CHAPTER

67 Cardiac Failure and the Kidney

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The kidney plays a central role in the sodium and water retention and edema formation associated with cardiac failure. Heart failure, like liver disease and the nephrotic syndrome, represents another edematous state in which renal sodium and water retention is observed despite an excess of total body sodium and water. This finding of continued renal sodium and water retention despite total body sodium and water excess, in part, defines the clinical syndrome of heart failure. In this regard, the pathophysiology of heart failure has been described as a cardiorenal syndrome, where left ventricular systolic and/or diastolic dysfunction leads to renal sodium and water retention that in turn produces the clinical syndrome of heart failure. Manifestations of cardiac failure are almost always associated with fluid volume retention resulting in hemodynamic and clinical congestion, where the former is measured as elevated ventricular filling pressures and the latter is seen as congestive signs and symptoms. Although an abnormal cardiac output initiates renal sodium and water retention, as will be discussed later in this chapter, most of the cardinal signs and symptoms of heart failure are attributable to fluid retention rather than to an abnormal cardiac output (Table 67.1).

Moreover, worsening fluid retention is the proximate cause of heart failure hospitalization (i.e., morbidity) in nearly 90% of cases.[1,2] As will be discussed in subsequent text of this chapter, renal dysfunction as measured simply by elevated blood urea nitrogen (BUN) and/or serum creatinine portends a very poor prognosis in both acutely decompensated patients and patients with chronic heart failure.[3–6] Consequently, the kidney provides a sensitive bioassay for prognosis in patients with heart failure. This observation underscores the importance of cardiorenal interactions in the natural history of heart failure. This chapter reviews the mechanisms of edema formation and sodium and water retention associated with cardiac failure, discusses the clinical implications of cardiorenal interactions in heart failure, and reviews current and future treatment options.

THE MECHANISM OF EDEMA FORMATION

Edema is a clinical sign that indicates an increase in the volume of sodium and water in the interstitial space. This increase in interstitial-space volume is caused by an alteration of the Starling forces that govern the transfer of fluid from the vascular compartment into the surrounding tissue spaces.[7] Edema may result from local factors such as an obstruction of lymphatic or venous flow. However, the type of edema considered in this chapter reflects a generalized disturbance of sodium and water balance and is associated with a net increase in extracellular fluid (ECF) volume, a situation that is usually not present when edema results from a local disruption of normal capillary mechanisms. Generalized edema results when altered Starling forces affect all capillary beds. The development of generalized edema thus indicates a widespread disturbance in the normal balance between tissue capillary and interstitial hydrostatic and colloid osmotic pressures, which control the distribution of ECF between the vascular and extravascular (interstitial) compartments. In edematous disorders such as cardiac failure, sodium and water retention by the kidney leads to the progressive expansion of the ECF volume and alteration of the Starling forces that subsequently result in edema formation.

Transcapillary solute and fluid transport consists of two types of flow: convective and diffusive. Bulk water movement occurs via convective transport induced by the imbalance between transcapillary hydraulic pressure and colloid osmotic pressure.[7] Transcapillary hydraulic pressure is influenced by a number of factors, including systemic arterial and venous blood pressures, regional blood flow, and the resistances imposed by the precapillary and postcapillary sphincters. Cardiac output, intravascular volume, and systemic vascular resistance, in turn, determine systemic arterial blood pressure. Systemic venous pressure is determined by right atrial pressure, intravascular volume, and venous capacitance. These latter hemodynamic parameters are largely determined by sodium and water balance and by various neurohormonal factors. For

67.1 Common Signs and Symptoms of Congestive Heart Failure

Primarily Related to Fluid Retention/Increased Ventricular Filling Pressures	Primarily Related to Abnormal Cardiac Output
Ascites	Cool extremities
Dyspnea (at rest or with exertion)	Fatigue
Hepatomegaly (RUQ fullness, pain)	Low blood pressure/narrow pulse pressure
Jugular venous distension	Poor capillary refill
Orthopnea	
Paroxysmal nocturnal dyspnea	
Peripheral edema	
Pleural effusions	
Pulmonary rales	
Third heart sound	

RUQ, right upper quadrant.

example, right atrial pressure or right ventricular preload is modulated both by changes in the intravascular volume, which are largely determined by the kidney, and alterations in venous capacitance, which are governed in part by neuroendocrine mechanisms such as the sympathetic nervous system, the renin–angiotensin system, the nonosmotic release of arginine vasopressin (AVP), and the natriuretic peptides. As discussed in this chapter, activation of these two mechanisms (i.e., renal sodium and water retention and neurohormonal activation), which may influence transcapillary hydraulic and oncotic pressures, is observed with cardiac failure.

Several mechanisms are capable of minimizing edema formation or diminishing the transudation of solute and water across the capillary bed. In several vascular beds, the local transcapillary hydraulic pressure gradient exceeds the opposing colloid osmotic pressure gradient throughout the length of the capillary bed, so that filtration occurs across its entire length.[8] Filtered fluid consequently must return to the circulation via lymphatics. Increased lymphatic drainage and the ability of lymphatic flow to increase may thus be seen as one protective mechanism that minimizes edema formation. Other protective mechanisms that reduce interstitial fluid accumulation include precapillary vasoconstriction, increased net filtration with a resultant rise in intracapillary plasma protein concentration, and increased interstitial fluid volume with a resultant augmentation of tissue hydraulic pressure. For example, increased net filtration itself, such as that associated with hypoalbuminemia and the resultant decreased plasma oncotic pressure, leads to a dissipation of capillary hydraulic pressure, a dilution of interstitial fluid protein concentration, and a corresponding rise in intracapillary protein concentration, all of which alter the balance of the Starling forces to mitigate further interstitial fluid accumulation.

These buffering factors directed against interstitial fluid accumulation may explain why, in patients with congenital analbuminemia, positive sodium and water balance, and edema formation do not occur consistently and sodium loads are excreted.[9] Because the continued loss of intravascular fluid volume to the interstitial space without renal sodium and water retention may result in the cessation of interstitial fluid formation, the presence of generalized edema, therefore, implies concomitant renal sodium and water retention. This is unquestionably the case in cardiac failure, as well as in liver disease and the nephrotic syndrome. The disturbances in microcirculatory hemodynamics associated with edema and expansion of the ECF volume are described in Table 67.2.

THE MECHANISMS OF FLUID RETENTION IN CARDIAC FAILURE

Cardiac failure may be defined as the inability of the heart to deliver enough blood to peripheral tissues to meet metabolic demands. In the case of low-output cardiac failure, a decrease in cardiac output initiates a complex set of compensatory mechanisms in an attempt to maintain circulatory integrity. The adjustments that serve to stabilize cardiac performance and arterial perfusion in such patients include increases in plasma volume, atrial and ventricular filling pressures, peripheral vasoconstriction, and cardiac contrac-

67.2 Disturbances in Microcirculatory Hemodynamics Associated with Edema and Expansion of Extracellular Fluid Volume

Increased venous pressure transmitted to the capillary
Adjustments in precapillary and postcapillary resistances to favor interstitial fluid accumulation
Inadequate lymphatic flow of drainage
Altered capillary permeability (K_f)

tility and heart rate. The retention of sodium and water is a major renal compensation for a failing myocardium, but it also accounts to a great extent for the familiar clinical syndrome of heart failure, which consists of pulmonary and/or peripheral edema and exercise intolerance. In fact, the inability to excrete a sodium load has been used as an index of the presence of heart failure,[10] and a defect in water excretion is regularly encountered in such patients.[11]

Classically, two theories have attempted to explain how the kidney becomes involved in renal sodium and water retention of heart failure. According to the "backward failure" hypothesis advanced by Hope[12] and Starling,[7] central venous pressure rises and then peripheral venous pressure rises as the cardiac pump fails. With this increase in peripheral venous pressure, the hydraulic pressure in the capillaries exceeds opposing forces and causes the transudation of fluid from the intravascular compartment to the interstitial space, and thus the development of edema. This loss of intravascular fluid volume then signals the kidney to retain sodium and water in an attempt to restore the circulating volume to normal. The "forward failure" theory states that as the heart fails, there is inadequate perfusion of the kidney, resulting in decreased sodium and water excretion.[13] As will become apparent from the following discussion, both an increase in central venous pressure, or "backward failure," and a decrease in cardiac output, or "forward failure," may contribute to the sodium and water retention of low-output cardiac failure via systemic and renal hemodynamic effects and through the activation of various vasoconstrictor and antinatriuretic neuroendocrine systems. According to our unifying hypothesis of body fluid–volume regulation,[14–21] neurohormonal activation plays a central role in the efferent limb of the sodium and water retention in cardiac failure, liver disease, and the nephrotic syndrome, whereas the afferent limb of this volume regulatory system is initiated by altered systemic hemodynamics. The following discussion addresses this unifying hypothesis of body fluid–volume regulation and the afferent and efferent mechanisms for sodium and water retention in edematous disorders, in particular, heart failure.

Afferent Mechanisms for Renal Sodium and Water Retention in Heart Failure

The kidney alters the amount of dietary sodium excreted in response to signals from volume receptors and chemoreceptors in the circulation. These receptors may affect kidney function by altering renal sympathetic nerve activity and changing levels of circulating hormones with vasoactive and nonvasoactive (e.g., direct sodium-retaining) effects on the kidney. Important "effector" hormones include angiotensin II (AT-II), aldosterone, AVP, endothelin, nitric oxide (NO), prostaglandins (PGs), and the natriuretic peptides, especially atrial and brain natriuretic peptides (ANP and BNP, respectively). Both high- and low-pressure baroreceptors as well as cardiac and hepatic chemoreceptors have been implicated in the activation of these neurohormonal systems.

High-Pressure Baroreceptors

In humans, evidence for the presence of volume-sensitive receptors in the arterial circulation originated from observations in patients with traumatic arterial-venous (AV) fistulae.[22] Closure of AV fistulae is associated with a decreased 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 results in an immediate increase in renal sodium and water excretion without changes in either glomerular filtration rate (GFR) or renal blood flow.[22] This observation implicates the "fullness" of the arterial vascular tree as a "sensor" in modulating renal sodium and water excretion. In fact, the fullness of the arterial vascular compartment, or the so-called effective arterial blood volume (EABV),[23] has been proposed as a major determinant of renal sodium and water handling according to the unifying hypothesis of body fluid volume regulation.[14–21]

The EABV is a measure of the adequacy of arterial blood volume to "fill" the capacity of the arterial circulation. Normal EABV exists when the ratio of cardiac output to peripheral vascular resistance maintains venous return and cardiac output at normal levels. Arterial or high-pressure volume receptors, therefore, may be stimulated when either cardiac output falls or peripheral vascular resistance diminishes to such an extent that the arterial circulation is no longer effectively "full" (Fig. 67.1). Therefore, in the case of low-output cardiac failure, it is the diminution of cardiac output that is perceived by the arterial circulation as inadequate to maintain EABV. In high-output cardiac failure, decreased peripheral vascular resistance may serve as the signal for arterial underfilling.[14–21] The concept of arterial underfilling in low- and high-output cardiac failure is discussed in the following paragraphs.

Studies using one model of low-output cardiac failure—constriction of the vena cava in the dog—support the notion that a fall in cardiac output may be a primary stimulus for sodium and water retention by the kidney. Using this model, Schrier and associates[24–26] showed that constriction

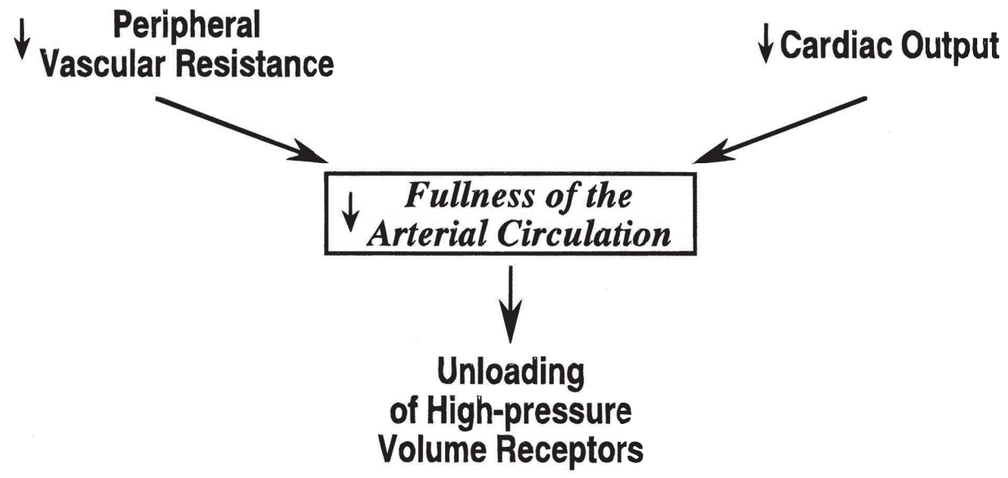

FIGURE 67.1 Peripheral vascular resistance and cardiac output as the determinants of arterial filling or the "effective arterial blood volume." Here, either a decrease in vascular resistance or diminished cardiac output results in decreased fullness of the arterial circulation with unloading of high-pressure volume receptors and activation of various neurohormonal responses (see text).

of the thoracic inferior vena cava (TIVC) is associated with a decrease in cardiac output, arterial pressure, and urinary sodium excretion, even when renal perfusion pressure and renal venous pressure were held constant. Of note, renal denervation and adrenalectomy did not abolish this antinatriuresis. Furthermore, sodium retention did not correlate with changes in GFR or renal vascular resistance. Constriction of the superior vena cava to cause a decrease in cardiac output similar to that observed in the TIVC studies resulted in a similar decrease in urinary sodium excretion despite the absence of concomitant hepatic, renal, and abdominal venous congestion. These findings support the hypothesis that the kidney decreases sodium excretion in response to a decrease in cardiac output and the associated arterial underfilling.

Migdal et al.[27] questioned this hypothesis by comparing the renal response in three different models of experimental heart failure. Specifically, they compared models of TIVC constriction, pulmonary artery occlusion (which is similar to caval constriction except that right-sided heart pressures are increased rather than decreased), and acute left ventricular infarction, another model of low-output heart failure but with increased left-sided heart pressures. This investigation demonstrated that with comparable decrements in cardiac output in all three models, only the TIVC constriction animals exhibited antinatriuresis. The authors concluded that low cardiac output per se is not the afferent signal for sodium retention in low-output heart failure. These authors[27] and others[28] suggested that in some way, decreased right-sided heart pressure mediates the antinatriuresis.

