Ascites and Renal Dysfunction in Liver Disease
Pathogenesis, Diagnosis, and Treatment

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Second Edition
Ascites and Renal Dysfunction in Liver Disease
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Dedicated to our wives, Nuria, Joana, Paula, and Barbara, in recognition of their contribution to our scientific careers.
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Preface to the Second Edition

It has been six years since we published the first edition of *Ascites and Renal Dysfunction in Liver Disease*. Since then, significant advances have been made in the pathogenesis of circulatory and renal dysfunction that occur in the setting of chronic liver diseases, particularly cirrhosis. Specifically, the role of vasodilatory factors, particularly nitric oxide, has been investigated extensively. Moreover, there is increased recognition of the mechanistic role of impaired heart function on the circulatory dysfunction of liver failure. In this second edition of *Ascites and Renal Dysfunction in Liver Disease*, these advances in pathogenesis are described in specific chapters.

Besides this increased knowledge on pathophysiology, major advances have been made in the clinical management of renal dysfunction in liver disease. A new therapeutic method, transjugular intravenous portosystemic shunts, has emerged for patients with ascites refractory to diuretic therapy. A large number of nonrandomized studies (as well as several randomized trials) have been published concerning the effects of this therapeutic approach. For the first time ever, an effective treatment has been described to treat hepatorenal syndrome in patients with cirrhosis, namely administration of vasoconstrictor drugs. Moreover, there are studies showing how hepatorenal syndrome can be effectively prevented in specific settings such as spontaneous bacterial peritonitis and alcoholic hepatitis. Finally, specific antagonists of the V2 vasopressin receptor are in advanced stages of clinical development. These drugs might prove to be useful in the management and prevention of dilutional hyponatremia, a complication for which there is currently no effective therapy. All these new topics, as well as other topics on the management of liver disease, are covered in this second edition.

The layout and look of the book have changed from the previous edition. The book has been divided into two sections: the first (Parts 1, 2 and 3) describes the pathophysiology of circulatory and renal abnormalities, whilst the second (Parts 4–7) relates to clinical management of patients. We hope this will make the book easier to read when looking for either pathogenic factors or answers to clinical questions.

Finally, we would like to acknowledge the work of the authors of the chapters, who are internationally recognised specialists in their fields and have done a tremendous job in summarizing the different topics inside the page limits. We thank both Nicki van Berckel and Janet Darling for their administrative assistance, and Blackwell Publishing for making the book appealing to the readers.

We hope that this second edition of *Ascites and Renal Dysfunction in Liver Disease* will be helpful not only to clinical researchers interested in complications of cirrhosis, but also to those clinicians – whether they be gastroenterologists, transplant hepatologists, nephrologists, or internists – caring for patients with liver diseases.

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2005
Part 1
Regulation of Extracellular Fluid Volume and Renal and Splanchnic Circulation
Chapter 1
Extracellular Fluid Volume Homeostasis

Brian D. Poole, William T. Abraham, and Robert W. Schrier

The development of ascites is the most common complication in patients with compensated cirrhosis, occurring in 58% of patients within 10 years of diagnosis. Ascites develops in the context of an increase in the extracellular fluid volume (ECF) and therefore it is essential to understand the regulation of body fluid volume to appreciate its pathogenesis. Knowledge of the intrarenal and extrarenal factors governing renal sodium excretion is crucial to understanding because the sodium ion is the principal determinant of ECF volume. In normal individuals, if the ECF is expanded by the administration of isotonic saline the kidney will excrete the excess sodium and water in the urine and return the ECF to normal values. However, in pathogenic disease states such as congestive heart failure (CHF) and cirrhosis the kidneys continue to retain sodium and water even in the presence of an increased ECF volume. In these edematous disorders the integrity of the kidney as the primary organ controlling ECF volume remains intact because transplantation of the kidney from an edematous, cirrhotic patient to a subject with normal liver function totally reverses the renal sodium and water retention (1). Moreover, transplantation of a normal liver into a cirrhotic patient with ascites and edema has been shown to abolish the renal sodium and water retention (2). Thus, the kidney must be responding to extrarenal signals from the afferent limb of a volume regulatory system in these edematous disorders. The study of these edematous states has led to a unifying hypothesis of body fluid volume regulation (3–8). This chapter will review the afferent and efferent mechanisms that contribute to extracellular fluid volume homeostasis in health and disease.

