

## Review Articles

*Mechanisms of Disease*FRANKLIN H. EPSTEIN, M.D., *Editor***HORMONES AND HEMODYNAMICS  
IN HEART FAILURE**ROBERT W. SCHRIER, M.D.,  
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**H**EART failure is a major cause of cardiovascular mortality and morbidity, resulting in more than 1 million hospitalizations per year, and is the most common hospital-discharge diagnosis among patients older than 65 years.<sup>1</sup> In recent years, much has been learned about the pathophysiology of heart failure, particularly in the area of fluid and electrolyte metabolism, and this will be the focus of the present review.

**REGULATION OF BODY-FLUID VOLUME**

There is considerable evidence in support of a unifying hypothesis of the regulation of body-fluid volume that is applicable to patients with edematous disorders such as cardiac failure, to patients with cirrhosis, and to normal pregnant women.<sup>2-4</sup> This hypothesis states that the integrity of the arterial circulation, as determined by cardiac output and peripheral arterial resistance, is the primary determinant of renal sodium and water excretion in health and disease. Specifically, either a primary decrease in cardiac output or arterial vasodilatation causes arterial underfilling, which results in the activation of neurohumoral reflexes that stimulate sodium and water retention. This integrated mechanism explains why plasma volume and blood volume increase in patients with heart failure, whether associated with low or high cardiac output, while their kidneys, which

are otherwise normal, continue to retain sodium and water. The retention of sodium and water may result in pulmonary congestion or peripheral edema and thus cause substantial morbidity and mortality in patients with heart failure. In fact, this state of excess total body-fluid volume in the presence of ventricular dysfunction defines the clinical syndrome of congestive heart failure.

The renal excretion of sodium and water normally parallels sodium and water intake, so that an increase in plasma and blood volume is associated with increased renal sodium and water excretion. In patients with heart failure, sodium and water are paradoxically retained, despite an increase in intravascular fluid volume. Renal sodium and water retention in these patients may be regulated not by the total blood volume, but by the degree of filling of another compartment, the so-called effective blood volume. Certainly, intrinsic renal mechanisms are not the primary cause of the sodium and water retention that results in pulmonary and peripheral edema in patients with heart failure, because renal sodium and water retention no longer occurs after successful heart transplantation.

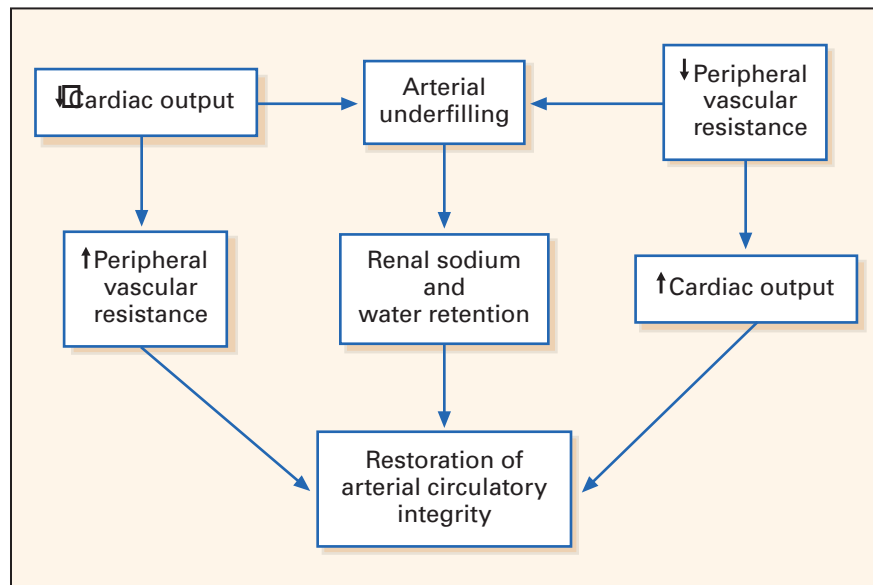
**ARTERIAL UNDERFILLING**

The integrity of the arterial circulation, as determined by cardiac output and peripheral vascular resistance or compliance, is the predominant determinant of renal sodium and water excretion (Fig. 1).<sup>2-4</sup> Several mechanoreceptors on the high-pressure side of the circulation can sense arterial underfilling and have been implicated in the regulation of body-fluid volume.<sup>5-7</sup> These receptors are found in the left ventricle, carotid sinus, aortic arch, and renal afferent arterioles. Decreased activation of these receptors due to a decrease in systemic arterial pressure, stroke volume, renal perfusion, or peripheral vascular resistance leads to an increase in sympathetic outflow from the central nervous system, activation of the renin-angiotensin-aldosterone system, and the nonosmotic release of arginine vasopressin, as well as the stimulation of thirst (Fig. 2).