An alternative interpretation of the findings of Migdal et al.[27] is that a decrease in cardiac output is a stimulus for renal sodium and water retention, but an acute rise in atrial or ventricular end-diastolic pressures, in animals with acute pulmonary hypertension or acute left ventricular infarction, with the release of the natriuretic peptides ANP and BNP, initially obscures this effect. Support for this interpretation may be found in a report from Lee et al.,[29] who examined sodium excretion in two models of low-output heart failure in the dog, acute heart failure produced by rapid ventricular pacing, and a TIVC constriction model. Similar to the animals in the study of Migdal et al., the dogs with TIVC constriction demonstrated diminished cardiac outputs and arterial pressures without an increase in atrial pressures or plasma ANP level but with avid renal sodium retention. Of note, plasma renin activity (PRA) and plasma aldosterone concentrations were substantially elevated in these TIVC-constriction animals. In the case of pacing-induced heart failure, cardiac output and arterial pressure were similarly decreased, whereas atrial pressures and the plasma ANP concentration were significantly increased. In the animals with elevated rather than normal circulating ANP concentrations, urinary sodium excretion was maintained and PRA and plasma aldosterone concentrations were not increased. Finally, dogs with TIVC constriction were given exogenous ANP to achieve circulating concentrations comparable to that seen in the pacing-induced heart failure animals. Exogenous administration of ANP to such levels prevented sodium retention, renal vasoconstriction, and activation of the renin–angiotensin–aldosterone system. These observations support the notion that decreased cardiac output is a stimulus for renal sodium retention in heart failure and suggest an important role for the natriuretic peptides in acutely attenuating this renal response. A further discussion of the role of ANP and BNP in heart failure is presented elsewhere in this chapter.

Other experimental evidence supports a role for diminished cardiac output as a determinant of sodium and water retention in heart failure. Rats with small-to-moderate myocardial infarctions and decreased cardiac outputs exhibit decreased fractional sodium excretion despite normal right and left ventricular end-diastolic pressures.[30] Using the model of TIVC constriction, Priebe et al.[31] demonstrated that the renal retention of sodium and water was reduced markedly when cardiac output was restored to normal by autologous blood transfusions. Moreover, a reduction of pressure or stretch at the carotid sinus, like that produced by decreased cardiac output or arterial hypotension, activates the sympathetic nervous system and promotes renal sodium and water retention.[32,33] Pharmacologic or surgical interruption of sympathetic afferent neural pathways emanating from high-pressure baroreceptor sites also inhibits the natriuretic response to volume expansion.[25,26,34–38] High-pressure baroreceptors also appear to be important factors in regulating the nonosmotic release of AVP, thereby affecting renal water excretion.[39,40] Finally, the juxtaglomerular apparatus, an arterial baroreceptor located in the afferent arterioles within the kidney, has been implicated in the modulation of renal renin release[32,41,42] and thus may stimulate increases in circulating AT-II and aldosterone, both of which promote sodium retention by the kidney.

Low cardiac output cannot be the only cause of sodium and water retention in heart failure, because diminished renal sodium and water excretion is also observed in states of high-output cardiac failure. In heart failure secondary to beriberi, anemia, thyrotoxicosis, or AV fistulae, cardiac output is increased as a consequence of a decrease in peripheral vascular resistance. This decrease in vascular resistance diminishes EABV (i.e., causes arterial underfilling) and serves as the stimulus for neurohormonal activation and renal sodium and water retention in these instances of high-output heart failure.[14–21] As noted already in humans[22] and dogs,[43] closure of an AV fistula causes increased sodium excretion, whereas opening an AV fistula decreases urinary sodium excretion. These changes in renal sodium excretion correlate with changes in arterial pressure and peripheral vascular resistance rather than GFR or renal blood flow, supporting the importance of arterial circulatory "fullness" as a determinant of the renal response to heart failure.

These observations of decreased sodium and water excretion in both low- and high-output cardiac failure support the theory that arterial underfilling initiates reflex stimuli for the kidneys to retain sodium and water. In this regard, high-pressure baroreceptors in the carotid sinus, aortic arch, left

ventricle, or the juxtaglomerular apparatus may comprise an important part of this reflex loop. Although these data support a role for arterial underfilling as the primary stimulus of the renal sodium and water retention of heart failure, low-pressure baroreceptors also may play an important role.

Low-Pressure Baroreceptors

In addition to the high-pressure arterial baroreceptors, the venous side of circulation seems to be a logical place for receptors sensitive to changes in blood volume to be found. In fact, 85% of blood volume may be found in the venous circulation, whereas just 15% of circulatory volume resides in the arterial circulation.[44] Although the smaller arterial blood volume may result in a higher sensitivity to detect blood volume changes, the larger amount of venous blood volume also may constitute an important component of the body fluid–volume regulatory system.

The atria of the heart are highly distensible and densely populated with nerve endings that are sensitive to small changes in passive distention.[45] Similar afferent low-pressure volume receptors may also be found in the pulmonary vasculature.[46] Increased filling of the thoracic vascular and cardiac atria would be expected to signal the kidney to increase urinary sodium excretion in order to return the blood volume to normal. As expected, maneuvers that increase this thoracic or "central" blood volume, such as weightlessness, negative-pressure breathing, head-out water immersion, recumbency, and exposure to cold, all produce a natriuresis.[47–52] Similarly, measures that decrease intrathoracic blood volume, including positive-pressure breathing, upright posture, and the application of tourniquets to the lower extremities, result in renal sodium retention.[49,53,54] Therefore, effective "central" blood volume, in addition to EABV, may serve as the afferent stimulus for the regulation of renal sodium and water excretion.

Considerable evidence implicates the left atrium as an important site of low-pressure receptors.[55–57] It is believed that changes in pressure or distention within the left atrium modulate electrical activity of the atrial receptors, which in turn may regulate renal sympathetic nerve activity. Left atrial nerves, therefore, can alter blood volume through changes in sodium excretion[57–59] as well as solute-free water excretion by influencing AVP release.[60–62] Acutely increasing left atrial volume by inflation of a balloon within the left atrium results in increased urinary volume excretion,[56] whereas hypotensive hemorrhage[63,64] and atrial tamponade[65] cause decreased atrial volume and diminish urine volume. However, in the setting of chronic heart failure, renal sodium and water retention occur despite left atrial distention and, frequently, loading of the other central baroreceptors (pulmonary veins, right atrium). Therefore, in chronic heart failure, diminished cardiac output with arterial underfilling may exert the predominant effect via the unloading of high-pressure arterial baroreceptors. Chronic studies in animals employing either experimental tricuspid insufficiency[66] or right atrial distention with an inflatable balloon[67] support this hypothesis. In these animal models, the increase in right atrial pressure was associated with avid renal sodium retention rather than the expected natriuresis. However, a concomitant fall in cardiac output could explain the sodium retention. Alternatively, alterations in cardiopulmonary baroreceptor function may occur in chronic but not acute heart failure.

Zucker et al.[68] demonstrated that the inhibition of renal sympathetic nerve activity seen during acute left atrial distention is lost during chronic heart failure in the dog. Moreover, a decrease in cardiac preload fails to produce the expected parasympathetic withdrawal and sympathetic activation in humans with heart failure.[69–71] Nishian et al.[71] described paradoxical forearm vasodilation and hemodynamic improvement during acute unloading of cardiopulmonary baroreceptors in patients with severe chronic heart failure. This paradoxical response to lower body negative pressure was associated with static plasma norepinephrine levels,[71] rather than the expected increase in plasma norepinephrine concentrations, further demonstrating this altered response to low-pressure baroreceptor unloading in heart failure. These observations confirm those made in heart failure patients during other forms of orthostatic stress.[69,70] These findings are also consistent with the observation of a strong positive correlation between left atrial pressure and coronary sinus norepinephrine, a marker of cardiac adrenergic activity, in patients with chronic heart failure.[72] Finally, Fonarow et al.[73] have shown that a reduction in left ventricular filling pressure rather than an increase in cardiac output during tailored hemodynamic management of heart failure improves survival over a 2-year period of follow-up. Taken together, these findings suggest that the normal inhibitory control of sympathetic activation accompanying increased atrial pressures is lost in heart failure patients and somehow may be converted to a stimulatory signal.

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, phenyldiguanidine, bradykinin, substance P, and PGs. Baker et al.[74] demonstrated stimulation of sympathetic afferent nerve endings by bradykinin in the heart of the cat. In conscious dogs, the administration of PGE_2 and arachidonate inhibited the cardiac baroreflex.[75] Moreover, Zucker et al.[76] showed that PGI_2 attenuates the baroreflex control of renal nerve activity via an afferent vagal mechanism. Because substances such as bradykinin and PGs may circulate at increased concentrations in subjects with heart failure,[77] it is possible that altered central nervous system input from chemically sensitive cardiac or pulmonary afferents contributes to the neurohormonal activation and sodium retention of chronic heart failure. This possibility may have important implications for the treatment of heart failure, because commonly prescribed medications such as angiotensin-converting enzyme (ACE) inhibitors may alter circulating bradykinin and PG levels. At the present

time, however, the exact roles of these hormones and cardiac and pulmonary chemoreceptors in heart failure are incompletely understood.

Hepatic Receptors

Theoretically, the liver should be in an ideal position to monitor dietary sodium intake and thus adjust urinary sodium excretion. Indeed, when compared with peripheral venous administration, infusion of saline solution into the portal circulation was reported to result in greater natriuresis.[78,79] Similarly, the increment in urinary sodium excretion has been claimed to be greater when the sodium load is given orally than when given intravenously.[80–82] In addition, the pathophysiologic 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, some investigators[83,84] were unable to demonstrate a difference in sodium excretion between animals infused with 5% sodium chloride systemically and animals receiving the same solution via the portal vein. Moreover, Obika et al.[85] found similar sodium excretions after sodium loads given intravenously or by gastric lavage. Therefore, the experimental evidence in favor of sodium or volume hepatic receptors remains controversial.

In summary, the afferent mechanisms for sodium and water retention in chronic heart failure may be preferentially localized on the arterial or high-pressure side of the circulation where EABV may serve as the primary determinant of the renal response. However, reflexes from the low-pressure cardiopulmonary receptor system also may be altered so as to influence renal sodium and water handling in heart failure. In this regard, increases in atrial and ventricular end-diastolic pressures also stimulate the release of the natriuretic peptides and inhibit AVP release, which may be important attenuating factors in renal sodium and water retention. Finally, these afferent mechanisms for initiating sodium and water retention in chronic heart failure should not be confused with additional mechanisms that may be implicated in the setting of acute decompensated heart failure, where increased central venous pressure and renal venous congestion may also contribute to worsening renal function and sodium and water retention, as discussed later in this chapter.

Efferent Mechanisms for Renal Sodium and Water Retention in Heart Failure

The Neurohormonal Response to Cardiac Failure

As mentioned, the activation of various neurohormonal vasoconstrictor and antinatriuretic systems mediates to a large extent the renal sodium and water retention associated with the edematous disorders. Arterial underfilling secondary to a diminished cardiac output or peripheral vasodilation, perhaps in association with an alteration in low-pressure baroreceptor function, elicits these "compensatory" neuroendocrine responses in order to maintain the integrity of the arterial circulation by promoting peripheral vasoconstriction and expansion of the ECF volume through renal sodium and water retention (Fig. 67.2). The three major neurohormonal vasoconstrictor systems activated in response to arterial underfilling are the sympathetic nervous system, the renin–angiotensin–aldosterone system, and the nonosmotic release of AVP. Although other vasoconstrictor hormones may also be activated in heart failure (e.g., endothelin), their role in heart failure pathophysiology remains unclear.

The 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. The nonosmotic release of AVP involves sympathetic stimulation of the supraoptic and paraventricular nuclei in the hypothalamus,[86] whereas activation of the renin–angiotensin–aldosterone system involves renal β-adrenergic stimulation.[87] However, this latter system may provide positive feedback stimulation of the sympathetic nervous system and

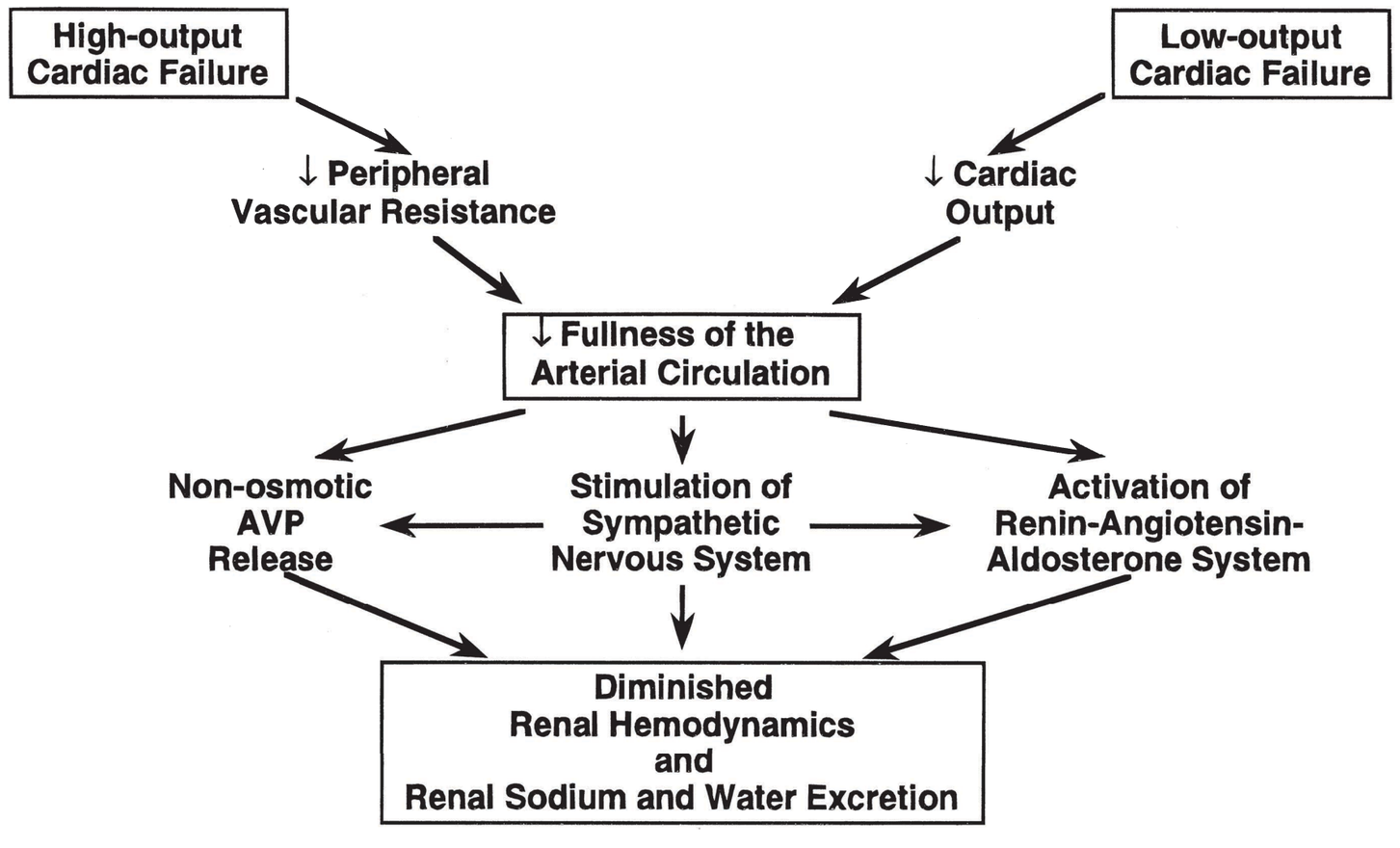

FIGURE 67.2 The mechanism explaining the defect in renal sodium and water excretion in both high- and low-output heart failure. *AVP*, arginine vasopressin.

nonosmotic AVP release. Various counterregulatory, vasodilatory, and natriuretic hormones, including the natriuretic peptides and PGs, are also activated in heart failure and the other edematous disorders, and may attenuate the renal effects of vasoconstrictor hormone activation. The effects of these neurohormonal systems, as well as the effects of alterations in systemic hemodynamics, on renal hemodynamics, and tubular sodium and water reabsorption in heart failure, are discussed in the following section.