Regulation of sodium excretion

Due to active transport processes, the sodium ion is primarily located in the ECF and, along with its major anions chloride and bicarbonate, constitutes more than 90% of the extracellular solute. Therefore, because sodium and its anions are the major osmotically active substances in the ECF, they are the major determinants of the ECF volume. With a positive sodium balance, the ECF volume will increase secondary to osmotically driven movement of water into the extracellular space. Sodium balance is determined by the equilibrium between sodium intake, extrarenal sodium loss, and renal sodium excretion. Practically, renal sodium excretion is the major determinant of sodium balance, given the ability of the kidney to excrete large amounts of sodium in response to a sodium load. In addition, sodium loading, by increasing serum osmolality, stimulates the hypothalamic thirst center leading to increased fluid intake as well as the osmotic release of arginine vasopressin (AVP). The release of AVP from the posterior pituitary decreases water excretion by increasing the permeability of the collecting duct epithelium to water. If the increase in ECF volume is sufficient to alter the Starling forces governing the transfer of fluid from the vascular to the interstitial compartment then edema results.

One of the major regulators of sodium excretion is the mineralocorticoid hormone aldosterone. Aldosterone is produced in the zona glomerulosa of the adrenal gland and acts to increase sodium reabsorption by increasing the number of epithelial sodium channels in the cortical collecting duct. In states of volume depletion, the renin–angiotensin–aldosterone system (RAAS) is stimulated causing an increase in sodium reabsorption that leads to expansion of the ECF. With expansion, the stimulus for aldosterone secretion is removed and sodium reabsorption is diminished, thereby stabilizing volume status. In states of mineralocorticoid excess such as primary hyperaldosteronism there is unregulated secretion of aldosterone leading to an increase in sodium reabsorption with resultant volume expansion and hypertension. The effect of aldosterone to cause renal sodium retention can be overridden, however, by the phenomenon of aldosterone escape. In this circumstance the ECF reaches a new, higher steady state, but does not continue to expand despite increased levels of aldosterone. This has been postulated to be mediated by hemodynamic mechanisms whereby an increase in renal artery pressure secondary to expansion of the ECF causes a pressure natriuresis. The increase in renal artery pressure subsequently increases the glomerular filtration rate (GFR) and the fractional excretion of sodium (FeNa). Recently it was reported that the chief molecular target of the escape phenomenon is the thiazide-sensitive NaCl.
cotransporter. In a rat model of aldosterone infusion coupled with a high sodium diet, it was found that levels of the epithelial sodium channel were unchanged during the escape phenomenon, but the amount of the thiazide-sensitive NaCl cotransporter was significantly diminished. Therefore it appears that the so-called pressure natriuresis is mediated at least in part by downregulation of the thiazide-sensitive NaCl cotransporter.

Homeostasis of the ECF is also mediated by the hormone atrial natriuretic peptide (ANP) and, as mentioned previously, AVP. ANP has been shown to be released from the myocardium in response to volume expansion and it has two major actions contributing to maintenance of volume status. It is a direct vasodilator that can lower systemic blood pressure and it also increases the urinary excretion of sodium and water. The natriuresis appears to be mediated by an increase in GFR secondary to afferent arteriole vasodilation coupled with efferent arteriole vasoconstriction. Furthermore, ANP has been shown to directly decrease tubular sodium reabsorption. In another rat model of hyperaldosteronism, it has been shown that the level of ANP increases coinciding with an increase in sodium excretion. Therefore the authors postulate that ANP may also mediate aldosterone escape. It is not known whether ANP has an effect on the thiazide-sensitive NaCl cotransporter.

