition, renal lymph was obtained by inserting micropipettes (outer tip diameter of ≅25 μm) into an intact renal hilar lymph vessel. Since renal lymph is thought to originate primarily in the cortex (9–12), interstitial oncotic pressure (Π_I) was estimated from the value of protein concentration of this lymph fluid, using Eq. 2.

Late-clamp (LC) group (n = 7 rats). 10 min after completion of control measurements and collections at normal renal perfusion pressures, the infusion of isotonic saline was increased to a rate calculated to deliver a volume of 8% body wt in 60 min. 60 min later, RAP to the left kidney was reduced to ≅75 mm Hg by means of partial constriction of the abdominal aorta and RAP was maintained at this level for the remainder of the experiment. Partial aortic constriction was achieved by applying tension to a 000 silk ligature encircling the abdominal aorta between the origins of the renal arteries. Concomitantly, the infusion rate of isotonic saline was reduced to 30 ml/kg per h for the remainder of the experiment. 15 min later, measurements and collections specified above were repeated, again in random order. Re-collections of late proximal tubule fluid were obtained from previous puncture sites of the same tubules studied in the initial period.

Early-clamp (EC) group (n = 7 rats). After completion of control measurements at normal renal perfusion pressures, RAP was reduced to ≅75 mm Hg and maintained at this level for the remainder of each experiment, employing the technique of partial aortic constriction described above. After reducing RAP (beginning 10 min after the completion of initial measurements), the infusion of isotonic saline was increased to a rate computed to deliver a volume of 8% body wt in 60 min. 60 min later, the rate was again reduced to 30 ml/kg per h and maintained at this level for the remainder of the experiment. 15 min later, measurements and collections specified above were repeated.

Analytical. The volume of fluid collected from individual end-proximal tubules was estimated from the length of the fluid column in a constant-bore capillary tube of known internal diameter. The concentration of inulin in tubule fluid was measured in duplicate by the microfluorescence method of Vurek and Pegram (13). Inulin concentrations in plasma and urine were determined by the macroanthrone method of Führ et al. (14). C_A and C_E were determined, usually in duplicate, using the fluorometric method of Viets et al. (15). Protein concentration in hilar lymph fluid was determined with an ultra-microcolorimeter, using a microadaptation (16) of the method of Lowry et al. (17). Sodium concentrations of plasma and urine were determined by flame photometry.

Calculations

Single nephron glomerular filtration rate: $SNGFR = (TF/P)_{In} \times V_{TF}$, where $(TF/P)_{In}$ and V_{TF} refer to tubule fluid-to-plasma inulin concentration ratio and tubule fluid flow rate, respectively. Absolute proximal reabsorption: $APR = SNGFR - V_{TF}$. Single nephron filtration fraction: $SNFF = 1 - (C_A/C_E)$. Initial glomerular plasma flow rate: $Q_A = SNGFR/SNFF$. Efferent arteriolar plasma flow rate: $Q_E = Q_A - SNGFR$.

According to the Starling relationship, the rate of peritubular uptake of APR is given by:

$$APR = K_r \times \bar{P}_r, \tag{1}$$

where K_r and $\bar{P}_r$ represent peritubular capillary reabsorption coefficient and mean net reabsorptive pressure, respectively. Local net reabsorptive pressure (P_r) at any point along a capillary is given by: $P_r = \Delta\Pi - \Delta P = (\Pi_C - \Pi_I) - (P_C - P_I)$, where Π_C and P_C are the local peritubular capillary oncotic and hydraulic pressures, respectively, and Π_I and P_I are the corresponding pressures in the surrounding cortical interstitium. Thus, the value of P_r at the inlet of the peritubular capillary (P_{r^o}) is given by: $P_{r^o} = (\Pi_E - \Pi_I) - (P_E - P_I)$. Likewise, the value of P_r at the distal-most surface branch of a peritubular capillary (P_{r^1}) is given by the expression: $P_{r^1} = (\Pi_{C^1} - \Pi_I) - (P_{C^1} - P_I)$.

