

Gibbs Memorial Lecture

Unifying Hypothesis of Body Fluid Volume Regulation:

Implications for Cardiac Failure and Cirrhosis

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Abstract

Body fluid volume regulation is critically important in maintaining life. In this paper, we review our unifying hypothesis of body fluid volume regulation, which maintains arterial circulatory integrity in health and disease. The integrity of the arterial circulation, as determined by cardiac output and peripheral vascular resistance, is the predominant determinant of renal sodium and water retention. Arterial circulatory integrity can be disturbed either by a decrease in cardiac output, as in low-output cardiac failure, or by a decrease in peripheral vascular resistance, as in high-output states such as high-output cardiac failure and cirrhosis. The resulting arterial underfilling is sensed by baroreceptors that are located in the left ventricle, the aortic arch, the carotid sinus and the renal afferent arterioles. Decreased activation of these receptors during arterial underfilling leads to neurohumoral compensatory responses, which include the stimulation of the sympathetic nervous system, activation of the renin-angiotensin-aldosterone system (RAAS) and the non-osmotic release of vasopressin. These compensatory responses maintain arterial circulatory integrity by increasing peripheral and renal arterial vascular resistance together with renal sodium and water retention. However, over the long term, these adaptive responses may have detrimental effects, such as pulmonary congestion, increased myocardial demand, increased cardiac afterload, ascites and hyponatremia. The intensity of the neurohumoral responses correlates with the progression and severity of both cardiac failure and cirrhosis. The understanding of the pathogenesis of sodium and water retention in cardiac failure and cirrhosis has led to therapies that favorably affect the morbidity and mortality of these patients.

Key Words: Body fluid volume regulation, arterial underfilling, cardiac failure, low-output cardiac failure, high-output cardiac failure, cirrhosis.

Introduction

BODY FLUID VOLUME REGULATION has been a focus of research of investigators for decades. In the 19th century, the famous French physiologist Claude Bernard expressed the importance of the homeostatic mechanisms for humans when he wrote that “the constancy of the *milieu interieur* is the condition of free and independent existence” (1). In 1909, Ernest Starling emphasized the critical role of the kidney in body fluid homeostasis when he stated that “the kidney presents in the highest degree the phe-

nomenon of ‘sensibility,’ the power of reacting to various stimuli in a direction which is appropriate for the survival of the organism, a power of adaptation which gives one the idea that its component parts must be endowed with intelligence” (2).

The kidney’s role in sodium and water retention, both in cardiac failure and in cirrhosis, has been studied with many paradoxical results. It was initially thought that the reason for the increased sodium and water retention in these disorders was a decrease in plasma volume (3). However, after accurate measurement methods became available, plasma volume was found to be increased in both cardiac failure and cirrhosis (4, 5). Intrinsic renal mechanisms are not the primary cause of the sodium and water retention in these diseases. Specifically, it is known that successful heart and liver transplantations totally reverse the renal sodium and water retention in cardiac failure and cirrhosis (6). Moreover, a kidney transplanted from a cirrhotic patient with ascites to a recipient

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with normal liver function also functions normally without causing sodium and water retention (7).

Borst and De Vries (8) suggested that the afferent signal for renal sodium and water retention in edematous disorders was diminished cardiac output as seen in low-output cardiac failure. However, sodium and water retention can occur in conditions of increased cardiac output, such as cirrhosis, sepsis, large arteriovenous fistula and pregnancy (9–11). Thus, cardiac output alone could not explain the sodium and water retention in edematous disorders.

The efferent limb of the body fluid volume regulation was also associated with perplexing findings. It is known that a decrease in glomerular filtration rate (GFR) leads to sodium and water retention. However, renal sodium and water retention can occur in patients with cardiac failure or cirrhosis before the GFR falls (12, 13). Thus, decreased GFR is not the primary factor for sodium and water retention in these disorders.

The regulation of arginine vasopressin (AVP) is very sensitive to osmotic changes. A 1–2% change in extracellular fluid osmolality alters AVP release in a manner that maintains normal osmolality. However, patients with both advanced heart failure and cirrhosis may have severe hypo-osmolality (14). Thus, factors other than the osmotic regulation of AVP must be involved in water retention in these edematous disorders.

The renin-angiotensin-aldosterone system (RAAS) is activated in patients with advanced heart failure (15) and cirrhosis (16), suggesting that it may play a role in enhanced sodium and water retention. However, pharmacological doses of the mineralocorticoid hormone, aldosterone, cause only limited sodium retention and do not produce edema in normal subjects (17). In contrast, patients with cardiac failure or cirrhosis do not demonstrate this “escape” from the sodium-retaining effect of aldosterone, and become more edematous (15, 18, 19).

The discovery of the hormone atrial natriuretic peptide (ANP) provided another possible explanation for sodium retention in cardiac failure and cirrhosis (20). It was thought that sodium retention in these disorders could be due to a deficiency of this hormone. However, plasma ANP level was found to be increased, not decreased, in heart failure (21, 22) and cirrhosis (23–25). These are some of the perplexities that challenged biomedical scientists for many years — in their efforts to understand

how body fluid volume and composition are regulated.