In most patients with heart failure, cardiac output is lower than normal. Beriberi, thyrotoxicosis, and other disease syndromes, however, can cause a form of heart failure in which cardiac output is higher than normal. In most of these latter disorders, arterial underfilling resulting from arterial vasodilatation leads to sodium and water retention, just as vasodilatation caused by cirrhosis, a large arteriovenous fistula, pregnancy, or a potent vasodilator such as minoxidil can lead to sodium and water retention.<sup>2-4</sup>

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**Figure 1.** Causes and Consequences of Arterial Underfilling in Patients with Heart Failure, Including the Mechanisms Activated to Counterbalance the Underfilling.

### THE SYMPATHETIC NERVOUS SYSTEM

The baroreceptor-mediated increase in sympathetic tone that occurs with ventricular dysfunction has several consequences, including increased myocardial contractility, tachycardia, arterial vasoconstriction and thus increased cardiac afterload, and venoconstriction with increased cardiac preload.  $\beta$ -Adrenergic receptors in the heart either are down-regulated ( $\beta_1$ -adrenergic receptors) or have abnormalities in signal-transduction activity that effectively uncouple them from effector mechanisms ( $\beta_1$ - and  $\beta_2$ -adrenergic receptors).<sup>8</sup>

Increased local and circulating concentrations of norepinephrine may contribute to myocyte hypertrophy, either directly through stimulation of  $\alpha_1$ - and  $\beta$ -adrenergic receptors or secondarily by activating the renin-angiotensin-aldosterone system.<sup>8</sup> Norepinephrine is directly toxic to myocardial cells, an effect mediated through calcium overload, the induction of apoptosis, or both.<sup>9</sup> Norepinephrine-induced death of myocytes can be prevented by concomitant nonselective  $\beta$ -adrenergic blockade or combined  $\beta$ - and  $\alpha$ -adrenergic blockade.<sup>9</sup> Patients with plasma norepinephrine concentrations greater than 800 pg per milliliter (4.7 nmol per liter) have a one-year survival of less than 40 percent,<sup>10</sup> unless there has been a reversible insult.

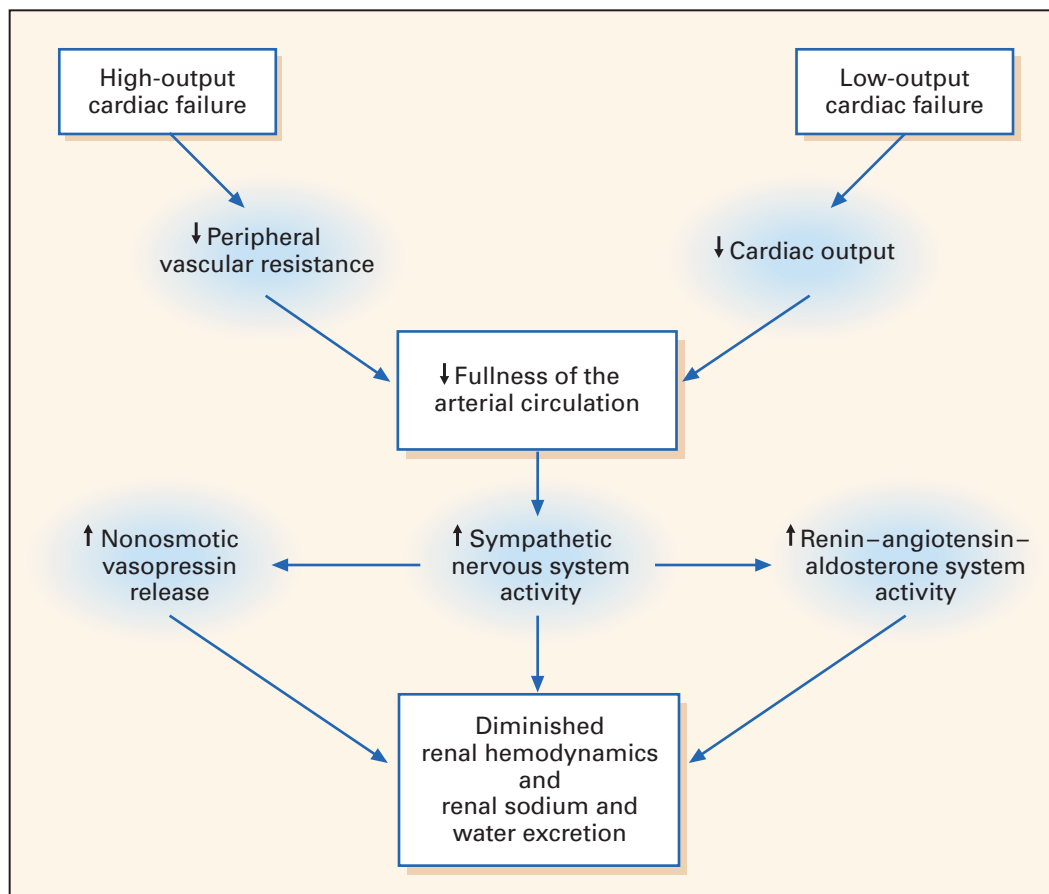
Through renal vasoconstriction, stimulation of the renin-angiotensin-aldosterone system, and direct effects on the proximal convoluted tubule, increased renal adrenergic activity contributes to the avid renal sodium and water retention that occurs in patients