For the equations for P_{r^o} and P_{r^1} as well as Eqs. 3 and 4 given below, oncotic pressures (Π) were calculated from the values of corresponding protein concentrations (C) with the following relationship (18, 19):

$$\Pi = a_1 C + a_2 C^2, \tag{2}$$

where $a_1 = 1.63$ and $a_2 = 0.249$ (for $4 \leqq C \leqq 10$ g/dl) for plasmas, assuming an albumin-to-globulin concentration ratio (A/G) of 1.0, the ratio found in normal rats by us and others (20–22). For renal lymph, $a_1 = 1.89$ and $a_2 = 0.469$ (for $0 \leqq C \leqq 2$ g/dl), assuming an A/G of 2.0, the ratio also found in rats by us and others (21, 22).

Protein concentration at the distal-most surface branch of peritubular capillary is given by: $C_{C^1} = C_E/[1 + (APR/Q_E)]$.[2] Furthermore, an estimate of $\bar{P}_r$ is defined as

$$\bar{P}_r = \int_0^1 [(\Pi_{Cx^*} - \Pi_I) - (P_{Cx^*} - P_I)]dx^*, \tag{3}$$

where x^* is fractional distance along the peritubular capillary and $\bar{P}_r$ is the integrated mean value between P_{r^o} and P_{r^1}. $\Pi_{Cx}{}^*$ and $P_{Cx}{}^*$ are local peritubular capillary oncotic and hydraulic pressures, respectively, at point x^*.

Because Π_I and P_I are constant in Eq. 3, $\bar{P}_r$ may also be expressed as

$$\bar{P}_r = \overline{\Delta\Pi} - \overline{\Delta P} = (\bar{\Pi}_C - \Pi_I) - (\bar{P}_C - P_I), \tag{4}$$

where $\bar{P}_C$ is estimated[3] to be $0.5 \times (P_E + P_{C^1})$.

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obtaining stable subcapsular pressures, pipettes were advanced into a nearby proximal convolution and difference in magnitude of hydraulic pressure ($P_T \gg P_I$) was confirmed each time.

[2] Since distal convoluted tubules of superficial nephrons are also perfused with surface peritubular capillaries, APR undoubtedly underestimates true peritubular capillary fluid uptake in absolute terms. In view of the small amount of reabsorption by cortical distal convolutions (≅5% of filtered load), however, the magnitude of this underestimation is quite small. Moreover, probably less than one-half of all superficial nephrons have distal convolutions on the renal cortical surface. We have therefore chosen, as have others (19, 23), to neglect this distal reabsorptive component, which we estimate to be <1.5 nl/min, compared to measured APR values averaging >12 nl/min, and usually >20 nl/min.

[3] Although the true profile of P_C with distance along peritubular capillaries may not be strictly linear, this assumption is a reasonable approximation in view of our findings that values of P_C measured at second-order branches of efferent arterioles are roughly midway between measured values for P_E and P_{C^1}.

K_r and $\bar{P}_r$ were calculated with a differential equation which gives the rate of change of intravascular protein concentration with distance along an idealized peritubular capillary. This equation, together with the method for its solution and a discussion of its validity, is given in detail elsewhere (18, 19).

Blood flow rate per single afferent arteriole or glomerulus: $GBF = Q_A/(1 - Hct_A)$, where Hct_A, the hematocrit of afferent arteriolar blood, is taken as equal to femoral arterial hematocrit. Efferent arteriolar blood flow rate: EABF = GBF − SNGFR. Resistance per single afferent arteriole: $R_A = [(RAP - \bar{P}_{GC})/GBF] \times 7.962 \times 10^{10}$, where the factor 7.962×10^{10} is used to give resistance in dyn-s-cm^{-5}, when RAP and $\bar{P}_{GC}$ are expressed in mm Hg and GBF in nl/min.

Resistance per single efferent arteriole (excluding peritubular capillary): $R_E = [(\bar{P}_{GC} - P_E)/EABF] \times 7.962 \times 10^{10}$.

Statistical analyses were performed by the paired and unpaired *t* test, where appropriate. Statistical significance is defined as $P < 0.05$.

RESULTS

Control period. Mean values for body wt, RAP, and a number of pertinent measures of plasma and urine composition and single nephron function in LC and EC groups are summarized in Table I. Mean body wt in LC and EC were essentially identical, as were control values for RAP, Hct, C_A, whole kidney GFR, SNGFR, Q_A, $U_{Na}V$, and FE_{Na}. As shown in Table I, values for $(TF/P)_{In}$ and APR were likewise similar in the control period of each group.