AVP is the chief regulator of renal water excretion and as such can be expected to have a major role in ECF volume regulation. It is known that in edematous disorders like CHF and cirrhosis there are inappropriate levels of AVP relative to plasma osmolality that results in water retention and hyponatremia. However, it has been shown that there is also counterregulation of this system. In rats administered AVP plus a water load it was shown that after an initial period of water retention there was subsequently an increase in urine volume that corresponded to a downregulation of the renal water channel aquaporin 2 despite continued elevated levels of AVP. Therefore, the authors conclude there is a vasopressin-independent downregulation of aquaporin 2 and therefore a limit on water reabsorption in this model.

Unlike in conditions such as primary hyperaldosteronism where there is an escape from continued sodium reabsorption despite elevated levels of aldosterone, in the edematous disorders there is impaired escape and continuous sodium and water reabsorption. It seems that the difference in these disorders is in how the kidney is responding to the afferent limb of the volume regulatory system.

Afferent mechanisms governing extracellular fluid volume homeostasis

An increase in sodium and water intake is associated with an expansion of the extracellular fluid volume. This includes expansion of the interstitial fluid and plasma components of total body fluid volume. Under normal circumstances, this expansion of total body fluid volume results in an increase in renal sodium and water excretion followed by restoration of the normal extracellular fluid volume. However, in patients with edematous disorders, avid sodium and water retention persists despite expansion of total extracellular fluid and blood volume. Thus, the afferent volume receptors governing extracellular fluid volume must not primarily sense total extracellular fluid or blood volume. In such instances, there must be some body fluid compartment that is still inadequately filled even in the presence of expansion of these body fluid compartments.

Effective blood volume and the concept of arterial underfilling

John Peters first coined the term effective blood volume in allusion to the component of blood or body fluid volume to which the volume regulatory system responds by altering the renal excretion of sodium and water. Peters suggested that extrarenal signals that enhance tubular sodium and water reabsorption by the otherwise normal kidney are initiated by this decrease in effective blood volume in the setting of cardiac failure or cirrhosis. In support of this claim is the observation that renal sodium and water retention can occur in patients with cardiac or liver failure before any decrease in glomerular filtration rate. Borst and deVries (10) first suggested cardiac output as the primary regulator of renal sodium and water excretion, thus constituting effective blood volume. While this notion is attractive, there exist several states of sodium and water retention that are associated with an augmented rather than a decreased cardiac output. For example, a significant increase in cardiac output may occur in the presence of avid renal sodium and water retention and expansion of extracellular fluid volume in association with cirrhosis, high-output cardiac failure, pregnancy, and large arteriovenous fistulae. Hence, cardiac output must not constitute the sole or primary determinant of effective blood volume.

The unifying hypothesis of body fluid volume regulation suggests that the relative integrity or fullness of the arterial circulation constitutes the primary afferent signal through which the kidneys either increase or decrease their excretion of sodium and water (3–8). This theory explains how an increase in the volume of blood on the venous side of the circulation may cause a rise in total blood volume, whereas a decrease in the relative volume of blood in the arterial circulation may promote continued renal sodium and water retention. A reduction in cardiac output is one way in which a decrease in arterial circulatory integrity may occur. However, as mentioned above, diminished cardiac output cannot be the only afferent signal for underfilling of the arterial circulation.
The unifying hypothesis of body fluid volume regulation proposes peripheral arterial vascular resistance and the compliance of the arterial vasculature as the second major determinant of the fullness of the arterial circulation (3–8). Thus, peripheral arterial vasodilation may provide another afferent signal for arterial underfilling, which causes renal sodium and water retention.

In summary, either a decrease in cardiac output or peripheral arterial vasodilation may constitute the afferent signal for arterial underfilling with resultant renal sodium and water retention that leads to expansion of the total blood volume. The afferent receptors or sensors of arterial underfilling must be responsive to small changes in effective arterial blood volume since the steady-state arterial blood pressure is not a sensitive index of the presence of arterial underfilling. For example, the rapidity of the compensatory response to arterial underfilling may obscure a fall in blood pressure until this efferent response becomes inadequate to maintain effective arterial blood volume. The mechanisms involved in this volume regulatory system are summarized in Figs 1.1 and 1.2, and the sensors of arterial underfilling are discussed next.