with heart failure. Renal denervation has been shown to decrease sodium retention in experimental cardiac failure.<sup>11</sup>

In the past,  $\beta$ -adrenergic blockade was thought to be contraindicated in patients with heart failure. However, if patients can tolerate short-term  $\beta$ -adrenergic blockade, ventricular function subsequently improves. In randomized, placebo-controlled clinical trials, the nonselective  $\beta$ -adrenergic antagonist carvedilol and the selective  $\beta_1$ -adrenergic antagonists bisoprolol and metoprolol decreased morbidity and mortality in patients with heart failure.<sup>12-14</sup> In 1997 the Food and Drug Administration approved carvedilol as the first  $\beta$ -adrenergic-antagonist drug indicated for the treatment of patients with New York Heart Association class II or III heart failure. Although the benefits of carvedilol in heart failure may be due primarily to its  $\beta$ -adrenergic effects, it also has  $\alpha_1$ -adrenergic-blocking effects (antiproliferative and vasodilating effects). The antioxidant properties of carvedilol may also contribute to its efficacy in heart failure, either by direct chemical redox effects or by indirect effects as a consequence of decreased oxygen consumption or oxidative stress.

### THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

The activity of the renin-angiotensin-aldosterone system is also increased in most patients with heart failure. As with plasma norepinephrine, the degree of increase in plasma renin activity provides a



**Figure 2.** Mechanisms by Which High-Output or Low-Output Heart Failure Leads to the Activation of Neurohormonal Vasoconstrictor Systems and Renal Sodium and Water Retention.