After saline load and aortic clamp. Identical degrees of volume expansion and reduction in RAP were achieved in LC and EC groups. Values for Hct and C_A fell in LC and EC, on average by 4.3±0.8% and 1.3±0.1 g/dl, respectively, in LC and by 4.5±0.7% and 1.3±0.1 g/dl in EC (Table I), indicating comparable degrees of hemodilution in LC and EC as well. With reduction in RAP in these volume-expanded rats, whole kidney GFR, SNGFR, and Q_A fell significantly, and to a similar extent in LC and EC (on average by 0.37±0.08 ml/min, 10.2±1.6 nl/min, and 32±4 nl/min, respectively in LC, and by 0.30±0.07 ml/min, 7.1±1.0 nl/min, and 26±4 nl/min in EC). Despite these similarities in the changes of RAP, Hct, C_A, GFR, SNGFR, and Q_A, marked differences in $U_{Na}V$, FE_{Na}, $(TF/P)_{In}$, and APR were observed between LC and EC. Thus, with volume expansion followed by delayed reduction in RAP in LC rats, values for both $U_{Na}V$ and FE_{Na} increased, on average, more than fourfold above control levels (i.e., by 7.5±1.5 μeq/min and by 5.0±0.6%). With volume expansion after aortic clamp, however, the increments in $U_{NA}V$ and FE_{Na} above control were much less, averaging only 0.5±0.4 μeq/min and 0.6±0.2%, respectively. Likewise, in contrast to the marked falls in average values for $(TF/P)_{In}$ and APR found in LC rats, aortic clamp before saline loading largely (although not completely) prevented declines in these two indices in EC rats (Table I). Thus, our findings accord well with previous observations by Fitzgibbons et al. (2), Osgood et al. (4), and Gennari et al. (5). Individual values for $U_{Na}V$ and APR in these 14 rats are given in Fig. 1.

Determinants of peritubular transcapillary fluid exchange

Control period. Mean values for the various determinants of peritubular transcapillary fluid exchange measured before and after saline load plus aortic clamp in these two groups of rats are given in Table II. During the control period, values for Π_E (i.e., intravascular oncotic pressure at the beginning of the peritubular capillary network), were similar between LC and EC groups, averaging 31.9±0.9 mm Hg and 32.8±1.0, re-

TABLE I

Mean Values for Whole Animal and Single Nephron Data in LC and EC Studies

	Body wt	RAP	Hct	C_A	GFR	$U_{Na}V$	FE_{Na}	SNGFR	Q_A	$(TF/P)_{In}$	APR
	g	*mm Hg*	*vol%*	*g/dl*	*ml/min*	*μeq/min*	%	*nl/min*			*nl/min*
LC group (n = 7 rats)											
Control	282±8	114±2	46.4±1.0	5.1±0.1	1.39±0.07	2.3±0.4	1.1±0.2	51.2±2.6	144±10	1.82±0.07	22.7±1.8
Saline load		72±0	42.1±1.1	3.8±0.1	1.01±0.08	9.8±1.7	6.0±0.7	41.0±2.5	112±9	1.43±0.06	12.2±1.5
P value*		<0.001	<0.005	<0.001	<0.005	<0.005	<0.001	<0.001	<0.001	<0.001	<0.001
EC group (n = 7 rats)											
Control	295±13	115±3	47.5±0.9	5.1±0.1	1.35±0.07	2.2±0.6	1.0±0.3	53.4±2.8	146±9	1.85±0.11	23.3±1.6
Saline load		73±1	42.9±0.6	3.9±0.2	1.05±0.10	2.7±0.8	1.6±0.3	46.3±3.3	120±7	1.84±0.13	20.2±2.1
P value‡	>0.40	>0.50	>0.20	>0.50	>0.50	>0.50	>0.50	>0.50	>0.50	>0.50	>0.50
P value*		<0.001	<0.001	<0.001	<0.001	>0.20	<0.025	<0.001	<0.001	>0.50	<0.05
P value§		>0.20	>0.50	>0.50	>0.50	<0.001	<0.001	>0.10	>0.20	<0.01	<0.001

Values expressed as means±1 SE.

* Calculated from paired data in each rat by Student's *t* test.

‡ Calculated from unpaired data for the values in control of LC group vs. control of EC group.

§ Calculated from unpaired data for the changes in LC group vs. EC group.