Glomerular Filtration Rate

The GFR is usually normal in mild heart failure and is reduced only as cardiac performance becomes more severely impaired. Until 1961, it was generally accepted that the rate of glomerular filtration was a major determinant of renal sodium excretion. In 1961, de Wardener et al.[88] published their classic paper indicating that acute expansion of ECF volume by saline loading was accompanied by a brisk natriuresis even when GFR was reduced. Moreover, in sodium-retaining heart failure patients, GFR is often normal and may even be elevated in states of high-output cardiac failure. These observations argue against an important role for diminished GFR in the sodium retention of heart failure per se (i.e., in the initiation of sodium retention), although a diminished GFR may be a contributing factor in patients with advanced heart failure or comorbid disorders that directly impair this aspect of renal function. It also should be emphasized that the contribution of GFR to sodium balance is difficult to evaluate because very minute changes in GFR are difficult to measure and may account for important changes in sodium excretion. For example, under normal conditions, with a GFR of 100 mL per minute, the filtered load of sodium amounts to approximately 20,000 mEq per day. This amount of filtered sodium is enormous compared to the normal urinary sodium excretion of approximately 200 mEq per day. In view of this considerable difference, it is apparent that very small changes in GFR can result in major alterations in sodium excretion if tubular reabsorption remains unaltered. In any event, although GFR may be diminished in patients with advanced heart failure, a reduction in GFR alone is probably not an important cause of fluid retention in these patients because sodium retention can be observed in heart failure patients who have GFRs comparable to normal subjects who are capable of maintaining sodium balance.

Renal Blood Flow

Heart failure is commonly associated with an increase in renal vascular resistance and a decrease in renal blood flow.[89] In general, renal blood flow decreases in proportion to the decrease in cardiac output. Some investigators also showed a redistribution of renal blood flow from the outer cortical nephron to juxtaglomerular nephrons during experimental heart failure.[90,91] It was proposed that deeper nephrons with longer loops of Henle reabsorb sodium more avidly. Therefore, the redistribution of blood flow to these nephrons in patients with heart failure might account for or substantially contribute to the renal sodium retention observed. However, other investigators were not able to demonstrate such a redistribution of blood flow in other models of cardiac failure.[92,93] At the present time, the role of redistribution of renal blood flow in the sodium retention of cardiac failure therefore remains uncertain.

The increased renal vascular resistance in heart failure could be caused by enhanced renal sympathetic activity or increased circulating concentrations of AT-II, norepinephrine, vasopressin, or other vasoconstricting substances. Alternatively, or in addition, decreased synthesis of or the development of tachyphylaxis to known vasodilating substances such as the natriuretic peptides and PGE_2 and PGI_2 may contribute to the increased renal vascular resistance. Studies performed in rats demonstrated the ability of the adrenergic neurotransmitter norepinephrine and AT-II to promote glomerular arteriolar constriction.[94,95] In a rat model of low-output heart failure caused by myocardial infarction, the marked elevation in efferent arteriolar resistance was abolished after the infusion of an ACE inhibitor,[95] thereby implicating the renal vasoconstrictor properties of AT-II in heart failure. Clinical results from our laboratory also favor AT-II as a major renal vasoconstrictive substance in patients with heart failure.[96] In patients with advanced heart failure, GFR was improved after 1 month of treatment with the ACE inhibitor captopril. However, similar patients receiving another vasodilating agent, prazosin, with identical improvement in cardiac output and left ventricular end-diastolic pressure but without any effect on the renin–angiotensin system had no improvement in GFR.[96] Moreover, a published review of the literature on renal function alterations induced by ACE inhibition during heart failure concluded that the net effect of ACE inhibitors in patients with heart failure is to augment renal blood flow to a greater extent than cardiac output.[97] This observation also supports an important role for AT-II in the renal hemodynamic alterations of heart failure. However, the renal response to ACE inhibition in patients with heart failure is variable; as a result, it is acknowledged that volume status and the degree of neurohormonal activation may influence this response (see the following).

In heart failure, the interaction between norepinephrine or AT-II and PGs may also provide a means of preserving near constancy of renal blood flow in response to arterial underfilling. Although the inhibition of PG synthesis does not generally impair GFR in normovolemic animals[98,99] or humans,[100] in states of high plasma concentrations of endogenous AT-II induced by volume depletion, the blockade of PG synthesis may be associated with substantial declines in renal blood flow and GFR.[98,99] Recent clinical results have underscored the importance of PGs in the maintenance of renal function in patients with heart failure.[77,101] In patients with heart failure, PG activity is increased and correlates with the severity of disease as assessed by the degree of hyponatremia.[77] In these 15 patients, plasma levels of the

metabolites of vasodilator PGI_2 and PGE_2 were found to be elevated 3 to 10 times above those seen in normal subjects. Of note, plasma levels of both metabolites also correlated positively with PRA and plasma AT-II concentrations. The administration of the PG synthesis inhibitor indomethacin in three of the hyponatremic heart failure patients resulted in a marked increase in peripheral vascular resistance and a fall in cardiac output. Riegger et al.[101] recently evaluated the renal effects of another PG synthesis inhibitor, acetylsalicylic acid, in patients with moderate heart failure consuming a normal sodium diet. In these patients, acetylsalicylic acid in doses that decreased the synthesis of renal PGE_2 resulted in a significant reduction in urinary sodium excretion. Moreover, the administration of a cyclooxygenase inhibitor in heart failure patients occasionally may result in acute reversible renal failure, an effect proposed to be due in part to the inhibition of vasodilating renal PGs and the resultant renal vasoconstriction.[102] It should be noted, however, that the extent to which the effects on renal function and sodium and water handling result from renal hemodynamic or the tubular actions of the PGs remains unclear.

As mentioned, norepinephrine may also contribute to the increased renal afferent arteriolar resistance in heart failure patients. In this regard, Oliver et al.[103] demonstrated that the venous to arterial norepinephrine concentration gradient across the kidney, a crude measure of renal nerve traffic, is increased in response to acute reduction of cardiac output. Moreover, Hasking et al.[104] showed that during a steady-state tritiated norepinephrine infusion, the spillover of norepinephrine to plasma from the kidney is significantly elevated in patients with heart failure. In these patients, the increased renal norepinephrine spillover substantially contributed to the increase in whole-body norepinephrine spillover. These findings demonstrate that renal adrenergic activity is increased in patients with heart failure, and thus contributes to the renal vasoconstriction. In support of this latter hypothesis, the administration of α-adrenergic receptor antagonists increased renal blood flow in edematous patients with heart failure.[105] Renal denervation studies in patients with refractory hypertension also underscore the role of renal sympathetic nerve activation in cardiovascular disease. In such patients, the catheter ablation of renal nerves reduces norepinephrine spillover from the kidneys and lowers blood pressure.[106–108] Ongoing renal denervation studies in patients with heart failure may shed further light on the role of renal sympathetic activation and the potential for catheter ablation of renal nerves in the treatment of heart failure.

Filtration Fraction, Proximal Tubular Sodium and Water Reabsorption, and Factors Acting Beyond the Proximal Tubule

Because renal blood flow falls as cardiac output decreases and GFR is usually preserved, the filtration fraction often is increased in early heart failure. An increase in the filtration fraction results in increased protein concentration and oncotic pressure in the efferent arterioles and the peritubular capillaries that surround the proximal tubule.[95] Such an increase in peritubular oncotic pressure has been proposed to increase sodium and water reabsorption in the proximal tubule.[109–113] Direct evidence for increased single-nephron filtration fraction was provided by micropuncture studies in rats with myocardial infarction induced by coronary ligation.[95] In rats with large myocardial infarctions involving approximately 40% of the left ventricular circumference, the single-nephron filtration fraction was markedly elevated (0.38 ± 0.02 versus 0.25 ± 0.02, $P < .005$) when compared with that in sham-operated control rats. The measurement of preglomerular, glomerular, and postglomerular pressures and flows revealed that these reductions in glomerular plasma flow rate and elevations in filtration fraction were associated with a profound constriction of the efferent arterioles. The effect of the latter was to sustain glomerular capillary hydraulic pressure, thereby preventing a marked fall in GFR. Significantly, fractional proximal fluid reabsorption was elevated in this model. Of interest, in these animals with myocardial infarction, the intravenous infusion of the ACE inhibitor teprotide led to the return of glomerular plasma flow rate, single-nephron filtration fraction, single-nephron GFR, efferent arteriolar resistance, and fractional proximal fluid reabsorption to or toward the levels found in the control rats.[95] Consistent with these experiments, micropuncture studies performed in other models of heart failure such as acute TIVC constriction[114] and acute cardiac tamponade[115] in dogs showed that the proximal tubule was at least one major nephron site responsible for renal sodium retention or a blunted response to saline infusion.

Despite the convincing nature of many studies, not all investigators have been able to detect an effect of peritubular oncotic pressure on proximal tubular sodium and water reabsorption. Rumrich and Ullrich,[116] Lowitz et al.,[117] Bank et al.,[118] and Holzgreve and Schrier[119] were unable to find changes in proximal reabsorption despite marked changes in peritubular oncotic pressures. Moreover, Conger et al.[120] directly perfused peritubular capillaries with either a protein-free or protein-rich solution and found that neither perfusate influences the rate of proximal reabsorption. Trying to reconcile these observations, Ott et al.[121] found that proximal reabsorption was different after changes in peritubular oncotic pressure in volume-expanded dogs compared with hydropenic animals. These authors suggested that the expansion of ECF volume resulted in an increased passive back leak that could be reversed by raising the peritubular oncotic pressure. During hydropenia, however, when passive back leak was relatively less, raising the peritubular capillary oncotic pressure did not influence proximal reabsorption.

The effects of increased filtration fraction might be expected to be exerted primarily on proximal tubular sodium reabsorption. Nevertheless, although clearance and micropuncture studies in animals with heart failure have demonstrated increased sodium reabsorption in the proximal tubule, distal

sodium reabsorption also seems to be involved. In this regard, clearance and micropuncture studies performed in dogs with AV fistulae,[122] chronic pericarditis,[115] and chronic partial thoracic vena caval obstruction[123] documented enhanced distal nephron sodium reabsorption. Levy[123] also showed that the inability of dogs with chronic vena caval obstruction to excrete a sodium load is a consequence of enhanced reabsorption of sodium at the loop of Henle. This nephron segment was similarly implicated in rats with AV fistulae.[93] Physical factors also could be involved in the augmented reabsorption of sodium chloride by the loop of Henle in dogs with constriction of the vena cava.[123]

Intrarenal mechanisms, specifically decreased delivery of tubular fluid to the distal diluting segment of the nephron, may also contribute to the impaired water excretion observed in heart failure. Evidence supporting this intrarenal mechanism of water retention in heart failure has been provided by studies involving the administration of mannitol[124] or the loop diuretic furosemide[125] to patients with heart failure and hyponatremia. The administration of either of these agents converted the cardiac patient's hypertonic urine to a dilute urine.[124,125] Both mannitol and furosemide may diminish the tubular reabsorption of sodium and water in the more proximal portions of the nephron, thus increasing fluid delivery to the more distal nephron sites of urinary dilution. Other factors may, however, be implicated to explain these results: (1) the infusion of mannitol may produce volume expansion, thereby suppressing the baroreceptor-mediated release of AVP; and (2) the furosemide-induced hypotonic urine was found to not be responsive to the administration of exogenous AVP, thus suggesting antagonism of AVP by furosemide.[125] In support of this latter hypothesis, Szatalowicz et al.[126] provided further evidence that furosemide interferes with the renal action of AVP in humans.

In summary, the exact contribution of proximal versus distal nephron sites in the augmented sodium and water reabsorption seen in heart failure may depend on the severity of the heart failure and the concomitant degree of arterial underfilling. The fact that changes in the filtration fraction have been observed in patients with heart failure before changes in sodium balance occur may question the dominance of peritubular factors and proximal reabsorption in the sodium retention characteristic of heart failure.[127] This observation suggests that other factors, such as the direct tubular effects of neurohormonal activation, may play a significant role in the renal sodium and water retention of heart failure. The renal effects of these various neurohormonal systems are discussed in detail in the following section, starting with activation of the vasoconstrictor mechanisms.

Vasoconstrictor Systems

Activation of the sympathetic nervous system in heart failure. The sympathetic nervous system is activated early in patients with heart failure. Numerous studies have documented elevated peripheral venous plasma norepinephrine concentrations in heart failure patients.[104,128–131] In advanced heart failure, using tritiated norepinephrine to determine norepinephrine kinetics, Hasking et al.[104] and Davis et al.[130] demonstrated that both increased norepinephrine spillover and decreased norepinephrine clearance contribute to the elevated venous plasma norepinephrine levels seen in these patients, suggesting that increased sympathetic nerve activity is at least partially responsible for the high circulating norepinephrine levels. Our laboratory[131] has demonstrated that in earlier stages of heart failure, the rise in plasma norepinephrine in patients with heart failure was due solely to increased norepinephrine secretion (Fig. 67.3), supporting the notion that sympathetic nervous system activity is increased early in the course of heart failure. Significantly, in our heart failure patients with mild-to-moderate symptoms, plasma epinephrine, a marker of adrenal activation, was not substantially elevated, confirming the neuronal source of the increased norepinephrine.

