Pathophysiology of Vasopressin in Edematous Disorders

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Abstract

Sodium and water retention is characteristic of edematous disorders including cardiac failure, cirrhosis, nephrotic syndrome and pregnancy. In recent years the use of a sensitive radioimmunoassay for plasma vasopressin has implicated the role of nonosmotic vasopressin release in the water retention of these edematous disorders. In experimental studies and studies in humans it has been found that the nonosmotic release of vasopressin is consistently associated with activation of the sympathetic nervous and renin-angiotensin-aldosterone systems. Moreover, the sympathetic nervous system has been shown to be involved in the nonosmotic release of vasopressin (carotid and aortic baroreceptors) and activation of the renin-angiotensin system (renal beta-adrenergic receptors). These findings have led to our proposal that body fluid volume regulation involves the dynamic interaction between cardiac output and peripheral arterial resistance. In this context neither total extracellular fluid (ECF) volume nor blood volume are determinants of renal sodium and water excretion. Rather, renal sodium and water retention is initiated by either a fall in cardiac output (e.g. ECF volume depletion, low-output cardiac failure, pericardial tamponade or hypovolemic nephrotic syndrome) or peripheral arterial vasodilation (e.g. high-output cardiac failure, cirrhosis, pregnancy, sepsis, arteriovenous fistulae and pharmacologic vasodilators). With a decrease in effective arterial blood volume (EABV), initiated by either a fall in cardiac output or peripheral arterial vasodilation, the acute response involves vasoconstriction mediated by angiotensin, sympathetic mediators and vasopressin. The slower response to restoring EABV involves vasopressin-mediated water retention and aldosterone-mediated sodium retention. The renal vasoconstriction which accompanies those states that decrease EABV, by either decreasing cardiac output or causing peripheral arterial vasodilation, limits the distal tubular delivery of sodium and water thus maximizing the water-retaining effect of vasopressin and impairing the normal escape from the sodium-retaining effects of aldosterone. The elevated glomerular filtration rate and filtered sodium load in pregnancy allows increased distal sodium and water delivery in spite of a decrease in EABV, thus limiting edema formation during gestation.

Introduction

Patients with generalized edema by definition have an excess of extracellular fluid (ECF). The ECF resides in two compartments, the vascular and interstitial compartments.

In edematous states, it is the interstitial compartment which is increased, while the vascular compartment may be increased, normal, or decreased.

The important role of the kidney in volume regulation has been recognized for many years. If the ECF is expanded by administration of isotonic saline in a normal subject, the kidney will excrete sodium and water in the urine and return the ECF volume to normal. The central issue in patients with edematous disorders is why does the kidney continue to retain sodium and water in spite of expansion of ECF and development of edema.

If kidneys from patients with edematous disorders are transplanted into a normal environment, excessive renal sodium and water retention no longer occurs. The conclusion therefore emerged that neither expansion of total ECF nor the interstitial compartment was the modulator of renal sodium and water excretion. Peters, in the 1950's, suggested that another body fluid compartment must be the regulator of renal sodium and water excretion¹⁾.

Cardiac output was then suggested as the stimulus for sodium and water retention. This concept could not provide a universal explanation for generalized edema because patients with low-output congestive heart failure and patients with decompensated cirrhosis, who frequently have normal or increased cardiac outputs, both avidly retain sodium and water. Next, decreased total plasma or blood volume was postulated as the stimulus for renal sodium and water retention. Further studies revealed that increased plasma and blood volumes were frequently present in patients with congestive heart failure and cirrhosis. At this point the venous component of body fluids was proposed as the modulator of renal sodium and water excretion. A rise in left atrial pressure is known to increase atrial natriuretic peptide and stimulate a sodium and water diuresis. Increased venous pressures are routinely seen in congestive heart failure patients, while renal sodium and water retention persists.

Our proposal identifies the fullness of the arterial vascular circulation, or effective arterial blood volume (EABV), as the modulator of renal sodium and water excretion. The EABV is determined primarily by cardiac output and peripheral arterial resistance²⁾³⁾. A decrease in either cardiac output or peripheral arterial resistance may therefore initiate and sustain a sodium and water retaining state which leads to edema formation. Since the arterial component of blood volume constitutes only 15 percent of total blood volume, it is possible for arterial blood volume to be decreased by either a decrease in cardiac output or peripheral arterial resistance, even though total blood volume is increased secondary to a rise in its venous component. Those states of renal sodium and water retention initiated by a fall in cardiac output are shown in Figure 1, while those states initiated by a fall in peripheral arterial resistance are shown in Figure 2.

Two compensatory mechanisms occur to protect EABV. One compensatory mechanism consists of a rapid neurohumoral and systemic hemodynamic response, whereas the other somewhat slower mechanism involves renal sodium and water retention. The neurohumoral response to a decreased EABV involves the stimulation of three vasoconstrictor

Fig. 1. Decreased cardiac output as the initiator of diminished effective arterial blood volume (EABV). (With permission from Schrier RW: Nephrology Manual. Ed Schrier RW, 3rd edition, Little Brown, Boston, 1990.)