Unifying Hypothesis of Body Fluid Volume Regulation

It is known that plasma volume is expanded in patients with advanced cardiac failure and cirrhosis, yet the normal kidneys are retaining sodium and water (4, 5). About 85% of the plasma volume is located on the venous side of the circulation and only about 15% on the arterial side. The arterial blood volume comprises less than 2% of the total body fluid. It can therefore be hypothesized that total plasma volume, which is mostly on the venous side of the circulation, could be expanded in cardiac failure and cirrhosis, yet arterial underfilling could occur due to a decrease in cardiac output. As noted already, however, renal sodium and water retention can occur in conditions of increased cardiac output, such as pregnancy, cirrhosis and high-output cardiac failure. Based on this, a unifying hypothesis of the body fluid volume regulation has emerged (Fig. 1) (26, 27). According to this hypothesis, arterial underfilling can be caused by a decrease in either cardiac output or arterial vasodilation, as occurs with a decrease in peripheral vascular resistance. All the responses after initiation of arterial underfilling are compensatory, in order to restore arterial circulatory integrity. In low-output cardiac failure there would be a secondary increase in peripheral vascular resistance, whereas in circumstances of decreased peripheral vascular resistance there would be a secondary increase in cardiac output because of the decreased cardiac afterload. In both conditions, renal sodium and water retention would occur to maintain arterial circulatory integrity.

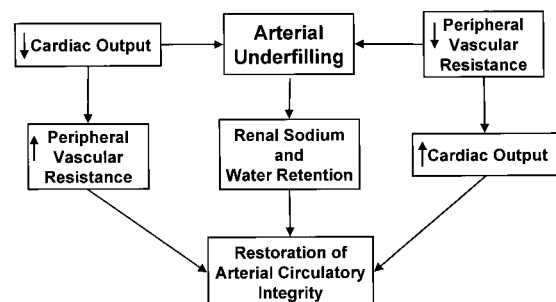


Fig. 1. Body fluid volume regulation hypothesis. Reprinted with permission (27).

Low-Output Cardiac Failure

Low-output cardiac failure may lead to arterial underfilling due to a decrease in cardiac output. Other conditions of decreased cardiac output, such as volume depletion, pericardial tamponade, constrictive pericarditis, decrease in oncotic pressure due to protein-losing states and hypersensitivity reactions which increase capillary permeability and loss of colloid from capillaries, may cause arterial underfilling (Fig. 2) (26). The arterial underfilling is sensed by baroreceptors that are located in the left ventricle, the aortic arch, the carotid sinus and the renal afferent arterioles. The resulting activation of these baroreceptors stimulates the sympathetic nervous system (SNS), which activates the RAAS and causes the non-osmotic release of AVP. Increased levels of angiotensin II contribute to the impaired renal escape from the sodium-retaining action of aldosterone in cardiac failure. The non-osmotic release of AVP contributes to the water retention.

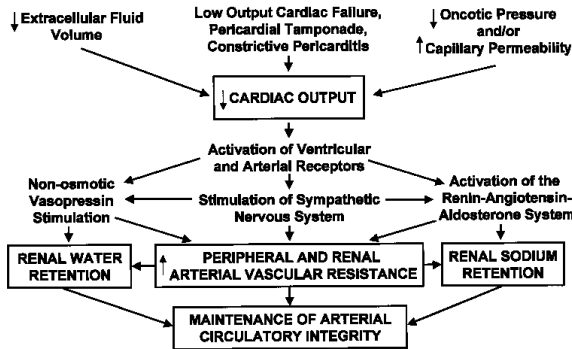


Fig. 2. Sequence of events in which reduced cardiac output initiates renal sodium and water retention. Reprinted with permission (26).

In the progression of cardiac failure, as cardiac index decreases, a compensatory increase in neurohumoral response and plasma volume is observed (Fig. 3) (28). The neurohumoral response is characterized by increased plasma levels of AVP, renin, aldosterone and norepinephrine. These neurohumoral changes compensate for the arterial underfilling by causing sodium and water retention, which increases total plasma volume. Even the “normal” levels of these hormones in early cardiac failure are in fact excessively increased, considering the plasma volume expansion, which would actually suppress these hormones in a normal individual.

	CLASS II	CLASS III	CLASS IV
Cardiac index	↓	↓↓	↓↓↓
Plasma hormones (AVP, renin, aldosterone, NE)	Normal	↑	↑↑
Plasma volume	↑	↑↑	↑↑↑

Fig. 3. Neurohumoral and plasma volume responses to progressive cardiac failure. New York Heart Classifications II, III and IV. AVP = arginine vasopressin; NE n Norepinephrine. Reprinted with permission (28).

The intensity of the neurohumoral response correlates with the severity of cardiac failure. Plasma norepinephrine concentrations provide a prognostic index of survival in heart failure (29). As shown in Fig. 4, patients with heart failure who have plasma norepinephrine concentrations greater than 800 pg/mL have the worst prognosis, with a one-year survival rate of 20%. Pretreatment serum sodium concentrations in patients with heart failure correlate with plasma renin activities (Fig. 5). Moreover, serum sodium concentration is a powerful predictor of cardiovascular mortality in heart failure (30). As shown in Fig. 6, patients with a pretreatment serum sodium concentration of less than 130 mEq/L have a one-year survival rate of about 20%.

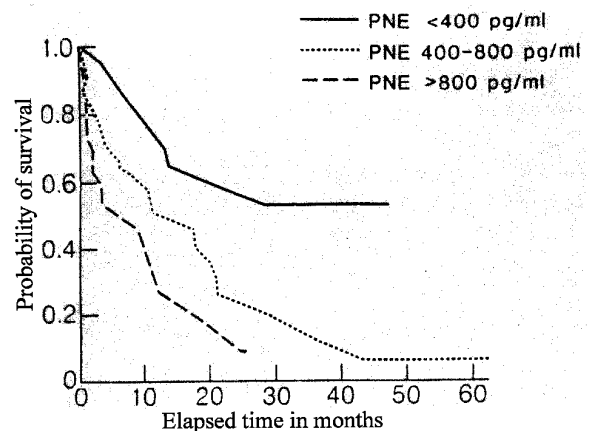


Fig. 4. Life-table analysis of survival, according to tercile, based on level of plasma norepinephrine (PNE). The probability of survival in each group was significantly different from the probabilities in the other two groups. Reprinted with permission (29).