Adapted from Schrier.<sup>2</sup>

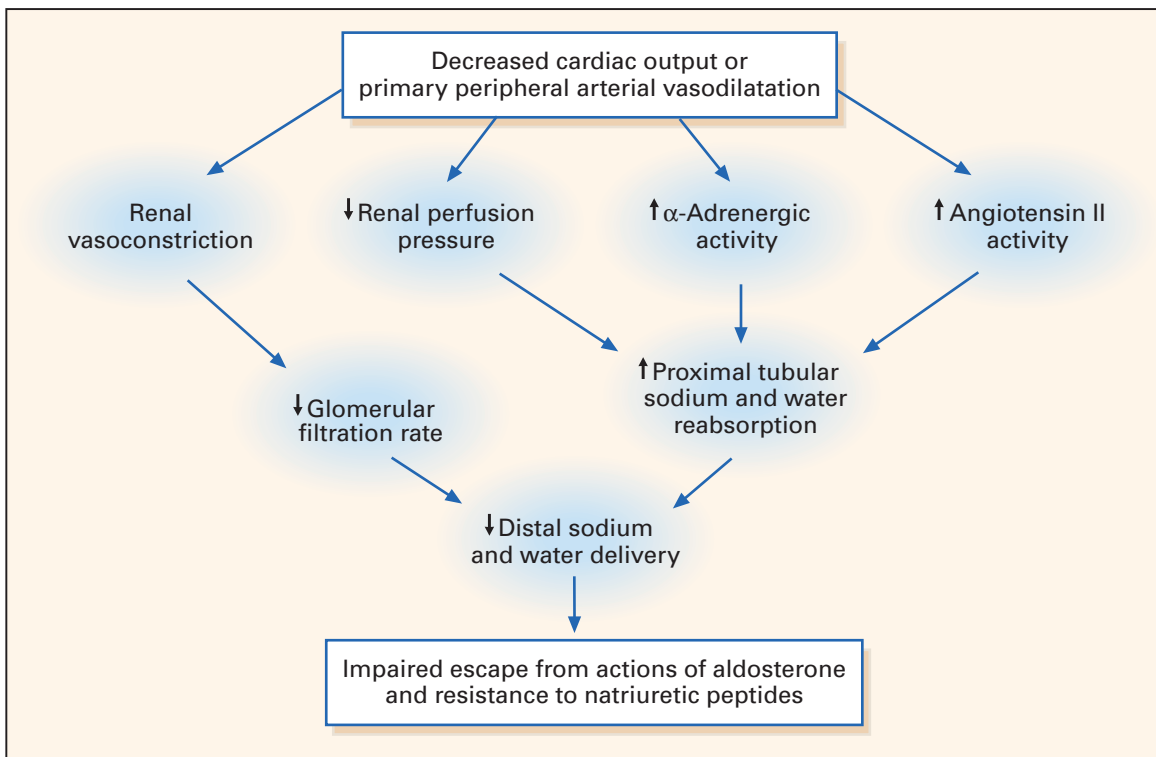
prognostic index in these patients.<sup>15,16</sup> Patients with mild heart failure may have little or no increase in either plasma renin activity or the plasma aldosterone concentrations. However, normal plasma renin and aldosterone values would be inappropriate in these patients because of their increased extracellular-fluid and total blood volumes. Among patients with severe heart failure, the values for plasma renin and aldosterone are high.

Not only is the activity of the renin-angiotensin-aldosterone system increased in heart failure, but also the action of aldosterone is more persistent than in normal subjects. In normal subjects, high doses of mineralocorticoid initially increase renal sodium retention so that the volume of extracellular fluid is increased by 1.5 to 2 liters. However, renal sodium retention then ceases, sodium balance is reestablished, and there is no detectable edema. This escape from mineralocorticoid-mediated sodium retention explains why edema is not a characteristic feature of primary hyperaldosteronism. The escape is depend-

ent, at least in part, on an increase in delivery of sodium to the site of action of aldosterone in the collecting ducts.<sup>17</sup>

Escape from the sodium-retaining action of aldosterone does not occur in patients with heart failure, and therefore they continue to retain sodium in response to aldosterone. Accordingly, they have substantial natriuresis when given spironolactone, which blocks mineralocorticoid receptors.<sup>18</sup> Since  $\alpha$ -adrenergic stimulation and angiotensin II increase sodium transport in the proximal tubule,<sup>19,20</sup> sodium delivery to the distal portion of the nephron, and thus the collecting duct, would be expected to decrease in patients with heart failure in whom the renin-angiotensin-aldosterone system is activated. Decreased sodium delivery to the collecting duct is therefore the most likely explanation for the persistent aldosterone-mediated sodium retention and the absence of the escape phenomenon in these patients (Fig. 3).

Renewed interest in therapy with aldosterone antagonists for patients with heart failure has been stim-



**Figure 3.** Mechanisms by Which Arterial Underfilling Leads to Diminished Distal Tubular Sodium and Water Delivery, Impaired Aldosterone Escape, and Resistance to Natriuretic Peptide Hormone.