The Studies of Left Ventricular Dysfunction (SOLVD) investigators[132] reported the presence of adrenergic activation in patients with asymptomatic left ventricular dysfunction. In this substudy of the SOLVD trials, neurohormonal activation was assessed in 56 control subjects, 151 patients with left ventricular dysfunction (ejection fractions ≤ 35%) but no overt heart failure, and 81 patients with overt heart failure, prior to randomization to receive placebo versus an ACE inhibitor. The plasma norepinephrine concentration

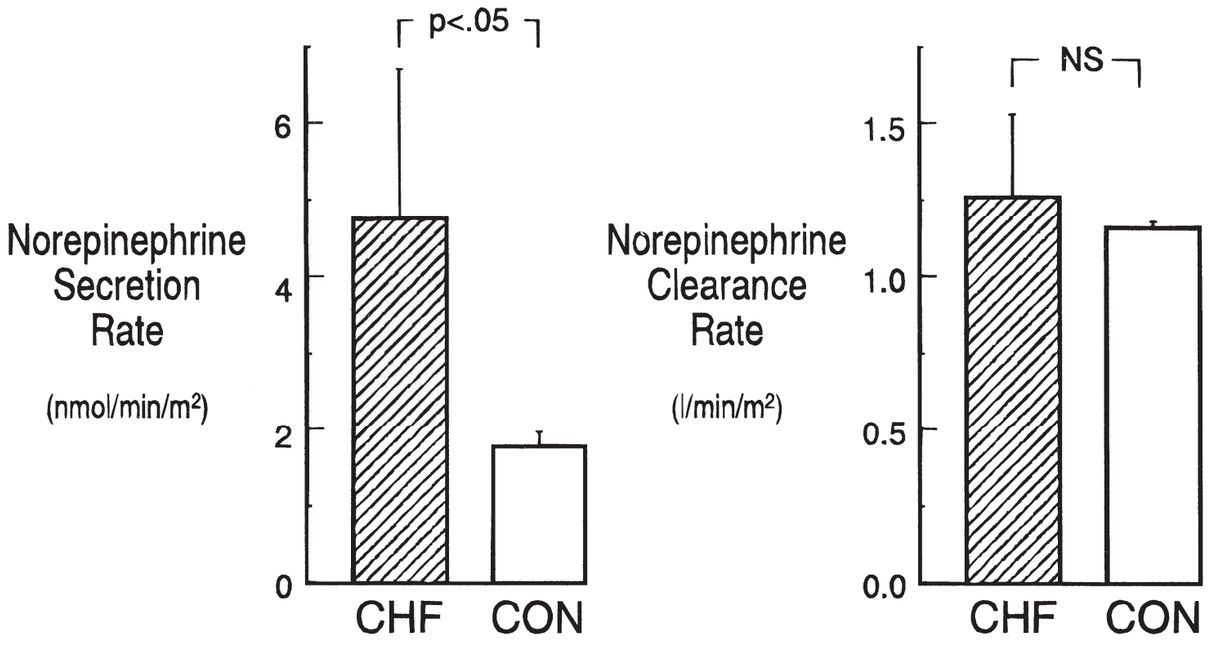

FIGURE 67.3 Plasma norepinephrine secretion and clearance rates in patients with mild-to-moderate heart failure (CHF) and in normal control subjects (CON). The findings of increased norepinephrine secretion and normal norepinephrine clearance in the CHF patients are consistent with early activation of the sympathetic nervous system in cardiac failure. *NS*, not significant. (From Abraham WT, Hensen J, Schrier RW. Elevated plasma noradrenaline concentrations in patients with low-output cardiac failure: dependence on increased noradrenaline secretion rates. *Clin Sci.* 1990;79:429, with permission.)

was significantly increased by 35% in subjects with asymptomatic left ventricular dysfunction compared to healthy control subjects, and by 65% greater than control values in the overt heart failure patients. These data also demonstrate that adrenergic activation occurs early in the course of heart failure or left ventricular dysfunction and are consistent with the observation that plasma norepinephrine concentrations or the degree of adrenergic activation are directly correlated with the degree of left ventricular dysfunction in patients with heart failure.[128,129,133,134] Finally, studies employing peroneal nerve microneurography to directly assess sympathetic nerve activity to muscle (MSNA) confirmed increased adrenergic nerve traffic in patients with heart failure.[135]

As mentioned, studies in human heart failure demonstrated the presence of renal adrenergic activation.[104] In this study of whole-body and organ-specific norepinephrine kinetics in heart failure patients, cardiac and renal norepinephrine spillovers were increased 504% and 206%, respectively, whereas norepinephrine spillover from the lungs was normal. These findings demonstrate the presence of selective cardiorenal adrenergic activation in heart failure. A discussion of the cardiac effects of this adrenergic activation is beyond the scope of this chapter. However, low heart rate variability (indicative of high cardiac sympathetic and low cardiac parasympathetic activity) assessed continuously by implantable pacemaker and/or defibrillator devices is a predictor of hospitalization for worsening heart failure.[136] Of note, in this report most hospitalizations for worsening heart failure were associated with fluid–volume overload. Therefore, measuring heart rate variability may provide insight into the systemic as well as the cardiac effects of heightened adrenergic activity. Moreover, numerous adverse effects of increased cardiac adrenergic activity have been documented in humans,[137] and positive experience with the use of β-adrenergic receptor antagonists in heart failure patients[137–143] supports the hypothesis that norepinephrine is harmful to the myocardium. In this regard, blocking the deleterious effects of norepinephrine on the heart results in the reverse of ventricular remodeling; that is, the dilated failing heart becomes smaller and stronger following chronic β-adrenergic blockade. Finally, it should be noted that a single resting venous plasma norepinephrine level provides a better guide to prognosis than do many other commonly measured indices of cardiac performance in which high plasma norepinephrine levels are associated with a poor prognosis in patients with heart failure.[144]

Renal tubular effects of adrenergic activation in heart failure. Renal nerves exert a direct influence on sodium reabsorption in the proximal tubule. Bello-Reuss et al.[58] demonstrated this direct effect of renal nerve activation to enhance proximal tubular sodium reabsorption in whole-kidney and 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, a result of increased fractional sodium and water reabsorption in this segment of the nephron. On the basis of results of an elegant series of studies, DiBona et al.[145] implicated the activation of the renal nerves in the sodium and water retention observed in the various edematous disorders. Experiments were conducted in conscious, chronically instrumented rats with either heart failure (myocardial infarction), cirrhosis (common bile duct ligation), or the nephrotic syndrome (doxorubicin injection). In each experimental model, renal sodium or water excretion of an acutely administered oral or intravenous isotonic saline load was significantly less than that in control rats. Bilateral renal denervation in the experimental rats restored their renal excretory response to normal. Moreover, in response to the acute administration of a standard intravenous isotonic saline load, the decrease in efferent renal adrenergic nerve activity was significantly less in all three experimental models than in control animals. These results support an increased basal efferent renal sympathetic nerve activity in heart failure and the other edematous disorders that fail to suppress normally in response to the isotonic saline load. These findings also are consistent with the aforementioned alterations in low-pressure baroreceptor function observed in human heart failure, where adrenergic activation is seen despite chronic increased loading of these cardiopulmonary receptors.

In dogs[146] and in humans[105] with heart failure, α-adrenergic receptor blockade induces a natriuresis. Moreover, adrenergic blockade with either phenoxybenzamine or hexamethonium abolishes the sodium retention seen in acute TIVC constriction.[25] Furthermore, the comprehensive adrenergic blocking agent carvedilol, but not metoprolol, increases renal blood flow and GFR in patients with chronic heart failure.[147] Conversely, sodium retention persists in dogs with denervated transplanted kidneys and chronic vena caval constriction.[148] In addition, in dogs with pacing-induced heart failure, no differences in renal hemodynamic or electrolyte excretion between innervated or denervated kidneys in compensated or decompensated animals were observed.[149] These latter observations implicate factors in addition to renal nerves in the sodium retention of heart failure. However, in these renal denervation experiments and in human heart failure, other hormonal factors (e.g., AT-II, aldosterone, AVP) may play an important role in the sodium and water retention.

Experience with the partial β_1-adrenergic receptor agonist xamoterol in heart failure suggests a role for the renal β-receptor in modulating proximal tubular sodium reabsorption.[150] Bøtker et al.[150] examined the acute renal effects of xamoterol in 12 patients with mild-to-moderate heart failure. Each patient was given xamoterol (0.2 mg per kilogram) or placebo in random order separated by 2 weeks of a clinically stable drug washout period. Renal clearance and excretion measurements were made with the patient in the supine position at 30- to 60-minute intervals before, during, and up to 6 hours after infusion. Lithium clearance was used as a measure of proximal tubular sodium handling.[151] Blood pressure, heart rate, renal plasma flow, GFR, and urinary

flow rate remained unchanged, whereas xamoterol significantly decreased renal sodium excretion by 30%. This acute decrease in sodium excretion with xamoterol was associated with an increase in proximal tubular sodium reabsorption, as indicated by decreased lithium clearance. Of note, plasma concentrations of AT-II and aldosterone were unaffected by xamoterol. These observations suggest a direct effect of acute xamoterol to enhance proximal tubular sodium reabsorption in heart failure. In patients with heart failure, the endogenous adrenergic receptor agonist and neurotransmitter norepinephrine may exert a similar effect on the proximal renal tubule.

Finally, as noted, renal nerves have been implicated as a stimulus for renin release from the kidney.[87] Therefore, with heart failure, adrenergic activation may lead to the activation of the renin–angiotensin–aldosterone system. Conversely, β-adrenergic receptor blockade may decrease renin release and improve the neurohormonal milieu in heart failure patients. In this regard, Eichhorn et al.[152] showed that the third-generation β-adrenergic receptor blocker bucindolol lowers PRA in patients with mild-to-moderate heart failure. The renal tubular effects of AT-II and aldosterone are discussed in the following paragraphs.

Activation of the renin–angiotensin–aldosterone system in heart failure. The renin–angiotensin–aldosterone system is usually activated in patients with heart failure, as assessed by PRA and plasma aldosterone.[133,153,154] In the substudy report from the SOLVD investigators,[132] PRA was increased not only in patients with established heart failure but also in subjects with asymptomatic left ventricular dysfunction. Of note, activation of the renin–angiotensin–aldosterone system is associated with hyponatremia and an unfavorable prognosis in patients with heart failure.[77,155] Dzau et al.[77] first described the association of PRA and hyponatremia in a group of 15 heart failure patients. These data showed that normal or suppressed PRA is associated with a normal serum sodium level, whereas the highest PRA is associated with the lowest serum sodium concentrations. Lee and Packer[155] subsequently confirmed this association between PRA and hyponatremia in a larger cohort of heart failure patients. Moreover, these investigators demonstrated the association of this hyponatremic, hyperreninemic state with poor survival. Finally, the proven beneficial effects of ACE inhibition or AT-II receptor blockade (ARB) on symptoms, hemodynamics, exercise capacity, and survival in heart failure patients further underscore the deleterious effects of AT-II and aldosterone in these patients.[156–161]

Recently, a positive feedback between the renin–angiotensin–aldosterone system and sympathetic activation was proposed.[162] This interaction is based in part on the ability of AT-II to augment neuronal norepinephrine release at the presynaptic level.[163] In humans, the presynaptic facilitation of norepinephrine release by AT-II may play a role in the cardiorenal adrenergic activation of heart failure. Clemson et al.[164] demonstrated AT-II–mediated increases in norepinephrine spillover in the human forearm. In heart failure patients, we demonstrated increased neuronal norepinephrine release from the heart during AT-II infusion, whereas cardiac adrenergic activity was decreased by the bolus injection of the ACE inhibitor enalaprilat.[165] In addition, Gilbert et al.[166] showed that chronic ACE inhibition with lisinopril lowers cardiac adrenergic activity in patients with chronic symptomatic heart failure. Thus, the activation of renal nerves is a stimulus for renal renin release, thereby activating the renin–angiotensin–aldosterone system, whereas activation of the renin–angiotensin–aldosterone system may further stimulate adrenergic activity at the presynaptic level.

Renal tubular effects of angiotensin II and aldosterone in heart failure. In animal models, AT-II has a direct effect on enhancing proximal tubular sodium reabsorption.[167] In these studies of the rat proximal tubule, the administration of AT-II resulted in a marked increase in the rate of sodium chloride reabsorption, whereas the infusion of the AT-II receptor antagonist saralasin significantly reduced proximal tubular sodium chloride reabsorption. Moreover, in a study from Abassi et al.,[168] the administration of the AT-II receptor antagonist losartan to decompensated sodium-retaining rats with heart failure secondary to AV fistulae produced a marked natriuresis. Although proximal tubular sodium handling was not examined in this study, the observation that losartan restored renal responsiveness to ANP is consistent with a losartan-induced increase in the delivery of sodium to the distal tubular site of ANP action. The role of distal tubular sodium delivery in the renal sodium retention of heart failure is discussed in the following paragraphs.

In humans with heart failure, the finding that urinary sodium excretion correlates inversely with PRA and urinary aldosterone excretion also supports a role for AT-II or aldosterone, or both, in renal sodium retention.[169] However, the administration of ACE inhibitors to patients with heart failure results in inconsistent effects on renal sodium excretion, despite a consistent fall in plasma aldosterone concentration.[170] A simultaneous fall in blood pressure or a decline in renal hemodynamics owing to decreased circulating AT-II concentrations, however, could obscure the beneficial renal effects of lowered AT-II and aldosterone concentrations. Support for this hypothesis may be found in a report from Motwani et al.[171] These investigators examined the hemodynamic and hormonal correlates of the initial effect of ACE inhibition with captopril on blood pressure, GFR, and natriuresis in 36 patients with moderate heart failure. In these subjects, a captopril-induced fall in GFR was predicted by a decrease in renal plasma flow, low pretreatment GFR, and a low absolute posttreatment serum AT-II concentration. A decrease in urinary sodium excretion was related to this fall in GFR. Conversely, Good et al.[172] showed in eight patients with chronic heart failure that long-term AT-II suppression with captopril enhances renal responsiveness to the loop diuretic furosemide. This observation also supports a role for AT-II in the renal sodium retention of heart failure.

The role of aldosterone in the renal sodium retention of heart failure has been debated for many years. In the presence of a high sodium intake, dogs with caval constriction retain sodium even after surgical removal of the adrenal source of aldosterone.[173] Moreover, patients with heart failure do not always show increased urinary sodium excretion after the administration of the aldosterone antagonist spironolactone.[174] In addition, Chonko et al.[175] showed that patients with heart failure may have edema without increased aldosterone secretion. However, a normal plasma aldosterone level in heart failure patients may be relatively high in the presence of excess total body sodium. A role for aldosterone in the renal sodium retention of human heart failure was demonstrated by our group.[176] We examined the effect of spironolactone on urinary sodium excretion in patients with mild-to-moderate heart failure who were withdrawn from all medications prior to the study. Sodium was retained in all subjects throughout the period prior to aldosterone antagonism (Fig. 67.4). With an average sodium intake of 97 ± 8 mmol per day, the average sodium excretion before spironolactone treatment was 76 ± 8 mmol per day. During therapy with spironolactone, all heart failure patients demonstrated a significant increase in urinary sodium excretion to 131 ± 13 mmol per day. Moreover, the urine sodium-to-potassium concentration ratio significantly increased during spironolactone administration, which is consistent with a decrease in aldosterone action in the distal nephron. Of note, norepinephrine concentration and PRA increased and ANP decreased during spironolactone administration, suggesting a possible explanation for the attenuation of the natriuretic effect of spironolactone in long-term studies. Therefore, the combined use of an aldosterone antagonist with other neurohormonal antagonists (e.g., ACE inhibitors, ARBs, and β-blockers) may result in an optimal long-term benefit. Several observations support this notion, including randomized controlled trials in patients with chronic heart failure or postmyocardial infarction (MI) left ventricular dysfunction.[177–180] For example, the Randomized Aldactone Evaluation Study (RALES) demonstrated that the addition of spironolactone (25 mg per day) to ACE inhibition decreased both hospitalizations and mortality by more than 30% as compared to controls in patients with advanced heart failure.[179] Another trial[180] of the selective aldosterone antagonist, eplerenone, demonstrated a 15% reduction in all-cause mortality in patients with post-MI heart failure. Although blocking aldosterone-mediated cardiac fibrosis was proposed to explain these survival benefits of aldosterone antagonism, a contribution to improved survival attributable to the renal effects of these agents cannot be excluded.