**Figure 1.1** Mechanism by which decreased cardiac output results in renal sodium and water retention and peripheral and renal vasoconstriction. (Reproduced with permission from Schrier R, Niederberger M. Paradoxes of body fluid volume regulation in health and disease: a unifying hypothesis. West J Med 1994; 16:393–407.)

**Figure 1.2** Mechanism by which peripheral arterial vasodilation results in renal sodium and water retention, increased cardiac output, and peripheral and renal vasoconstriction. (Reproduced with permission from Schrier R, Niederberger M. Paradoxes of body fluid volume regulation in health and disease: a unifying hypothesis. West J Med 1994; 16:393–407.)
Sensors of arterial underfilling

High-pressure baroreceptors

Afferent receptors for this volume regulatory system must reside in the arterial vascular compartment. In this regard, high-pressure baroreceptors in the left ventricle, carotid sinus, aortic arch, and juxtaglomerular apparatus have been implicated as the primary afferent receptors involved in the regulation of renal sodium and water excretion and extracellular fluid volume homeostasis (11–19). The presence of volume-sensitive receptors in the arterial circulation in humans was initially suggested by observations made in patients with traumatic arteriovenous fistulae (20). In such patients, closure of the fistulae results in a decrease in the rate of emptying of the arterial blood into the venous circulation, as demonstrated by closure-induced increases in diastolic arterial pressure and decreases in cardiac output. This increase in arterial fullness produces an immediate increase in renal sodium excretion without changes in either glomerular filtration rate or renal blood flow (20).

Various denervation experiments also implicate high-pressure volume receptors, and thus the integrity of the arterial circulation, as primary afferent receptors in modulating renal sodium and water excretion. In these studies, pharmacological or surgical interruption of sympathetic afferent neural pathways arising from high-pressure areas inhibited the natriuretic response to volume expansion (21–27). In addition, reduction of pressure or stretch at the carotid sinus has been shown to activate the sympathetic nervous system and to cause renal sodium and water retention (28,29). High-pressure baroreceptors also appear to be important factors in regulating the non-osmotic release of vasopressin and thus renal water excretion (30,31).

The juxtaglomerular apparatus is a high-pressure receptor located in the afferent arterioles within the kidney. It responds to decreased stretch or increased renal sympathetic activity with enhanced secretion of renin (28). Thus, this renal baroreceptor is an important factor in the control of angiotensin II formation and aldosterone secretion and ultimately in the regulation of renal sodium excretion.

Low-pressure baroreceptors

The low-pressure baroreceptors of the thorax, including the atria, right ventricle, and pulmonary vessels, may also contribute to extracellular fluid volume homeostasis. Loading of these volume-sensitive receptors results in enhanced cardiac release of natriuretic peptides (32) and suppression of non-osmotic vasopressin release from the neurohypophysis (33). Since patients with advanced cardiac failure exhibit avid sodium and water retention and activation of neurohormonal vasoconstrictor systems—including enhanced non-osmotic vasopressin release—despite elevated atrial pressures and increased circulating concentrations of the natriuretic peptides, high-pressure baroreceptors must predominate over these low-pressure ones. This observation also supports the primacy of the arterial circulation as the determinant of extracellular fluid volume homeostasis.

Cardiac and pulmonary chemoreceptors

In the heart and lungs, both vagal and sympathetic afferent nerve endings respond to a variety of exogenous and endogenous chemical substances, including capsaicin, phenyl diguanidine, bradykinin, substance P, and prostaglandins (34–36). Since substances such as bradykinin and prostaglandins may circulate at increased concentrations in subjects with edematous disorders (37), it is possible that altered central nervous system input from chemically sensitive cardiac and/or pulmonary afferents contributes to the sodium and water retention characteristic of these disease states. This possibility may have important implications for the treatment of some sodium-retaining disorders. For example, in heart failure, commonly prescribed medications such as angiotensin-converting enzyme inhibitors may alter circulating bradykinin and prostaglandin levels, thus potentially influencing cardiopulmonary chemoreceptor activity. At the present time, however, the exact role of these cardiac and pulmonary chemoreceptors in body fluid volume regulation remains unknown.

