Nephritic Edema

By Neil A. Kurtzman

Nephritic edema results from the primary retention of salt. Acute glomerulonephritis is the prototypical form of the disorder. The stimulus for the salt retention arises within the kidney by an unknown mechanism. As effective arterial blood volume (EABV) was normal at the start of the disease process, it becomes expanded as salt and water are added to it. The pathophysiological sequelae of this process are compared with those which follow the salt retention of congestive heart failure (CHF). The latter is a syndrome in which salt retention is secondary, driven by the contraction of EABV which is at the heart of CHF. Finally, mechanisms responsible for the salt retention of nephrosis are considered. It is possible, and even likely, that most patients with nephrotic edema have primary salt retention, rather than secondary edema. If this view is correct, salt is retained not because of urinary protein loss and its consequent hypoalbuminemia, but rather because of the glomerulopathy which caused the syndrome in the first place.
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THE TOPIC OF this review is something of a poor relation. The most recent edition (the sixth) of Brenner and Rector's *The Kidney* does not mention it in its chapter on edema and barely refers to it in the chapter on glomerulonephritis. The reasons for this snub are not immediately apparent, but may be symptomatic of the decline of organ physiology in the age of exons, to the antiquity of much of the relevant work on the subject, to the infrequency of nephritic edema's occurrence in the developed world, and to simple inadvertence.

The edema of renal disease has long been classified into 2 types, nephritic and nephrotic. The former exemplified by salt-retaining glomerulonephritis, the latter typically attributed to the hypoalbuminemia characteristic of the nephrotic syndrome. In this article I will compare the features of nephritic edema to those seen in congestive heart failure (CHF). I will then consider in which category to place the patient with nephrotic syndrome.

The edema of heart, kidney, and liver disease is the result of renal salt retention. The failure of a normal kidney to excrete appropriate amounts of salt in patients with CHF and cirrhosis has intrigued clinicians and renal physiologists for more than half a century. Peters[1] reasoned that CHF must induce volume contraction and introduced the concept of effective arterial blood volume (EABV) into the clinical consciousness. He proposed that EABV was contracted in CHF and that the relentless salt retention so often a feature of that malady was an appropriate, although maladaptive, response by the kidney. In other words, the kidney was a dumb beast just carrying out orders — volume contracted, salt retained. A mechanism useful when absolute volume was diminished could cause lethal edema when the heart failed.

EABV is not a measurable entity. Its state must be inferred. It does not necessarily correlate with blood volume, extracelluar volume, or interstitial volume. Failure to distinguish between effective and absolute volume has caused much medical mischief. For example, finding an increased total blood volume in patients with advanced liver disease tells us nothing about their EABVs.[2] Table 1 lists some of the features of patients with a contracted EABV. The essence of a contracted EABV is arterial underfilling that results in impaired organ perfusion. If the patient has diarrhea, his total blood volume is likely decreased; if organ ischemia is secondary to CHF, the patient will probably have an increase in total blood volume although EABV is contracted. The kidney responds to volume contraction by increasing reabsorption and releasing renin, hence reduced salt excretion, a high urea to creatinine ratio, decreased urate excretion, and secondary hyperaldosteronism characteristic of states of both absolute and effective volume contraction. Vasopressin release also increases because it too is sensitive to volume.

Expansion of EABV will have opposite effects. The markers of volume will be oppositely expressed. The urea to creatinine ratio will fall. Likewise, renin, aldosterone, and vasopressin will decrease. The blood pressure which decreases when volume is contracted may rise to life-threatening

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Table 1. Contracted EABV

1. History—blood loss, no intake, vomiting, diarrhea, and so on
2. Physical examination—orthostatic rise in pulse, fall in blood pressure
3. ↑ (BUN/Cr)
4. ↑ Uric acid
5. ↑ Renin
6. ↑ Aldosterone
7. ↑ AVP
8. ↓ U_{NaCl} (assuming renal function is normal)

levels. Urine sodium concentration will rise, provided that the kidney is normal. A low urine sodium concentration in the face of increased EABV denotes renal disease.