Reprinted from Schrier and Better<sup>17</sup> with the permission of the publisher.

ulated by the results of the two-year Randomized Aldactone Evaluation Study of 1663 patients, which demonstrated a 30 percent reduction in the risk of death among those given a low dose of spironolactone (25 to 50 mg per day) as compared with those given placebo.<sup>21</sup>

In addition to increasing aldosterone secretion and proximal tubular sodium transport, angiotensin II has other renal effects in patients with heart failure. It causes vasoconstriction of both the afferent and efferent renal arterioles. In glomeruli it stimulates mesangial contraction, thereby diminishing the glomerular filtration surface.<sup>22</sup> The constrictor action of angiotensin II on afferent arterioles is caused by calcium influx into the arteriolar cells and can be inhibited by calcium-channel-blocking drugs.<sup>23</sup> On the other hand, the constrictor action on efferent arterioles is caused by mobilization of calcium from stores within the arteriolar cells and is not inhibited by calcium-channel blockers.<sup>23</sup> In patients with severe heart failure, angiotensin II helps to maintain glomerular capillary pressure, and thus the glomerular filtration rate, by constricting the efferent arterioles.

The administration of angiotensin-converting-enzyme inhibitors has been associated with an acute

deterioration of renal function in some patients with severe heart failure. This effect is attributed to blocking of the constrictor action of angiotensin II on efferent arterioles, which decreases glomerular capillary pressure and the glomerular filtration rate.<sup>24</sup> A recent clinical trial (Evaluation of Losartan in the Elderly) compared the angiotensin-converting-enzyme inhibitor captopril with losartan, an angiotensin II subtype 1 (AT<sub>1</sub>)-receptor antagonist, in 722 elderly patients with heart failure. There was no difference between the groups in serum creatinine concentration, and hyperkalemia was not a problem. In both groups, only 10.9 percent of patients had an increase in the serum creatinine concentration that was greater than 0.3 mg per deciliter (26.5 μmol per liter).<sup>25</sup>

An angiotensin-converting-enzyme inhibitor is now considered first-line therapy in patients with heart failure. These drugs have improved survival in patients with chronic heart failure of all degrees of severity and in patients with left ventricular systolic dysfunction, with or without heart failure, after myocardial infarction.<sup>26,27</sup> Moreover, angiotensin-converting-enzyme inhibition reverses left ventricular hypertrophy, a common harbinger of heart failure.<sup>28</sup>

There is mounting evidence that the beneficial ef-

fects of angiotensin-converting-enzyme inhibition in patients with heart failure are due to direct actions on myocardial cells in addition to decreases in cardiac afterload and blood pressure. Angiotensin II may have a mitogenic effect on cardiac myocytes. The resultant cardiac remodeling may lead to a decrease in the size of the capillary network relative to that of the whole myocardium, thus predisposing the patient to ischemic insults.<sup>29</sup> Angiotensin-converting-enzyme inhibition may reverse this remodeling process. The effects of angiotensin-receptor antagonists on cardiac remodeling appear to be similar to those of angiotensin-converting-enzyme inhibition. However, the effects of angiotensin-receptor antagonists on mortality in patients with heart failure remain to be determined. Among the aforementioned 722 elderly patients with chronic heart failure, those taking losartan had lower mortality than those taking captopril over a 48-week follow-up period.<sup>25</sup> However, mortality was a secondary end point; the incidence of the primary end point, a change in the serum creatinine concentration, did not differ between the two groups of patients.

Patients with heart failure have increased thirst even though they often have low serum osmolality, which normally inhibits thirst. Angiotensin II may increase thirst by stimulating the central thirst center.<sup>30</sup> Patients with heart failure who have hyponatremia may be more prone to cardiac arrhythmias and have greater sensitivity to angiotensin-converting-enzyme inhibitors than those with normal serum sodium concentrations.

#### NONOSMOTIC RELEASE OF ARGININE VASOPRESSIN

Water retention in excess of sodium retention may occur in patients with heart failure and lead to hyponatremia. In fact, hyponatremia is a very ominous prognostic indicator in patients with heart failure.<sup>30</sup> Hyponatremia may be partly due to the increased water intake caused by the increased thirst associated with heart failure.<sup>31</sup> However, increased water intake alone rarely causes hyponatremia, because the normal renal capacity to excrete solute-free water is substantial (about 10 to 15 liters a day). In patients with heart failure and hyponatremia, hypo-osmolality, which inhibits the release of arginine vasopressin in normal subjects, is associated with persistently high plasma concentrations of arginine vasopressin.<sup>32</sup> This observation suggests a pivotal role for arginine vasopressin in hyponatremia. In rats with acute low-output cardiac failure, a peptide antagonist of arginine vasopressin increases water excretion.<sup>33</sup> Unfortunately, these antagonists act as partial agonists in humans.<sup>34</sup> However, in preliminary studies of patients with heart failure, a nonpeptide, orally active antagonist of arginine vasopressin proved effective in reversing impaired urinary diluting capacity, increasing