Hepatic receptors

Conceptually, the liver should be in an ideal position to monitor dietary sodium intake and thus adjust urinary sodium excretion. In support of this notion, infusion of saline into the portal circulation has been reported to result in a greater natriuresis when compared with peripheral venous saline administration (38,39). Similarly, the increase in urinary sodium excretion has been shown to be greater when the sodium load is given orally than when it is given intravenously (40–42). Moreover, the pathophysiologically retention of sodium in patients with severe liver disease is also consistent with an important role for the liver in the control of sodium excretion. However, the experimental evidence in favor of hepatic sodium or volume receptors remains controversial since some investigators have been unable to confirm the above observations of increased sodium excretion in response to portal vein or gastric sodium loading (43–45).

In summary, the afferent mechanisms for sodium and water retention appear to be preferentially localized to the arterial or high-pressure side of the circulation, where arterial fullness may serve as the primary determinant of the renal response. Reflexes emanating from low-pressure cardiopulmonary receptors may also be altered so as to influence renal sodium and water handling in
heart failure. In this regard, increases in atrial pressure also stimulate the release of the natriuretic peptides and inhibit vasopressin release, which may be important attenuating factors in renal sodium and water retention. At the present time, the role of cardiac and pulmonary chemoreceptors and possibly hepatic volume receptors and osmoreceptors remains unclear.

**Efferent mechanisms involved in extracellular fluid volume homeostasis**

The kidney alters the amount of dietary sodium excreted in response to signals from high-pressure and low-pressure volume receptors in the circulation. These receptors may affect renal function by altering renal sympathetic nerve activity and by altering levels of circulating hormones with vasoactive (renal hemodynamic) and nonvasoactive (direct sodium- and/or water-retaining) effects on the kidney. In addition to the sympathetic neurotransmitter norepinephrine, angiotensin II, aldosterone, arginine vasopressin, and other vasoconstrictor hormones may contribute to renal sodium and water retention. Nitric oxide, vasodilating prostaglandins, bradykinin, and the natriuretic peptides may play important counterregulatory roles attenuating both the renal vasoconstriction and antinatriuresis caused by norepinephrine, angiotensin II, and other vasoconstrictor hormones.

**Renal hemodynamics**

The glomerular filtration rate is usually normal early in the course of arterial underfilling and is reduced only as the disease state becomes more advanced. Renal vascular resistance, however, is often increased early, with a concomitant decrease in renal blood flow (46,47). Thus, the ratio of glomerular filtration rate to renal blood flow, or the filtration fraction, is often increased in such patients. This increased filtration fraction is a consequence of predominant constriction of the efferent arterioles within the kidney. These changes in renal hemodynamics alter the hydrostatic and oncotic forces in the peritubular capillaries to favor increased proximal tubular reabsorption of sodium and water. These renal hemodynamic changes are primarily mediated by the neurohormonal response to arterial underfilling.

**The neurohormonal response to arterial underfilling**

Arterial underfilling secondary to a diminished cardiac output or to peripheral arterial vasodilation elicits a series of initially compensatory neuroendocrine responses in order to maintain the integrity of the arterial circulation by promoting increased cardiac inotropy, peripheral vasoconstriction, and expansion of the extracellular fluid volume through renal vasoconstriction and renal sodium and water retention (Figs 1.1 and 1.2). The three major neurohormonal vasoconstrictor responses to arterial underfilling are activation of the sympathetic nervous system and the RAAS, and the non-osmotic release of vasopressin.

Baroreceptor activation of the sympathetic nervous system appears to be the primary integrator of the hormonal vasoconstrictor systems involved in renal sodium and water retention, since the non-osmotic release of vasopressin involves sympathetic stimulation of the supraoptic and paraventricular nuclei of the hypothalamus (48), and activation of the RAAS involves renal β-adrenergic stimulation (49). In addition, the renin-angiotensin system may provide positive feedback stimulation of the sympathetic nervous system and non-osmotic vasopressin release (50), thus indicating that these vasoconstrictor systems may be co-regulated in various pathophysiological states. The effects of these neurohormonal systems on renal hemodynamics and tubular sodium and water handling are discussed below.