It was previously thought that the water retention in cardiac failure must be mediated totally by intrarenal mechanisms, because the

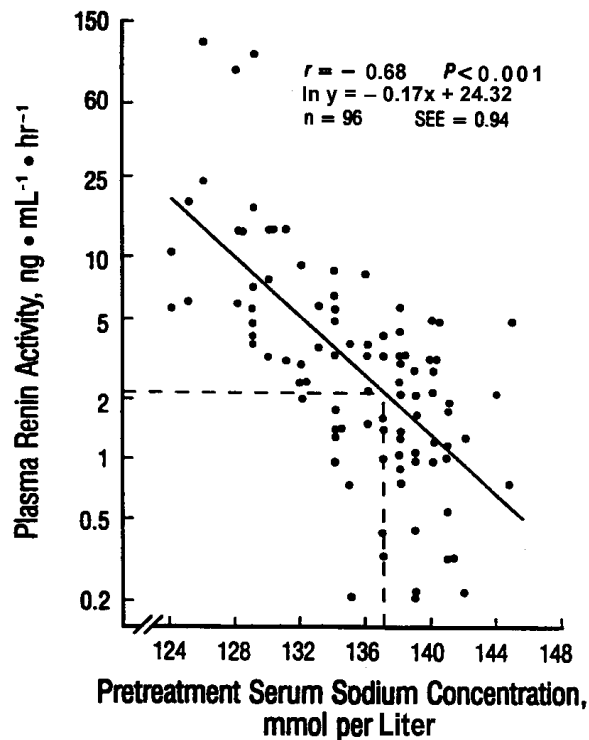


Fig. 5. Relationship between serum sodium concentration and plasma renin activity before vasodilator therapy in 96 patients with severe chronic heart failure. SEE = standard error of the estimate. Reprinted with permission (30).

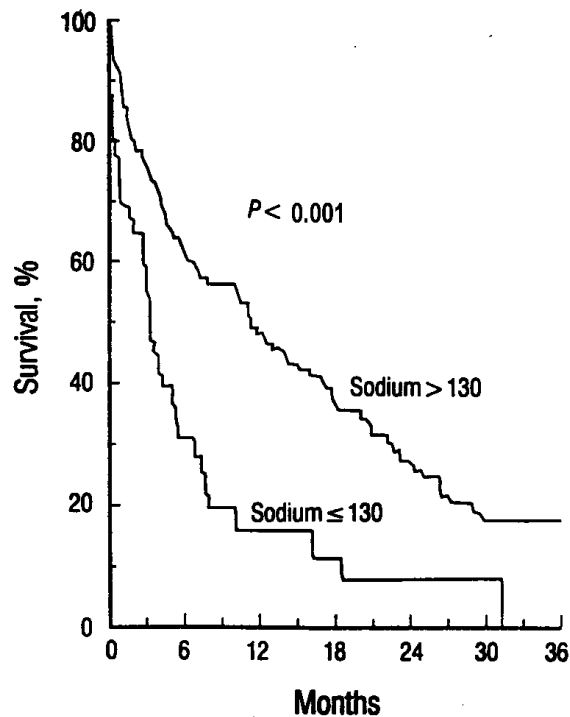


Fig. 6. Kaplan-Meier analysis showing cumulative rates of survival in patients with heart failure stratified into two groups based on pretreatment serum sodium concentration (>130 vs. 130 mEq/L). Reprinted with permission (30).

bioassay method could not consistently detect increased AVP levels in cardiac failure patients who were hyponatremic. However, this bioassay method was insensitive and could only detect plasma AVP concentrations above 10 pg/mL. After the development of a sensitive radioimmunoassay, it was shown that normal urine concentration and dilution occur in response to plasma AVP levels between 0.5 and 4 pg/mL, values that were not detectable with the bioassay. Szatalowicz et al. (31), by using a sensitive radioimmunoassay technique to measure AVP, showed that plasma AVP levels were not suppressed, despite the presence of hyponatremia in patients with congestive heart failure (Fig. 7). This study was the first to demonstrate the non-osmotic release of AVP in hyponatremic heart failure patients. Kim et al. (32) extended this observation by showing that messenger RNA (mRNA) for AVP was significantly

