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NEPHROLOGY FORUM

# Renal and circulatory mechanisms in congestive heart failure

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## Case presentation

A 65-year-old white man with long-standing ischemic cardiomyopathy and congestive heart failure was hospitalized because of 2 weeks of increasing dyspnea at rest, weight gain, and the onset of rapid atrial fibrillation.

Fifteen years earlier, the patient had an acute myocardial infarction complicated by congestive heart failure; digoxin and thiazide diuretics were prescribed. Over the ensuing years, he had progressive angina and required diagnostic cardiac catheterization, which revealed three-vessel disease. The patient had undergone coronary artery bypass surgery 3 years earlier. The postoperative course was complicated by a "post-cardiotomy syndrome." A postoperative echocardiogram showed persistent left ventricular enlargement with marked dysfunction. Over the next year, the patient noted 6-pillow orthopnea, nocturia, and exertional dyspnea of 4 to 5 steps. Blood pressure was 170/100 mm Hg and serum creatinine was 1.8 mg/dl. Methyldopa, 500 mg four times daily, and later hydralazine, 25 mg orally twice daily, were added to the patient's regimen. Ibuprofen was given intermittently for chest wall pain. Eventually hydrochlorothiazide administration was discontinued and furosemide was prescribed in a dose of 40 mg/day.

Two years before the current admission, the patient was admitted to the hospital for worsening congestive heart failure. Furosemide was increased to 80 mg daily, and captopril, 50 mg three times a day, was added. Methyldopa and hydralazine were discontinued. Over the next 22 months, the patient was admitted to the hospital five times for management of increasing congestive heart failure. Serum creatinine increased gradually to 4.3 mg/dl while he was receiving captopril and returned to 2 mg/dl when captopril was stopped. Medications 2 months prior to the current admission included diltiazem, furosemide, long-acting nitrates, prazosin, and metolazone.

Examination at the time of admission revealed a dyspneic white male with a protuberant abdomen who was lying in bed at an angle of 40°. The respiratory rate was 25/min. Blood pressure was 125/75 mm Hg supine and 112/75 mm Hg sitting. Pertinent physical findings included jugular venous pressure of 11 cm with hepatojugular reflux. Cardiac examination revealed a dyskinetic and diffuse apical impulse displaced laterally to the anterior axillary line; S1 and S2 were audible, and a II/VI holosystolic murmur was heard at the apex radiating to the axilla. Bilateral inspiratory rales were evident at both lung bases. He had a distended abdomen with shifting dullness and a fluid wave. The liver span was 10 cm by percussion; the edge was not palpable. No splenomegaly was present. Bowel sounds were normal. Pulses were 2+ throughout without bruits. There was bilateral 1+ pedal edema. The neurologic examination was essentially normal.

Admission laboratory data included: serum sodium, 129 mEq/liter; potassium, 3.9 mEq/liter; chloride, 88 mEq/liter; and bicarbonate, 27 mEq/liter. The BUN was 60 mg/dl and the serum creatinine 3.2 mg/dl. Calcium was 6.3 mg/dl; phosphate, 4.3 mg/dl; and glucose, 88 mg/dl. The alkaline phosphatase was 134 units; LDH, 263 units; and SGOT, 41 units. Total bilirubin was 0.5 mg/dl; albumin, 2.4 g/dl; and uric acid, 11 mg/dl. Urinalysis showed 1+ protein as well as 0 to 1 white blood cells, 0 to 1 red blood cells, and a few hyaline casts/high-power field. Arterial blood gases at room air revealed a $PO_2$ of 36 mm Hg; pH, 7.5; and 97% $O_2$ saturation. An electrocardiogram disclosed atrial fibrillation with a ventricular response of approximately 150/min, axis of -20°, and Q waves in V 1-4 with poor R-wave progression consistent with an anteroseptal myocardial infarction of indeterminate age; lateral ST- and T-wave abnormalities were consistent with strain, ischemia, or the effect of digitalis. Chest x-ray showed cardiomegaly, pulmonary vascular redistribution, and a blunted left costophrenic angle.