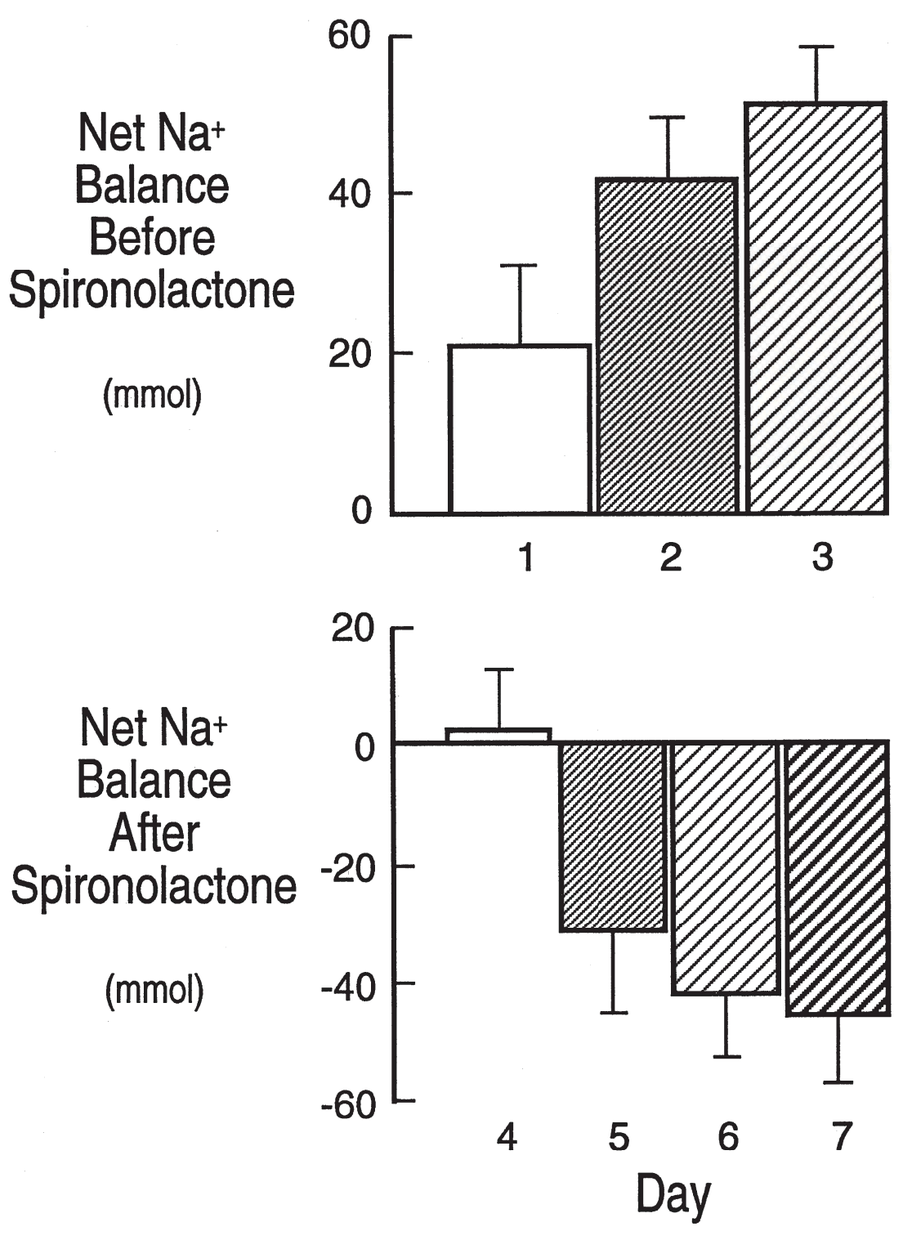

FIGURE 67.4 Reversal of sodium retention with aldosterone antagonism in patients with heart failure. The net positive cumulative sodium balance, by day, for the period before spironolactone therapy (*upper panel*) and the net negative cumulative sodium balance after the initiation of spironolactone, 400 mg per day (*lower panel*) are shown. (From Hensen J, et al. Aldosterone in congestive heart failure: analysis of determinants and role in sodium retention. *Am J Nephrol.* 1991;11:441, with permission of S. Karger AG, Basel.)

The nonosmotic release of vasopressin in heart failure. Plasma AVP is usually elevated in patients with advanced heart failure and correlates with the clinical and hemodynamic severity of disease and the serum sodium concentration.[181–186] Several clinical and experimental observations indicate that nonosmotic mechanisms are responsible for increased AVP release in heart failure. A study from our laboratory[186] found plasma AVP concentrations to be inappropriately elevated in 30 of 37 hyponatremic patients with heart failure. The 30 patients with detectable plasma AVP levels had higher levels of BUN and serum creatinine and higher ratios of BUN to serum creatinine than did the 7 patients with undetectable plasma AVP levels. This latter finding could be dissociated from diuretic use because it was also observed in 14 patients who had never received diuretics. The presence of prerenal azotemia in these patients is consistent with diminished cardiac output as a mediator of the nonosmotic AVP release. Alternatively, this observation of prerenal azotemia in association with hyponatremia also supports an intrarenal component of the impaired water excretion.

Osmotically inappropriate elevations of plasma AVP in human heart failure were also later reported by Riegger et al.,[184] Rondeau et al.,[185] and Goldsmith et al.[181] The study by Riegger et al.[184] demonstrated a decrease in the elevated plasma AVP levels after improvement in cardiac function by hemofiltration, whereas no change in plasma AVP was observed after decreasing left atrial pressure with prazosin.

Moreover, the elevated plasma AVP levels seen in patients with heart failure often,[183,187] but not always,[11] failed to suppress normally in response to acute water loading. Taken together, these observations demonstrate that there is an enhanced nonosmotic release of AVP in heart failure and support the hypothesis that diminished cardiac output, rather than alterations in atrial pressures, is responsible. As previously mentioned, the baroreceptor activation of the sympathetic nervous system in response to arterial underfilling likely mediates this nonosmotic AVP release.[86]

To shed further light on the mechanism of nonosmotic stimulation of AVP in heart failure patients and, more specifically, to determine the precise relationship between AVP release, cardiac hemodynamics, and the renin–angiotensin system, we studied 25 consecutive patients with severe heart failure (cardiac index 2.1 ± 0.1 L/minute/m^2 and pulmonary capillary wedge pressure 27.5 ± 1.5 mm Hg).[96] These patients received two water loads of 15 mL per kilogram of body weight, the first load without drugs on day 1 and the second on day 3 after receiving vasodilator therapy with either captopril or prazosin for 2 days. Baseline and hourly hemodynamic, renal, and hormonal measurements were obtained for 5 hours following the water load. Basal plasma AVP was detectable (mean 3.0 ± 0.4 pg per milliliter) in 17 of the 25 patients (group 1) despite a diminished plasma sodium concentration (P_{Na}, 133.5 mmol per liter) and low effective plasma osmolality (E_{osm}, 262 ± 3 mOsm per kilogram of H_2O). The remaining eight patients (group 2) had appropriately suppressed plasma AVP (< 0.5 pg per milliliter, undetectable) for their P_{Na} (136.5 ± 0.9 mmol per liter) and E_{osm} (268 ± 2 mOsm per kilogram of H_2O). Cardiac index (1.9 versus 2.6 L/minute/m^2, $P < .005$) and the percentage of water load excreted (31.4% versus 57.1%, $P < .005$) were lower in group 1 than in group 2 patients, but GFR was similar (55 versus 54 mL/min/1.73 m^2). The PRA and plasma aldosterone concentrations were higher in group 1 patients, suggesting arterial underfilling. In group 1 patients, vasodilators increased the cardiac index from 1.9 to 2.1 L/min/m^2 and the percentage of water load excreted from 31% to 53% (both $P < .001$). In these same patients, plasma AVP decreased from 3.0 to 1.8 pg per milliliter ($P < .01$), platelet-associated AVP decreased from 8.6 to 5.1 pg per milliliter ($P < .005$), and minimal urinary osmolality decreased from 375 to 208 mOsm per kilogram of H_2O ($P < .001$). There was no change in GFR. In group 1 patients in the control condition as well as after vasodilator therapy, plasma AVP decreased with plasma osmolality during the water load, suggesting some preservation of the osmoregulation of AVP, but with a lower osmotic threshold in these patients. Moreover, changes in the renin–angiotensin–aldosterone system were unrelated to changes in water excretion after vasodilator therapy. We consequently concluded that plasma and platelet AVP levels were the major determinants of the abnormal water excretion in many patients with heart failure. These results, therefore, favor a role of impaired cardiac function to cause arterial underfilling with resultant nonosmotic AVP release as a mediator of "resetting" the osmotic threshold for AVP in patients with heart failure. Improved cardiac function secondary to afterload reduction diminishes this resetting of the osmotic threshold. Of interest, our results are reminiscent of earlier studies that suggested that an occasional hyponatremic cardiac patient responds to a large water load by the prompt onset of a water diuresis.[11] Also, more recently, AVP secretion was found to respond in exaggerated fashion to osmotic loading in patients with heart failure undergoing radiologic procedures with radiocontrast hyperosmolar agents.[188] This latter finding also suggests a form of reset osmostat.

The renal effects of vasopressin in heart failure. Vasopressin, via the stimulation of its renal V_2 receptor,[189] induces the insertion of the aquaporin-2 (AQP2) water channel into the collecting duct apical membrane with resultant water reabsorption. Elevations in plasma vasopressin concentration and AQP2 are believed to contribute to water retention in heart failure. In animal models of heart failure, the absence of a pituitary source of AVP is associated with normal or near normal water excretion.[190,191] For example, in intact dogs with diminished cardiac outputs owing to TIVC constriction, the removal of the pituitary with glucocorticoid replacement results in the normalization of the impaired water excretion.[190] In these animals, acute constriction of the TIVC caused a significant fall in cardiac output associated with a marked increase in urinary osmolality and a decrease in solute-free water clearance. The effects of TIVC constriction were dissociated from renal hemodynamic changes and the presence or absence of renal sympathetic innervation. However, in hypophysectomized, steroid-replaced animals, both urinary osmolality and solute-free water clearance were maintained at basal levels during constriction of the TIVC. Impaired water excretion also occurs in rats with heart failure because of AV fistulae.[191] Significantly, the impairment in water excretion seen in this high-output model of heart failure was not demonstrable in Brattleboro rats with central diabetes insipidus (i.e., AVP deficiency), supporting a role for persistent AVP release in the abnormality in water excretion associated with high-output cardiac failure. Similar results were obtained by Riegger et al.[192]

Further evidence implicating a role for AVP in the water retention of heart failure comes from studies using selective peptide and nonpeptide V_2 receptor AVP antagonists in several animal models of heart failure.[193–196] Ishikawa et al.[193] assessed the antidiuretic effect of AVP in a low-output model of acute heart failure secondary to TIVC constriction in the rat. In these animals, plasma AVP concentrations were increased and a peptide antagonist of the V_2 receptor of AVP reversed the defect in solute-free water excretion. Yared et al.[194] showed a similar reversal of water retention using another peptide antagonist to the antidiuretic effect of AVP in rats with cardiac failure owing to coronary artery ligation. An orally active nonpeptide V_2 receptor AVP antagonist, OPC-31260, was described.[197] The intravenous

administration of OPC-31260 during a dose-ranging study in normal human subjects increased urine output to a similar extent as 20 mg of furosemide given intravenously.[198] In these healthy volunteers, urine osmolality was significantly lower after administration of the V_2 receptor antagonist, thus indicating an increase in solute-free water clearance. Moreover, this agent reversed the impairment in renal water excretion in rats with experimental heart failure owing to myocardial infarction[195] and in dogs with pacing-induced heart failure,[196] further supporting a role for AVP in the renal water retention of heart failure. This effect of the nonosmotic release of AVP to cause water retention in cardiac failure was associated with increased transcription of messenger RNA (mRNA) for the AVP preprohormone in the rat hypothalamus.[199]

The effects of V_2 receptor antagonists on water metabolism in heart failure have now been studied at the molecular level. Kidney AQP2 expression is increased in experimental heart failure. Rats with cardiac failure due to coronary ligation demonstrate an increase in renal AQP2 expression[200,201] that was reversed with nonpeptide V_2 receptor antagonism.[186] The V_2 receptor antagonism also reversed water retention in rats with heart failure. Recent studies have been undertaken in hyponatremic heart failure patients treated with various V_2 receptor antagonists.[202–206] One investigational agent, lixivaptan, produced a dose-related increase in water excretion, a correction of hyponatremia, and a decrease in urinary AQP2 excretion.[202,205] It is known that 3% to 6% of AQP2 water channels that traffic to the luminal membrane are excreted in the urine.[207] Therefore, urine AQP2 excretion can serve as an index of AVP effect and thus V_2 receptor antagonism in vivo in humans and experimental animals. Other investigational agents, such as tolvaptan and conivaptan, have demonstrated similar effects on diuresis (aquaresis) and a correction of hyponatremia in heart failure.[203,204,206] The SALT-1 and SALT-2 studies demonstrated this effect of V_2 receptor antagonism to correct hyponatremia not only in cardiac failure but also in cirrhosis and the syndrome of inappropriate antidiuretic hormone secretion.[208] Interestingly, preliminary data suggest that AVP antagonists, like inhibitors and antagonists of the sympathetic and renin–angiotensin–aldosterone systems, may prolong survival in heart failure patients.[206] However, the large randomized Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) study failed to demonstrate such an effect on survival in cardiac failure patients.[209]

Endothelin in heart failure. Endothelin is a potent vasoconstrictor, and its concentration is increased in patients with heart failure.[210] Results of a study from Teerlink et al.[211] suggest that endothelin plays an important role in the maintenance of arterial pressure in experimental heart failure, as shown by a significant decrease in blood pressure following the administration of the endothelin antagonist bosentan in rats with coronary artery ligation. In the kidney, mesangial cells, endothelial cells, epithelial glomerular cells, and inner medullary collecting duct cells are capable of synthesizing endothelin.[212] In this regard, recent studies in experimental heart failure demonstrate the early activation of the cardiac and renal endothelin systems.[213] Unfortunately, the role of increased endothelin in the pathogenesis of the renal sodium and water retention of heart failure is currently unknown. However, endothelin may be a potent mediator of renal vasoconstriction via the stimulation of endothelin A (ETA) receptors and thus may influence renal sodium and water handling. In experimental cardiac failure, endothelin has been associated with an antinatriuresis.[214–217] Conversely, experimental evidence suggests that the endothelin B (ETB) receptor may play a role in renal vasodilation and/or natriuresis.[216,217] In this regard, the clinical effects of investigational nonselective endothelin antagonists in heart failure have been disappointing. The use of these agents has been associated with a greater likelihood of worsening heart failure—associated with fluid volume overload—and worse clinical outcomes.[218] Consistent with the aforementioned postulated differences between ETA and ETB receptor functions, the selective antagonism of ETA receptors may produce a more desirable effect on renal function and excretory capacity in heart failure.