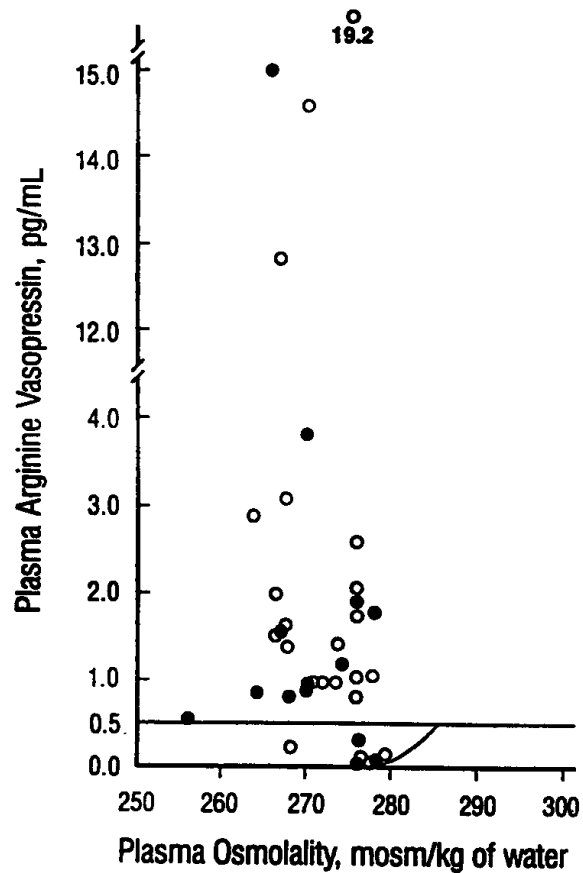


Fig. 7. Plasma arginine vasopressin (AVP) in 37 hyponatremic patients with congestive heart failure. Patients who never received diuretics before measurement of AVP are represented by solid circles, and those who received diuretics within 24 hours of blood sampling for AVP measurement are represented by open circles. Reprinted with permission (31).

increased in the hypothalamus of rats with chronic heart failure as compared to sham-operated controls. Therefore, in addition to the increased plasma levels of AVP, increased gene expression of AVP was shown to be associated with cardiac failure.

Bichet et al. (33) further investigated the relationship between cardiac function and non-osmotic release of AVP. They showed that patients with non-osmotic release of AVP had significantly lower cardiac indices, higher pulmonary capillary wedge pressures and higher plasma renin and aldosterone concentrations. When these patients were treated with an angiotensin converting enzyme (ACE) inhibitor, cardiac index increased significantly, suggesting amelioration of arterial underfilling. The reversal of arterial underfilling was associated with an improvement in urinary dilution and increased water excretion. Moreover, plasma and platelet AVP levels were significantly reduced following afterload reduction with the ACE inhibitor and improvement in cardiac output.

The V2 receptor is the antidiuretic receptor for AVP on the basolateral surface of the collecting duct, while the V1 receptor is the vascular smooth muscle receptor. In a rat model of cardiac failure, administration of a non-peptide V2 receptor antagonist has been shown to reverse the impaired water excretion (34). In a randomized, double-blind, placebo-controlled study, the orally active, non-peptide, selective V2 receptor antagonist, WAY-VPA-985, was used in humans with congestive heart failure (35). This agent decreased urine osmolality and increased urine flow, and serum sodium concentration.

Aquaporin-2 (AQP-2) is the AVP-regulated water channel that mediates water transport through the renal collecting duct. Activation of V2 receptors by AVP increases intracellular cyclic adenosine monophosphate (cAMP) level by activating adenylate cyclase. Subsequently, through activation of protein kinase A, cytoplasmic vesicles containing AQP-2 water channels "traffic" to the apical membrane of the collecting duct to make the membrane permeable to water. In the absence of AVP, endocytic retrieval of the AQP-2 water channels into the cytoplasm occurs and the membrane becomes impermeable to water. This phenomenon of the trafficking of AQP-2 water channels has confirmed the shuttle hypothesis (36).

Studies of rats with chronic heart failure have showed increased papillary AQP-2 protein expression (37, 38). This overexpression of

AQP-2 decreased significantly when these rats were treated with the V2 antagonist, OPC-31260 (38). Moreover, this decrease was associated with the reversal of water retention in these animals.

It is known that about 3–6% of AQP-2 water channels that traffic to the luminal membrane of the collecting duct are excreted in the urine (39, 40). Thus, in the case of increased trafficking to the membrane, an increased level of AQP-2 can be detected in the urine. In this regard, Saito et al. (41) showed that when plasma AVP levels were increased with hypertonic saline, the urinary AQP-2 was increased in a linear manner. A recent study of hyponatremic heart failure patients demonstrated that treatment with a selective V2 receptor antagonist was associated with a dose-related increase in water excretion, correction of hyponatremia and a decrease in urinary AQP-2 excretion (Fig. 8) (42).

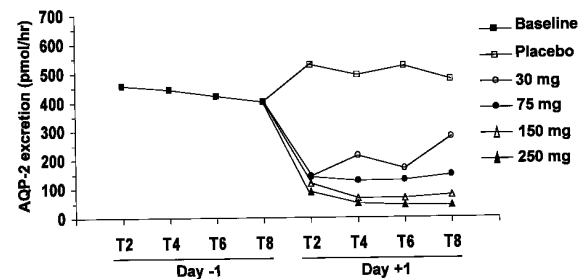


Fig. 8. Selective V2 receptor antagonism decreases 24-hour urinary aquaporin-2 (AQP-2) excretion in human heart failure. Reprinted with permission (42).

In normal subjects, high doses of aldosterone initially increase renal sodium retention. However, after an increase of 1.5–2 L of extracellular fluid volume, renal sodium retention ceases. This "escape" from the sodium-retaining action of aldosterone is due, at least in part, to an increased distal delivery of sodium to the site of action of aldosterone (19). However, patients with heart failure show an impaired escape from the effect of aldosterone because the activated neurohumoral mechanisms which maintain arterial pressure also decrease sodium delivery to the distal nephron (Fig. 9) (19). In this regard, the aldosterone antagonist, spironolactone, causes a marked natriuresis when given in sufficient doses to patients with heart failure (43).