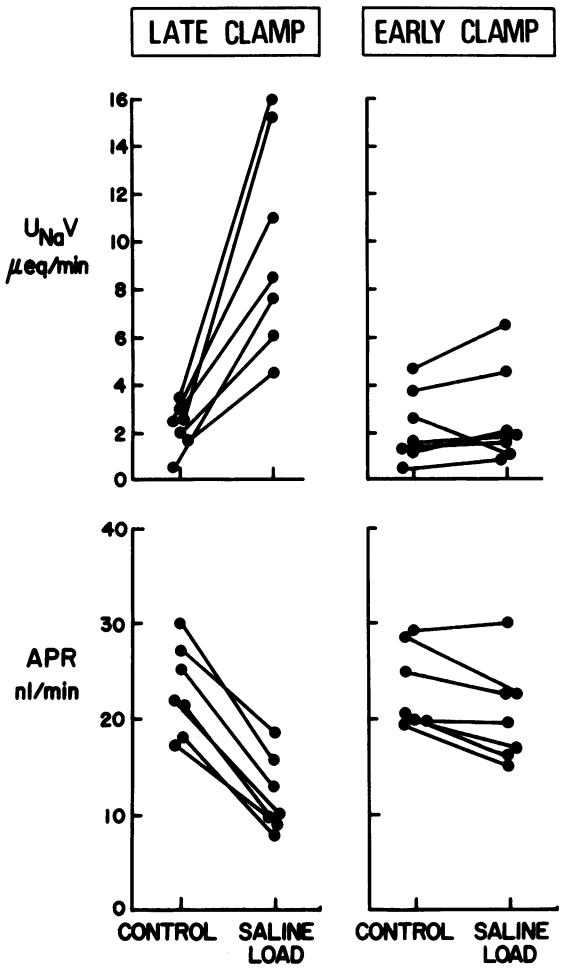

FIGURE 1 Individual values for $U_{Na}V$ and APR measured before and after saline loading in LC (left) and EC (right) rats.

spectively. Likewise, average values for Q_E were similar in these two groups (Table II). Since $\bar{\Pi}_C$ is determined both by the efferent arteriolar plasma protein concentration and by subsequent dilution of peritubular capillary blood by APR,[2] the measured near-equality in values for APR, Π_E, and Q_E between LC and EC resulted in values for $\bar{\Pi}_C$ which were likewise essentially identical in these two groups, as shown in Table II. As also shown, average values for Π_I did not differ between LC (3.0±0.5 mm Hg) and EC (2.7±0.2). In consequence, $\overline{\Delta\Pi}$, which is given by $\bar{\Pi}_C - \Pi_I$, was found to be similar, on average between LC and EC groups (23.4±0.5 for the former and 23.9±1.0 mm Hg for the latter). Peritubular capillary hydraulic pressures measured at proximal- (P_E) and distal-most sites (P_{C_1}) were both slightly lower in LC than in EC, averaging 18.4±0.8 vs. 19.1±0.7 mm Hg, and 7.3±0.5 vs. 9.1±0.4 mm Hg, respectively, but the differences were not statistically significant. $\bar{P}_C$, therefore, was slightly but not significantly higher in EC than LC (Table II). Together with nearly equal average values for P_I (2.9±0.3 mm Hg in LC and 3.1±0.3 mm Hg in EC), $\overline{\Delta P}$ ($=\bar{P}_C - P_I$) was essentially the same in both LC and EC groups, averaging 9.9±0.4 and 11.0±0.4 mm Hg, respectively. Thus, during the control study period, these two groups were indistinguishable with respect to $\overline{\Delta\Pi}$ and $\overline{\Delta P}$. Therefore, $\bar{P}_r$ averaged 13.5±0.5 mm Hg in LC and 13.0±1.0 in EC. Moreover, in view of essentially identical control values for APR and $\bar{P}_r$ in LC and EC groups, values for the reabsorption coefficient, K_r, likewise were similar, on average, between LC and EC (Table II).

