VASOPRESSOR-INDUCED NATRIURESIS AND ALTERED INTRARENAL HAEMODYNAMICS IN CIRRHOTIC MAN

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SUMMARY

1. The influence of two intravenous vasopressors (angiotensin II and norepinephrine) on renal function and intrarenal blood flow distribution was studied in thirteen cirrhotic subjects and the results compared with those from eight non-cirrhotics.

2. Increased sodium excretion occurred in four of eight cirrhotics with ascites who received comparable pressor doses of angiotensin II and one of five similar subjects who received norepinephrine. In contrast, sodium excretion fell or remained the same in all eight non-cirrhotics.

3. Renal plasma flow fell and filtration fraction rose in nearly all subjects who did not respond to vasopressors with a natriuresis but changed little in those who did.

4. Vasopressor-induced changes of the multicompartmental 133 xenon washout curve were qualitatively different in the group who responded with a natriuresis in comparison to the others. Whereas the distribution of flow to the fastest component fell in the non-responder, it remained the same or rose in those who developed a natriuresis.

5. We interpret these results as suggesting a state of relative renal vasopressor resistance allowing the induced systemic hypertension to reduce tubular sodium reabsorption in some cirrhotics by influencing peritubular 'physical factors'.

Key words: cirrhotics, natriuresis, intrarenal blood flow.

Doses of intravenous angiotensin II and norepinephrine resulting in similar rises of systemic blood pressure may produce a natriuresis in cirrhotic men with ascites and an antinatriuresis in normotensive non-cirrhotics (Laragh, Cannon, Bentzel, Sicinski & Meltzer, 1963). Studies of vasopressor administration in dogs with inferior vena caval ligation have suggested that the response of sodium excretion is similar to that observed in cirrhotic man (Cannon, Ames &
Laragh, 1966; Porush, Kaloyanides, Cacciaguida & Rosen, 1967). This paradoxical natriuresis has been attributed to intrarenal haemodynamic events that differ from those of healthy subjects (Laragh et al., 1963) but the nature and relative contribution of specific determinants have not been defined. Changes of glomerular and/or peritubular capillary physical factors such as hydrostatic pressure or oncotic pressure have been implicated (Earley & Daugharty, 1969). It is conceivable that there could be a family of haemodynamic responses to vasopressors, which under certain circumstances could combine to produce either a natriuresis or an antinatriuresis and that the cirrhotic kidney is somehow pre-conditioned to respond paradoxically. During a vasopressor-induced increase of systemic blood pressure, there might also be vasoconstriction of both efferent and afferent arterioles, disproportionately greater in the efferent limb. This might be expected to cause: (1) reduction of renal plasma flow; (2) increase of filtration fraction and, since these changes affect the character of the blood leaving the glomerular tuft by increasing its resistance to flow and its protein concentration; (3) decrease of peritubular capillary hydrostatic pressure; (4) increase of oncotic pressure in these same vessels and thus (5) increase in fractional reabsorption of sodium. But if systemic blood pressure rises in association with a smaller degree or absent arteriole vasoconstrictor response, renal blood flow and filtration fraction might remain more nearly the same so that peritubular capillary hydrostatic pressure rises, causing decreased fractional sodium reabsorption (Schrier & de Wardener, 1971).

Direct demonstration of such complex phenomena in man appears to be impossible but further characterization of the haemodynamic events may be useful. The recording of washout patterns of diffusible gas (krypton and xenon) has provided provocative data on the intrarenal distribution of blood flow in several normal and abnormal states (Barger, 1966; Hollenberg, Epstein, Rosen, Basch & Merrill, 1968; Rosen, Hollenberg, Dealy & Merrill, 1968; Epstein, Berk, Hollenberg, Adams, Chalmers, Abrams & Merrill, 1970; Hollenberg, Epstein, Guttmann, Conroy, Basch & Merrill, 1970). The results of these studies have been consistent with the view that a reduction of outer cortical blood flow is accompanied by a reduction of sodium excretion and that increased outer cortical blood flow is associated with increased sodium excretion. This relationship has usually been attributed to a disproportionate increase in the number of glomeruli with longer tubules that exist in the inner cortex which would presumably facilitate increased fractional reabsorption of sodium (Barger, 1966). Other mechanisms may explain this relationship. For example, cortical ischaemia, as recognized by the washout curves, may reflect changes in peritubular haemodynamics rather than regional redistribution of glomerular filtration rate. In any case, it remains to be shown that the paradoxical natriuresis might be associated with a similar alteration of haemodynamic response.