**The sympathetic nervous system**

The sympathetic nervous system is unquestionably activated in patients with arterial underfilling. In edematous states such as heart failure and cirrhosis, this sympathetic activity has been documented by both indirect (51–61) and direct (62,63) measures. For example, Leimbach et al. (62) in the case of heart failure and Floras et al. (63) in the case of cirrhosis have demonstrated increased central sympathetic outflow to skeletal muscle using direct intraneuronal recordings of the peroneal nerve. Similarly, employing continuous infusion of tritiated norepinephrine in patients with mild to moderate heart failure or cirrhosis, whole-body norepinephrine kinetics studies have shown increased norepinephrine secretion rates and normal norepinephrine clearance rates, compatible with activation of the sympathetic nervous system (55,61). Finally, using similar techniques, renal sympathetic activation has been demonstrated in patients with such edematous disorders as heart failure (51). Significantly, the degree of activation of the sympathetic nervous system strongly correlates with disease severity and poor prognosis in both heart failure and cirrhosis (64,65).

Through renal vasoconstriction, stimulation of the RAAS, and direct effects on the proximal convoluted tubule, enhanced renal sympathetic activity may contribute to the avid sodium and water retention associated with arterial underfilling. Indeed, intrarenal adrenergic blockade has been shown to cause a natriuresis in experimental animals and humans with heart failure or cirrhosis (21,66,67). In the rat, renal nerve stimulation has been demonstrated to produce an approximately 25% reduction in sodium excretion and urine volume (68).
The diminished renal sodium excretion that accompanies renal nerve stimulation may be mediated by at least two mechanisms. Studies performed in rats have demonstrated that norepinephrine-induced efferent arteriolar constriction alters peritubular hemodynamic forces in favor of increased tubular sodium reabsorption (69). As previously mentioned, the increase in filtration fraction with a normal or only slightly reduced glomerular filtration rate that is often seen in edematous patients is due to efferent arteriolar constriction. Constriction of the efferent arterioles in such states has been confirmed by renal micropuncture studies performed in rats (70) and is at least partially mediated by increased renal sympathetic activity and also by angiotensin II. Thus, efferent arteriolar constriction in states of arterial underfilling shifts the balance of hemodynamic forces in the peritubular capillaries in favor of enhanced proximal tubular sodium reabsorption.

In addition, renal nerves have been shown to exert a direct influence on sodium reabsorption in the proximal convoluted tubule (66,68). Bello-Reuss et al. (68) demonstrated this direct effect of renal nerve activation to enhance proximal tubular sodium reabsorption in whole-kidney and individual nephron studies in the rat. In these animals, renal nerve stimulation produced an increase in the tubular fluid to plasma inulin concentration ratio in the late proximal tubule, an outcome of increased fractional sodium and water reabsorption in this segment of the nephron (68). Hence, increased renal nerve activity may promote sodium retention by a mechanism independent of changes in renal hemodynamics.

The renin–angiotensin–aldosterone system

The RAAS is also activated in response to arterial underfilling, as assessed by plasma renin activity and plasma aldosterone concentration (71–73). Moreover, activation of the RAAS is associated with hyponatremia and an unfavorable prognosis in edematous disorders (74,75). Angiotensin II may contribute to sodium and water retention through direct and indirect effects on proximal tubular sodium reabsorption and by stimulating the release of aldosterone from the adrenal gland. Angiotensin II causes renal efferent vasoconstriction, resulting in decreased renal blood flow and an increased filtration fraction. As with renal nerve stimulation, this results in increased peritubular capillary oncotic pressure and reduced peritubular capillary hydrostatic pressure, which favor the reabsorption of sodium and water in the proximal tubule (70,76). In addition, angiotensin II has been shown to have a direct effect of enhancing sodium reabsorption in the proximal tubule (77). Finally, angiotensin II enhances aldosterone secretion by the adrenal gland, which promotes tubular sodium reabsorption in the cortical and medullary ducts.