Intravenous furosemide (up to 200 mg per dose) produced only a mild diuresis. Quinidine was given for atrial fibrillation, and the patient eventually underwent electrical cardioversion. Normal sinus rhythm was achieved, but he continued to complain of anorexia, fatigue, and shortness of breath. Concomitantly, the BUN and serum creatinine rose to 80 and 4.5 mg/dl, respectively. Urine output remained at approximately 1400 cc/day. Urinalysis continued to reveal trace protein, hyaline casts, and 0 to 1 white blood cells per/high-power field. A Swan-Ganz catheter was inserted. Initial pulmonary capillary wedge pressure was 20 mm Hg, cardiac index was 1.6 liters/min/1.73 $m^2$, and the calculated systemic vascular resistance was approximately 2000 dynes $sec^{-1}$ $cm^{-5}$. Dobutamine administration increased the cardiac index to 2.2 liters/min/1.73 $m^2$ and decreased the systemic vascular resistance to 1600 dynes $sec^{-1}$ $cm^{-5}$. Dobutamine was stopped, and low-dose dopamine and increasing doses of sodium nitroprusside were given. However, the patient developed transient marked oliguria (<10 cc/hr) while the blood pressure hovered at 90/60 mm Hg. Dopamine and nitroprusside administration were halted. Captopril was tried, but oliguria persisted despite a transient increase in the cardiac index.

A renal arteriogram was performed to evaluate the possibility of bilateral renal artery stenosis and correctable lesions. Renal angiogram revealed right renal artery occlusion and left renal artery ostial stenosis; angioplasty with a 6 mm balloon dilated the left stenosis successfully. Immediately after dilation, dobutamine and nitroprusside were given, and the patient responded to intravenous furosemide with a remarkable

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diuresis. Dobutamine and nitroprusside were discontinued gradually, and oral captopril was prescribed. In addition to a 4 kg diuresis with symptomatic improvement, the patient's BUN and serum creatinine fell to 37.0 and 2.0 mg/dl respectively. At discharge the blood pressure was 105–125/60–75 mm Hg. Discharge medications were captopril, 37.5 mg three times daily; digoxin, .125 mg each day; and furosemide, 120 mg daily. The patient currently is clinically stable.

## Discussion

DR. VICTOR J. DZAU (*Chief, Division of Vascular Medicine and Atherosclerosis, Brigham and Women's Hospital, and Harvard Medical School, Boston, Massachusetts*): This case provides a good illustration of the central role of the kidney in the pathogenesis and clinical management of congestive heart failure. The patient had bilateral renal artery stenosis and ischemic cardiomyopathy. Renal hypoperfusion as a result of anatomic as well as functional abnormalities rendered this patient particularly refractory to conventional therapy with diuretics and digitalis. The use of captopril was complicated by the development of acute renal insufficiency. We and others previously have reported that captopril can produce acute renal insufficiency in patients with bilateral renal arterial stenosis and in those with unilateral arterial stenosis in a solitary functioning kidney [1, 2]. This process can explain the rise in serum creatinine in response to captopril in this patient. The mechanism of captopril-induced renal insufficiency in patients with bilateral renal arterial stenosis is complex. In this setting, angiotensin II constricts the renal efferent arterioles, thus maintaining glomerular filtration rate and filtration fraction. Converting enzyme inhibitors can cause efferent arteriolar dilation and simultaneous reduced renal perfusion pressure [1–3]. These renal hemodynamic alterations can lead to reduced glomerular filtration rate and an increased serum creatinine level. The diagnosis of renal vascular hypertension should have been entertained in this patient prior to this admission. He developed hypertension after age 60, which was first noted 4 years prior to admission, and which was associated with a serum creatinine of 1.8 mg/dl. The refractoriness of the hypertension to control by methyldopa and hydralazine as well as the increase in serum creatinine over the ensuing years are further clues. Interestingly, over the year prior to admission, the patient became normotensive coincident with a progressive deterioration of cardiac function. Finally, the worsening in renal function following captopril therapy provided the most important clue to this diagnosis. The dramatic diuresis seen after angioplasty in this patient demonstrates the critical importance of renal perfusion to the therapeutic renal response in congestive heart failure [4].

The cardiorenal interaction in congestive heart failure is complex. In addition to the contribution of primary renal dysfunction to worsening cardiac failure in a patient with already compromised cardiac function, secondary functional changes in the kidney also occur as a direct result of cardiac failure. These functional changes contribute to the pathophysiology of congestive heart failure. This subject has been previously reviewed by several investigators. My goal in today's presentation is to provide an update on the current understanding of the neurohormonal and renal mechanisms in cardiac failure, and to review the therapeutic modalities, especially converting enzyme inhibition, relating to the renal function and natural history of patients with advanced cardiac failure.