Fig. 2. Peripheral arterial vasodilation as the initiator of diminished EABV. (With permission from Schrier RW: Nephrology Manual. Ed Schrier RW, 3rd edition, Little Brown, Boston, 1990.)

pathways: ¹⁾ the sympathetic nervous system, ²⁾ the renin-angiotensin system, and ³⁾ vasopressin. The sympathetic nervous system plays a major role in the compensatory mechanism since increased central sympathetic hypothalamic input results in non-osmotic vasopressin release and beta-adrenergic input via the renal nerves stimulates the renin-angiotensin system.

Vasopressin release can occur in the absence of changes in plasma osmolality⁴⁾. The stimuli for this nonosmotic release of vasopressin generally are circumstances associated with changes in autonomic neural tone such as physical pain, emotional stress, hypoxia, liver disease⁵⁾, adrenal insufficiency⁶⁾, cardiac failure⁷⁾, and volume depletion⁸⁾. It appears that afferent vagal and glossopharyngeal pathways from low pressure left atrial and high pressure carotid sinus baroreceptors modulate this nonosmotic release of vasopressin. Non-osmotic release of vasopressin consistently occurs with activation of the renin-angiotensin-aldosterone system and the sympathetic nervous system^{5~7)}.

These compensatory mechanisms are rarely able to totally reverse the decreased cardiac output or decreased peripheral arterial resistance which initiated the response. Therefore these compensatory mechanisms remain chronically stimulated with resultant continuous renal sodium and water retention. Another factor involved in edema formation in patients with decreased EABV is failure to escape from the sodium retaining effects of aldosterone as shown in Figure 3. Renal vasoconstriction resulting from the neurohumoral compensatory response is associated with a decrease in sodium and water delivery to the distal nephron thus limiting the aldosterone escape phenomenon. With this background,

Fig. 3. Aldosterone escape in normal subject (left side) and failure of aldosterone escape in patients with diminished EABV (right side). (With permission from Schrier RW: Nephrology Manual. Ed Schrier RW, 3rd edition, Little Brown, Boston, 1990.)

several major edematous disorders including cardiac failure, cirrhosis, nephrotic syndrome, and pregnancy will be discussed.

Cardiac Failure

In low-output and high-output cardiac failure, the previously discussed roles of decreased cardiac output and decreased peripheral arterial resistance become the respective major factors in sodium and water retention. Specifically, in high-output cardiac failure, as is seen in patients with hyperthyroidism, an arteriovenous fistula, anemia, or beriberi, a decrease in peripheral arterial resistance causes a decrease in EABV and initiates the sodium and water retention. In low-output cardiac failure, a decrease in cardiac output is proposed as the initiating event to decrease EABV and lead to sodium and water retention. Although the initiating event differs in high- and low-output cardiac failure, the subsequent events leading to renal sodium and water retention are similar (Figure 4).

Plasma vasopressin, as measured by radioimmunoassay, is consistently elevated in patients and animals with low-output cardiac failure^{7)9~11)} and in animals with high-output cardiac failure¹²⁾¹³⁾. Ishikawa et al¹⁴⁾ have studied the role of vasopressin using a low-output model of cardiac failure secondary to constriction of the vena cava in rats. Plasma vasopressin levels were increased, and a V2 receptor antagonist of vasopressin reversed the defect in water excretion. Yared et al¹⁵⁾ have also shown that water retention

Fig. 4. High-output and low-output cardiac failure. Although the initiating “underfill” event differs in high- and low-output failure, the subsequent pathways leading to renal sodium and water retention are similar. (With permission from Schrier RW: Pathogenesis of sodium and water retention in high-output and low-output cardiac failure, nephrotic syndrome, cirrhosis, and pregnancy. *N Engl J Med* 319: 1065–1072, 1988.)

can be reversed using a V2 receptor antagonist in a heart failure model secondary to coronary ligation. These results are quite similar to those of Anderson et al⁹⁾ in which the removal of the pituitary source of vasopressin virtually abolished the defect in water excretion in dogs with acute vena cava constriction. The increased release of vasopressin in response to nonosmotic stimuli in cardiac failure is also associated with increased transcription of vasopressin messenger RNA in the rat hypothalamus¹⁶⁾.

What is the stimulus for nonosmotic release of vasopressin in cardiac failure? A decrease in mean arterial pressure of 7 to 10 percent is necessary to stimulate nonosmotic vasopressin release⁸⁾ and such a decrement may not occur in some water-retaining patients with cardiac failure. Experimental studies however have implicated ventricular receptors¹⁷⁾ and baroreceptors that sense stroke volume¹⁸⁾ in the modulation of vasopressin release. Thus, a decrease in stroke volume and cardiac output, rather than a decrease in mean arterial pressure, may be the primary stimulus for nonosmotic release of vasopressin in low-output cardiac failure. In support of this interpretation is the finding that an increase in cardiac output, achieved with either the converting-enzyme inhibitor captopril or the alpha 1-adrenergic blocker prazosin, is associated with improvement in water excretion and suppression of vasopressin release in patients with Stage III and IV congestive heart failure in the absence of a rise in arterial pressure¹⁹⁾.

In addition to its antidiuretic effect on the kidney, vasopressin also is a potent vasoconstrictor, particularly at high circulating levels of the hormone. In experimental low-output cardiac failure, a V1 receptor antagonist of vasopressin decreased vascular resistance and lowered blood pressure¹⁵⁾. No such similar effect of V1 receptor antagonism was seen in high-output cardiac failure¹²⁾. In patients, there is also some evidence of a vascular effect of vasopressin in congestive heart failure. Creager and associates²⁰⁾ have shown that the afterload reduction and enhanced cardiac output during vascular antagonism of vasopressin correlated with high plasma concentrations of vasopressin in patients with congestive heart failure. Since the vascular effects of vasopressin occur at much higher concentrations than the antidiuretic effects, vasopressin mediated effects on water retention are likely to occur before a vascular effect on cardiac afterload is demonstrable.