A role for aldosterone in the renal sodium retention of human heart failure has been demonstrated (78). The effect of spironolactone on urinary sodium excretion was examined in patients with mild to moderate heart failure, who were withdrawn from all medications prior to study. Sodium was retained in all subjects throughout the period prior to aldosterone antagonism (Fig. 1.3). On an average sodium intake of $97\pm 8$ mmol/day, the average sodium excretion before spironolactone was $76\pm 8$ mmol/day. During therapy with spironolactone, all heart failure patients demonstrated a significant increase in urinary sodium excretion to $131\pm 13$ mmol/day. Moreover, the urine sodium concentration to potassium concentration ratio significantly increased during spironolactone administration, consistent with a decrease in aldosterone action in

![Figure 1.3](image-url)
the distal nephron. Similarly, there also have been reports of natriuresis occurring in cirrhosis after the administration of spironolactone (79). The near-uniform response to spironolactone in cirrhosis suggests that the high plasma levels of aldosterone frequently seen in these subjects contribute to the increased distal sodium reabsorption.

The non-osmotic release of vasopressin

Elevated plasma vasopressin levels have been demonstrated in patients with heart failure and cirrhosis and correlate with the clinical and hemodynamic severity of disease and with the serum sodium concentration (80–89). Through the use of a single intravenous bolus technique, we determined vasopressin clearance to be normal in six patients with mild to moderate heart failure (unpublished observations). Moreover, plasma vasopressin concentrations are inappropriately elevated in hyponatremic patients with heart failure or cirrhosis, and these levels fail to suppress normally with acute water loading (82,84,85), suggesting that the enhanced release of vasopressin in these settings is due to non-osmotic stimulation. As already suggested, baroreceptor activation of the sympathetic nervous system probably mediates this non-osmotic release of vasopressin in states of arterial underfilling.

Arginine vasopressin, via stimulation of its renal or V$_2$ receptor, enhances water reabsorption in the cortical and medullary collecting ducts. Two lines of evidence implicate non-osmotic vasopressin release in the abnormal water retention seen in the edematous disorders. First, in animal models of heart failure, the absence of a pituitary source of vasopressin is associated with normal or near-normal water excretion (17,90). This observation was first made by Anderson and colleagues in the dog during acute thoracic veno caval constriction (17). In these animals, acute removal of the pituitary source of vasopressin by surgical hypophysectomy virtually abolished the defect in water excretion. Abnormal water excretion occurring in the rat with high-output cardiac failure due to aortocaval fistula also appears to be the result of abnormal vasopressin release, since the defect is not demonstrable in rats with central diabetes insipidus (90). The second line of evidence supporting a role for vasopressin in the water retention of heart failure and cirrhosis may be found in studies of selective V$_2$ receptor antagonists. These agents have been shown to reverse the impairment in water excretion in animal models of cardiac failure and cirrhosis and in human heart failure (91–95). Thus, while diminished fluid delivery to the distal diluting segment may also contribute to the abnormal water excretion seen in states of arterial underfilling, increased vasopressin appears to exert the predominant effect.

In summary, baroreceptor activation of the three major neurohormonal vasoconstrictor systems is involved in the avid renal sodium and water retention characteristic of the edematous disorders. Increased adrenergic nervous system activity in response to arterial underfilling appears to orchestrate this neurohormonal response. Renal nerves, angiotensin II, aldosterone, and vasopressin all may play a role as important effector mechanisms in the abnormal retention of sodium and water.

While the aforementioned neuroendocrine systems conspire to promote sodium and water retention in states of arterial underfilling, counterregulatory vasodilatory or natriuretic substances may attenuate, to some degree, this neurohormonal vasoconstrictor activation. Chief among these are the natriuretic peptides and vasodilating prostaglandins.

