SESSION II

ELECTROLYTE METABOLISM

Chairman: PROFESSOR H. E. DE WARDENER

Factors relating to sodium excretion in experimental ascites

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Summary

Although there is some disagreement about the role of the proximal convoluted tubule in the sodium retention of caval dogs, most authors agree that the major site of increased sodium resorption is the ascending loop of Henle. Furthermore, although the majority of experimental evidence suggests that the increase in sodium resorption is caused by alteration in physical factors, presumably in the vasa recti, there is some evidence that circulating substances may also be involved.

Experiments in oedematous animals

Much is now known about the mechanisms of sodium handling by the normal kidney, in the dehydrated animal and those acutely and chronically salt loaded as well as in the experimentally diseased kidney (Schrier and De Wardener, 1971). However, as far as the clinical situation is concerned, we have far less knowledge about the oedematous state. Thus, the study of sodium handling in the oedematous animal is of considerable relevance in our understanding and treatment of fluid retention.

Animal models

Various oedematous animal models have been used over the past 20 years including cellophane bands around the major portal veins (Volwiler, Grindlau and Bollman, 1950) and chronic constriction of the thoracic vena cava (TVC dog) to simulate ascites (Davis and Howell, 1953). The later model has been the one most extensively investigated and the results obtained in these studies will be discussed.

In dogs, chronic constriction of the thoracic vena cava (TVC) above the entry of the hepatic veins is obtained via a left thoracotomy. These will subse-

quently be referred to as caval dogs. The vein is tied with a tantalum band or linen tape until the pressure in the inferior vena cava is greater than 18 cm of saline. Usually dogs in whom the TVC is tied too tightly, i.e. pressure greater than 40 cm of water, do not survive. During the next 48 hr there is almost total urinary sodium retention with urinary sodium excretion varying from 4.5 to 8.5 mEq/day, compared to control values of about 60 mEq/day (Davis and Howell, 1953). Ascites is normally detectable from 24 to 48 hr and continues to accumulate subsequently. The liver pathology is one of hepatic venous congestion (Table 1) which, together with a fibrinous

TABLE 1. The comparison between chronic thoracic vena caval dogs and patients with cirrhosis and ascites

	TVC dog	Cirrhosis and ascites
Hepatic portal vein pressure	++	++
Inferior vena cava pressure	++	±
Haemodilution	+	+
Sodium excretion	0	0
GFR	N or ↓	↓
RPF	N or ↓	↓
Water load	N	Variable
Renin	++	++
Aldosterone	+++	+++
Abnormal LFTs	±	+++
Histology	Passive venous congestion	Fibrosis and regeneration nodules
Lymphatic congestion	++	++

exudate, is apparently essential for ascites formation (Davis, Lindsay and Southworth, 1952) since constriction of the abdominal inferior vena cava (AVC) fails to develop ascites (Volwiler *et al.*, 1950).

Mechanism of sodium retention in caval dogs

Sodium retention in caval dogs cannot be explained by changes in glomerular filtration rate (GFR) or total renal blood flow (RBF) which do not fall significantly in these animals. These dogs do develop increased serum aldosterone levels, of up to seven times the control values, owing to increased secretion and decreased hepatic degradation of aldosterone (Ayers *et al.*, 1962). However, ascites continues to form in adrenalectomized caval dogs who are either given minimal amounts of mineralocorticoids (Davis, Howell and Shuttleworth, 1953) or solely kept on a high salt intake (Davis *et al.*, 1956). The possibility that sodium retention in these dogs is due to increased renal vein pressure or to an hepatorenal nervous pathway has been ruled out by persistent sodium retention after transplantation of the kidney from the abdomen to the neck (Carpenter *et al.*, 1961).