In summary, the activation of the three major neurohormonal vasoconstrictor systems—the sympathetic nervous system, the renin–angiotensin–aldosterone system, and the nonosmotic release of AVP—is implicated in the renal sodium and water retention of heart failure. The role of other vasoconstrictor systems (e.g., endothelin) is less well defined. These neuroendocrine systems exert direct (tubular) and indirect (hemodynamic) effects on the kidneys to promote the retention of sodium and water. Furthermore, these observations provide the rationale for the use of neurohormonal antagonists in the treatment of heart failure (see the following paragraphs). In this regard, endogenous counterregulatory vasodilatory and natriuretic hormones may play an important attenuating role in heart failure, and the exogenous administration of these agents may be important in the treatment of heart failure.

Vasodilator Systems

Natriuretic peptides in heart failure. The natriuretic peptides, including but not limited to ANP and BNP, circulate at increased concentrations in patients with heart failure.[219–225] These peptide hormones possess natriuretic and vasorelaxant properties as well as renin, aldosterone, and possibly AVP and sympathetic-inhibiting properties.[226–231] Both of these peptide hormones appear to be released primarily from the heart in response to increased atrial or ventricular end-diastolic pressure or to increased transmural cardiac pressure.[232,233] In a study of ANP kinetics in patients with cardiac dysfunction, we demonstrated that increased ANP production rather than decreased metabolic clearance was the major factor contributing to the elevated plasma ANP concentrations in these patients.[234] This finding is consistent

with the observed increase in the expression of both ANP and BNP mRNA in the cardiac ventricles of humans and animals with heart failure.[235,236] However, given the peripheral vasoconstriction and sodium retention associated with heart failure, these elevated circulating natriuretic peptide levels must be inadequate to fully block vasoconstrictor hormone activation. In this regard, volume expansion experiments performed in dogs with heart failure demonstrated a deficiency to further increase the elevated ANP levels.[237] This relative deficiency of ANP secretion may contribute to the body's limited ability to maintain hemodynamic and renal function during the advanced stages of heart failure. In a coronary ligation model of heart failure in the rat, the infusion of a monoclonal antibody shown to specifically block endogenous ANP in vivo caused a significant rise in right atrial pressure, left ventricular end-diastolic pressure, and peripheral vascular resistance.[238] Alternatively, a study by Colucci et al.[239] found that a 6-hour infusion of the recombinant human BNP, nesiritide, significantly decreased pulmonary-capillary wedge pressure and improved symptoms in patients hospitalized with symptomatic heart failure. In a pivotal trial leading to U.S. Food and Drug Administration (FDA) approval of nesiritide, infused BNP was shown to improve both hemodynamics and symptoms of decompensated heart failure.[240]

Renal effects of the natriuretic peptides in heart failure. In normal humans, ANP and BNP increase GFR and urinary sodium excretion with no change or only a slight fall in renal blood flow.[232,241] The changes in renal hemodynamics are likely mediated by afferent arteriolar vasodilation with constriction of the efferent arterioles, as indicated by micropuncture studies in rats.[242,243] In addition to increasing GFR and filtered sodium load as a mechanism of their natriuretic effect, ANP and BNP are specific inhibitors of sodium reabsorption in the collecting tubule.[244–246] An important role for endogenous ANP in the renal sodium balance of heart failure was demonstrated by the aforementioned study of Lee et al.[28] However, the administration of synthetic ANP to patients with low-output heart failure results in a much smaller increase in renal sodium excretion and less significant changes in renal hemodynamics as compared to normal subjects.[232] Like ANP, the natriuretic effect of BNP is blunted in rats with high-output heart failure produced by AV fistulae.[247] Nevertheless, in hypertensive patients with mild-to-moderate heart failure and normal renal sodium excretory capacity, the natriuretic effect of BNP appears comparable to that in control subjects.[248] Because ANP and BNP appear to share the same receptor sites,[249] it is possible that the natriuretic effect of BNP is also blunted in sodium-retaining patients with more advanced heart failure. Support for this hypothesis may be found in reports from our group[250] and from Wang et al.[251] In our study, in 16 patients with advanced decompensated New York Heart Association (NYHA) class III heart failure due to either ischemic or idiopathic dilated cardiomyopathy (left ventricular ejection fraction 18 ± 2%, cardiac index 1.84 ± 0.15 L/minute/m^2, pulmonary capillary wedge pressure 27 ± 3 mm Hg), the administration of BNP at either 0.025 or 0.050 μg/kg/min for 4 hours produced a natriuresis in only 4 patients. The effect of BNP on GFR and renal blood flow was inconsistent in these patients and did not predict the natriuretic response. It is noteworthy that the doses of BNP infused in this study were 2.5 to 5 times greater than that currently approved as an initiating dose for the treatment of heart failure. In any event, although the renal effects of BNP were blunted in some of these heart failure patients, BNP did produce a significant (50%) decrease in pulmonary capillary wedge pressure. At the higher dose, BNP also significantly lowered peripheral vascular resistance and improved cardiac performance. Wang et al.'s study[251] demonstrated essentially the same lack of beneficial renal effects of infused BNP in a similarly small group of patients with heart failure.

Concern has been raised regarding the renal effects of BNP in heart failure. A meta-analysis of five trials suggested a higher rate of worsening renal dysfunction (defined as an increase in serum creatinine of at least 0.5 mg per deciliter) in nesiritide-treated subjects compared to controls.[252] However, this analysis had several limitations including the pooling of studies using different starting doses of nesiritide. Because it is likely that the renal hemodynamic effects of BNP in heart failure relate to the relative degree of renal versus peripheral vasodilation (i.e., the distribution of regional blood flow) induced by the drug, higher doses associated with more profound reductions in peripheral vascular resistance and systemic blood pressures may be expected to produce worsening renal function, whereas lower doses may actually preserve (or perhaps improve) renal hemodynamics. Support for this hypothesis and for the renal safety of nesiritide, when used as recommended, may be found in the results of the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) trial.[253] In ASCEND-HF, 7,141 patients who were hospitalized with acute heart failure were randomized to receive either nesiritide or placebo for 24 to 168 hours in addition to standard care. Using the approved dose of nesiritide, there were no significant differences in rates of death from any cause at 30 days or rates of worsening renal function, defined by more than a 25% decrease in the estimated glomerular filtration rate, between the two groups.

In contrast to the previously mentioned findings of ANP and BNP resistance in heart failure, Elsner et al.[254] recently suggested that renal responsiveness to urodilatin ($ANP_{95–126}$), a slightly extended form of $ANP_{99–126}$, is preserved in heart failure. Urodilatin appears to be produced in the kidney by different posttranslational processing of the ANP prohormone $ANP_{1–126}$.[255] Endogenous urodilatin appears to be confined to the kidney[256]; that is, it is not a circulating hormone like ANP and BNP. In normal humans, exogenously administered urodilatin produces hemodynamic and renal effects similar to those of ANP.[228,257] In the report from Elsner et al.,[219] 12 patients with class II or III heart failure received

urodilatin, 15 ng/kg/min, or placebo (n = 6 in each group) for 10 hours. Although the urodilatin-treated patients did demonstrate a modest natriuresis during urodilatin infusion, it should be noted that (1) digoxin and furosemide were continued during the study, (2) the patients were maintained on an 8 g of sodium per day intake, and (3) the patients received a 500-mL water load (300 mL orally and 200 mL intravenously) during the hour preceding the study drug infusion. In the former instance, furosemide likely facilitated the delivery of sodium to the distal nephron. In the latter two cases, the high daily sodium intake and oral water load would be expected to diminish the degree of vasoconstrictor neurohormone activation. In fact, plasma vasoconstrictor hormone concentrations were, at most, mildly elevated in these patients. Therefore, these findings do not exclude the existence of renal resistance to urodilatin in patients with heart failure and more advanced degrees of neurohormonal activation. On the other hand, urodilatin is less sensitive to degradation by the neutral endopeptidase (EC 3.4.24.11) and thus, more stable in comparison to ANP.[258] Furthermore, in the kidney, ANP solely binds to cortical receptors, whereas urodilatin can also be found in medullary structures.[259] Thus, the renal effects of urodilatin in human heart failure remain uncertain. Ongoing studies of urodilatin in heart failure promise to clarify these issues.

The mechanism of the relative resistance to the natriuretic effect of ANP (and possibly BNP and urodilatin) in heart failure remains controversial. Possible mechanisms include: (1) the downregulation of renal ANP receptors,[260,261] (2) the secretion of inactive immunoreactive ANP,[262] (3) enhanced renal neutral endopeptidase activity limiting the delivery of ANP to receptor sites,[263] (4) hyperaldosteronism by an increased sodium reabsorption in the distal renal tubule,[264] and (5) diminished delivery of sodium to the distal renal tubule site of ANP action.[244–246] In sodium-retaining patients with heart failure, we found a strong positive correlation between plasma ANP and urinary cyclic guanosine monophosphate (cGMP, the second messenger for the natriuretic effect of ANP, BNP, and urodilatin in vivo).[265,266] This observation supports the active biologic responsiveness of renal ANP receptors in heart failure and thus suggests that diminished distal tubular sodium delivery may be involved in the natriuretic peptide resistance observed in patients with cardiac failure. Further support for this hypothesis is found in our experience with cirrhosis, another edematous disorder associated with renal ANP resistance, in which maneuvers that definitely increase distal tubular sodium delivery reversed the ANP resistance[267] (see the following). In addition, heart failure maneuvers that are expected to increase distal tubular sodium delivery, such as the administration of an AT-II receptor antagonist or furosemide, also improve the renal response to ANP.[170,268] Finally, studies in rats with experimental heart failure demonstrated that renal denervation reverses the ANP resistance.[269] Because proximal tubular sodium reabsorption is enhanced by adrenergic stimulation, this effect of renal denervation to enhance ANP sensitivity in experimental cardiac failure is also compatible with a role in distal sodium delivery. The proposed role of diminished distal tubular sodium delivery in natriuretic peptide resistance and impaired aldosterone escape is shown in Figure 67.5.

Summary

As the heart begins to fail, the renal tubule reabsorbs sodium and water more avidly. The afferent stimuli for this "compensatory" volume retention may involve aspects of both the forward and backward theories of heart failure. An acute fall in cardiac output may inactivate (unload) high-pressure baroreceptors located in the aortic arch, the carotid sinus, and the juxtaglomerular apparatus and thus may activate the afferent adrenergic nervous system. Diminished renal perfusion and increased renal sympathetic tone enhance the release of renin and thus activate the renin–angiotensin–aldosterone system. In acute high-output heart failure, in which the cardiac output is insufficient to meet circulatory demands, the fall in peripheral vascular resistance provides the stimulus for arterial underfilling and deactivates high-pressure receptors. Although acute loading of the low-pressure receptors of the thorax may inhibit AVP release and stimulate the release of

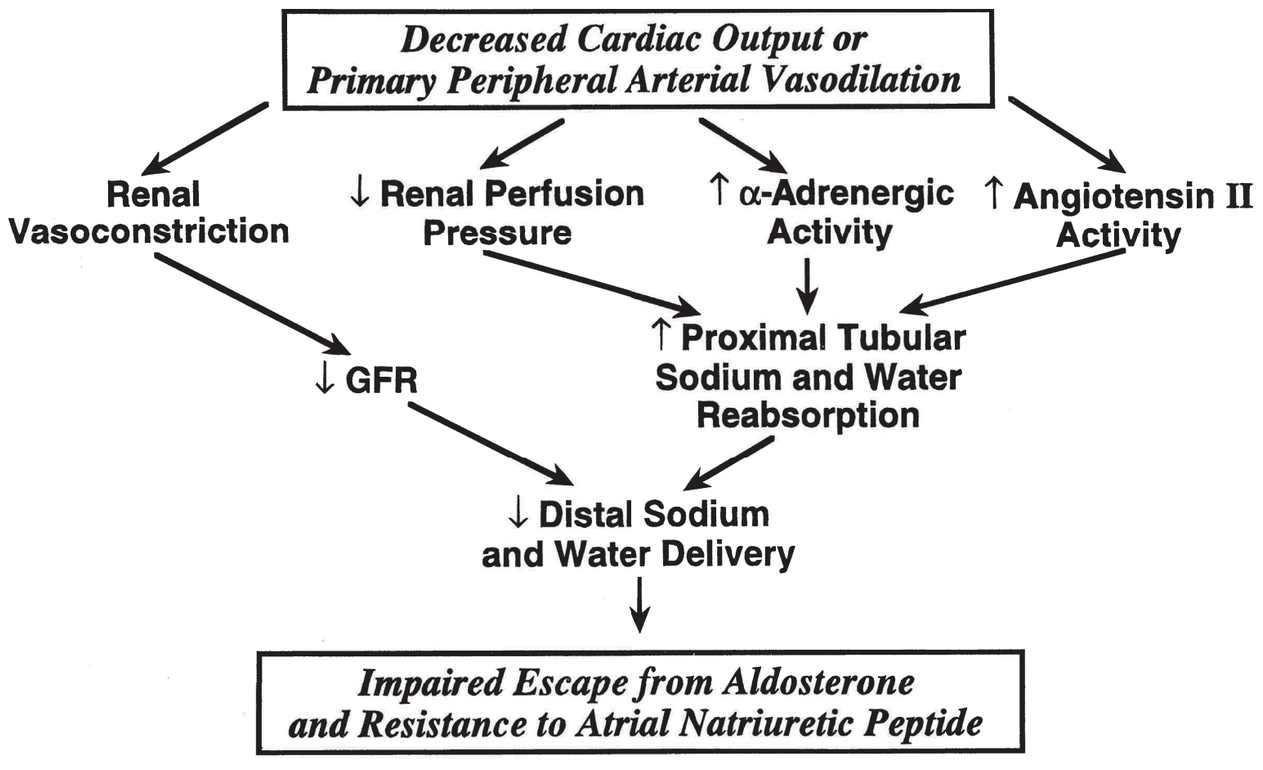

FIGURE 67.5 The proposed mechanism of natriuretic peptide resistance and impaired aldosterone escape in states of arterial underfilling. *GFR*, glomerular filtration rate. (From Schrier RW, Better OS. Pathogenesis of ascites formation. *Eur J Gastroenterol.* 1991;3:721, with permission.)

natriuretic peptides, this counterregulatory response to sodium and water retention may become ineffective because of progressive insensitivity of the cardiopulmonary receptors in the setting of chronic heart failure. Further cardiac compromise, resulting from either the progression of the primary cardiac pathology or increased cardiac demand, results in further renal sodium and water retention, expansion of the ECF volume, and overt edema formation. The development of increased cardiac filling pressures with subsequent pulmonary or peripheral edema substantially contributes to the high morbidity and mortality of heart failure.