After saline load and aortic clamp. Mean values for APR measured after volume expansion and aortic clamp in LC and EC groups are also shown in Table II. As

TABLE II

Mean Values for APR and the Determinants of Peritubular Transcapillary Fluid Exchange in LC and EC Studies

	APR	Π_E	Q_E	$\bar{\Pi}_C$	Π_I	$\overline{\Delta\Pi}$	P_E	P_{C_1}	$\bar{P}_C$	P_I	$\overline{\Delta P}$	$\bar{P}_r$	K_r
	nl/min	*mm Hg*	*nl/min*					*mm Hg*					*nl/(s·mm Hg)*
LC group (n = 7 rats)													
Control	22.7±1.8	31.9±0.9	93±9	26.4±0.6	3.0±0.5	23.4±0.5	18.4±0.8	7.3±0.5	12.9±0.3	2.9±0.3	9.9±0.4	13.5±0.5	0.028±0.003
Saline load	12.2±1.5	20.3±0.3	71±8	18.6±0.9	2.0±0.4	16.6±0.9	20.3±0.8	10.4±0.6	15.4±0.6	6.4±0.5	9.0±0.8	7.7±0.9	0.029±0.006
P value*	<0.001	<0.001	<0.001	<0.001	<0.005	<0.001	<0.025	<0.005	<0.005	<0.001	>0.05	<0.001	>0.50
EC group (n = 7 rats)													
Control	23.3±1.6	32.8±1.0	92±7	26.6±1.1	2.7±0.2	23.9±1.0	19.1±0.7	9.1±0.4	14.1±0.5	3.1±0.3	11.0±0.4	13.0±1.0	0.032±0.005
Saline load	20.2±2.1	22.4±1.3	72±4	18.3±1.3	1.5±0.2	16.8±1.2	10.9±0.6	6.5±0.5	8.7±0.5	3.7±0.6	5.0±0.6	11.8±1.2	0.032±0.007
P value‡	>0.50	>0.50	>0.50	>0.20	>0.50	>0.50	>0.50	>0.05	>0.05	>0.20	>0.05	>0.50	>0.50
P value*	<0.05	<0.001	<0.005	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	>0.20	<0.001	>0.10	>0.50
P value§	<0.001	>0.40	>0.50	>0.50	>0.50	>0.50	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	>0.50

Values expressed as means±1 SE.

* Calculated from paired data in each rat by Student's t test.

‡ Calculated from unpaired data for the values in control of LC group vs. control of EC group.

§ Calculated from unpaired data for the changes in LC group vs. EC group.

described above, values for APR decreased markedly with volume expansion in LC rats, on average by nearly 50% (from 22.7±1.8 to 12.2±1.5 nl/min). By contrast, in volume expanded EC rats, APR decreased only slightly, as shown. In association with reduction in C_A, C_E, and therefore Π_E, fell to a similar extent with saline loading in both groups (on average by 11.6±0.8 mm Hg in LC and by 10.4±1.3 mm Hg in EC). SNFF remained essentially constant in both groups (averaging 0.36±0.02 before and 0.37±0.02 after volume expansion in LC and 0.37±0.02 and 0.38±0.01 in EC). Furthermore, as shown in Table II, since Q_E fell to a similarly small extent with volume expansion in both LC and EC, values for $\bar{\Pi}_C$ also fell essentially equally in LC (by 7.8±0.6 mm Hg) and EC (by 8.2±0.5 mm Hg). Given the numerically trivial reductions in Π_I of ≅1 mm Hg seen with volume expansion in both groups, values for $\overline{\Delta\Pi}$ were found to fall essentially equally in LC (by 6.8±0.6 mm Hg) and EC (by 7.1±0.6 mm Hg).

In contrast to the impressive resemblance of LC and EC groups noted thus far in terms of the changes in oncotic pressure profiles with saline loading, we observed marked differences in the patterns of hydraulic pressure between LC and EC. Whereas both P_E and P_{C^1}, and therefore $\bar{P}_C$, tended to increase in all volume expanded LC rats, on average by 1.9±0.6, 3.1±0.7, and 2.5±0.5 mm Hg, these measures decreased substantially in saline loaded EC rats, on average by 8.2±0.4, 2.6±0.3, and 5.4±0.2 mm Hg, respectively. In LC rats P_I increased, on average, by 3.5±0.3 mm Hg, thereby offsetting the rise in $\bar{P}_C$ so that $\overline{\Delta P}$ remained essentially constant (Table II). By contrast, because of the little change in P_I in EC rats, the marked reduction in $\bar{P}_C$ with saline loading resulted in a similarly large fall in $\overline{\Delta P}$, averaging 5.9±0.5 mm Hg (Table II). Collectively, in conjunction with the reduction in $\overline{\Delta\Pi}$ (≅7 mm Hg) and near constancy of $\overline{\Delta P}$, $\bar{P}_r$ fell markedly in volume expanded LC rats, on average by 5.8±0.5 mm Hg, whereas $\bar{P}_r$ remained essentially constant with volume expansion in EC owing to the offsetting effects of the decrease in $\overline{\Delta\Pi}$ (≅7 mm Hg) and the nearly equivalent concomitant fall in $\overline{\Delta P}$ (≅6 mm Hg). As indicated by the proportional reduction of APR and $\bar{P}_r$ with volume expansion in LC rats, calculated values for K_r remained essentially constant, as shown in Table II. K_r also remained unchanged with volume expansion in EC, reflecting, in this case, near constancy of both APR and $\bar{P}_r$.