In normal subjects, infusion of ANP causes increased natriuresis. However, patients with cardiac failure are resistant to this natriuretic effect of exogenously administered ANP (22). In patients with chronic heart failure, a linear

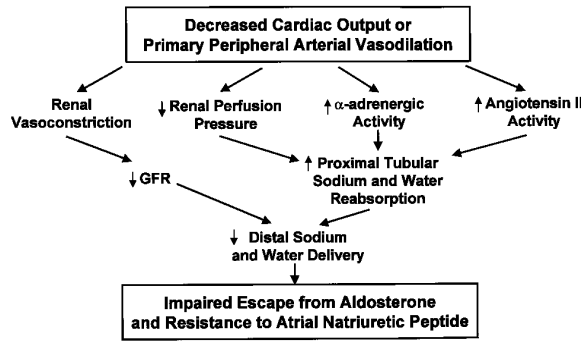


Fig. 9. A decrease in cardiac output or peripheral arterial vasodilation can initiate events that diminish distal sodium delivery, thereby impairing aldosterone escape and causing resistance to the natriuretic response of atrionatriuretic peptide (ANP). Reprinted with permission (19).

correlation was found between plasma concentrations of ANP and urinary excretion of cyclic guanosine monophosphate (cGMP), which is the intracellular secondary messenger of ANP (44). This finding suggests that the resistance to ANP is not at the receptor level in cardiac failure patients. Pettersson et al. (45) demonstrated that the resistance to ANP can be reversed after renal denervation in rats with heart failure. Since renal denervation decreases proximal tubular sodium reabsorption and thus increases distal sodium delivery, resistance to ANP in patients with cardiac failure is probably due to decreased distal sodium delivery to the collecting duct site of the hormone's action.

High-Output Cardiac Failure

Sodium and water retention occurs not only in low-output cardiac failure but also in high-output cardiac failure, e.g., thyrotoxicosis, beriberi and large arteriovenous fistulae. In conditions associated with high cardiac output, the reason for arterial underfilling is arterial vasodilatation (Fig. 10) (26).

Riegger et al. (46) showed that plasma renin, norepinephrine and AVP levels were elevated and plasma osmolality was decreased in a rat model of high-output cardiac failure secondary to an aortocaval fistula. These same compensatory neurohumoral responses occur in both high- and low-output cardiac failure. Thus, as proposed by the body fluid volume regulatory hypothesis, the trigger for arterial underfilling is decreased peripheral vascular resistance in high-output cardiac failure and decreased cardiac output in low-output cardiac failure (Fig. 11).

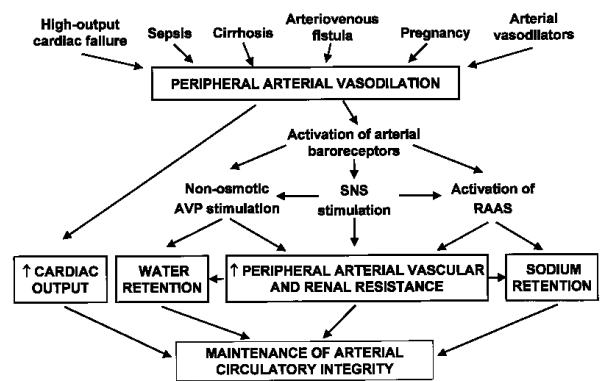


Fig. 10. Sequence of events in which peripheral arterial vasodilation is the central initiator of renal sodium and water retention. SNS = sympathetic nervous system; RAAS = renin-angiotensin-aldosterone system. Reprinted with permission (26).

In advanced cardiac failure, the compensatory responses to arterial underfilling may lead to maladaptive consequences, which include pulmonary congestion, increased myocardial demand and increased cardiac afterload (Fig. 12). Understanding the pathophysiology of the vicious cycle of chronic congestive heart failure has led to various advances in treating heart failure patients (Fig. 13) (47). Myocardial injury causes depressed ventricular performance, which leads to reduced cardiac output. As a compensatory response to the reduced cardiac output, the SNS, the RAAS system and non-osmotic release of AVP are stimulated to maintain blood pressure. However, these responses lead to a vicious cycle, since the resulting systemic vasoconstriction and renal sodium and water retention increase ventricular pre- and afterload and myocardial hy-

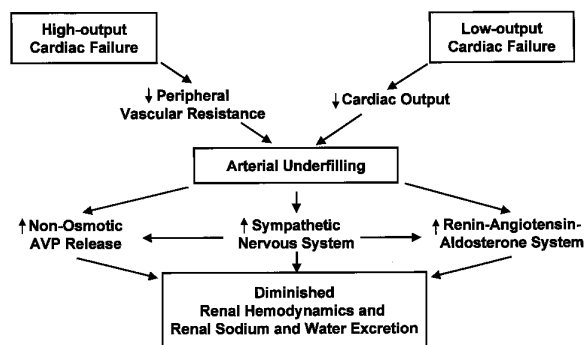


Fig. 11. High-output and low-output cardiac failure. Although the initiating "underfill" event differs in high- and low-output failure, the subsequent compensatory pathways leading to renal sodium and water retention are similar. Reprinted with permission (12).

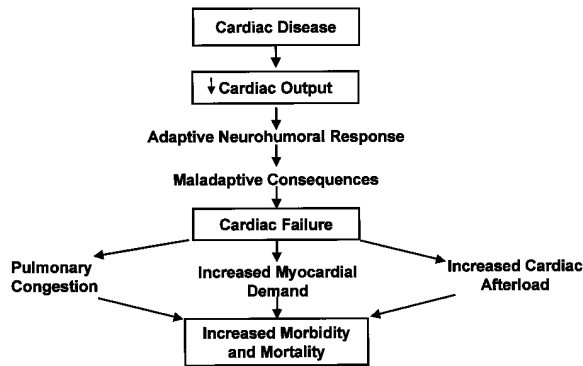


Fig. 12. Compensatory responses become maladaptive in advanced cardiac failure. Reprinted with permission (28).