The efferent mechanisms for renal sodium and water retention in heart failure are multifactorial. Inactivation of receptors in the high-pressure circulation and blunting of receptors in the low-pressure system initiate reflexes in which renal sympathetic tone is augmented and renal vasoconstriction results. Renal blood flow decreases to a greater extent than GFR, and therefore the filtration fraction rises. This increase alters the ultrafiltration of plasma and peritubular physical forces, which may in turn increase proximal tubular sodium reabsorption. Changes in cardiac output, ventricular filling pressures, and renal perfusion pressure also activate the renin–angiotensin–aldosterone system and the nonosmotic stimulation of AVP, and increase the secretion and/or production of PGs and the natriuretic peptides. At some point in the natural history of cardiac failure, the vasoconstrictive forces overcome the vasodilating effects of PGs, natriuretic peptides, and other vasodilating substances, and peripheral vasoconstriction and renal sodium and water retention occur. Increases in ventricular preload and afterload ensue, resulting in a further deterioration in cardiac performance and a further stimulation of neurohormonal vasoconstrictor systems.

Once initiated by arterial underfilling, sodium and water retention in heart failure leads to another vicious cycle of increasing central venous pressure, venous congestion, and worsening heart failure signs and symptoms often leading to acute decompensation, hospitalization, and worsening renal function. This cardiorenal syndrome of heart failure is associated with poor outcome (as discussed in the following section) and may be perpetuated not only by arterial underfilling but also by renal venous congestion. Support for this notion comes from a prospective cohort study of 145 patients, where an elevated central venous pressure was the most important hemodynamic factor associated with worsening renal function in patients with acute decompensated heart failure.[270] Moreover, in a retrospective analysis of 2,557 patients who underwent cardiac catheterization for hemodynamic assessment, elevated central venous pressure was the single most important prognostic factor for worsening renal function and mortality.[271] These observations are mechanistically plausible, because the transmission of venous pressure to renal veins impairs renal blood flow and glomerular filtration. Of note, diuresis in patients with right ventricular dysfunction, despite decreased cardiac output, leads to a decrease in venous congestion and a resultant improvement in renal function during the treatment of decompensated heart failure.[272] However, cardiac output remains a significant predictor of change in GFR during hospitalization in those patients without significant right ventricular dysfunction.[272] These findings speak to the importance of venous congestion and confirm the primacy of cardiac output in determining cardiorenal interactions in heart failure.

THE CLINICAL SIGNIFICANCE OF CARDIORENAL SYNDROME

As mentioned in the introduction to this chapter, the kidney represents an important marker of heart failure clinical status and a sensitive predictor of clinical outcomes in both chronic and acutely decompensated heart failure. In the PRIME II trial, an estimated GFR less than 60 mL per minute was associated with a significantly worse mortality in 1,708 chronic heart failure patients who were followed for more than 2 years.[3] Reduced GFR was a more potent predictor of mortality than many other common predictors of outcome such as the left ventricular ejection fraction, NYHA functional class ranking, hypotension, tachycardia, and the presence of comorbidity. Similarly, in 2,086 chronic heart failure patients followed in the Italian Network Project (IN-CHF), a serum creatinine level greater than 2.5 mg per deciliter was associated with a relative risk for 1-year mortality of 4.33 (95% confidence interval, 1.79 to 10.44).[4] In multivariable regression analysis, other independent clinical predictors of poor outcome included advanced NYHA class, advanced age, the presence of a third heart sound, and no ACE-inhibitor therapy. However, none of these predictors was as strong as an elevated serum creatinine. Even modest elevations of serum creatinine have been associated with an increased risk for morbidity and mortality in cardiac failure patients. A retrospective analysis of 6,797 heart failure patients enrolled in the SOLVD trial demonstrates this association.[5] The SOLVD trial excluded patients with baseline serum creatinine levels greater than 2.0 mg per deciliter. Dries et al.[5] stratified patients on the basis of serum creatinine levels into two groups, those with serum creatinine levels less than 1.5 mg per deciliter and those with serum creatinine levels between 1.5 mg per deciliter and 2.0 mg per deciliter. Those in the elevated serum creatinine group demonstrated increased risk for all-cause mortality (relative risk, 1.41; 95% confidence interval, 1.25 to 1.59), mortality due to pump failure (relative risk, 1.5; 95% confidence interval, 1.25 to 1.8), and sudden cardiac death (relative risk, 1.28; 95% confidence interval, 0.99 to 1.63). Therefore, impairment in glomerular filtration as measured by serum markers represents a potent predictor of mortality in patients with chronic heart failure.

Similarly, renal dysfunction predicts in-hospital mortality in patients with acutely decompensated heart failure. Definitive observations come from the Acute Decompensated Heart Failure National Registry (ADHERE), which has enrolled more than 150,000 patients from approximately 275 community, tertiary, and academic hospitals in the

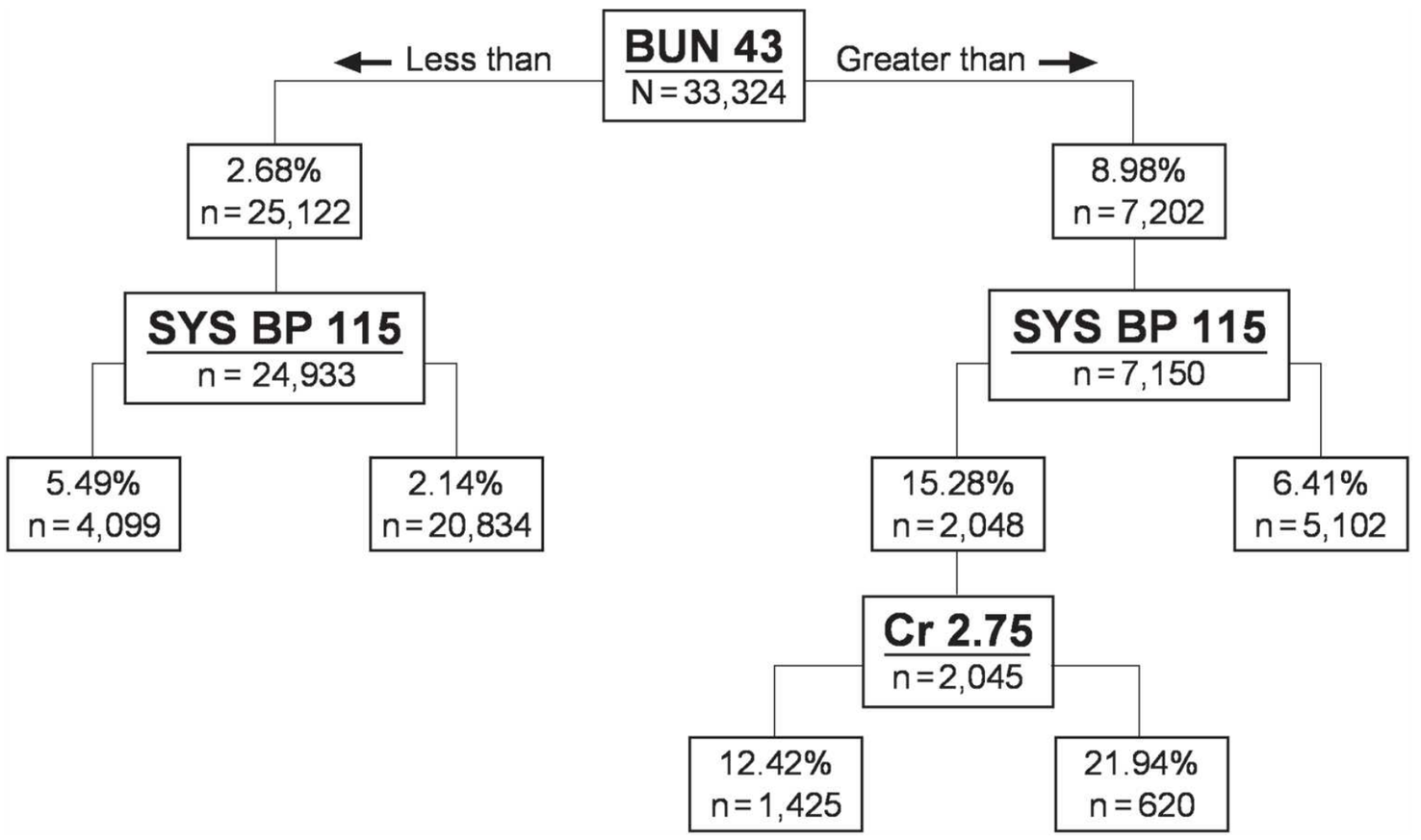

FIGURE 67.6 The ADHERE risk assessment tree from CART analysis. Numbers and percentages come from the derivation dataset and have been confirmed in a separated validation dataset (not shown). Note that two of the three predictors are measures of renal function. *BUN*, blood urea nitrogen; *SYS BP*, systolic blood pressure; *Cr*, creatinine. (From Fonarow GC, et al., for the ADHERE Scientific Advisory Committee, Study Group, and Investigators. Risk stratification for in-hospital mortality in acutely decompensated heart failure: classification and regression tree [CART] analysis. *JAMA*. 2005;293:572, with permission.)

United States.[1,6] Using classification and regression tree (CART) analysis to define covariate adjusted odds ratios of death, a practical user-friendly bedside tool for risk stratification of patients hospitalized with acute decompensated heart failure was developed.[6] Specifically, CART analysis of the ADHERE database was performed using the first 65,235 discharges enrolled. The first 33,046 hospitalizations (from October 2001 through February 2003) served as the derivation cohort and were analyzed to develop the risk-prediction model. Then, the validity of the model was prospectively tested using data from 32,229 subsequent hospitalizations (validation cohort) enrolled in ADHERE from March 2003 through July 2003. In-hospital mortality was similar in the derivation (4.2%) and validation (4.0%) cohorts. Recursive partitioning of the derivation cohort for 39 variables indicated that the best single predictor for mortality was high admission levels of BUN ($\geq$ 43 mg per deciliter), followed by low admission systolic blood pressure ($<$ 115 mm Hg), and then by high levels of serum creatinine ($\geq$ 2.75 mg per deciliter). A simple risk tree identified patient groups with mortality ranging from 2.1% to 21.9% (Fig. 67.6). The odds ratio for mortality between patients identified as high and low risk was 12.9 (95% confidence interval, 10.4 to 15.9) and similar results were seen when this risk stratification was applied prospectively to the validation cohort. These results suggest that acute decompensated heart failure patients at low, intermediate, and high risk for in-hospital mortality can be easily identified using vital sign and laboratory data obtained on hospital admission. In the context of the present chapter, it is noteworthy that two of the three most potent predictors of in-hospital mortality in ADHERE are measures of renal function. The importance of serum creatinine as a predictor of in-hospital mortality for acute decompensated heart failure was also demonstrated by the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF).[273]

THE PHYSIOLOGIC BASIS FOR THE TREATMENT OF SODIUM AND WATER RETENTION IN HEART FAILURE

In heart failure, as in all of clinical medicine, effective therapy should be dictated by an understanding of the pathophysiologic process involved. Depressed ventricular function is associated with a vicious cycle of maladaptive responses, including increased neurohormonal activation, systemic vasoconstriction and renal sodium and water retention, and increased ventricular preload and afterload (Fig. 67.7). Treatment of heart failure should be directed at modifying the afferent and efferent factors responsible for the salt and water retention. Therefore, the primary goal in the treatment of cardiac failure is to improve the function of the heart as a pump. This increases the integrity of the arterial circulation and decreases the venous hypertension, thereby interrupting two of the major afferent mechanisms leading to sodium and water retention. Unfortunately, this goal of improving the contractile state of the heart is often difficult to accomplish. In certain cases of heart failure, however, left ventricular function may be improved by surgical intervention. For example, some patients with coronary artery disease and ischemic cardiomyopathy may exhibit improved cardiac function and less severe heart failure after surgical or percutaneous transluminal revascularization of the ischemic myocardium. However, a randomized controlled comparison of medical versus surgical therapies for ischemic heart failure failed to demonstrate the superiority of surgical revascularization on outcomes in a large cohort of patients.[274] Moreover, the assessment of myocardial viability did not identify patients with a differential survival benefit from bypass surgery, as compared with medical therapy alone, in this study.[275] A more classic example of surgically correctable heart failure is that seen in the setting of severe aortic stenosis. Patients with critical aortic stenosis often exhibit a severe degree of low-output heart failure with very avid