The sympathetic nervous system and the renin-angiotensin-aldosterone system are also activated in patients with congestive heart failure. Plasma norepinephrine levels have been shown to correlate with the degree of left ventricular dysfunction²¹⁾²²⁾. An increase in plasma renin activity is another marker of the severity of congestive heart failure¹⁹⁾²³⁾. Stimulation of nonosmotic release of vasopressin, activation of the sympathetic nervous system, and activation of the renin-angiotensin-aldosterone system have been shown to occur in high-output as well as low-output cardiac failure. The lower the cardiac output in low-output failure or in high-output failure the lower the arterial resistance, the more profoundly these three hormonal factors will increase vascular tone and cause sodium and water retention.

Cirrhosis

Early attempts to explain sodium and water retention in cirrhosis invoked the “under-filling” hypothesis, which stated that ascites formation led to circulatory hypovolemia and secondary renal sodium and water retention. This theory could not account for sodium and water retention in all patients with cirrhosis since some patients were found to have increased plasma volumes which were not altered with diuresis²⁴⁾²⁵⁾. Therefore, an “overflow” hypothesis for ascites formation was proposed. This hypothesis stated that primary renal sodium and water retention, which was not related to hypovolemia, led to a secondary formation of ascites. It has been shown in experimental cirrhotic models that renal sodium retention preceded ascites formation or overt hypoalbuminemia with a reduction of plasma oncotic pressure^{26~28)}. It has also been shown that renal sodium retention occurs even when a portacaval shunt is created to prevent portal hypertension²⁷⁾. Thus, the mechanism for primary renal sodium retention with the overflow hypothesis remained obscure. Moreover, studies in patients are in conflict with the overflow hypothesis since the volume expansion in this model should suppress activation of the sympathetic nervous system, the renin-angiotensin-aldosterone system, and nonosmotic release of vasopressin, however, these hormonal systems have been shown to be activated in patients with decompensated cirrhosis⁵⁾²⁹⁾.

The current hypothesis, as shown in Figure 5, invokes a reduction in peripheral arterial resistance as the initiating factor for renal sodium and water retention in patients with cirrhosis³⁰⁾. A fall in peripheral arterial resistance has been shown to occur early in rats³¹⁾ and dogs²⁸⁾ with experimental cirrhosis. In addition, patients with advanced cirrhosis and renal sodium and water retention are known to have decreased peripheral arterial resistance with lowered arterial blood pressure and normal or high cardiac output³²⁾. Patients with cirrhosis develop arteriovenous fistulas in the splanchnic, dermal, and pulmonary circulations and renal sodium retention is known to occur in patients with decreased peripheral arterial resistance secondary to an arteriovenous fistula³³⁾. An increase in the total plasma volume occurs with this renal sodium and water retention while the arterial compartment of the plasma volume remains decreased. This decrease in EABV is associated with continued stimulation of the sympathetic nervous system, the renin-angiotensin-aldosterone system, and nonosmotic release of vasopressin in the presence of an increased plasma volume. Increases in these hormones have been demonstrated in animals with aortocaval fistulas¹²⁾¹³⁾, while venous filling pressures are increased as reflected by elevated plasma atrial natriuretic factor levels³⁴⁾. Further studies on the initiating role of decreased peripheral arterial resistance in the renal sodium and water retention associated with cirrhosis are needed since one study suggests that sodium retention may occur prior to a detectable decrease in peripheral arterial resistance²⁸⁾. However, since the mean daily sodium retention was very small (20mEq) and mean arterial pressure fell, it seems likely that the cardiac measurements were not sensitive enough to detect a fall in the calculated peripheral vascular resistance.

Fig. 5. Cirrhosis and pregnancy. The primary peripheral vasodilation is the primary “underfill” event in both cirrhosis and pregnancy. However the reduction in oncotic pressure and portal hypertension further reduce EABV and thus enhance sodium and water retention in the patient with cirrhosis. Portal hypertension and increased intrahepatic pressure have also been shown to initiate a hepatorenal reflex, which causes renal sodium and water retention. In pregnancy the rise in glomerular filtration rate enhances the amount of sodium and water filtered and increases distal sodium and water delivery thus attenuating the sodium and water retention secondary to the decreased EABV. (With permission from Schrier RW: Pathogenesis of sodium and water retention in high-output and low-output cardiac failure, nephrotic syndrome, cirrhosis, and pregnancy. *N Engl J Med* 316: 1065–1072, 1988.)