The studies presented here were undertaken to obtain further data on the relation of haemodynamic phenomena to sodium excretion in cirrhotics in an attempt to discover directional changes which might explain the paradoxical natriuresis.

METHODS

On one day, renal function was measured before and during the infusion of the selected vasopressor [either angiotensin II (Hypertensin®—Ciba) or norepinephrine]. The measurements included clearance of p-aminohippurate (PAH) and [125I]iothalamate and excretion rates of sodium and potassium. On a separate, usually following, day we estimated intrarenal blood flow using the 133Xenon washout technique (Rosen et al., 1968).
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Two groups of volunteers were recruited: (1) eight non-cirrhotic, apparently healthy men with a history of severe drinking problems, and (2) thirteen hospitalized patients with the clinical diagnosis of cirrhosis with ascites. Both groups gave their fully informed consent. The study was approved by the Human Experimentation Committees of the University of Washington and the Seattle Veterans Administration Hospital.

History and physical examinations of the non-cirrhotic subjects revealed no evidence of chronic illness other than weight loss attributed to a recent drinking episode in some. Laboratory findings on their blood and urine were normal. They were placed on a diet containing at least 150 mmol of sodium and 100 mmol of potassium per day for 3 days. The patients with cirrhosis were moderately to severely wasted, had exhibited ascites at least once, were jaundiced, had hard enlarged livers by physical examination and liver function tests gave abnormal results. Liver biopsy was not performed routinely but advanced cirrhosis was observed in the five patients so studied. Our studies were done after variable periods (1–4 weeks) in the hospital on low sodium (under 50 mmol/day) diets and mild thiazide diuretic therapy. Diuretics were always discontinued 3 days before the test day. All patients were ambulatory and able to void freely. None was oliguric and serum creatinine concentration was always within the normal range. The patients differed from one another principally in the degree of ascites which was present at the time of the study. Ascites was arbitrarily classified as follows: 1+ = barely detectable ascites in an individual known to have recently had ascites; 2+ = detectable but not obvious ascites; 3+ = obvious abdominal distention; 4+ = tense and incapacitating ascites.

For purposes of presentation and analysis, the cirrhotic patients were divided into two groups according to the natriuretic response to vasopressor administration. A ‘responder’ was arbitrarily defined as a patient whose sodium excretion increased at least ninefold during vasopressor infusion. All others were termed ‘non-responders’. No clinical or laboratory feature was observed which would have allowed us to predict whether they would be responders or non-responders.

The design of the study was similar in all subjects. A water diuresis (urine osmolality: 46–188 mosm/kg of water) was initiated by the infusion of 1 litre of dextrose (5 g/100 ml) in water over 30–45 min and sustained thereafter by oral ingestion of 500 ml of water per h. Standard renal clearance techniques were then used to obtain sequential estimates of glomerular filtration rate, renal plasma flow, clearance of free water and electrolyte excretion rates before and during the constant intravenous infusion of either angiotensin II or norepinephrine in doses sufficient to maintain diastolic blood pressure 20 mmHg above resting levels. This required 12–32 μg/min of norepinephrine or 1·6–6·0 μg/min of angiotensin II in the non-cirrhotics and 14–64 μg/min of norepinephrine or 3·0–12·0 μg/min of angiotensin II in the cirrhotics.

Three consecutive 30 min clearance periods in a comfortable supine position were performed before the infusion of the vasopressor. After the vasopressor was started, there was a 30 min equilibration period and then three more clearance periods while the infusion was maintained. The patients stood briefly to void (usually less than 2 min); no catheter was used. Glomerular filtration rate (GFR) was measured as clearance of [125I]iothalamate and effective renal plasma flow (ERPF) estimated as the clearance of PAH. Loading doses of [125I]iothalamate and PAH were given 60 min before the first clearance period and levels were sustained by constant infusion throughout the study. Sodium and potassium excretion rates were measured and clearance of free water calculated.
On the following day, under as identical conditions as were possible, the effects of angiotensin
and norepinephrine on intra-renal blood flow was studied, using the $^{133}$Xe
renal washout technique described by Hollenberg et al. (1968) and Rosen et al. (1968). Under fluoroscopy, a
catheter (6 Fr Becton-Dickinson polyethylene with i.d. of 1.58 mm, o.d. of 1.80 mm) was
placed into the renal artery via the femoral artery. The first study was made using 300 μCi of
$^{133}$Xe in less than 0.5 ml after a 30 min rest period and before the infusion of the vasopressor
was started. The second study using 600 μCi in less than 1.0 ml was made 30 min after starting the
infusion. The vasopressor was the same as had been used on the previous day and the
dosage found necessary to maintain the same blood pressure response was always similar. The background radioactivity before the first injection was at baseline indicating no interfer-
cence from the $^{125}$Ijodothalamate used the previous day. Background radioactivity was
usually two to six times higher before the second injection. Peak count rates were always 80
times background or more.