'Third factor' in caval dogs

That the known factors for controlling renal sodium secretion could not explain the sodium retention found in chronic caval dogs was further emphasized by the failure of the animals to have a natriuresis after an acute saline load. When a normal dog receives an intravenous infusion of saline from 5 to 10% body weight, a brisk natriuresis occurs at a rate of between 600 and 1200 mEq/min. After these dogs had been converted to chronic caval dogs the natriuretic response fell to between 10 and 100

TABLE 2. The effect of acute saline loading on caval dogs (Levinsky and Lalone, 1965)

	Saline loading Mean U_{NaV}		Mean ΔU_{NaV}	P
	Pre	Post		
Controls	48	908	860	
Caval dogs	4	52	48	< 0.01
AVC dogs*	20	360	340	< 0.01

* Constriction of abdominal vena cava.

mEq/min (Table 2) (Levinsky and Labone, 1965). This failure to respond to an acute expansion of the extracellular volume, the classical 'third factor experiment', could not be explained by significant decreases in GFR, RBF or in the filtered sodium load. In dogs in whom the abdominal vena cava (AVC) had been ligated, there was also a significant decrease in the natriuretic response but this was still significantly greater than in the chronic caval dogs (Table 2). This change in the AVC dogs may be explained by a failure of the GFR to rise following saline expansion as compared to the chronic TVC dogs.

The site of sodium resorption

Attempts to elucidate the site and mechanisms of sodium retention have been performed using both clearance experiments and micropuncture studies. In clearance studies, Kaloyanides and his colleagues (1969) showed that the fractional distal sodium load during water diuresis, as approximated by $C_{H_2O} + C_{Na}/C_{IN}$, was significantly lower in caval dogs (9.1 ml/min/100 ml GFR) than in normal dogs (11.7 ml/min/100 ml GFR). However, free water clearance in the two groups was similar. This suggested that the caval dogs must be resorbing a larger fraction of the distal sodium load in the ascending loop of Henle. Using $C_{H_2O}/C_{H_2O} + C_{Na}$ as an index of fractional sodium resorption in the distal segment, caval dogs were found to resorb 93% of the distal sodium load compared to 83% in control animals. Similar results were obtained using hypotonic sodium chloride diuresis and in this instance proximal sodium resorption in caval dogs was significantly increased—81.5% of filtered sodium compared to 68% in controls.

Further clearance experiments with simultaneous measurements of urine and renal papillary tip failed to reveal any specific abnormality in the mechanisms of urine concentration in caval dogs apart from increased sodium resorption in the ascending loop of Henle (Porush *et al.*, 1971).

The effect of acute saline infusion on proximal sodium resorption in caval dogs was studied by micropuncture and, in disagreement with the clearance data, proximal fractional sodium resorption was found to be depressed normally, i.e. 31% compared to 39% in normals (Auld, Alexander and Levinsky, 1971). Despite this, sodium excretion was only 41 μ Eq/min compared to 584 mEq/min in the control kidneys. Thus, these authors concluded that enhanced distal resorption must play a major role in the sodium retention of caval dogs. This suggestion was supported by further micropuncture evidence following sampling from both proximal and distal convoluted tubules in caval dogs (Levy, 1970). The findings here were that the majority of sodium delivered to the distal segment was resorbed proximal to the sampling site early along the distal convoluted tubule, i.e. in the ascending loop of Henle.

Thus, in summary, although there was disagreement as to whether the proximal convoluted tubule was involved in the sodium retention in caval dogs, both clearance and micropuncture studies indicate that the major site of increased sodium resorption is the ascending loop of Henle.

The nature of the sodium retaining lesion in caval dogs

As with all aspects relating to 'third factor' in sodium handling by the kidney, the question of whether the increased resorption in the ascending

TABLE 3. Changes in micropuncture results in the proximal tubule of superficial nephrons in saline loaded dogs following the addition of vaso-active drugs (VAD)

	Saline	Saline and VAD	
$U_{Na}V$ mEq/min	28.1 $\pm$ 7.7	391 $\pm$ 77.8	
TF/P In*	1.36 $\pm$ 0.04	1.27 $\pm$ 0.04	$P < 0.005$
Fractional sodium resorption (%)	25.05 $\pm$ 2.4	19.3 $\pm$ 2.4	$P < 0.005$
Superficial nephron filtration rate (SNFR)	91.5 $\pm$ 9.7	106.5 $\pm$ 18.2	$P < 0.1$
SNFR/GFR $\times 10^{-6}$	3.40 $\pm$ 0.42	3.52 $\pm$ 0.42	N.S.