Patients with cirrhosis who excrete less than 80 percent of a water load in 5 hours have higher plasma concentrations of vasopressin, renin, aldosterone, and norepinephrine than cirrhotic patients who excrete the water load normally³⁵). Patients who excrete less than 20 percent of an acute water load had significantly higher concentrations of the hormones than patients who excreted between 20 and 80 percent of a water load; those patients with the most severe water retention also had a much worse prognosis³⁶). Plasma vasopressin, renin, aldosterone, and norepinephrine were decreased as sodium and water excretion increased using head-out water immersion to expand central blood volume in these nonexcretor patients. These results are compatible with underfilling of the arterial compartment of plasma volume, secondary to a decreased peripheral arterial resistance, as the initiator of sodium and water retention in cirrhosis. In experimental models of cirrhosis induced by carbon tetrachloride and phenobarbital³⁷) or longterm bile-duct ligation³⁸), nonosmotic release of vasopressin has also been implicated in water retention associated with cirrhosis.

Head-out water immersion improves but does not normalize renal sodium and water excretion in nonexcretor patients with cirrhosis³⁵). In these studies mean arterial pressure

did not rise due to further peripheral vasodilatation even though intracardiac pressures and cardiac output improved with head-out water immersion³⁵⁾. This increased peripheral vasodilatation may in part be due to suppression of the renin-angiotensin and sympathetic nervous systems and may have accounted for incomplete recovery of renal sodium and water excretion. When head-out water immersion is combined with exogenous norepinephrine to prevent the further peripheral vasodilatation, renal sodium and water excretion was normalized³⁹⁾. The only hemodynamic difference noted with this combined treatment when compared to head-out water immersion alone was an increase in mean arterial pressure from 105/64 mm Hg to 135/75 mm Hg. No difference in cardiac output, right atrial pressure, pulmonary artery pressure, or pulmonary capillary wedge pressure occurred. Also the suppression of plasma vasopressin and aldosterone was similar with both maneuvers, thus suggesting that the increased sodium and water excretion was due to increased distal delivery of sodium and water.

As stated earlier, activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system also occurs in patients with cirrhosis. An increase in plasma norepinephrine occurs secondary to enhanced norepinephrine secretion since the metabolic clearance of norepinephrine remains unchanged in cirrhotic patients⁴⁰⁾. Antagonism of the tubular action of aldosterone with spironolactone is associated with improvement in ascites⁴¹⁾ and enhancement of the natriuretic response to head-out water immersion in cirrhosis⁴²⁾. Angiotensin appears to play a crucial role in maintaining blood pressure in patients with cirrhosis since administration of saralasin, an antagonist of angiotensin, produces a reversible decrease in blood pressure⁴³⁾.

A profile of peripheral arterial resistance, plasma hormones and plasma volume in the various stages of cirrhosis is shown in Figure 6.

Nephrotic Syndrome

Initial investigators believed that the blood volume in patients with nephrotic syndrome was decreased secondary to the diminished plasma oncotic pressure that accompanied the albuminuria and hypoalbuminemia⁴⁴⁾. Recently this issue has been more controversial since, when corrected for dry weight, normal or increased blood volumes have been measured in some patients with nephrotic syndrome and renal sodium and water retention⁴⁵⁾. Intrarenal mechanisms have also been postulated to account for renal sodium and water retention in patients with nephrotic syndrome. In one study, the ability to excrete a water load correlated with the glomerular filtration rate in adult patients with nephrotic syndrome⁴⁶⁾. In an experimental study using a unilateral intrarenal injection of an amino-nucleoside and micropuncture techniques, an increase in tubular sodium reabsorption was found in the collecting duct of the ipsilateral but not the contralateral kidney⁴⁷⁾.

Other studies investigating the role of aldosterone in patients with nephrotic syndrome initially appeared to exclude hypovolemia-induced aldosterone as a stimulus for renal sodium retention in nephrotic patients^{48) 49)}. Specifically, reduction of aldosterone levels

by converting-enzyme inhibitors did not result in an increase in sodium excretion by the kidney⁴⁹⁾. In addition, renin and aldosterone levels were the same during periods of edema and periods of steroid-induced remission of the nephrotic syndrome. Moreover, Meltzer et al⁵⁰⁾ identified a group of nephrotic patients with suppressed plasma levels of renin and aldosterone. These nephrotic patients had significantly lower glomerular filtration rates and higher blood pressures than the other patients who demonstrated the hormonal characteristics of hypovolemia.

There is however considerable evidence that a decrease in blood volume as the initiating factor in renal sodium and water retention occurs in some patients with nephrotic syndrome. In a group of children with nephrotic syndrome secondary to minimal change disease, administration of hyperoncotic albumin and head-out water immersion suppressed elevated concentrations of plasma vasopressin, renin, aldosterone and norepinephrine and increased plasma atrial natriuretic factor in association with diuresis and natriuresis⁵¹⁾⁵²⁾.

Fig. 6. Peripheral vasodilation hypothesis. (#) The peripheral arterial vasodilation hypothesis can explain virtually all of the manifestations of the spectrum of systemic and renal hemodynamics, plasma hormones and effects on sodium and water excretion observed in the cirrhotic patient. (+) In many cirrhotic patients the peripheral vasodilation decreases cardiac pre-load and is associated with an increase in cardiac output. (*) Some patients (approximately one-third) with decompensated cirrhosis, as defined by the presence of ascites, may have normal renal hemodynamics because of increasing synthesis of renal vasodilating prostaglandins. These patients demonstrate a severe diminution in renal function with administration of nonsteroidal antiinflammatory drugs in contrast to no effect observed in the compensated (i.e. no ascites) cirrhotic patient. (With permission from Schier RW, Arroyo V, Bernardi M, et al: Peripheral arterial vasodilation hypothesis: A proposal for the initiation of renal sodium and water retention in cirrhosis. *Hepatology* 8: 1151-1157, 1988.)