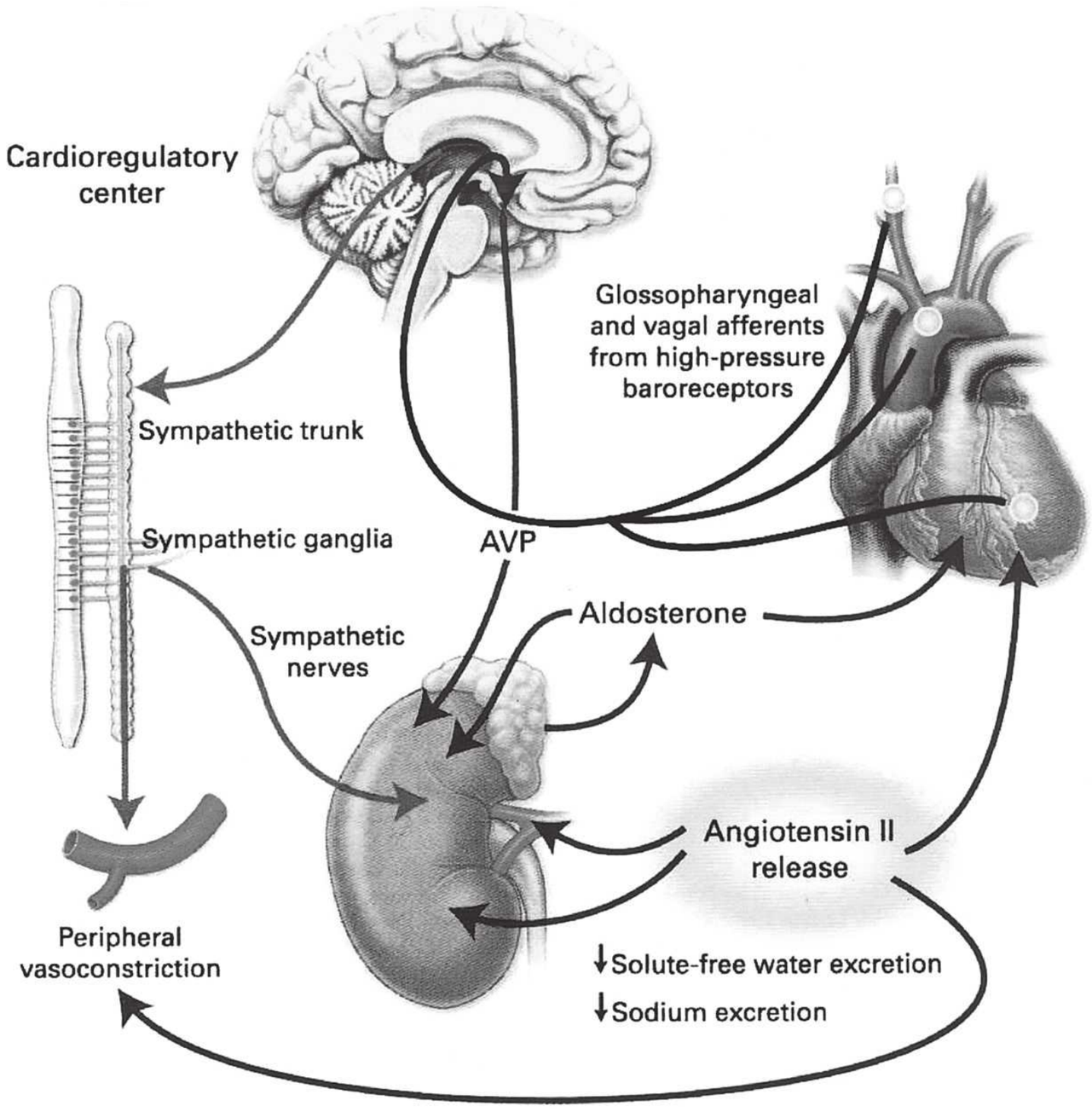

FIGURE 67.7 The pathophysiology of heart failure. Unloading of high-pressure baroreceptors (*circles*) in the left ventricle, carotid sinus, and aortic arch generates afferent signals (*black*) that stimulate cardioregulatory centers in the brain, resulting in the activation of efferent pathways in the sympathetic nervous system. The sympathetic nervous system appears to be the primary integrator of the neurohumoral vasoconstrictor response to arterial underfilling. Activation of renal sympathetic nerves stimulates the release of renin and angiotensin II, thereby activating the renin–angiotensin–aldosterone system. Concomitantly, the sympathetic stimulation of the supraoptic and paraventricular nuclei in the hypothalamus results in the nonosmotic release of arginine vasopressin (AVP). Sympathetic activation also causes peripheral and renal vasoconstriction, as does angiotensin II. Angiotensin II constricts blood vessels, stimulates the release of aldosterone from the adrenal gland, and also increases tubular sodium reabsorption and causes remodeling of cardiac myocytes. Aldosterone may have direct cardiac effects, in addition to increasing the reabsorption of sodium and the secretion of potassium and hydrogen ions in the collecting duct. The lines designate circulating hormones. (From Schrier RW, Abraham WT. Hormones and hemodynamics in heart failure. *N Engl J Med.* 1999;341:577, copyright © 2000, Massachusetts Medical Society. All rights reserved.)

renal sodium and water retention that is usually completely reversible following a replacement of the stenotic aortic valve. An emerging alternative to surgical replacement of a critically stenosed aortic valve is transcatheter aortic-valve implantation (TAVI). In patients with severe aortic stenosis who are not candidates for surgery, TAVI has been shown to significantly improve outcomes as well as cardiac symptoms, as compared with standard therapy.[276]

In other instances of heart failure, cardiac function may be augmented by the cardiac glycosides, such as digoxin, which modestly improve cardiac contractility and may favorably influence baroreceptor function.[277] However, digoxin does not improve survival in heart failure patients[278] and is thus used much less frequently than before in the treatment of chronic heart failure. Vasodilators, such as nitrates and hydralazine, and ACE inhibitors may improve cardiac function by decreasing cardiac preload and afterload.[279] The addition of a fixed dose of isosorbide dinitrate plus hydralazine to standard therapy for heart failure including neurohormonal blockers has been shown to improve survival among black patients with advanced heart failure.[280] The efficacy of ACE inhibitors in heart failure is discussed in the following paragraphs. Investigational nonglycoside inotropic agents may acutely improve cardiac output, but longer term use has been shown, thus far, to increase mortality.[281–283]. β-Adrenergic receptor antagonists, once thought to be contraindicated in patients with low-output heart failure, can exhibit a favorable effect on cardiac function and outcome in patients with chronic heart failure. In fact, these agents improve the left ventricular ejection fraction to a greater extent than do any other forms of heart failure drug therapy.[137] Carvedilol, a nonselective third-generation β-blocker/vasodilator with α_1-adrenergic receptor–blocking properties, produces a dose-related improvement in ejection fraction

and a reduction in mortality in patients with class II to IV heart failure.[139] In the U.S. Carvedilol Heart Failure Trials Program, this agent reduced all-cause mortality by 65% compared to placebo in patients with mild-to-moderate heart failure.[140] Likewise, the Second Cardiac Insufficiency Bisoprolol Study demonstrated a 34% reduction in all-cause mortality versus placebo during the treatment of heart failure with this β_1 selective agent.[141] In a randomized study of metoprolol CR/XL treatment of 3,991 patients with class II to IV heart failure, treatment with metoprolol CR/XL was associated with a 34% decrease in all-cause mortality, a 38% decrease in cardiovascular mortality, a 41% decrease in sudden death, and a 49% decrease in death owing to progressive heart failure as compared to controls.[142] β-Blockers have also been shown to improve outcome in post-MI left ventricular dysfunction with or without heart failure and in severe heart failure.[133,143] However, these effects are not seen with all β-blockers.[284]

Another strategy for improving pump function and outcome in selected heart failure patients (i.e., those with ventricular dyssynchrony) is the use of cardiac resynchronization therapy. This device-based treatment for heart failure works to optimize ventricular filling and to improve the contraction pattern via atrial-synchronized biventricular pacing. Resynchronization therapy has been shown to improve hemodynamics, quality of life, functional status, and exercise capacity while reducing the risks of heart failure hospitalization and all-cause mortality.[285–291] Cardiac resynchronization has been associated with the preservation of renal function[292] and, anecdotally, a reduction in the diuretic dose in patients with chronic heart failure.

Because an improvement in pump function is a primary goal in the treatment of heart failure, agents that might further impair cardiac contractility should be avoided in this setting. Unfortunately, many medications that have been demonstrated to produce a negative effect on cardiac inotropy are commonly prescribed in cardiac disease patients. For example, most antiarrhythmic drugs and the commonly prescribed first-generation calcium channel antagonists exhibit some degree of negative inotropy in vivo.[293] Newer vascular-selective calcium channel blockers may be better tolerated in patients with heart failure but should not be used as a heart failure therapy per se.

The neuroendocrine activation in patients with heart failure provides another target for therapy. In fact, recent experience with various neurohormonal antagonists suggests that the inhibition or antagonism of neurohormonal vasoconstrictor systems may be more beneficial than nonspecific diuretic or vasodilator therapy. This is certainly the case with adrenergic blockade, as noted in the preceding text. AT-II is known to mediate myocardial hypertrophy, increase fibrosis and collagen deposition, and cause the activation of the sympathetic nervous system. Therefore, the administration of ACE inhibitors would be anticipated to decrease myocardial remodeling and hypertrophy and to decrease the activation of the sympathetic nervous system. ACE inhibition also decreases the degradation of bradykinin, which is a well-known vasodilator that can reduce cardiac afterload. The proven beneficial effects of ACE inhibition on symptoms, hemodynamics, exercise capacity, and survival in heart failure patients support this hypothesis.[147,156,282] Moreover, in the patients of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS), all with class IV heart failure, significant reductions in mortality were consistently found in the patients treated with enalapril who had baseline hormone levels greater than median values.[156] In the group of patients treated with the ACE inhibitor, there were significant reductions from baseline to 6 weeks in levels of AT-II, aldosterone, norepinephrine, and ANP, but not epinephrine. These results suggest that the effect of enalapril on mortality was related to diminished hormonal activation in general and to the renin–angiotensin system in particular.[294] In the SOLVD studies[157] of less severe heart failure, the addition of enalapril to conventional therapy also significantly reduced mortality and hospitalization rates. Studies support the use of ACE inhibition in post-MI left ventricular dysfunction with or without clinical heart failure, as well.[158] Recent data support the noninferiority of ARBs in the treatment of post-MI ventricular dysfunction or chronic heart failure.[159–161] Such studies have led to the perceived interchangeability of ACE inhibitors and ARBs. Hospital-based quality measures from the Centers for Medicare and Medicaid Services endorse the equivalency of ACE inhibitors and ARBs in the treatment of heart failure, as do the 2005 Update to the American College of Cardiology/American Heart Association Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult.[295]

Diuretics are indicated to restore the ECF volume toward normal as heart failure becomes more advanced and when edema formation occurs. Diuretic therapy is discussed extensively elsewhere. Of note, although most patients with cardiac failure respond to a potent loop diuretic (e.g., furosemide), and this agent can increase solute-free water clearance in patients with cardiac edema,[125] cardiac output may actually decline during acute treatment due to the further activation of vasoconstrictor hormone systems.[296] Volume depletion owing to overzealous diuretic treatment must also be considered in any acute or chronic heart failure patient with worsening signs or symptoms of a low-output state. For example, diminished renal perfusion may occur in the setting of excessive diuretic treatment, resulting in elevations in BUN and serum creatinine concentrations. On the other hand, the belief that heart failure patients require elevated ventricular filling pressures to maintain an adequate cardiac output has been proved erroneous, because recent experience with heart failure management guided by implantable hemodynamic monitors demonstrates that most patients with chronic heart failure can be treated with diuretics to normalize or nearly normalize intracardiac and pulmonary artery pressures to reduce the risk of hospitalization for worsening heart failure.[297,298] One particular challenge in diuretic therapy, however, is the common circumstance of

worsening renal function despite the persistence of ECF volume overload. That is, BUN and serum creatinine may rise in the face of continued fluid volume overload during diuresis. This may relate to a further reduction in cardiac output. However, in many instances, the worsening renal function appears to be due to the diuretic therapy per se. In this regard, loop diuretics have been shown to reduce GFR on average in heart failure patients.[299]

This situation of worsening renal function despite ECF volume excess during diuresis may also be associated with diuretic resistance. Diuretic resistance is not an uncommon finding in patients with advanced heart failure. Because the intraluminal delivery of loop diuretics via tubular secretion is necessary for these agents to inhibit sodium chloride reabsorption in the thick ascending limb of Henle, renal vasoconstriction may play an important role in diuretic resistance associated with heart failure (Fig. 67.8). Moreover, increased distal tubule sodium reabsorption further contributes to diuretic resistance in this condition. Therefore, the addition of a more distal acting diuretic, such as metolazone or hydrochlorothiazide, may reverse resistance to loop diuretics. In some cases, however, diuretic resistance is impossible to overcome. Such patients are often unable to be safely discharged from the hospital or are repetitively readmitted to the hospital, if discharged.

Fluid removal by intermittent or continuous ultrafiltration has been suggested to have several advantages over diuretic therapy.[300–305] In addition to the reduction of excess ECF volume in heart failure patients, it has been suggested that the ultrafiltration of cytokines, which suppress myocardial contractility, may improve cardiac function. This remains to be proven, however. As compared to diuretics, fluid/electrolyte and acid–base disturbances may be more easily corrected and avoided with ultrafiltration. Furthermore, for the same amount of fluid removal, more sodium is removed with ultrafiltration than with diuretics because the sodium concentration in the ultrafiltrate is equivalent to plasma, whereas with diuretic therapy the urinary sodium concentration is virtually always less than plasma. Recently, a simple approach to ultrafiltration using peripherally inserted catheters has been introduced for the treatment of heart failure.[304] The efficient removal of fluid has been demonstrated using this technique. Small case series support the use of ultrafiltration in hospitalized patients and intermittently in outpatients with refractory heart failure. A randomized controlled trial of ultrafiltration versus diuretics in hospitalized decompensated heart failure patients supports the benefits of this approach.[305] In the Ultrafiltration Versus IV Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure (UNLOAD) trial, patients with acute decompensated heart failure randomized to early ultrafiltration compared with those assigned to standard intravenous diuretic therapy demonstrated significantly more weight and net fluid loss at 48 hours and significantly decreased rehospitalization rates at 90 days, without significant renal function differences.

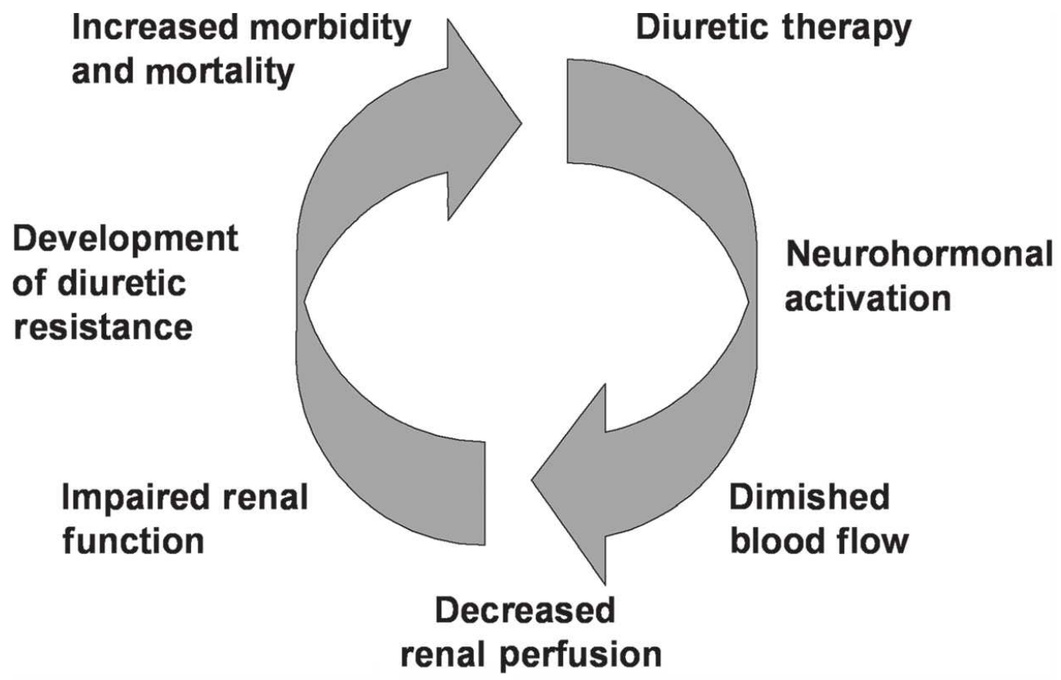

FIGURE 67.8 The "iatrogenic" cardiorenal syndrome of heart failure. A scheme by which diuretic therapy may worsen the neurohormonal and renal hemodynamic milieu of heart failure, leading to diuretic resistance and poor outcomes in heart failure patients.

Water restriction remains the mainstay of therapy in patients with heart failure who are hyponatremic. Studies also suggested that in hyponatremic patients with heart failure receiving furosemide and captopril, plasma sodium values tended to normalize, whereas they did not in patients receiving other vasodilators.[306,307] These data support the concomitant use of ACE inhibitors and loop diuretics in hyponatremic heart failure patients. Alternatively, selective V_2-receptor AVP antagonists have been shown to correct the hyponatremia of heart failure.

Finally, other measures, including sodium restriction and oxygen administration, contribute to the overall management of patients with heart failure. Special emphasis should be placed on the salutary influence of bed rest, which increases osmolar and solute-free water clearances, cardiac output, renal plasma flow, and GFR and decreases plasma catecholamines and PRA.[308] Such considerations lay the foundation for the physiologic basis of therapy in heart failure.

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