Myocardial failure activates a series of compensatory mechanisms for maintaining cardiovascular homeostasis. These compensatory mechanisms increase vascular tone and promote sodium retention [5, 6]. Increased systemic vascular resistance maintains systemic blood pressure in the presence of a declining cardiac output. Similarly, increased sodium and water retention increases plasma volume and ventricular filling pressure, and theoretically should augment stroke volume. Excessive and intense systemic vasoconstriction, however, imposes an increased "afterload" on the failing heart and impedes left ventricular ejection. Markedly expanded plasma volume can result in transudation of fluid from the capillaries and can lead to edema. Thus the renal and circulatory responses to the diminished cardiac output play central roles in the pathophysiology of congestive heart failure.

### *Renal hemodynamics in cardiac failure*

The renal adaptive responses to cardiac dysfunction can occur extremely early in cardiac failure. Hostetter and coworkers studied renal function in rats after experimental myocardial infarction induced by coronary artery ligation [7]. Rats with small to moderate-sized myocardial infarctions, despite maintenance of normal arterial pressure and "peak" pumping ability of the left ventricle, exhibited a distinct impairment in their ability to excrete sodium in response to an acute sodium load. Both absolute and fractional sodium excretion were impaired. This impairment in sodium handling occurred despite only mild reductions in effective renal plasma flow (ERPF) and glomerular filtration rate (GFR), and in the absence of overt cardiac failure. In rats with large infarctions, ERPF and GFR were both reduced, and urinary sodium excretion in response to acute sodium chloride loading was significantly attenuated. The intrarenal hemodynamic changes in response to experimental myocardial infarction and ventricular dysfunction were examined further by Ichikawa and coworkers. They observed that glomerular plasma flow rate ($Q_A$) was markedly impaired, while the reduction in single-nephron glomerular filtration rate (SNGFR) was proportionally less, and that these changes resulted in an increase in single-nephron filtration fraction (SNFF) [8]. Measurement of preglomerular, glomerular, and postglomerular pressures and flows revealed that the reduction in $Q_A$ and the increase in SNFF were due to intense constriction of the efferent arterioles. The increased resistance in the efferent arterioles promoted the maintenance of glomerular capillary hydraulic pressure and thus prevented a more marked fall in GFR. These alterations in glomerular hemodynamics might contribute to the increase in sodium retention in cardiac failure via a decrease in peritubular hydraulic pressure and an increase in peritubular oncotic pressure, thereby resulting in increased proximal tubular fluid reabsorption [6]. In addition, neurohormonal mechanisms may also affect tubular sodium reabsorption in cardiac failure. DiBona and colleagues reported that increased renal sympathetic nerve activity directly stimulates proximal tubular sodium reabsorption [9, 10]. Angiotensin II, aldosterone, and vasopressin all affect renal tubular sodium handling [6]. I would now like to turn to an in-depth analysis of these important neurohormonal mechanisms that influence renal and electrolyte status in cardiac failure.

**Table 1.** Neurohormonal systems in cardiac failure

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|---|
| 1. Vasoconstricting-sodium retentive systems |
| Renin-angiotensin-aldosterone system |
| Sympathetic nervous system |
| Vasopressin |
| 2. Vasodilating natriuretic systems |
| Prostaglandins ($PGE_2$, $PGI_2$) |
| Dopamine |
| Atrial natriuretic factor |

### *Neurohormonal mechanisms in cardiac failure*

The neurohormonal mechanisms activated in cardiac failure include the sympathetic nervous system, the renin-angiotensin system, vasopressin, prostaglandins, and atrial natriuretic factor [5, 11–14]. Each of these systems or hormones influences systemic and renal vascular resistances and the renal handling of sodium and water (Table 1). These neurohormonal systems can be divided into two general classes: those that induce vasoconstriction and promote sodium retention, and those that stimulate vasodilation and induce natriuresis. The latter class of hormones offsets or balances ("counter-regulates") the former class. The sympathetic nervous and renin-angiotensin systems and vasopressin belong to the first class, whereas prostaglandins, atrial natriuretic factor, and dopamine belong to the second class of hormones.