solute-free water excretion, and correcting hyponatremia.<sup>35</sup>

Activation of carotid baroreceptors has been implicated in the nonosmotic release of arginine vasopressin during arterial underfilling in patients with heart failure.<sup>7</sup> Since atrial pressures increase in heart failure, it might be expected that the Henry-Gauer atrial reflex would lead to the suppression of arginine vasopressin and water diuresis.<sup>36</sup> However, since patients with heart failure have impaired urinary dilution, activation of arterial baroreceptors must override activation of atrial receptors to maintain the nonosmotic release of arginine vasopressin.<sup>3-7</sup>

Arginine vasopressin causes antidiuresis by activating vasopressin  $V_2$  receptors on the basolateral surface of the principal cells in the collecting duct.<sup>37</sup> Activation of these receptors initiates a cascade of intracellular signaling events by means of the adenyl cyclase pathway, leading to translocation of aquaporin-2 water channels from cytoplasmic vesicles to the apical surface of the collecting duct.<sup>38</sup> These water channels then allow a single file of water molecules to traverse the apical membrane in response to the osmotic gradient generated by the countercurrent urinary concentrating mechanism. Arginine vasopressin not only increases the shuttling of aquaporin-2 water channels to the apical surface, but also increases aquaporin-2 synthesis. Aquaporin-2 water channels are increased in the cortex and papilla of rats with heart failure, an effect that is reversed by a nonpeptide  $V_2$ -receptor antagonist.<sup>39</sup> The vasopressin-mediated shuttling of aquaporin-2 water channels to the apical membrane of the collecting duct is associated with an increase in urinary excretion of the aquaporin. In the aforementioned study of the antagonist of arginine vasopressin in humans with heart failure,<sup>35</sup> the drug decreased urinary aquaporin-2 excretion, and this correlated with the increase in solute-free water excretion.

Activation of vasopressin  $V_1$  receptors in vascular smooth muscle by arginine vasopressin may contribute to cardiac dysfunction in patients with severe heart failure. In dogs with heart failure induced by tachycardia, a vasopressin  $V_1$ -receptor antagonist decreased systemic vascular resistance and increased cardiac output.<sup>40</sup> Moreover, the effect of the vasopressin  $V_1$  antagonist on cardiac output was more sustained when a vasopressin  $V_2$ -receptor antagonist was given at the same time. Administration of a vasopressin  $V_2$ -receptor antagonist increased survival in rats with heart failure.<sup>41</sup> It therefore seems possible that in heart failure the combination of a vasopressin  $V_1$ -receptor antagonist and a vasopressin  $V_2$ -receptor antagonist might be more effective than either alone.

#### NATRIURETIC PEPTIDES

Atrial natriuretic peptide is a 28-amino-acid peptide that is normally synthesized in the atria and to

a lesser extent in the ventricles and is released into the circulation during atrial distention.<sup>42</sup> In patients with heart failure, plasma atrial natriuretic peptide concentrations rise as atrial pressures increase. Brain or B-type natriuretic peptide is a 32-amino-acid peptide that is synthesized primarily in the ventricles, and its release into the circulation is also increased in patients with heart failure.<sup>43</sup> Because plasma concentrations of brain natriuretic peptide are increased in patients with early heart failure or left ventricular dysfunction, plasma brain natriuretic peptide may be a sensitive diagnostic marker of heart failure.<sup>44</sup>

Atrial natriuretic peptide exerts its effects on the kidney primarily at the levels of the glomerulus and collecting duct.<sup>45</sup> In the glomerulus, it causes efferent arteriolar constriction and afferent arteriolar dilation, thereby increasing the glomerular filtration rate.<sup>46</sup> In the collecting duct, it decreases sodium reabsorption, thereby increasing sodium excretion. Atrial natriuretic peptide also inhibits the secretion of renin and aldosterone.<sup>47</sup> The effects of brain natriuretic peptide on the kidney and on plasma renin activity and the plasma aldosterone concentration appear to be similar to those of atrial natriuretic peptide.<sup>42</sup>