Thus, in the absence of significant changes in K_r and $\overline{\Delta P}$, the observed marked average decline in APR with volume expansion in LC rats occurred in association with a major reduction in $\overline{\Delta\Pi}$, a consequence of reduction in $\bar{\Pi}_C$ (attributable to the fall in Π_E). With saline loading in EC rats, however, despite an average fall in $\overline{\Delta\Pi}$ (and Π_E) equivalent to that seen in LC, APR failed to decline. In this case, we found an EC-related fall in $\overline{\Delta P}$. This decline in $\overline{\Delta P}$ served to offset the concomitant fall in $\overline{\Delta\Pi}$.

Microvascular resistances in LC vs. EC

In 12 of these animals (seven in the LC group and five in EC) $\bar{P}_{GC}$ was measured directly in surface glomeruli both before and after saline infusion and aortic clamp. As shown in Fig. 2, whereas $\bar{P}_{GC}$ failed to change with volume expansion in LC (averaging 49.1 ±0.5 mm Hg and 47.1±0.4, $P > 0.05$), a marked fall in $\bar{P}_{GC}$ was detected in EC (from 49.3±0.8 to 39.1±0.4, $P < 0.005$), which paralleled the decline in $\bar{P}_C$, the latter also confined to the seven rats in the EC group. Efferent arteriolar resistance (R_E) increased to a similar small extent with volume expansion plus aortic clamp in LC and EC groups (Fig. 2). With volume expansion, afferent arteriolar resistance, R_A, fell twice as much, on average, in LC than EC, thereby resulting in more effective autoregulation of $\bar{P}_{GC}$ and $\bar{P}_C$ in LC than EC.

DISCUSSION

Fitzgibbons et al. (2) showed in rats that the natriuresis induced by saline loading was largely abolished when renal perfusion pressure was reduced to ≅70 mm Hg immediately before (EC), but not after (LC), the volume load. These findings, which have since been confirmed by others (3–6), were also duplicated in the present study. We also duplicated the findings by Osgood et al. (4) of an inverse correlation between changes in $U_{Na}V$ and APR. In the Osgood study, as well as in the present effort, a marked fall in APR accompanied the large increase in $U_{Na}V$ with volume expansion in the LC group, whereas neither of these measures changed significantly despite an equivalent degree of volume expansion in the EC group. Not only were the findings by these previous investigators taken as evidence against an important role for systemic or circulating humoral factor(s) in mediating saline-induced natriuresis (especially because contralateral kidneys in both groups displayed marked natriuresis [4]), but they were also interpreted as failing to support a significant role for peritubular capillary oncotic pressure in determining APR and sodium excretion insofar as systemic protein concentration (4) and filtration fraction (2) were affected equally by EC and LC. Whether or not changes in the other peritubular capillary Starling forces were responsible for the observed differences in APR noted between EC and LC in these previous studies is unknown because these additional forces and flows were not evaluated.

We therefore carried out the present systematic analysis of the various Starling forces operating across renal cortical peritubular capillaries under these conditions. With saline loading, marked declines in $\overline{\Delta\Pi}$