Let us consider 2 edematous patients — the first with salt-retaining acute glomerulonephritis (AGN), and a second with CHF. Furthermore, let's assume that each of these hypothetical patients has every feature of his respective disease. I realize, of course, that no patient has every feature of any disease; thus the assumption is heuristic. I am indebted to the pioneering work of Eichna,[3] almost half a century old, for the formulation that follows. Although I have added to it, the basic concept is his. Table 2 presents the expected finding in 2 such patients.

Both are edematous and both have pulmonary edema because they have relentless renal salt-retention. The resultant expansion of extracellular volume raises the central venous pressure. Heart size is increased in both, as is end diastolic pressure. Each has a second heart sound. Thus, at the bedside they appear very much alike. They are edematous and have rales. But the first patient does not have heart disease, whereas the second has normal kidneys. There must be differences between them.

As heart failure develops, cardiac output decreases. Thus, the blood pressure tends to decrease as the syndrome progresses. Blood pressure tends to rise with the onset of nephritic edema. This distinction is not very useful clinically because hypertension is so common a cause of CHF and because sequential blood pressure values are rarely available from just before to just after the onset of CHF. The location of edema fluid, however, is helpful. Facial edema is typical in AGN whereas dependent edema is the rule in CHF.

Secondary hyperaldosteronism is a well-recognized accessory of CHF. It was difficult to predict before their initial measurements what renin levels would be in AGN; they turned out to be low.[4] One might have predicted that inflammatory disease could have triggered renin release, but it does not. The kidney with AGN seems to respond to volume expansion, with respect to renin release, as does a normal kidney. Vasopressin levels are well known to be elevated in CHF.[5-7] They have not been measured in patients with AGN. Nevertheless, it's safe to posit that they are low.

A favorable response to digitalis — increased cardiac output, urine flow, and salt excretion — is a feature of CHF. Patients with AGN are indifferent to its administration. As mentioned earlier, cardiac output is low in CHF; it's low even when it's high. Heart failure is the syndrome that results from a cardiac output inadequate to meet the metabolic requirements of the body — inadequate because of heart disease. Patients with high-output cardiac failure have a cardiac output higher than normal, but lower than needed. Patients with AGN have a normal or high cardiac output. Inadequate organ perfusion forces maximal oxygen extraction across the capillary bed. Thus, an increased A-VO_2 difference is an invariable feature of CHF. Unless pulmonary edema has rendered the patient hypoxemic, the A-VO_2 difference is normal or decreased in patients with AGN. Tissue hypoxia stimulates lactic acid generation causing the A-V pH difference also to rise in CHF. This variable is normal or decreased in AGN.

By now it should be obvious that although EABV is contracted in CHF, it is markedly expanded in patients with salt-retaining AGN. The latter represents a congested state, not CHF. The

Table 2. Comparison of CHF With AGN

	Edema	Palm Edema	Urine Na	CVP	Heart Size	S3	EDP	BP	Facial Edema	Renin	Aldosterone	AVP	Response to Digitalis	Cardiac Output	A-VO_2 Difference	A-V pH Difference
CHF	+	+	Low	High	+	+	High	Falls	–	High	High	High	+	Low	Increased	Increased
AGN	+	+	Low	High	+	+	High	Rises	+	Low	Low	Low	–	High	Decreased	Decreased

Table 3. Characteristics of Edema-Forming States

	Primary Edema	Secondary Edema
Synonyms	Overflow Nephritic Renal	Underfill Nephrotic Cardiac
ECF volume	↑	↑
Plasma volume	↑	
Blood pressure	NI-↑	NI-↓
Cardiac output	NI-↑	↓
GFR	↓	NI-↓
Renal blood flow	NI	↓
FF	↓	↑
PRA	↓	↑
Aldosterone	↓	↑
Sympathetic nervous activity	NI	↑
Plasma ADH	?	↑
Fractional sodium	↓	↓

Abbreviation: NI, normal.

edema of the renal patient results from salt and water added to a normal circulation which then "overflows" into the interstitium. It is an edematous state associated with an expanded EABV. In endocrinological terminology, it is primary edema. Primary because the usual stimulus for salt retention, a contracted EABV, is absent. The edema of CHF is secondary. Secondary because the kidney is responding appropriately, although maladaptively, to volume contraction. Table 3 summarizes the characteristics of these 2 states.