Counts were recorded by a collimated sodium iodide crystal via a pulse height analyser
(window 70–100 keV) and high-speed printer and with a digital integrator (Nuclear Chicago). Three-minute curves were recorded using the convention of Rosen et al. (1968), in which the counts recorded at the third minute are assumed to be equivalent to the extrapolated value of the third and fourth components of the renal washout curve which would otherwise require
40 min to record. With this method, we calculated the flow rates (slope of log c.p.m. against
time) and fractional distribution (relative zero-time intercept) of the first two components. The first component may represent outer cortical blood flow under normal conditions but its anatomical counterpart is not precisely defined and probably varies in size with the situation (Carriere, Thorburn, O’Morchoe & Barger, 1966). The second component includes blood flow in the outer medulla, the juxtedudillary cortex and, at times, the inner part of the superficial cortex [the so-called ‘cortex A’ as defined by Carriere et al. (1966) using the radioautographic technique]. Curve analysis for the first two components was done by an iterative computer routine modified for use on these data from the computer routine of Worsley & Lax (1962) by
one of us (A.W.F.). This method is similar to that described by Ladefoged (1968). Partition
coefficient for the xenon was adjusted for the haematocrit (Ladefoged, 1966). The curves
were also analysed in duplicate by the standard graphic technique and were reproducible by
two observers within 10%. The computer routine gives almost perfect reproducibility and is
not dependent on subject analysis. Yet the results of the two analyses were highly correlated
($r = 0.73$ for first component blood flow and $r = 0.93$ for first component fractional distribu-
tion). Curves which could not be resolved into two components by the iterative routine always
appeared to be mono-exponential or a ‘fusion curve’ and no further interpretation was made of
first component values. We report the results of the blood flow analysis of both components
and the fractional distribution to the first component. The fractional distribution of the second
component tends to be the reciprocal of the first and, as noted, its anatomical counterpart is
less well defined. Average flow rate is derived from the initial slope of the xenon disappearance
curve as an estimate of the harmonic mean (Rosen et al., 1968).

RESULTS

General

The individual responses of selected aspects of renal function are portrayed in Figs. 1–8, each
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contrasting the response to the two pressor agents in the three groups of patients. Overall, the data suggest that cirrhotic responders differed from the other two groups in several ways; they tended to have an increase in urine volume and potassium excretion as well as of sodium excretion and they exhibited a lesser change of certain renal haemodynamics in response to vasopressor administration. A full table (Clinical Science No. 73/9) of renal and haemodynamic data is deposited with the Librarian, The Royal Society of Medicine, 1 Wimpole Street, London, W.1, from whom copies are available on request.

Responses of the non-cirrhotic subjects

The response of the eight non-cirrhotic subjects to angiotensin II and norepinephrine was
similar. Urinary sodium, potassium, and free water were reduced in all (Figs. 1, 3 and 4). Urine flow rate fell in all but two patients (Fig. 2). In three of these subjects negative free water formation was observed—probably due to the release of endogenous antidiuretic hormone. The mean glomerular filtration rate fell slightly but significantly (Fig. 5, \( t = 2.81, P<0.05 \)). The clearance of PAH showed an appreciable reduction in each case (Fig. 6, \( t = 7.87, P<0.001 \)). As a result, whole kidney filtration fraction rose substantially (Fig. 7), perhaps effecting a parallel reduction of post-glomerular blood flow.

![Graph showing urine volume response to vasopressors](image)

**Fig. 2.** Urine volume (\( \dot{V} \)) response to two vasopressors showing that mean urine volume increased in the sodium excretion 'responders' and not in the 'non-responders'.