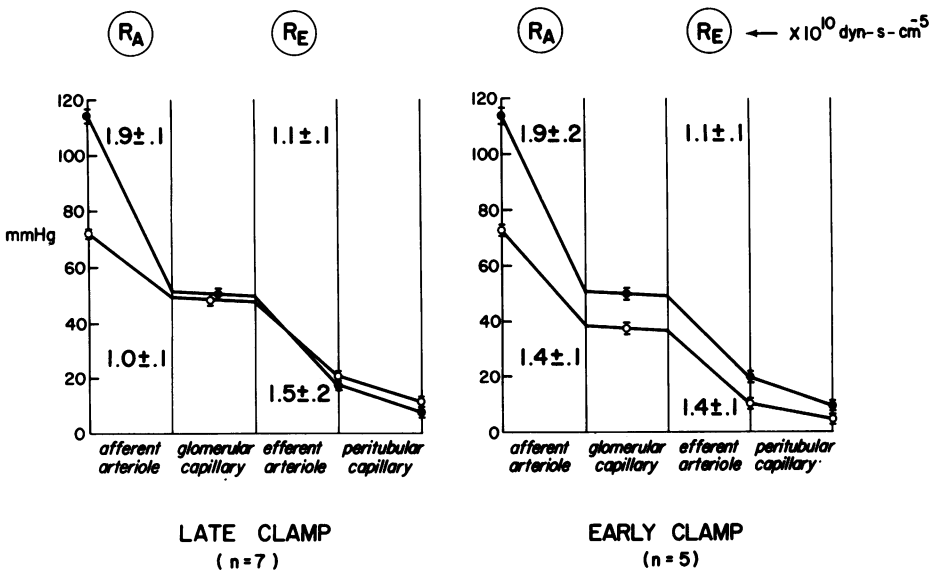

FIGURE 2 Profiles of intravascular hydraulic pressure from renal artery to terminal portions of peritubular capillaries in LC and EC rats. Average values obtained in control period are depicted as solid circles; values after saline load are shown as open circles. Calculated average values for R_A and R_E are also provided. Values are expressed as mean±1 SE.

were observed in both EC and LC groups. These comparable declines in $\overline{\Delta\Pi}$ resulted from reductions in the two components of this quantity, i.e., $\overline{\Pi}_C$ and Π_I, the former more than the latter and primarily because of saline-induced declines in systemic oncotic pressure, together with near-constancy of SNFF.

Such reductions in $\overline{\Pi}_C$ and $\overline{\Delta\Pi}$, which have been observed consistently in response to acute saline loading by many investigators (16, 19, 23–27), would, if unopposed by other intrarenal hemodynamic adjustments, be expected to result in a net reduction in APR (18, 19, 28, 29). In LC, where APR declined markedly and $U_{Na}V$ increased markedly, the decline in $\overline{\Delta\Pi}$ was indeed unopposed. In EC, however, where the responses of APR and $U_{Na}V$ to volume expansion were dramatically blunted, these changes in $\overline{\Pi}_C$ and $\overline{\Delta\Pi}$ were essentially offset by a concurrent decline in $\overline{\Delta P}$. Thus, in LC rats, P_E and P_{C_1}, and therefore $\overline{P}_C$, all increased slightly but significantly (Table II). Despite the increase in $\overline{P}_C$, $\overline{\Delta P}$ remained essentially constant because of an opposing small average increase in P_I. By contrast, with saline loading in EC rats, P_E, P_{C_1}, and $\overline{P}_C$ fell markedly, without an accompanying change in P_I, thereby resulting in a decline in $\overline{\Delta P}$, which essentially offset the measured fall in $\overline{\Delta\Pi}$. In consequence, $\overline{P}_r$ remained constant with volume expansion in EC rats but fell markedly in LC. Since $\overline{P}_r$ either fell in proportion to the fall in APR (LC) or remained unchanged, as did APR (EC), it follows from Eq. 1 that K_r was not altered by volume expansion in either LC or EC groups.

Apart from the obvious strong correlation between the degree of saline-induced natriuresis (and fall in APR) and $\overline{P}_r$ observed in the present study, it was also evident that these reabsorptive parameters correlated closely with changes in P_I. Similar observations were made by Marchand (6) in a recent series of experiments in saline-loaded dogs also studied with early clamp. So far as peritubular capillary fluid uptake is concerned, however, we believe this relationship between P_I and APR to be fortuitous rather than causal in that, as given by Eq. 4, a rise in P_I per se would favor an increase, not a decrease, in peritubular uptake of APR.