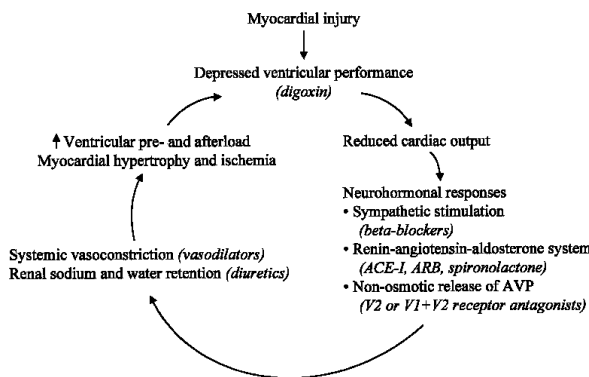


Fig. 13. Vicious cycle of depressed ventricular function. Potential therapies are in parentheses. ACE-I = angiotensin converting enzyme inhibitors; ARB = angiotensin receptor blockers; AVP = arginine vasopressin. Reprinted with permission (47).

pertrophy and ischemia, further decreasing myocardial performance.

In recent years, there have been major advances in the treatment of heart failure, directed toward the pathophysiological mechanisms (Fig. 13). Clinical studies have shown that ACE inhibitors improve survival not only in patients with cardiac failure (48, 49), but also in asymptomatic patients with left ventricular dysfunction (49). Moreover, ACE inhibitors significantly decrease the incidence of heart failure and cardiovascular death in patients with vascular disease but normal ejection fractions, and in diabetic patients with cardiovascular risk factors (50). Recent trials have showed that beta blockers are beneficial in reducing mortality in patients with cardiac failure (51–53). Another important advance in the treatment of cardiac failure is the finding that the aldosterone antagonist, spironolactone, significantly reduces morbidity and mortality in patients

with severe heart failure (54). This effect of spironolactone appears to be extrarenal, perhaps by decreasing cardiac fibrosis. Vasodilators, diuretics and digoxin are the other classes of drugs that are being used in the treatment of heart failure.

Cirrhosis

The sodium and water retention in cirrhosis can also be explained by the unifying hypothesis of body fluid volume regulation, as is the case with low- and high-output cardiac failure. In both cardiac failure and cirrhosis, the kidney is responding in a similar manner to compensate for arterial underfilling.

For decades, there were two hypotheses to explain renal sodium and water retention in cirrhotic patients. According to the “underfilling hypothesis,” portal hypertension leads to ascites formation, and the subsequent decrease in plasma volume causes the kidneys to retain sodium and water (55). However, when the plasma volume was measured in cirrhotic patients, it was found to be increased, and this increase in plasma volume antedated the ascites formation (56, 57). Thus, the “overflow hypothesis” was proposed; it suggested that a hepatorenal reflux mechanism is initiated in cirrhosis, whereby the kidneys retain sodium and water and cause plasma volume expansion and ascites formation (58). However, this “overflow” hypothesis does not explain the neurohumoral responses during the progression of cirrhosis. As cirrhosis progresses from the compensated to the decompensated (ascitic) phase, toward the hepatorenal syndrome, the neurohumoral responses are aggravated as a result of the increase in peripheral arterial vasodilation (Fig. 14) (58, 59). If primary plasma volume expansion (of both the venous and arterial compartments) occurs as suggested by the “overflow

	Compensated cirrhosis (no ascites)	Decompensated cirrhosis (ascites)	Hepatorenal syndrome
Peripheral arterial vasodilation	↑	↑↑	↑↑↑
Plasma hormones (AVP, renin, aldosterone, NE)	Normal	↑	↑↑
Plasma volume	↑	↑↑	↑↑↑

Fig. 14. Progressive hemodynamic and hormonal changes in cirrhosis. NE = norepinephrine. Reprinted with permission (59).

hypothesis,” the plasma hormones of AVP, aldosterone and norepinephrine should be suppressed, not stimulated, as actually occurs with the progression of cirrhosis.

Since neither the “underfilling” nor the “overflow” hypothesis could totally explain the sodium and water retention in cirrhosis, the “peripheral arterial vasodilation hypothesis” has been proposed (60). According to this hypothesis, splanchnic vasodilation occurs early in the course of cirrhosis. The resulting arterial underfilling stimulates neurohumoral responses, which lead to renal sodium and water retention. This hypothesis explains the increased cardiac output and the enhanced neurohumoral changes over the entire spectrum of cirrhosis.

Recent studies using Doppler ultrasonography have demonstrated increased brachial, femoral, renal and cerebral vascular resistances in cirrhosis (61–63). However, the overall total systemic vascular resistance is decreased. Moreover, there is a correlation between the decrease in peripheral vascular resistance and the increase in plasma volume in cirrhotic patients (64). The central blood volume (i.e., the blood volume present in the central part of the circulation), which modulates the tone in the arterial and cardiopulmonary receptors, is decreased in cirrhosis (64). There is also a significant correlation between the decrease in central volume and the increase in portal venous pressure, as assessed by the hepatic venous pressure gradient (64).

Albillos et al. (65) studied rats with portal hypertension due to portal vein constriction to elucidate the relationship between portal hypertension, splanchnic vasodilation and sodium retention. In this study, systemic vascular resistance decreased within 24 hours of the constriction of the portal vein, and an increase in total body sodium was observed within 48 hours. These findings show that arterial underfilling due to arterial vasodilation precedes the sodium retention in portal hypertension.