In a group of 16 adult patients with a variety of causes of nephrotic syndrome, blood volumes were significantly less than controls when expressed per kilogram of wet body weight⁵³⁾. Blood volume was inversely and significantly related to plasma renin activity. In addition, plasma vasopressin was not suppressed during water loading and correlated significantly with blood volume in nephrotic patients. These results supported the role of nonosmotic release of vasopressin in water retention secondary to hypovolemia in these patients with nephrotic syndrome.

Evidence also exists to support the role of aldosterone in sodium retention in nephrotic patients⁵⁴⁾. In nephrotic patients on a controlled sodium diet, spironolactone totally reversed the nearly 100mEq/day positive sodium balance. This natriuretic effect of spironolactone was not seen in control patients receiving the same 400mg daily dose of this aldosterone antagonist.

The current proposal regarding the pathogenesis of renal sodium and water retention in nephrotic syndrome is shown in Figure 7. Depending on the degree of intrarenal sodium retention, patients with nephrotic syndrome may be categorized as either the hypovolemic, vasoconstrictor or hypervolemic variety.

Fig. 7. Nephrotic syndrome. The albuminuria and decrease in plasma oncotic pressure initiate the underfilling in the nephrotic syndrome. Renal impairment and intrarenal factors may intervene, however, and in some circumstances restore or even expand effective blood volume. (With permission from Schrier RW: Pathogenesis of sodium and water retention in high-output and low-output cardiac failure, nephrotic syndrome, cirrhosis, and pregnancy. *N Engl J Med* 319: 1065–1072, 1988.)

Pregnancy

Increases in plasma volume, extracellular fluid volume, cardiac output and renal hemodynamics during pregnancy of 30 to 50 percent have led some to the conclusion that pregnancy is an “overflow” state secondary to primary renal sodium and water retention. During the first trimester of pregnancy, however, blood pressure is lower than in non-pregnant normal subjects⁵⁵⁾. Primary renal sodium and water retention with volume expansion can not account for this fall in blood pressure. Phippard and colleagues have studied the hormonal and hemodynamic changes accompanying pregnancy in baboons⁵⁶⁾. They have found an early peripheral vasodilatation and increased cardiac output which precedes the volume expansion of pregnancy. Since the increase in cardiac output does not completely compensate for the peripheral vasodilatation, the result is a lower blood pressure in the first trimester of pregnancy.

The cause of peripheral vasodilatation in pregnancy may be multifactorial. The placenta creates an arteriovenous fistula in the maternal circulation and contributes to peripheral vasodilatation. In addition, increased synthesis of vasodilating prostaglandins, such as prostaglandin E₂ and prostacyclin, may contribute to peripheral vasodilatation^{57) 58)}. As in the other diseases discussed, a decrease in peripheral arterial resistance leads to a decreased EABV and stimulation of the sympathetic nervous and renin-angiotensin-aldosterone systems and nonosmotic release of vasopressin (Figure 5).

Plasma vasopressin plays a role in the decreased plasma osmolality and plasma sodium concentrations which accompany pregnancy in animals⁵⁹⁾ and humans⁶⁰⁾. Thirst stimulation also occurs at a lower plasma osmolality in pregnant women⁶⁰⁾. The importance of increased thirst and water intake can be demonstrated in Brattleboro rats, which lack vasopressin, but show the same fall in plasma osmolality during pregnancy as water intake doubles⁶¹⁾.

There is evidence to suggest that primary peripheral vasodilatation and decreased EABV may be responsible for the release of vasopressin and stimulation of thirst at a lower plasma osmolality in pregnant than non-pregnant rats. When water intake is restricted to that of nonpregnant rats, pregnant rats have significantly higher concentrations of vasopressin and aldosterone⁵⁹⁾. Moreover, the threshold for nonosmotic vasopressin release occurs at a 40 percent higher mean blood volume in pregnant rats when volume depletion is induced by intraperitoneal injection of polyethylene glycol⁶²⁾. Thus, the primary peripheral arterial vasodilatation of pregnancy seems most likely to be responsible for the increased thirst and lower threshold for osmotic and nonosmotic gonadotropin⁶³⁾ and the presence of a fetoplacental unit⁶⁴⁾, may also be involved in the “reset osmostat” of pregnancy.

Evidence for increased vasopressin synthesis during pregnancy can also be found at the gene level. Zingg and Lefebvre⁶⁵⁾ found a 2.5-fold increase in vasopressin messenger RNA in late pregnancy, while Van Tol et al⁶⁶⁾ found a 2-fold increase in vasopressin messenger RNA on the last day of gestation. These findings are most compatible with a decrease in EABV in pregnancy with enhanced vasopressin synthesis rather than merely an alteration

in osmotic threshold, i.e. reset osmostat.

The increase in plasma aldosterone that occurs during pregnancy would be expected to contribute to renal sodium retention and expansion of the extracellular volume. Renal excretion of a sodium load under steady-state conditions has been shown to be normal in pregnancy⁶²⁾, thus suggesting escape from the sodium retaining effects of aldosterone. This aldosterone escape is most likely related to the increased glomerular filtration rate and increased distal tubular delivery of sodium associated with pregnancy (Figure 5), since increased delivery of fluid and sodium to the distal tubule appears to be the mechanism responsible for escape from the effects of aldosterone⁶⁷⁾.