*Vasoconstrictive-sodium retentive hormones in cardiac failure.* My colleagues and I have studied the roles of the sympathetic nervous system and the renin-angiotensin system in the pathogenesis of experimental cardiac failure [15]. Acute experimental cardiac decompensation is associated with activation of the renin-angiotensin system and the sympathetic nervous system, as well as stimulation of vasopressin release. These systems maintain systemic blood pressure and promote renal sodium and water retention during acute decompensation. In the chronic "compensated" phase of experimental cardiac failure, which is associated with expansion of extracellular fluid volume and restoration of blood pressure, the plasma levels of the hormones generally return to normal [16]. Similar patterns have been reported in human cardiac failure [17]. Patients with acute, poorly compensated, severe cardiac failure have markedly elevated plasma renin activity, plasma norepinephrine, vasopressin levels, and urinary catecholamines [18]. In contrast, patients with chronic, stable cardiac failure have normal plasma levels of these same hormones. Confirmation of the importance of the clinical state in determining plasma neurohormonal levels arises from sequential measurements in patients followed from acute cardiac decompensation to the chronic stable stage. Both plasma renin activity and angiotensin II levels were elevated during the former but returned to normal during the latter stage [17]. Thus severe cardiac failure, either progressing relentlessly or suddenly aggravated, is associated with marked activation of the renin-angiotensin and sympathetic nervous systems, which then deactivate and return to normal as cardiac function stabilizes and circulatory compensation occurs.

Many patients with cardiac failure exhibit hyponatremia [19]. Serum sodium concentration has been shown to be a useful predictor of the state of the renin-angiotensin and sympathetic nervous systems in cardiac failure. Indeed, an inverse correlation has been reported between serum sodium concentration and plasma renin activity [19–21]. When patients with congestive heart failure were divided according to their serum sodium concentration, hyponatremic patients (serum sodium concentration <135 mM) had significantly higher levels of plasma renin activity, angiotensin II, and aldosterone than did normonatremic patients [22]. Concentrations of other vasoactive hormones, including norepinephrine, epinephrine, cortisol, dopamine, and vasopressin, also were increased (Fig. 1). In contrast, normonatremic CHF patients had normal or nearly normal plasma levels of these hormones. The current evidence thus suggests that individuals with cardiac failure and hyponatremia form a specific subgroup of patients characterized by clinical decompensation and elevated levels of "stress" hormones. These patients also have higher serum creatinine and blood urea nitrogen concentrations because of prerenal azotemia [15, 22, 23]. Finally, they have a reduced ability to respond to circulatory alterations such as orthostasis [24], even though their ventricular function may be similar to that in the clinically compensated patient with a normal serum sodium concentration.

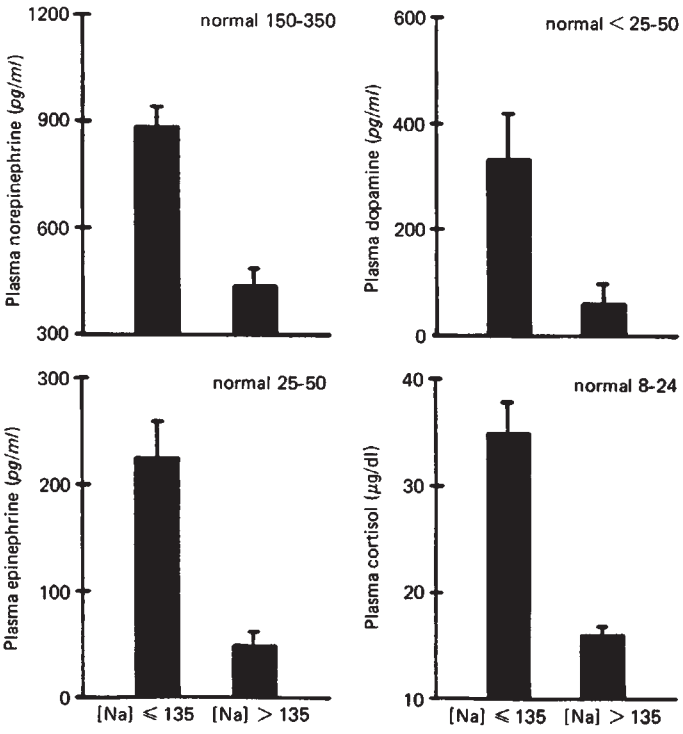


**Fig. 1.** *Plasma norepinephrine, epinephrine, dopamine, and cortisol concentrations in CHF patients with hyponatremia* (serum Na ≤ 135 mEq/liter) *and normonatremia* (serum Na > 135 mEq/liter). All hormones were significantly higher in the hyponatremic patients ($P < .01$).