La Villa et al. (66) administered large doses of mineralocorticoid to compensated cirrhotic patients, to investigate the characteristics of the patients who failed to “escape” from the sodium retaining effects of the hormone and thus developed ascites. The cirrhotic patients who failed to escape demonstrated significantly higher cardiac output and lower systemic vascular resistance (i.e., arterial underfilling) compared to those patients who demonstrated mineralocorticoid escape and did not develop ascites.

As with cardiac failure, the neurohumoral response correlates with the severity of the cir-

rhosis. Patients with the highest plasma renin and norepinephrine concentrations have the poorest survival rates (60). There is also a correlation between plasma norepinephrine and AVP concentrations, suggesting that the increased activity of the SNS stimulates the non-osmotic release of AVP (67). As in cardiac failure, the presence of hyponatremia in cirrhotic patients is associated with a poor outcome (68).

The bioassay method suggested that AVP could not be detected in hyponatremic cirrhotic patients, as was also noted in heart failure patients. However, after the development of the radioimmunoassay method, it was clearly shown that an acute waterload did not suppress plasma AVP in hyponatremic cirrhotic patients (69). In rats with experimental cirrhosis, the increased plasma levels of AVP are accompanied by increased expression of hypothalamic mRNA for AVP (70). The collecting duct AQP-2 mRNA expression is also significantly increased in cirrhotic animals as compared to controls (71). This high expression of AQP-2 was not suppressed with an acute waterload. However, its expression diminished significantly after the administration of a V2 receptor antagonist. Moreover, Tsuboi et al. (72) showed that the non-peptide AVP antagonist OPC-31260 significantly increased urine volume and decreased urinary osmolality in cirrhotic rats.

The effect of V2 receptor antagonists has been investigated in cirrhotic patients. An orally active, non-peptide V2 receptor antagonist has been shown to increase urine volume and decrease urine osmolality in patients with cirrhosis (73). Serum sodium concentrations can also be corrected in hyponatremic cirrhotic patients with these agents (74).

In order to investigate the role of V1 AVP receptors in liver disease, Claria et al. (75) administered a V1 receptor antagonist to cirrhotic animals, after the blockade of angiotensin II with saralasin. A decrease in blood pressure was observed, suggesting that AVP also plays a role in maintaining arterial circulatory integrity in cirrhosis, along with the RAAS and SNS.

Gregory et al. (76) showed that treatment with the aldosterone antagonist, spironolactone, was associated with weight loss and disappearance of ascites in a majority of patients with cirrhosis. This finding corroborates the important role of aldosterone in sodium retention in cirrhosis, and is compatible with the failure of cirrhotic patients to demonstrate mineralocorticoid escape.

The findings relative to plasma ANP in cirrhosis are very similar to those in heart failure patients. Skorecki et al. (77) showed, in cirrhotic patients, that the plasma ANP levels and urinary excretion of cyclic GMP were increased in response to head-out water immersion (HWI), a maneuver used to increase the central blood volume. However, no change was observed in urinary sodium excretion, suggesting a resistance to ANP. As in heart failure, resistance to the natriuretic and diuretic response to ANP was shown to be reversed when the kidneys were denervated in rats with experimental cirrhosis (78).

In a study by Abraham et al. (79), patients with cirrhosis showed a marked natriuresis when ANP was given together with mannitol. This natriuresis was associated with increased distal tubular sodium delivery, as assessed by lithium clearance, during the infusion of mannitol. The lithium clearance was increased in responders receiving ANP together with mannitol, whereas it was not increased in nonresponder cirrhotic patients. There was no difference in the increase of urinary cGMP excretion between responders and nonresponders, thus providing evidence against a collecting duct receptor defect. The results of this study in cirrhotic patients thus supported decreased distal delivery as a major factor contributing to ANP resistance in cirrhosis.

Nicholls et al. (80) investigated the response to the combined treatment of HWI and norepinephrine in cirrhotic patients. Mean arterial pressure increased by HWI and norepinephrine treatment, but not by HWI alone. This combined treatment was also associated with an increase in urinary sodium excretion. In another study, the ability to excrete an acute waterload over a 5-hour period was also shown to increase from 28% to 90% with the combined treatment of HWI and norepinephrine in hyponatremic cirrhotic patients (81). In these studies, there was a linear correlation between the water excretion and increment of systemic vascular resistance, further supporting the peripheral arterial vasodilatation hypothesis of sodium and water retention in cirrhosis.

We then proposed that nitric oxide, which is a very potent vasodilator, mediates the vasodilation of the splanchnic bed in cirrhosis. Specifically, the increment of blood flow in the physiologic splanchnic shunts due to portal hypertension would increase shear-mediated endothelial nitric oxide activity, which could lead to arterial underfilling. The endothelial nitric

oxide synthase (eNOS) expression was indeed shown to be increased in the aortas and the mesenteric arteries of cirrhotic rats with ascites as compared to control animals (82). Oral administration of the nonspecific nitric oxide synthase (NOS) inhibitor, N^G-nitro-L-arginine methyl ester (L-NAME), for one week was associated with reversal of the upregulated eNOS expression in the aortas and mesenteric arteries of these cirrhotic animals. The aortic expression of the secondary messenger of nitric oxide, cGMP, was also shown to decrease in cirrhotic rats with ascites after treatment with L-NAME (Fig. 15, lower panel) (82). The hyperdynamic circulation was reversed with L-NAME as systemic vascular resistance, cardiac index and mean arterial pressure were normalized (Fig. 15, upper panel) (83). Furthermore, plasma renin activity, plasma concentrations of aldosterone, AVP and ANP were decreased, sodium and water excretion was increased (Fig. 16) and hyponatremia was corrected with L-NAME treatment (82).