The xenon washout patterns showed a reduction of mean blood flow as would be expected from the \( C_{PAH} \) results and a concomitant fall in fractional blood distribution to component I, the putative 'outer cortex' (Fig. 8). Two patients from each vasopressor study group developed fusion curves, a finding which has been interpreted as representing a large but unmeasured decrease in component I.
Response of the cirrhotic subjects

Cirrhotic subjects responded to vasopressor infusion in two qualitatively different ways with regard to sodium excretion. Four of the eight who received angiotensin II and one of the five who received norepinephrine increased sodium excretion greatly whereas the other eight (four

FIG. 3. Potassium excretion response (UxV) demonstrating that this, too, paralleled the sodium response for both groups of cirrhotics. The single patient receiving angiotensin II in the non-responders whose potassium excretion rose is the patient whose clearance of free water (C_H2O) rose (Fig. 4).

with each drug) exhibited a fall or no change at all (Fig. 1). The non-responders almost always differed from the responders in that urine flow and potassium excretion rose instead of falling (Figs. 2 and 3). Similarly, the clearance of free water (C_H2O) rose in all responders, virtually paralleling the rise in urine flow (Fig. 4).

The comparative haemodynamic responses of these two groups of cirrhotics reveal differences. The initial GFR among the angiotensin responders was reduced in comparison with the
angiotension non-responders. However, the one norepinephrine responder did not have a low value. The GFR rose during angiotensin infusion in all responders and three of the four non-responders. Renal plasma flow in the responders remained the same or rose during angiotensin infusion while it fell in the non-responders (Fig. 6). Hence, the filtration fraction remained the same (Fig. 7) rather than rising as it did in the two groups whose sodium excretion rate fell. This maintenance of filtration fraction did not occur in the one cirrhotic who developed a natriuresis in response to norepinephrine.

![Graph](Fig. 4: Free water clearance ($C_{H_2O}$) rose in all 'responders' suggesting increased proximal delivery of sodium in distal diluting segments. Not all patients maintained a dilute urine, however.)

The finding of a diminished vasoconstriction in response to vasopressor is supported in part by the results of the xenon washout study the following day. It should be noted that only one component of the washout curve was discernible during the first 3 min in four of the cirrhotic patients (Fig. 8). These so-called fusion curves have been noted in other studies of cirrhotics though they were generally found in more advanced states of renal dysfunction (Epstein et al., 1970). Two of these patients received angiotensin; one, a responder, developed a two-component washout curve and the other, a non-responder did not change from the single component curve. Of the other six who received angiotensin the three who failed to develop a natriuresis had a sharp reduction in component I contribution as was seen in the non-cirrhotics.
In contrast, three of the responders had virtually no change in component I and in a fourth, there was a rise.

The data from the norepinephrine group are again less clear. The two cirrhotics with initial fusion curves were not changed, there was no appreciable reduction of component I in any of the other three. The one responder had a slight rise in component I distribution but there was also a slight rise in component I in one of the norepinephrine non-responders (Fig. 8).

**DISCUSSION**

These observations confirm the previous finding that intravenous vasopressor in doses which cause reduction of sodium excretion in non-cirrhotic individuals may cause a natriuresis in
some cirrhotic patients with ascites. Our results are quite similar to the original work by Laragh et al. (1963) who demonstrated an impressive natriuresis to somewhat higher doses of intravenous angiotensin II and a similar but much smaller response to norepinephrine. In addition, we have demonstrated that this response is not always seen in such patients. This variation in the direction of response of sodium excretion was paralleled by changes in potassium excretion, urine flow rate and clearance of free water in most patients. Two of the cirrhotic non-responders actually increased potassium excretion and urine flow suggesting that they were, in fact, delivering more sodium to the distal tubular segments presumably a result of decreased proximal tubular sodium reabsorption. These data also suggest that this directional change in sodium excretion in response to vasopressor was accompanied by qualitatively different haemodynamic responses manifested by: (1) a tendency for $C_{\text{PAH}}$ to remain unchanged in the

![Graph](image-url)
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A cirrhotic responder rather than falling as it did in non-cirrhotics and non-responders; (2) stability of filtration fraction in the cirrhotic responder rather than a rise as observed in the other two groups, and (3) little or no fall in the relative contribution of component I of the xenon curve, in contrast to the usual reduction of this component during vasopressor administration. Two of the responders actually demonstrated an increase of this portion of the xenon curve.