Figure 1 schematically depicts the events that follow primary salt retention. The expansion of EABV simultaneously induces hypertension and edema while suppressing plasma levels of renin, aldosterone, and arginine vasopressin (AVP). Thus hyponatremia and hypokalemia are rarely seen in patients with AGN. Even though distal delivery of solute is reduced in AGN, it is very difficult (although not impossible) to retain sufficient water to markedly lower plasma sodium in the absence of increased vasopressin. Besides AGN, this type of edema is seen in patients with other forms of renal disease. Among these are acute and chronic renal failure associated with injudicious salt and water intake.

The pathophysiology of secondary edematous states is more complex. Classically, 3 syndromes have been thought to cause this form of pernicious fluid retention — CHF, the nephrotic syndrome, and cirrhosis.[8] Interestingly, there has been heated debate over the inclusion of liver cirrhosis in this category and much less over where to place the nephrotic syndrome. This despite little evidence supporting an expanded EABV in end-stage liver disease and a plethora of data suggesting that many, if not all, forms of nephrotic syndrome are associated with primary salt retention. I'll deal with nephrotic syndrome later.

EABV is contracted in patients with heart failure because cardiac output is inadequate. In liver failure the initial cause of diminished EABV is vasodilatation, in effect arteriovenous (A-V) shunting. Later, patients with more advanced liver disease sequester fluid in the peritoneal cavity secondary to portal hypertension. The combination of liver disease and portal hypertension is crucial. Portal hypertension alone does not cause ascites. For example, patients with schistosomiasis involving the portal circuit get varices but not ascites. The hypoalbuminemia so commonly observed in advanced liver disease likely plays little role in the fluid retention it accompanies. Albumin infusion to patients with ascites and edema attributable to cirrhosis is usually without effect.[9] Though there was a period of intense discussion about "overflow" edema early in the course of cirrhosis, there currently is no reason to believe that EABV is ever expanded in patients with progressive liver disease.[10]

Figure 2 depicts the pathophysiological events that cascade from a persistent contraction of EABV. Volume contraction (and probably angiotensin II, as well) stimulates the hypothalamus to produce and release vasopressin and to induce thirst. It also causes renal salt retention and renin release. Proximal tubular salt reabsorption in-

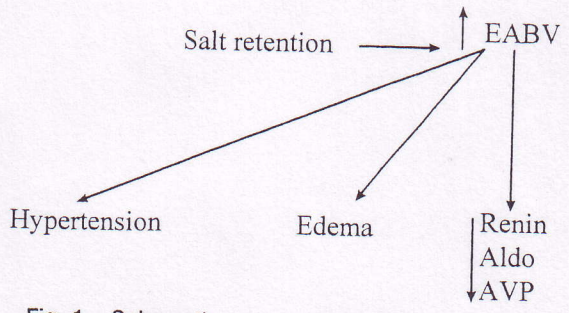

Fig 1. Schematic representation of the consequences of primary salt retention. Salt is retained because of a disorder arising within the kidney.

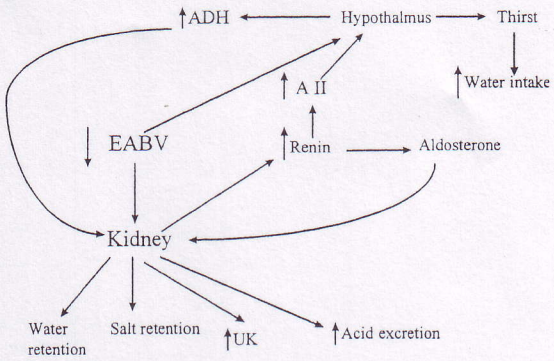

Fig 2. The pathophysiology of secondary salt retention. The initiating event is contraction of EABV.

creases because of the increased filtration fraction associated with volume contraction. Increased filtration fraction raises peritubular oncotic pressure and reduces hydrostatic pressure, both of which favor the movement of solute and water from the tubule to the capillary. Elevated renin concentrations raise angiotensin II and hence aldosterone which increases distal nephron sodium reabsorption while stimulating the secretion of potassium and protons.