Several possible explanations exist for the relationship between hyponatremia and elevated vasoconstricting-sodium retentive hormones. During cardiac decompensation these hormones are activated for cardiovascular homeostasis. Angiotensin and vasopressin as well as the sympathetic nervous system

all influence sodium and water clearance [5]. Furthermore, angiotensin can induce vasopressin release, and angiotensin may directly stimulate thirst [25]. Stimulation of thirst combined with the antidiuretic effect of vasopressin and the reduction of free-water clearance resulting from increased proximal tubular reabsorption of sodium can produce hyponatremia. Hyponatremia might further stimulate increased plasma renin activity [26]. Thus, a vicious cycle may be set up under these circumstances. I will return to a discussion of the mechanisms of hyponatremia later.

*Endogenous vasodilating-natriuretic hormones in cardiac failure.* Circulatory homeostasis is maintained by a balance between vasoconstrictor and vasodilator mechanisms [19, 27]. Like the control of vascular tone, renal sodium excretion also is controlled by a balance between opposing forces. Several endogenous local and circulating hormonal substances with natriuretic and vasodilatory properties have been reported. These hormones include dopamine, prostaglandin $E_2$, and atrial natriuretic factor [12, 14]. Evidence suggests that these hormones are counterregulatory forces to the vasoconstricting-sodium retentive forces. Indeed, studies in patients with congestive heart failure demonstrate a direct linear relationship between the magnitude of systemic vasoconstrictive forces (as reflected by plasma renin activity and angiotensin II concentration) and the magnitude of systemic vasodilator forces (as measured by circulating levels of prostaglandin $E_2$ and $I_2$ metabolites) [19] (Fig. 2). The close correlation between circulating levels of prostaglandin metabolites and angiotensin II in patients with cardiac failure might reflect stimulation of prostaglandin synthesis by angiotensin II, increased release of renin induced by prostaglandin, or, most likely, a common stimulus to both systems. Furthermore, a significant and striking inverse correlation is observed between serum sodium concentration and plasma $PGE_2$ metabolite concentration [19]. Indeed, hyponatremic patients have elevated plasma $PGE_2$ metabolite concentrations and increased 6 keto $PGF_{1\alpha}$ and dopamine levels [22]. Recently we observed that plasma atrial natriuretic factor is also elevated in hyponatremic patients with congestive heart failure as compared with normonatremic CHF patients. The close correlation between the vasoconstrictor forces (for example, angiotensin) and the vasodilator forces (such as prostaglandin) suggests that these substances modulate vascular tone. To further examine this possibility, we studied the hemodynamic effects of indomethacin, a prostaglandin synthetase inhibitor, in patients with cardiac failure [19]. When given indomethacin, hyponatremic patients with elevated vasodilating and vasoconstricting hormones had a significantly decreased cardiac index as well as increased pulmonary capillary wedge pressure, mean arterial pressure, and systemic vascular resistance. In contrast, normonatremic patients with normal concentrations of catecholamines, plasma renin activity, and prostaglandin $E_2$ metabolites exhibited no significant hemodynamic changes after administration of indomethacin. Administration of the widely used antiinflammatory agents to patients with severe cardiac failure may greatly alter this delicate balance between opposing vasodilating and vasoconstricting forces [28]. Many vasodilatory drugs currently in use in the treatment of cardiac failure might exert their effect, in part, by increasing endogenous production of prostaglandins $I_2$ and $E_2$. These effects may be attenuated by the administration of drugs that inhibit the production of vasodilatory prostaglandins (by blocking cyclooxygenase) [12]. Finally, nonsteroidal antiinflammatory drugs also might induce intense renal vasoconstriction by blocking renal prostaglandin production [29], and perhaps precipitate acute renal failure [22, 30]. Our data suggest that patients with hyponatremia are most likely to be affected, favorably or adversely, by an alteration in this delicate hormonal balance.