The renin-angiotensin system is known to be activated consistently in the first trimester of pregnancy⁶⁸⁾. Plasma norepinephrine levels have been studied in pregnancy but the results are inconclusive with increased⁶⁹⁾ or normal⁷⁰⁾ levels reported.

Summary

This review has examined the pathophysiology of vasopressin in the edematous disorders of cardiac failure, cirrhosis, nephrotic syndrome and pregnancy and proposed a unifying hypothesis of body fluid volume regulation. A decrease in the EABV secondary to either a decreased cardiac output or a decrease in peripheral arterial resistance is proposed as the initiator of sodium and water retention. This decreased EABV leads to nonosmotic release of vasopressin and to activation of the sympathetic nervous and renin-angiotensin-aldosterone systems. Nonosmotic release of vasopressin leads to water retention while increased secretion of aldosterone, and failure to escape from the hormones sodium-retaining effect, leads to sodium retention in edematous disorders.

Exceptions to the above statements may exist in nephrotic syndrome and pregnancy. In nephrotic syndrome, the kidney is diseased and intrarenal mechanisms may lead to expansion of the arterial vascular tree and suppression of the renin-angiotensin-aldosterone system. In pregnancy, the increased glomerular filtration rate and increased distal delivery of sodium and water "aldosterone escape" to occur.

References

- 1) Peters JP: The role of sodium in the production of edema. *N Engl J Med* 239: 353–362, 1948.
- 2) Schrier RW: Pathogenesis of sodium and water retention in high-output and low-output cardiac failure, nephrotic syndrome, cirrhosis, and pregnancy (First of two parts). *N Engl J Med* 319: 1065–1072, 1988.
- 3) Schrier RW: Pathogenesis of sodium and water retention in high-output and low-output cardiac failure, nephrotic syndrome, cirrhosis, and pregnancy (Second of two parts). *N Engl J Med* 319: 1127–1134, 1988.
- 4) Schrier RW, Berl T, Anderson RJ: Osmotic and nonosmotic control of vasopressin release. *Am J Physiol* 236: F321–F322, 1979.
- 5) Bichet D, Szatalowicz V, Chaimovitz C, et al: Role of vasopressin in abnormal water

- excretion in cirrhotic patients. *Ann Intern Med* 96: 413–417, 1982.
- 6) Linas SL, Berl T, Robertson G, et al: Evidence for vasopressin dependent and independent mechanisms in the impaired water excretion of glucocorticoid deficiency. *Kid Int* 18: 58–67, 1980.
- 7) Szatalowicz VL, Arnold PE, Chaimovitz C, et al: Radioimmunoassay of plasma arginine vasopressin in hyponatremic patients with congestive heart failure. *N Engl J Med* 305: 263–266, 1981.
- 8) Dunn FL, Brennan TJ, Nelson AE, et al: The role of blood osmolality and volume in regulating vasopressin secretion in the rat. *J Clin Invest* 52: 3212–3219, 1973.
- 9) Anderson RJ, Harbottle J, McDonald KM, et al: Mechanism of effect of thoracic inferior vena cava constriction on renal water excretion. *J Clin Invest* 54: 1473–1479, 1974.
- 10) Riegger GAJ, Liebau G, Koshiesk K: Antidiuretic hormone in congestive heart failure. *Am J Med* 72: 49–57, 1982.
- 11) Goldsmith SR, Francis GS, Cowley AW, et al: Increased arginine vasopressin levels in patients with congestive heart failure. *J Am Coll Cardiol* 1: 1385–1390, 1983.
- 12) Riegger GAJ, Liebau G, Bauer E, et al: Vasopressin and renin in high output heart failure of rats: Hemodynamic effects of elevated plasma hormone levels. *J Cardiovasc Pharmacol* 7: 1–5, 1985.
- 13) Riegger GAJ, Liebau G: The renin-angiotensin-aldosterone system, antidiuretic hormone, and sympathetic nerve activity in an experimental model of congestive heart failure in the dog. *Clin Sci* 62: 465–469, 1982.
- 14) Ishikawa S, Saito T, Okada K, et al: Effect of vasopressin antagonist on water excretion in inferior vena cava constriction. *Kid Int* 30: 49–55, 1986.
- 15) Yared A, Kon V, Brenner BM, et al: Role of vasopressin (AVP) in rats with congestive heart failure (CHF). *Kid Int* 27: 337, 1985 (abstract).
- 16) Kim JK, Michel J-B, Soubrier F, et al: Arginine vasopressin gene expression in congestive heart failure. *Kid Int* 33: 270, 1988 (abstract).
- 17) Thames MD, Peterson MG, Schmid PG: Stimulation of cardiac receptors with veratrum alkaloid inhibits ADH secretion. *Am J Physiol* 239: H784–788, 1980.
- 18) Hakumaki MO, Wang BC, Sundet WD, et al: Aortic baroreceptor discharge during nonhypotensive hemorrhage in anesthetized dogs. *Am J Physiol* 249: H393–403, 1985.
- 19) Bichet DG, Kortas C, Mettauer B, et al: Modulation of plasma and platelet vasopressin by cardiac function in patients with heart failure. *Kid Int* 29: 1188–1196, 1986.
- 20) Creager MA, Faxon DP, Cutler SS, et al: Contribution of vasopressin to vasoconstriction in patients with congestive heart failure: Comparison with the renin-angiotensin-aldosterone and the sympathetic nervous system. *J Am Coll Cardiol* 7: 758–765, 1986.
- 21) Levine TB, Francis GS, Goldsmith SR, et al: Activity of the sympathetic nervous system and the renin-angiotensin-aldosterone assessed by plasma hormone levels and their relation to hemodynamic abnormalities in congestive heart failure. *Am J Cardiol* 49: 1659–1666, 1982.
- 22) Thomas JA, Marks BH: Plasma norepinephrine in congestive heart failure. *Am J Cardiol* 41: 233–243, 1978.
- 23) Dzau VJ, Colucci WS, Hollenburg NK, et al: Relation of the renin-angiotensin-aldosterone system to clinical state in congestive heart failure. *Circulation* 63: 645–651, 1981.