* Tubular Fluid/Plasma (TF/P) Inulin concentration (Blendis *et al.*, 1972).

loop of Henle is due to alterations in physical factors within the kidney at that site, or to changes in concentration of a circulating substance, or to both, remains controversial. In normal man, angiotensin II causes sodium retention, whereas it can induce a natriuresis in cirrhotic patients with ascites (Laragh *et al.*, 1963). Similarly, Porush and his co-workers (1967) found that angiotensin II in an i.v. dose of 0.1 μ g/kg/min, resulted in a natriuresis during hydropenia which was significantly greater in caval than in normal dogs. This natriuresis was associated with an increase in the distal sodium load and a decrease in free water resorption, suggesting a site of action at both the proximal convoluted tubule and the ascending loop of Henle respectively. These changes could have been produced by systemic circulatory changes. Therefore, the authors attempted to answer this by infusing angiotensin II directly into one renal artery in another group of caval dogs. The result was a significant natriuresis on the ipsilateral side, sodium excretion increasing from 41.8 to 114 μ Eq/min. There was no change in the normal dogs receiving intrarenal angiotensin II. This suggested either localized changes in physical factors within the infused kidney, i.e. in intrarenal haemodynamics, or an alteration in secretion of an intrarenal hormone.

In the same year, Friedler and his colleagues (1967) showed that an acute saline infusion in caval dogs did not result in the rise in blood pressure seen in normal dogs. However, when the saline infusion was followed by local infusion of a vasodilator, acetylcholine, into one renal artery, this resulted in a moderate increase in sodium excretion, e.g. up to 200 μ Eq/min. With the further addition of a systemic hypertensive agent, e.g. angiotensin II or noradrenaline, there was a further and greater natriuresis, e.g. up to 600 μ Eq/min, equivalent to that in a normal dog. It was also significantly greater than that of the contralateral kidney which was not vasodilated. This effect of the combination of agents strongly suggested that the changes in physical factors within the kidney that might occur in caval dogs had been reversed. This study was then repeated with micropuncture sampling of the proximal tubule (Blendis *et al.*, 1972). It was found that this combination of

vasoactive drugs resulted, after saline loading, in a further considerable decrease in proximal resorption in caval dogs (Table 3). Simultaneous measurement of nephron filtration rate enabled the distal sodium load to be calculated, and this was found to be considerably increased (Table 3). These results suggested that the increased sodium resorption mechanism in the distal segment, whether it be physical factor or hormonal, had been overcome or saturated by the increased sodium load, and a natriuresis resulted.

Another physical factor that should be discussed is that of redistribution of blood flow within the kidney. There is considerable disagreement over the suggestion that redistribution of blood flow away from the superficial cortex would lead to sodium retention (Blantz, Kayz and Rector, 1971; Velasquez, Notargiacomo and Cohn, 1973). Nonetheless, it was recently demonstrated, using the ^{133}Xe washout technique, that, following acute partial occlusion of the TVC, significant reductions in superficial renal cortical blood flow occurred associated with sodium retention (Kilcoyne and Cannon, 1971). These changes did not occur with constriction of the AVC. Unfortunately, there are considerable differences in the renal handling of sodium between the acute and chronic caval dogs (Cirksena, Dirks and Berliner, 1966; Auld *et al.*, 1971) and so no firm conclusions can be drawn as to the role of redistribution in chronic caval dogs.

Finally, there is much recent evidence that one or more nonadrenal humoral factors may be involved in the regulation of renal sodium excretion (Sealey, Laragh and Krishman, 1969; Nutbourne *et al.*, 1970; Bricker, Klahrs and Purkerson, 1968). Plasma ultrafiltrates of dogs acutely expanded with saline inhibit load bladder transport (Buckalew, Martinez and Green, 1970). However, similarly prepared plasma from chronic caval dogs failed to show any activity, the short circuit current remaining unchanged (Buckalew and Lancaster, 1971).

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