Thus, there appears to be an alteration of the target organ (kidney) haemodynamic responsiveness in certain cirrhotic patients, an observation consistent with previous data suggesting a variable pre-existing abnormality of the xenon curves in similar patients (Epstein et al., 1970). This was interpreted as indicating an active cortical vasoconstriction, unresponsive to sympatholytic agents (Epstein et al., 1970). Our data suggest that in some cirrhotics the already partially constricted arterioles are relatively unresponsive to vasopressor as well.
It remains to be demonstrated that the altered haemodynamic response is responsible for the altered natriuretic response. Such a relationship could pertain in view of the known influence of haemodynamic factors on peritubular capillary uptake of sodium from the nephron (Schrier & de Wardener, 1971). For example, if the rise in systemic blood pressure caused by vaso-

pressor was accompanied by an overriding increase in pre- and post-glomerular capillary resistance, as it seems to be in the non-cirrhotics and some cirrhotics, then hydrostatic pressure within the peritubular capillary network might fall facilitating increased fractional reabsorption of sodium (Schrier & de Wardener, 1971). If the change of renal cortical vascular resistance is small in response to systemic vasopressor, then the rise in systemic blood pressure may be

![Diagram](image-url)

**Fig. 8.** The data from xenon washout studies performed on a separate day demonstrate a qualitative difference in the haemodynamic response of 'responders' versus both 'non-responders' and non-cirrhotics. None of the responders had an appreciable decrease of fractional flow to the first component \((C_1)\), and in two patients it rose appreciably. In contrast, seven of eight non-cirrhotic subjects experienced a fall in fractional flow to \(C_1\). Norepinephrine did not change fractional flow in the 'non-responder' cirrhotics but angiotensin caused reduction in the three with initially normal curves. Fusion curves were those in which no first component can be discerned.
directly reflected by a rise of hydrostatic pressure in the same area and result in exactly the opposite effect on tubular sodium reabsorption. These data do suggest that such a relationship might exist. The subjects who did not develop a natriuresis also increased filtration fraction, whereas those who experienced a natriuresis in response to angiotensin II maintained their filtration fraction and renal blood flow.

The lack of fall of component I in response to vasopressor may be a related phenomena. All five of the ‘responders’ maintained or developed a detectable first component contribution during vasopressor administration in contrast to the marked tendency for this same component to fall or disappear in non-cirrhotics and most cirrhotic non-responders. A fall in first component contribution to total flow has been interpreted as a change in the relative contribution to filtration made by outer cortical glomeruli (Barger, 1966). However, it may reflect an event more closely related to filtration fraction under these experimental conditions, in which the fall in post-glomerular flow accounts for a substantial fall in the amount of cortex being perfused at this relatively rapid rate. We do not attach quantitative importance to these data as they were obtained under very special circumstances in a small group. Nevertheless, qualitative differences of renal blood flow response do appear to be related to the paradoxical natriuresis. Unpublished observations (R. A. Gutman, A. W. Forrey, W. P. Fleet & R. E. Cutler) in a group of five non-cirrhotic alcoholics on low sodium (40 mmol/day) intake for 3 days showed a fall in sodium excretion in response to vasopressor suggesting that the paradoxical natriuresis may not be conditioned by sodium intake per se.

An alternative explanation of the correlation of our xenon data to the sodium excretion data can be found in the redistribution theory (Barger, 1966; Thurau & Horster, 1968), according to which the kidney is pictured as a group of nephrons differing from one another primarily in the length of their tubules and, therefore, in their sodium reabsorptive surface. Relative decrease in blood flow to the outer cortex would presumably limit filtration in nephrons with short loops of Henle and favour the juxtamedullary nephrons with their long loops of Henle. If this mechanism were important, one might picture the role of the vasopressor as primarily cortical constricting in the non-cirrhotics and some cirrhotics. But in the cirrhotics, who respond with a natriuresis to the vasopressor, the cortical nephron filtration may undergo relatively less constrictive response to the vasopressor; as a result, outer cortical blood flow might actually increase and, thereby, increase the filtration at the glomeruli with shorter nephrons. However, this attractive theory has not received full support in other research laboratories (Blantz, Katz, Rector & Seldin, 1971; Herrera-Acosta, Andreucci, Rector & Seldin, 1972).