Patients with heart failure are resistant to the natriuretic effect of exogenously administered natriuretic peptides.<sup>48</sup> The resistance may be due to down-regulation of renal natriuretic peptide receptors, increased degradation of natriuretic peptides by neutral endopeptidase in the proximal tubule, or decreased sodium delivery to the collecting duct as a result of a decrease in the glomerular filtration rate or increased sodium reabsorption in the proximal tubule (Fig. 3). Several observations support the role of decreased distal sodium delivery in the resistance to natriuretic peptides in heart failure. An argument against the existence of resistance at the receptor level is the finding of a linear correlation between plasma concentrations of atrial natriuretic peptide and urinary excretion of cyclic guanosine monophosphate, the secondary messenger of the hormone.<sup>49</sup> In patients with another edematous disorder (i.e., cirrhosis), resistance to atrial natriuretic peptide is reversed by increasing distal sodium delivery with an infusion of mannitol.<sup>50</sup> Finally, the best correlate of the natriuretic response to infused brain natriuretic peptide in patients with heart failure is distal tubular sodium delivery.<sup>51</sup>

In patients with early heart failure, increased secretion of atrial natriuretic peptide and brain natriuretic peptide may attenuate or delay systemic and renal arterial vasoconstriction, venoconstriction with increased cardiac preload, and renal sodium retention. For example, in animals with heart failure, administration of antibodies to atrial natriuretic peptide or antagonists to atrial natriuretic peptide receptors decreases renal blood flow; increases right atrial pressure, plasma renin activity, and sodium retention; and

worsens diastolic dysfunction by impairing myocardial relaxation.<sup>52</sup> Finally, the infusion of synthetic brain natriuretic peptide in patients with heart failure decreases pulmonary-capillary wedge pressure, diminishes systemic vascular resistance, and increases cardiac output.<sup>51</sup>

### ENDOTHELIAL HORMONES

Prostacyclin and prostaglandin E are vasodilating hormones produced from arachidonic acid in many cells. They are primarily autocrine hormones, and depending on the species, one or both are found in the glomerular afferent arterioles. Angiotensin II, norepinephrine, and renal nerve stimulation increase the synthesis of these vasodilating prostaglandins, which then attenuate the vasoconstrictor effects of these three stimuli.<sup>53</sup> These vasodilatory prostaglandins may thus counterbalance the neurohormone-induced renal vasoconstriction that occurs in heart failure. Support for this suggestion is found in the deterioration in kidney function, even to the point of acute renal failure, that can occur in patients with severe heart failure who are given a nonsteroidal antiinflammatory drug that blocks cyclooxygenase, a key enzyme in prostaglandin synthesis.<sup>54</sup>