The natriuretic peptides

The natriuretic peptides, including atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP), circulate at increased concentrations in patients with heart failure (96–98) and in some patients with cirrhosis (99,100). These peptide hormones possess natriuretic, vasorelaxant, and renin-, aldosterone-, and possibly vasopressin-and sympathoinhibiting properties (101–106). In normal humans, ANP and BNP increase glomerular filtration rate and urinary sodium excretion with no change or only a slight fall in renal blood flow (107,108). The changes in renal hemodynamics are probably mediated by afferent arteriolar vasodilation with constriction of the efferent arterioles, as discerned by micropuncture studies in the rat (109,110). In addition to increasing glomerular filtration rate and filtered sodium load as a mechanism of their natriuretic effect, ANP and BNP are specific inhibitors of sodium reabsorption in the collecting tubule (111–113).

Despite the above observations, the natriuretic effects of these peptide hormones are blunted in states of arterial underfilling such as heart failure and cirrhosis (107,114–116). Possible mechanisms for natriuretic peptide resistance in heart failure and cirrhosis include: (i) downregulation of renal natriuretic peptide receptors; (ii) secretion of biologically inactive, immunoreactive ANP or BNP; (iii) enhanced renal neutral endopeptidase activity that degrades natriuretic peptides, thus limiting the delivery of ANP and BNP to distal nephron receptor sites; (iv) hyperaldosteronism causing an increased sodium reabsorption in the distal renal tubule; (v) intracellular mechanisms, including increased phosphodiesterase activity; and (vi) diminished delivery of sodium to the distal renal tubule site of natriuretic peptide action. According to the unifying hypothesis of body fluid volume regulation, arterial underfilling results in renal vasoconstriction, decreased renal perfusion pressure, and activation of the sympathetic and renin–angiotensin systems. These renal hemodynamic and neurohormonal changes then decrease the glomerular filtration rate and

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increase proximal tubular sodium reabsorption, thereby resulting in diminished distal tubular sodium delivery that may explain the blunted natriuretic response to ANP and BNP (3–8). This notion is supported by several observations. In sodium-retaining patients with heart failure, a strong positive correlation between levels of plasma ANP and urinary cyclic guanosine monophosphate [the second messenger for the natriuretic effect of ANP in vivo (117)] has been reported, supporting the active biological responsiveness of renal ANP receptors in heart failure (118). Further, in cirrhosis, maneuvers that increase distal tubular sodium delivery have been shown to reverse ANP resistance (119). Finally, distal tubular sodium delivery has been reported to be the most potent predictor of renal responsiveness to BNP in heart failure patients (Fig. 1.4) (115).

Renal prostaglandins

In normal subjects and in intact animals, renal prostaglandins do not regulate renal sodium excretion or renal hemodynamics to any significant extent (120,121). In patients with heart failure or cirrhosis, vasodilating prostaglandins appear to play an important role in the maintenance of renal blood flow and glomerular filtration. For example, inhibition of prostaglandin synthesis in decompensated cirrhotic patients decreases renal blood flow, glomerular filtration rate, sodium excretion, and solute-free water excretion and impairs the natriuretic response to furosemide or spironolactone (122,123). Infusion of prostaglandin E1 has been shown to reverse these decreases in renal hemodynamics observed after prostaglandin inhibition (123). Similar observations have been made in patients with chronic heart failure (124). These findings support a counterregulatory role for vasodilating prostaglandins in the regulation of body fluid volume in patients with heart failure and cirrhosis.

Summary

The various neurohormonal systems activated in response to diminished effective arterial blood volume influence changes in renal hemodynamics and directly affect tubular sodium and water handling, resulting in an avid sodium- and water-retaining state in an attempt to restore the integrity of the arterial circulation. Activation of neurohormonal vasoconstrictor systems appears to be mediated primarily by high-pressure baroreceptor stimulation of the sympathetic nervous system, leading to activation of the RAAS and the non-osmotic release of vasopressin, in response to arterial underfilling. Counterregulatory vasodilator and natriuretic hormones, such as the natriuretic peptides and vasodilating prostaglandins, are also activated in edematous states such as heart failure and cirrhosis. These hormones may serve to attenuate to some degree the antinatriuretic and antiuretic effects of vasoconstrictor hormone activation.

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