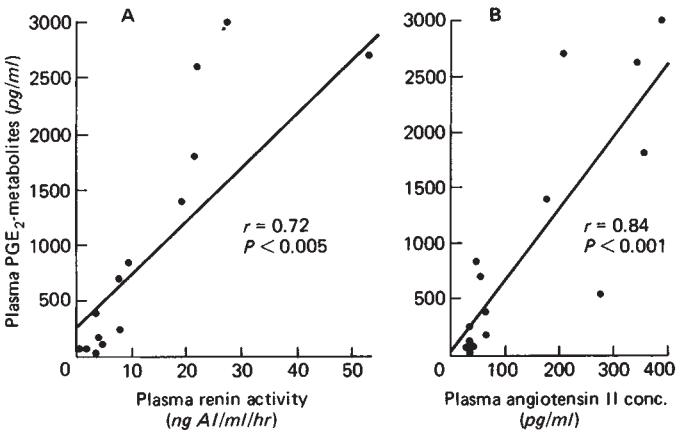


**Fig. 2.** *Relationship of plasma $PGE_2$ metabolite concentration to plasma renin activity and plasma angiotensin concentration in patients with CHF.* (From Ref. 19.)

Two other potential natriuretic factors should be considered in cardiac failure: dopamine and atrial natriuretic factor (ANF). Dopamine induces natriuresis and increases renal plasma flow and glomerular filtration rate. Two kinds of dopamine receptors (DA1 and DA2) have been identified in physiologic preparations [31, 32]. Located postsynaptically, DA1 receptors mediate vasodilation in coronary, renal, cerebral, and mesenteric blood vessels. In contrast, DA2 receptors are situated on autonomic ganglia and postganglionic sympathetic nerves. When DA2 receptors are stimulated, norepinephrine release from sympathetic nerve terminals is inhibited. Theoretically, activation of either DA1 or DA2 receptors in cardiac failure, endogenously or pharmacologically, could induce natriuresis. In the case of the DA1 receptor, natriuresis would be due to direct effects on renal hemodynamics or direct inhibition of tubular sodium reabsorption. With DA2 stimulation, natriuresis might result from inhibition of norepinephrine release, thus depriving the kidney of the antinatriuretic effects of sympathetic stimulation. Goldberg and Raifer have proposed that dopaminergic nerves exist in the kidney, and that dopamine is released locally to influence renal sodium excretion [31]. This hypothesis is supported by reports that urinary excretion of dopamine increases selectively with sodium loading in humans, and is correlated positively with natriuresis [31].

Little is known about the status of endogenous dopamine in cardiac failure. Circulating plasma levels of dopamine reportedly are increased in patients with congestive heart failure [33], and this increase is probably due to increased adrenal secretion of this catecholamine. Myocardial stores in animals and humans are increased relative to tissue stores of norepinephrine [34, 35],

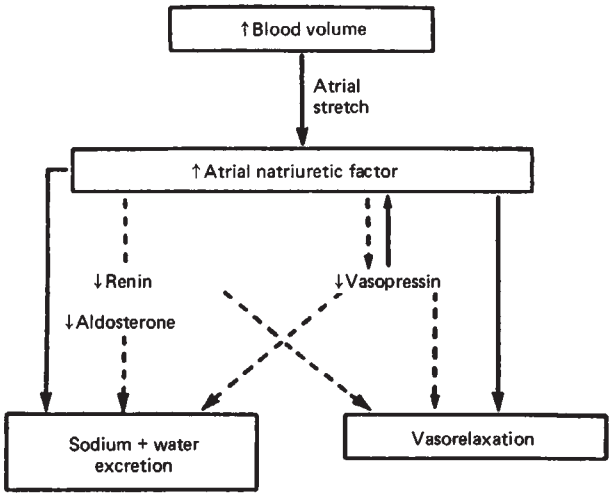


**Fig. 3.** *Contribution of atrial natriuretic factor to blood volume regulation.* Inhibitory signals are indicated by *dashed lines*, stimulatory signals by *solid lines*. Increased blood volume stimulates the release of atrial natriuretic factor and results in sodium and water excretion and vasorelaxation. Atrial natriuretic factor also affects blood pressure and sodium and water homeostasis by inhibiting the secretion of renin, aldosterone, and vasopressin.

probably because the failing heart cannot hydroxylate dopamine to norepinephrine [35]. The status of renal dopamine metabolism in cardiac failure has not been studied. Thus it is not known whether renal dopamine synthesis and its urinary excretion are increased or decreased. The kidney, however, remains responsive to infusions of exogenous dopamine despite cardiac failure. When given to patients with severe CHF, dopamine can increase renal blood flow out of proportion to the increase in cardiac index. This response suggests a selective renal vasodilatory effect [36]. Similar treatment with low doses of dopamine has been reported to initiate a diuresis in patients refractory to furosemide [37]. Moreover, oral dopaminergic therapy with levodopa [38], ibopamine [39], the DA2 agonist bromocryptine [40], and the DA1 agonist fenoldopam [41] has resulted in beneficial systemic hemodynamic effects in patients with cardiac failure. The increase in renal blood flow and natriuresis that results from DA1 receptor activation suggests a selective renal vasodilatory effect [42]. These studies indicate a therapeutic role for pharmacologic stimulation of renal DA1 and DA2 receptors with the neurohormone dopamine or a related agent in cardiac failure. The application of dopaminergic therapy to cardiac failure clearly merits further prospective study if this endogenous vasodilating system is to be used to greatest advantage.