By duplicating the findings of Fitzgibbons et al. (2), Osgood et al. (4), and Gennari et al. (5), of differing responses of $U_{Na}V$ and APR to EC vs. LC, despite equivalent degrees of volume expansion, we echo their conclusion that the changes in reabsorption observed in the LC group must occur by mechanism(s) independent of circulating humoral or blood compositional factors. As with these previous investigators, we too failed to see a causal relationship between APR and SNGFR in that the fall in APR in LC and near-constancy of APR in EC were associated with essentially equivalent declines in SNGFR. Moreover, P_T tended to increase in LC (on average by 1.7±0.4 mm Hg, $P < 0.05$) along with reduction in APR, and to decrease in EC (on average by 1.6±0.9 mm Hg, $P < 0.05$) where APR remained essentially unchanged.

Thus, in the present study, since $\overline{\Pi}_C$ and $\overline{\Delta\Pi}$ fell equally with volume expansion in LC and EC, the differing values for $\overline{P}_r$ between LC and EC are con-

sequences of the differing values for $\bar{P}_C$. As shown for LC rats in Fig. 3a, because of the fall in $\overline{\Delta\Pi}$ without a comparable fall in $\bar{P}_C$, $\bar{P}_r$, (the integrated area between the $[\Pi_C - \Pi_I]$ and $[P_C - P_I]$ curves) decreased by nearly 50% in LC. In EC, however, (Fig. 3b), despite a comparable fall in $\overline{\Delta\Pi}$, $\bar{P}_r$ remained unchanged from pre-expansion values because of the concurrent and equivalent decline in $\bar{P}_C$. The unopposed fall in $\overline{\Delta\Pi}$ in LC rats, therefore, served to lessen net peritubular capillary uptake of reabsorbate, and correlates well with the finding of a large fall in APR in this group. Net peritubular capillary fluid uptake is predicted not to change in EC rats, however, because the fall in $\overline{\Delta P}$ essentially nullified the impact on transcapillary exchange of the concomitant fall in $\overline{\Delta\Pi}$. The finding of little change in APR in EC rats is therefore in keeping with predictions based on the measured absence of change in the net peritubular transcapillary reabsorptive force. The present findings reinforce the view (16, 18, 24–29, 30–39) that peritubular capillary Starling forces play a major role in modulating APR, both in states of normal hydration as well as after extracellular fluid volume expansion.

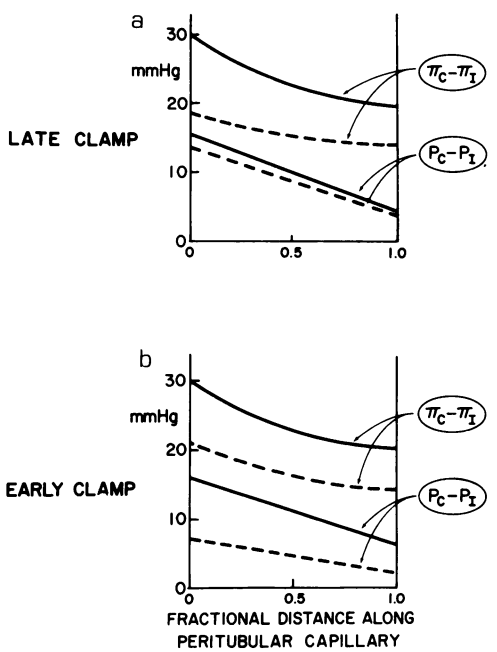

FIGURE 3 Comparison of profiles of $\Delta\Pi$ ($=\Pi_C - \Pi_I$), and ΔP ($=P_C - P_I$) along peritubular capillaries in LC and EC rats. Π_C and Π_I refer to oncotic pressures in peritubular capillary and in the surrounding cortical interstitium. P_C and P_I refer to corresponding hydraulic pressures. Solid and dashed curves refer to values obtained before and after saline loading, respectively. $\overline{\Delta\Pi}$, the integrated mean value of $\Pi_C - \Pi_I$ with distance along the peritubular capillary, fell to the same extent in LC and EC. $\overline{\Delta P}$, the corresponding mean value of $P_C - P_I$, remained essentially unchanged with volume expansion in LC but declined markedly in EC, thereby offsetting the fall in $\overline{\Delta\Pi}$ in this group. The area between $\Delta\Pi$ and ΔP curves, which describes the net capillary reabsorptive force, $\bar{P}_r$, thus declines in LC but remains essentially constant in EC. This fall in $\bar{P}_r$ in LC correlates well with the measured fall in APR; near constancy of $\bar{P}_r$ in EC also correlates well with the measured near constancy of APR in this group.

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