- 24) Lieberman FL, Denison EK, Reynolds TB: The relationship of plasma volume, portal hypertension, ascites, and renal sodium retention in cirrhosis: The overflow theory of ascites formation. *Ann NY Acad Sci* 170: 202–212, 1970.
- 25) Lieberman FL, Reynolds TB: Plasma volume in cirrhosis of the liver: Its relation to portal hypertension, ascites, and renal failure. *J Clin Invest* 46: 1297–1308, 1967.
- 26) Levy M: Observations on renal function and ascites formation in dogs with experimental portal cirrhosis, in Epstein M (ed): *The kidney in liver disease*. Elsevier, New York, pp 131–142, 1978.
- 27) Levy M, Wexler MJ: Renal sodium retention and ascites formation in dogs with experimental cirrhosis but without portal hypertension or increased splanchnic vascular capacity. *J Lab Clin Med* 91: 520–536, 1978.
- 28) Levy M, Allotey JB: Temporal relationships between urinary salt retention and altered systemic hemodynamics in dogs with experimental cirrhosis. *J Lab Clin Med* 92: 560–569, 1978.
- 29) Bichet DG, Van Putten VJ, Schrier RW: Potential role of increased sympathetic activity in impaired sodium and water excretion in cirrhosis. *N Engl J Med* 307: 1552–1557, 1982.
- 30) Schrier RW, Arroyo V, Bernardi M, et al: Peripheral arterial vasodilation hypothesis: A proposal for the initiation of renal sodium and water retention in cirrhosis. *Hepatology* 8: 1151–1157, 1988.
- 31) Fernandez Munoz D, Caramelo C, Santos JC, et al: Systemic and hemodynamic disturbances in conscious rats with experimental cirrhosis without ascites. *Am J Physiol* 249: G316–320, 1985.
- 32) Schrier RW, Caramelo C: Hemodynamics and vasoactive hormones in hepatic cirrhosis, in Epstein M (ed): *The kidney in liver disease*. 3rd ed.
- 33) Epstein FH, Post RS, McDowell M: The effect of an arteriovenous fistula on renal hemodynamics and electrolyte excretion. *J Clin Invest* 32: 233–241, 1953.
- 34) Villarreal D, Freeman RH, Davis JO, et al: Atrial natriuretic factor secretion in dogs with experimental high-output heart failure. *Am J Physiol* 252: H692–697, 1987.
- 35) Bichet DG, Groves BM, Schrier RW: Mechanisms of improvement of water and sodium excretion by immersion in decompensated cirrhotic patients. *Kid Int* 24: 788–794, 1983.
- 36) Nicholls KM, Shapiro MD, Groves BM, et al: Factors determining renal response to water immersion in non-excretor cirrhotic patients. *Kid Int* 30: 417–421, 1986.
- 37) Linas SL, Anderson RJ, Guggenheim SJ, et al: Role of vasopressin in impaired water excretion in conscious rats with experimental cirrhosis. *Kid Int* 20: 173–180, 1981.
- 38) Better OS, Aisenbrey GA, Berl T, et al: Role of antidiuretic hormone in impaired urinary dilution associated with chronic bile duct ligation. *Clin Sci* 58: 493–500, 1980.
- 39) Shapiro MD, Nicholls KM, Groves BM, et al: Interrelationship between cardiac output and vascular resistance as determinants of effective arterial blood volume in cirrhotic patients. *Kid Int* 28: 206–211, 1985.
- 40) Nicholls KM, Shapiro MD, Van Putten VJ, et al: Elevated plasma norepinephrine concentrations in decompensated cirrhosis: Association with increased secretion rates, normal clearance rates and suppressibility by central blood volume expansion. *Circ Res* 56: 457–461, 1985.
- 41) Gregory PB, Broekelschen PH, Hill MD, et al: Complications of diuresis in the alcoholic patients with