The paradoxical natriuresis could also be explained by the suggested dual role of angiotensin on the kidney, acting in part as a renal vasoconstrictor which would tend to inhibit sodium excretion and, in part, directly on the tubules as a diuretic (Bonjour, Regoli, Roch-Ramel & Peters, 1968). The paradoxical response to angiotensin has been shown to be dose-related in some animals, in that antinatriuresis occurred with low doses and natriuresis with higher doses and is compatible with this explanation (Levitin, Lehmann, Pigeon, Warren & Goldenberg, 1963; Louis & Doyle, 1965; Cannon, 1966; Malvin & Vander, 1967). However, the angiotensin dosage in responders and non-responders in this study was nearly the same. Moreover, a direct effect of angiotensin on sodium transport by isolated tubules could not be demonstrated (Healy, Douglas & Arnold, 1969). The similar paradoxical responsiveness in some cirrhotics to both angiotensin and norepinephrine (Laragh et al., 1963) also casts doubt
on the likelihood that a direct tubular effect is important in the natriuretic response. Malvin & Vander (1967) on the basis of their data and others suggested that the directional changes in sodium excretion were invariably associated with similar directional changes in total GFR but we observed no such general parallel effect.

The method employed in this study of recording the radioactive gas washout pattern has been used to demonstrate apparent outer renal cortical ischaemia in physiological and several abnormal sodium-retaining states. The method was first developed in dogs and radioautographs were used to suggest that the first component represented the outer cortical blood flow and the second component represented an ill-defined but deeper part of the kidney (Thorburn, Kopald, Herd, Hollenberg, O'Morchoe & Barger, 1963; Carriere et al., 1966). When one considers only the relative count rate at zero time of the extrapolated curves of component I compared to component II, it may be that the data offer a fairly useful approximation of the amount of blood reaching the outer cortex. The flow rates which are derived from the slopes of the two components must be expressed in rates per mass of tissue. Since the size of the compartment may be changing, it is difficult to assign physiological significance to this value. In any case, we observed no regular change of flow rate. Using other techniques in experimental animals, recent investigations have not been able to confirm that blood flow redistribution always occurs (Blantz et al., 1971; Herrera-Acosta et al., 1972). But recently, two laboratories have reported concordant results using radioactive microspheres and the $^{133}$xenon method (Solomon, Hollenberg & Merrill, 1971; Logan, Jose, Eisner, Lilienfield & Slotkoff, 1971). In both studies, redistribution of blood flow away from the outer cortex was demonstrated in sodium retaining states. However, other studies have failed to demonstrate close correlation of xenon washout results and microsphere distribution results in dogs receiving vasopressor (Rector, Stein, Bay, Osgood & Ferris, 1972). It may be that these changes in the pattern of xenon washout curves represent something far more complex than a reduction of so-called 'outer cortex' flow. Indeed, the emphasis on layering of function in the cortex may be inappropriate. Nevertheless, a qualitatively different xenon washout response to pressor agents did occur in the natriuretic responders in this study suggesting that areas which ordinarily reduce flow rates or distribution fail in this response in those patients with cirrhosis who develop a natriuresis. Since these patients also tend to have a baseline reduction of component I when they are antinatriuretic (Epstein et al., 1970; Kew, Brunt, Varma, Hourigan, Williams & Sherlock, 1971), the relationship between component I and sodium excretion is again seen. The presumed simultaneous reduction of component I and sodium excretion of normals in response to these same pressors is further evidence of this relationship (Hollenberg et al., 1970).

Although it remains unclear whether any identifiable area of the cortex is uniformly involved in the preferential vasoconstrictor response, it is possible that the modulation of that response influences sodium excretion by 'physical factors'. Since the majority of proximal tubules are present in the outer cortex, these blood flow distribution changes may occasionally be related to this anatomical area. These studies demonstrate a potentially important phenomena in man which raises more questions than it answers. Further analysis will require laboratory animals. It should be possible to demonstrate with micropuncture studies that the predicted changes in post-glomerular capillary hydrostatic and oncotic pressure is occurring in properly selected animal models such as the caval dog. Such studies may reveal the mediator for outer cortical constriction. In the meanwhile, it must be noted that these studies do not suggest that vasopressors are a proper form of therapy for cirrhotic patients.
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