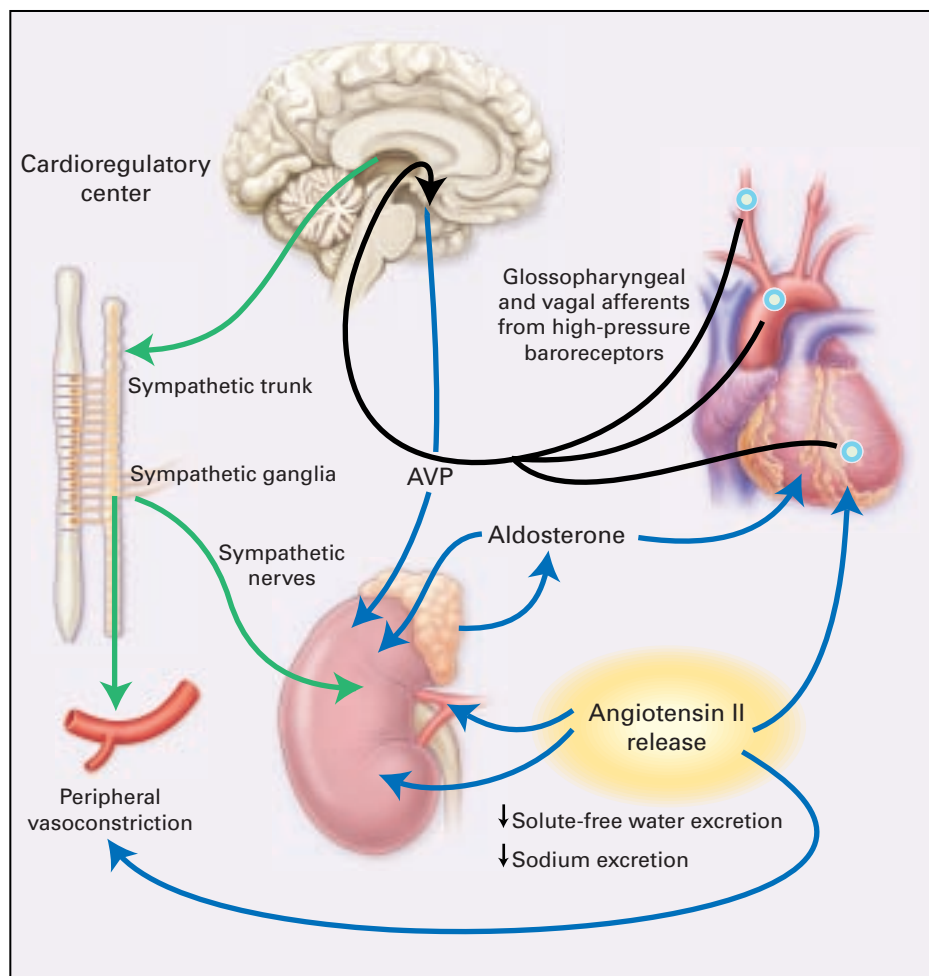
Nitric oxide is an even more potent vasodilator than prostacyclin and prostaglandin E. Endothelial cells contain a constitutive nitric oxide synthase,<sup>55</sup> the activity of which may be blunted in heart failure.<sup>56</sup> Thus, the constrictor action of the endogenous vasoconstrictors whose concentrations are elevated in heart failure, including angiotensin II, norepinephrine, and arginine vasopressin, may be increased by decreased nitric oxide synthesis in endothelial cells.

Endothelin is one of the most potent vasoconstrictors, and plasma endothelin concentrations are increased in some patients with heart failure.<sup>57</sup> High plasma endothelin concentrations are associated with a poor prognosis in patients with New York Heart Association class III or IV heart failure.<sup>57</sup> However, endothelin is more likely to contribute to the systemic and renal vasoconstriction associated with heart failure by local (autocrine) actions than by systemic (endocrine) actions. The endothelin receptor antagonist BQ-123 increased survival in rats with heart failure.<sup>58</sup>

The plasma concentrations of some cytokines, such as tumor necrosis factor, are increased in patients with heart failure.<sup>59</sup> Tumor necrosis factor depresses myocardial function, and the administration of antibodies to tumor necrosis factor improves cardiac function in patients with sepsis.<sup>60</sup> Tumor necrosis factor also increases nitric oxide synthase activity in vascular smooth muscle.

### CONCLUSIONS

Arterial underfilling due to diminished cardiac output in low-output heart failure or diminished periph-



**Figure 4.** The Pathophysiology of Heart Failure.

Unloading of high-pressure baroreceptors (blue 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 (green). 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, thus activating the renin–angiotensin–aldosterone system. Concomitantly, 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 and stimulates the release of aldosterone from the adrenal gland, and it also increases tubular sodium reabsorption and causes remodeling of cardiac myocytes. Aldosterone may also 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 blue lines designate circulating hormones.

eral vascular resistance in high-output heart failure initiates baroreceptor-mediated neurohumoral events, particularly the activation of the sympathetic nervous system, the activation of the renin–angiotensin–aldosterone system, and the nonosmotic release of vasopressin, all of which maintain arterial perfusion to vital organs. Over the long term, these neurohumoral reflexes may have deleterious effects that include pulmonary edema, hyponatremia, increased cardiac afterload and preload, and cardiac remodel-

ing. This complex sequence of events is depicted in Figure 4. The understanding of the long-term consequences of arterial underfilling in heart failure has led to beneficial therapies in addition to diuretics — namely, angiotensin-converting-enzyme inhibitors and  $\beta$ -adrenergic-receptor blockers.

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