A novel and probably important natriuretic hormone exists in granules in the mammalian cardiac atria. This hormone, atrial natriuretic factor (ANF), possesses potent vasodilatory and natriuretic properties. A detailed description of the properties of ANF is available in several reviews [43–47]. Briefly, ANF occurs naturally in human plasma, predominantly as a 28-amino acid peptide that contains a 17-amino acid ring held together by a disulfide bridge. The hormone is released in response to atrial stretch, volume loading, or both. The molecular form of ANF released by the atrium is reported to be pro-ANF (a 126-amino acid peptide) [48]. The circulating form, however, appears to be the 28-amino acid peptide. The hormone does not exhibit $Na^+$-$K^+$ ATPase inhibitory activity and shows no cross-reactivity with digoxin antibodies. Receptors to ANF have been localized in many tissues, including blood vessels and the adrenal capsule [49].

The study of ANF seems particularly relevant to cardiac failure. Atrial natriuretic factor in pharmacologic experiments inhibits renin and aldosterone secretion as well as vasopressin production [50], and blocks vasoconstrictor-augmented vascular contractility [51] (Fig. 3). When ANF is infused into animals, blood pressure falls, whereas glomerular filtration rate and filtration fraction increase and natriuresis ensues [52]. Thus ANF has the characteristics of an ideal counterregulatory natriuretic hormone in congestive heart failure, as it offsets the sodium-retaining potential of the renin-aldosterone system.

We know that acute atrial stretch stimulates ANF release. The critical question is whether ANF release also is stimulated during chronic atrial hypertension associated with congestive heart failure. Measurements of plasma ANF levels in human cardiac failure reveal that the levels are elevated [53]. Whether these elevated plasma ANF levels in chronic cardiac failure are the same or are attenuated, as compared with the response to comparable acute increases in atrial pressure, is not known. Altered sensitivity to stretch might occur with chronic atrial hypertension, leaving a blunted increase in plasma ANF levels that are insufficient to overcome the sodium retentive forces. Although studies in humans do not support a primary ANF defect in congestive heart failure, Chimosky and colleagues proposed that Syrian hamsters with congenital myopathic heart failure are deficient in ANF [54]. This group reported that the atrial ANF content is significantly reduced in these hamsters. Symbiosis of normal hamsters with their myopathic kin prevents development of fluid accumulation without altering the progression of the cardiac degeneration. These findings suggest that a primary defect in ANF synthesis contributes to increased sodium retention in this model of cardiac failure. However, other studies measuring plasma ANF levels disputed this proposal by demonstrating that the plasma levels are increased in these animals [55]. Further studies are necessary to elucidate the role of ANF in cardiac failure. The question remains, are elevations of plasma ANF in humans biologically significant? Are pharmacologic doses of ANF necessary to show a renal, endocrine, or vascular response to cardiac failure?

Scriven and Burnett administered synthetic ANF intrarenally to control dogs and dogs with experimental cardiac failure [56]. The natriuresis and increased glomerular filtration rate induced by ANF was blunted in the group with cardiac failure, demonstrating a decreased responsiveness to ANF in this condition. In humans with cardiac failure, such hyporesponsiveness may also be seen. Cody et al infused synthetic ANF in CHF patients and failed to observe a natriuresis despite a documented hemodynamic response [57]. Hyporesponsiveness in ANF release in response to acute stimuli also might exist in CHF. For example, oral water loading plus water immersion to the neck fails to correct the salt and water retention of the kidney in cardiac failure [58]. Our preliminary data suggest that water immersion failed to increase further the plasma ANF level in these patients

(unpublished observations). The theme of decreased responsiveness to volume regulatory signals is also supported by the data of Zucker and coworkers, who demonstrated impaired left atrial responsiveness to stretch in dogs with chronic, high-output congestive heart failure [59]. It may well be that altered stretch or barosensitivity occurs with chronic exposure to a high-pressure, high-volume circulation, keeping plasma ANF levels tonically elevated but insufficient to overcome depressed end-organ responsiveness or tachyphylaxis.