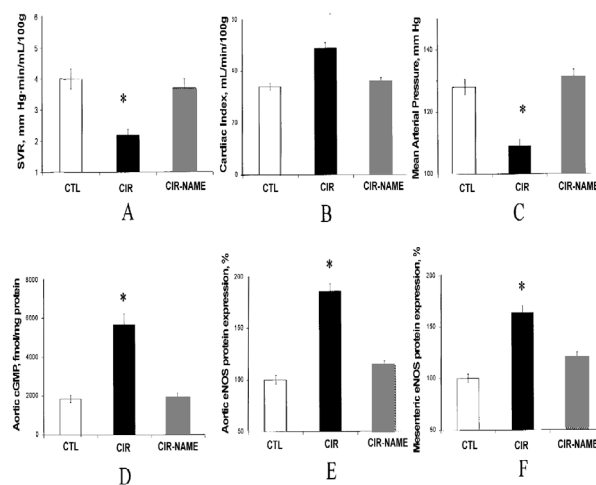


Fig. 15. (A) Systemic vascular resistance. (B) Cardiac index. (C) Mean arterial pressure. (D) Aortic concentrations of cGMP. (E) eNOS protein expression in aortas. (F) eNOS protein expression in mesenteric arteries. Chronic nitric oxide synthase (NOS) inhibition with 0.5 mg/kg/day L-NAME (CIR-NAME) for seven days by gavage increases systemic vascular resistance (SVR), decreases cardiac index, and increases mean arterial pressure. The concentration of cGMP and the expression of eNOS protein in the aorta and mesenteric arteries expression diminished in cirrhotic rats treated with L-NAME. Bars and segments represent the mean and the SEM, respectively. * $P < 0.01$ versus untreated cirrhotic rats. CTL = control rats; CIR = rats with untreated cirrhosis; CIR-NAME = cirrhosis with L-NAME treatment; eNOS = endothelial nitric oxide synthase. Reprinted with permission (82, 83).

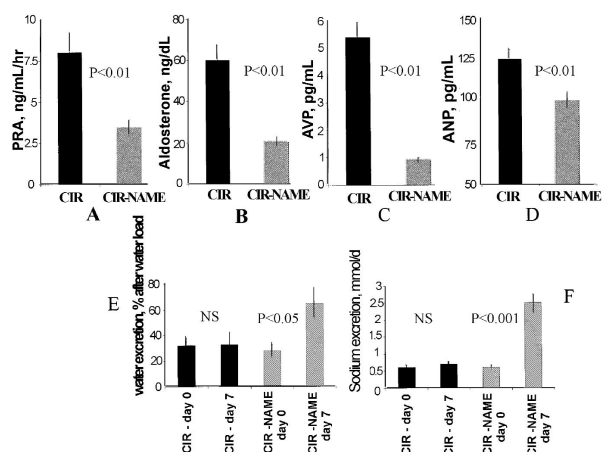


Fig. 16. (A) Plasma renin activity. (B) Aldosterone concentration. (C) AVP concentration. (D) ANP concentration. (E) Water excretion 3 hours following a water load of 30 mL/kg. (F) Sodium excretion. Concentrations of plasma renin, aldosterone, AVP and ANP decreased in cirrhotic rats with ascites with seven days of L-NAME treatment (CIR-NAME). Water and sodium excretion were impaired in both treated and untreated cirrhotic rats at day 0. After seven days of L-NAME a significant improvement in water and sodium excretion occurred in cirrhotic rats treated with L-NAME, but not in untreated cirrhotic rats. Bars and segments represent the mean and the SEM, respectively. PRA = plasma renin activity; AVP = arginine vasopressin; ANP = atrial natriuretic peptide; CIR = untreated cirrhosis; CIR-NAME = cirrhosis with L-NAME treatment. Reprinted with permission (82).

Spontaneous bacterial peritonitis (SBP) may occur as a complication in cirrhotic patients with ascites and is the most common cause of impairment in renal function in these patients (84). In this setting, the hyperdynamic circulation and arterial underfilling of cirrhosis worsens. A recent study showed that patients treated with intravenous albumin in addition to an antibiotic demonstrated a significant decrease in renal impairment and hospital mortality compared to patients treated with an antibiotic alone (85). Thus, an attenuation of the arterial underfilling by albumin administration altered mortality due to SBP.

Hepatorenal syndrome is a serious complication of cirrhosis, indicating an ominous prognosis. In a clinical study, the use of a V1 receptor blocker, terlipressin, together with albumin, was associated with a significant decrease in plasma renin activity and plasma norepinephrine (86). Most important, renal function improved and the hepatorenal syndrome was reversed with this treatment, which diminished the arterial underfilling and the resulting neurohumoral responses.

A recent randomized, prospective study compared therapeutic paracentesis with transjugular intrahepatic portosystemic shunt (TIPS) therapy in cirrhotic patients having refractory ascites (87). The result in this study differed from that in a previous study, which found no significant difference between the two treatments (88). However, unlike the earlier study, the more recent study included patients with better liver function (87). Thus, early reversal of portal hypertension with TIPS (e.g., Child-Pugh class B) may have a beneficial effect on decompensated cirrhotic patients with diuretic resistance.

Conclusion

Studies investigating the pathophysiology of sodium and water retention in cardiac failure and cirrhosis provided insights which have led us to the development of our unifying hypothesis of body fluid volume regulation. Treatment based on attenuation of the advanced responses to arterial underfilling by the sympathetic nervous system, the RAAS, and the non-osmotic release of AVP have been shown to benefit patients with cardiac failure and cirrhosis.

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