- ascites: A controlled trial. *Gastroenterology* 73: 534–538, 1977. 42) Epstein M, Pins DS, Schneider N, et al: Determinants of deranged sodium and water homeostasis in decompensated cirrhosis. *J Lab Clin Med* 87: 822–839, 1976. 43) Schroeder ET, Anderson GH, Goldman SH, et al: Effect of blockade of angiotensin II on blood pressure, renin and aldosterone in cirrhosis. *Kid Int* 9: 511–519, 1976.
- 44) Brown E, Hopper J Jr, Wennesland R: Blood volume and its regulation. *Annu Rev Physiol* 19: 231–254, 1957. 45) Dorhout Mess EJ, Roos JC, Boer P, et al: Observations on edema formation in the nephrotic syndrome in adults with minimal lesions. *Am J Med* 67: 378–384, 1979. 46) Shapiro MD, Nicholls KM, Groves BM, et al: Role of glomerular filtration rate in the impaired sodium and water excretion of patients with the nephrotic syndrome. *Am J Kid Dis* 8: 81–87, 1986.
- 47) Ichikawa I, Rennke HG, Hoyer JR, et al: Role for intrarenal mechanisms in the impaired salt excretion of experimental nephrotic syndrome. *J Clin Invest* 71: 91–103, 1983.
- 48) Brown EA, Markandu ND, Roulston JE, et al: Is the renin-angiotensin-aldosterone system involved in the sodium retention in the nephrotic syndrome? *Nephron* 32: 102–107, 1982. 49) Brown EA, Markandu ND, Sagnella GA, et al: Lack of effect of captopril on the sodium retention of nephrotic syndrome. *Nephron* 37: 43–48, 1984.
- 50) Meltzer JI, Keim HJ, Laragh JH, et al: Nephrotic syndrome: Vasoconstriction and hypervolemic types indicated by renin-sodium profiling. *Ann Intern Med* 91: 688–696, 1979. 51) Rasher W, Tulassey T, Seyberth HW, et al: Diuretic and hormonal responses to head-out water immersion in nephrotic syndrome. *J Pediatr* 109: 609–614, 1986. 52) Tulassey T, Rasher W, Long RE, et al: Atrial natriuretic peptide and other vasoactive hormones in nephrotic syndrome. *Kid Int* 31: 1391–1395, 1987.
- 53) Usberti M, Federico S, Meccariello S, et al: Role of plasma vasopressin in the impairment of water excretion in nephrotic syndrome. *Kid Int* 25: 422–429, 1984.
- 54) Shapiro M, Hasbargen J, Henson J, et al: Role of aldosterone in the sodium retention of patients with nephrotic syndrome. *Am J Nephrol* (in press).
- 55) MacGillivray I, Rose GA, Rowe B: Blood pressure survey in pregnancy. *Clin Sci* 37: 395–407, 1969. 56) Phippard AF, Horvath JS, Glynn EM: Circulatory adaptation to pregnancy—serial studies of haemodynamics, blood volume, renin and aldosterone in the baboon (*Papio homodryas*). *J Hypertens* 4: 773–779, 1986.
- 57) Whalen JB, Clancey CJ, Farley DB, et al: Plasma prostaglandins in pregnancy. *Obstet Gynecol* 51: 52–55, 1978. 58) Gerber JG, Payne NA, Murphy RC, et al: Prostacyclin produced by the pregnant uterus in the dog may act as a circulating vasodepressor substance. *J Clin Invest* 67: 632–636, 1981. 59) Durr JA, Stamoutsos B, Lindheimer MD: Osmoregulation during pregnancy in the rat: Evidence for resetting of the threshold for vasopressin secretion during gestation. *J Clin Invest* 68: 337–346, 1981. 60) Davison JM, Gilmore EA, Durr J, et al: Altered osmotic threshold for vasopressin and thirst in human pregnancy. *Am J Physiol* 246: F105–109, 1984. 61) Barron WM, Durr J, Stamoutsos BA: Osmoregulation and vaso-

- pressin secretion during pregnancy in Brattleboro rats. *Am J Physiol* 248: R29–37, 1985.
- 62) Barron WM: Volume homeostasis during pregnancy in the rat. *Am J Kid Dis* 9: 296–302, 1987.
- 63) Davison JM, Sheills EA, Philips PR, et al: Serial evaluation of vasopressin release and thirst in human pregnancy. *J Clin Invest* 81: 798–806, 1988.
- 64) Barron WM, Lindheimer MD: Osmoregulation in pseudopregnant and prolactin-treated rats: Comparison with normal gestation. *Am J Physiol* 254: R478–484, 1988.
- 65) Zingg HH, Lefebvre DL: Oxytocin and vasopressin gene expression during gestation and lactation. *Brain Res* 464: 1–6, 1988.
- 66) Van Tol HH, Bolwerk EL, Liu B, et al: Oxytocin and vasopressin gene expression in the hypothalamo-neurohypophyseal system of the rat during the estrous cycle, pregnancy, and lactation. *Endocrinology* 122: 945–951, 1988.
- 67) Gonzalez-Campoy JM, Romero JC, Knox FG: Escape from the sodium-retaining effects of mineralocorticoids: Role of ANF and intrarenal hormone systems. *Kid Int* 35: 767–777, 1989.
- 68) Symonds EM: Renin-angiotensin system in normal and hypertensive pregnancy, in Lewis PJ, Moncada S, O'Grady J (eds): *Prostacyclin in pregnancy*. New York, Raven Press, pp 91–98, 1983.
- 69) Whittaker PG, Gerrard J, Lind T: Catecholamine responses to changes in posture during pregnancy. *Br J Obstet Gynaecol* 92: 586–592, 1985.
- 70) Barron WM, Mujais SK, Zinaman M, et al: Plasma catecholamine responses to physiologic stimuli in normal human pregnancy. *Am J Obstet Gynecol* 154: 80–84, 1986.