The clinical presentation of patients with untreated CHF includes edema (the consequence of salt retention) and hyponatremia (caused by increased intake and reduced excretion of water); these patients rarely, however, suffer hypokalemia and metabolic alkalosis both of which might be expected to arise from their secondary hyperaldosteronism. This is because aldosteronism requires adequate distal sodium delivery for its expression, and virgin patients with CHF have reduced distal delivery of sodium. Treatment of these patients with diuretics, not unexpectedly, commonly induces hypokalemic metabolic alkalosis. The increased delivery of sodium caused by diuretics allows expression of the secondary hyperaldosteronism which was lying in wait like a viper in the renal tubular grass.

The treatment implications of these 2 forms of edema are profound. Treating a patient with secondary edema with diuretics will worsen his condition if not accompanied by an increase in EABV. Thus patients with CHF who are on the ascending limb of their Starling curve will respond to diuretic treatment with worsening cardiac and renal function. On the other hand, if they are on the descending limb, both cardiac and renal function will improve.

The situation is much simpler in the patient with nephritic edema. Here both EABV and total extracellular volumes are expanded. Diuresis cures the volume disorder. The underlying cause of the aberration, obviously, is unaddressed by this therapy.

The edema of the nephrotic syndrome presents a more ambiguous countenance. Traditionally, it has been attributed to a contracted EABV resulting directly from the hypoalbuminemia that is a cardinal feature of the disorder (Table 4). Toscanini remarked "Tradition is yesterday's mistake." This is even more so in medicine than in music. Dorhout Mees has been the most eloquent critic of this traditional view. Much of what follows is derived from his work and arguments.[11-14]

We've known for years that both analbuminemic humans and rats do not have edema.[15] This alone should have given pause to those (including me) who posited hypoalbuminemia as the sole cause of nephrotic edema. In experimental models of nephrotic syndrome, salt retention appeared to precede hypoalbuminemia.[16,17] In other models, salt retention did not occur despite hypoproteinemia.[18-20] There are reports in patents with the nephrotic syndrome that suggest contraction of EABV.[21] These include a natriuretic response to water immersion and to albumin infusion.[22-25] All of these studies suffer methodological difficulties. Other studies have shown no change in sodium excretion after albumin infusion.[14] These same patients responded dramatically to furosemide administration. Their natruresis was not augmented by concomitant albumin infusion.

Blood pressure fell after remission in nephrotic children. This strongly indicates that they were

Table 4. Observations Supporting Underfill and Overflow Mechanisms of Edema in Nephrotic Syndrome

Underfill
Plasma volume may be reduced
Evidence of sodium retention stimulated by renal hypoperfusion
Increase in sodium excretion after maneuvers that expand central blood volume
Activation of the sympathetic nervous system
Overflow
Plasma volume normal or expanded
Suppression of PRA
GFR often impaired
Blunted response or no response to plasma volume expansion

volume expanded when they were hypoalbuminemic and that restoration of normal oncotic pressure was accompanied by a fall in EABV to normal. Blood volume measurements, realizing that they do not necessarily correlate with EABV, have been high in nephrotic patients.[14] Plasma renin activity has been high in some patients with nephrotic syndrome, arguing for a contracted EABV.[21] But other observations have failed to disclose the expected relationship of blood volume to renin activity, suggesting that renin may not mark the state of EABV in nephrotic patients. Some studies have shown that atrial natriuretic peptide is high in nephrosis, again indicating that EABV may be expanded. The filtration fraction has been reported to be low in nephrotic syndrome of diverse origins.[14]

These data all suggest that, at least in some nephrotic patients, EABV is expanded. Thus, the category of "nephrotic edema" needs serious scrutiny. It is possible, although not yet definite, that there may be no such disorder, that patients with nephrotic syndrome may have nephritic edema. This would really not turn out to be all that startling because all these patients have a glomerulopathy.

Why does the kidney afflicted with AGN retain salt? Both proximal and distal tubular reabsorption are likely increased. Inflammation of the glomerulus must somehow be sending a signal to the tubules. Our lack of understanding about this process is not only the result of paucity of interest, but also is caused by the absence of a good experimental model. When such is discovered or invented, the intrarenal message demanding salt retention is sure to be molecular, thus ensuring that today's and tomorrow's investigators will find the problem interesting.

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