The ability of ANF to cause vasodilation, induce natriuresis, and block vasoconstricting-sodium retentive hormone secretion makes it an ideal agent for the treatment of human heart failure, at least theoretically. Riegger and colleagues studied the effect of infusions of ANF in 7 patients with severe congestive heart failure [60]. Dose-dependent increases in cardiac output, a fall in pulmonary arterial and systemic pressures, and suppression of plasma aldosterone and cortisol were observed. Both natriuresis and kaliuresis occurred. As mentioned earlier, other investigators also have administered ANF infusions to patients with cardiac failure and have observed mixed responses [60]. In some patients, ANF failed to induce natriuresis or diuresis ([57, 60]; Nicholls MG, Espiner E, personal communication).

It thus appears that circulating plasma ANF is increased in cardiac failure in response to the increase in blood volume. Although a variable response to pharmacologic doses of ANF occurs, the significance of physiologic changes in plasma ANF concentrations remains to be determined. Endogenous ANF likely will be shown to modulate natriuresis through at least a permissive action. Pharmacologically, ANF might prove useful in the therapy of congestive heart failure.

In summary, evidence suggests that a variety of endogenous natriuretic and vasodilatory substances—notably atrial natriuretic factor, dopamine, and prostaglandins—may play a collective, interdependent role in offsetting the sodium-retentive neurohormonal storm characteristic of congestive heart failure. Therapeutic advances in the treatment of cardiac failure may derive from avoidance of disruption of these natriuretic hormonal responses, from enhancement of these endogenous factors, or from pharmacologic administration of endogenous substances like ANF or their analogues. Future research on the body's natural defenses against volume overload in cardiac failure should provide new insights into pathophysiology and therapy.

### *Cardiorenal interactions in cardiac failure*

To achieve an understanding of the pathophysiology of cardiac failure, we first must examine the relationship of cardiac sensors and volume regulation. Stimulation of atrial or ventricular receptors by stretch or volume expansion results in withdrawal of renal sympathetic outflow and inhibition of renin and vasopressin release (Fig. 4) [61–64]. In addition, studies of total-body water immersion as well as sodium loading in humans have demonstrated increased urinary prostaglandin $PGE_2$ and dopamine excretion [31, 65], suggesting increased renal production of these natriuretic substances. Atrial natriuretic peptide also appears to be released in response to water immersion.

Patients with congestive heart failure have abnormalities in cardiopulmonary baroreflex function and hormonal secretion

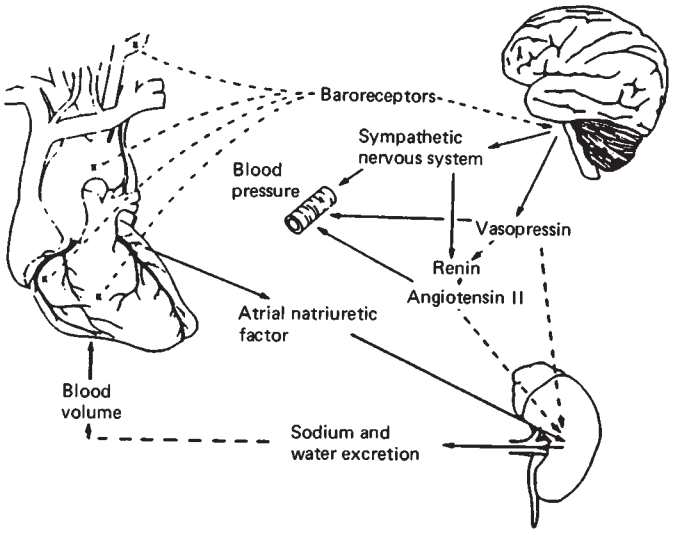


**Fig. 4.** *Overview of cardiovascular regulation of renal function.* Inhibitory signals to each organ are indicated by *dashed lines*, stimulatory signals are indicated by *solid lines*. Increases in blood volume stimulate cardiopulmonary baroreceptors and secretion of ANF. Increases in systemic arterial pressure stimulate arterial baroreceptors. Baroreceptor activation sends inhibitory signals to the central nervous system vasomotor center, and cause suppression of sympathetic efferent activity and increased vagal efferent activity (not shown).

[66]. In a dog model of cardiac failure, atrial receptors with myelinated afferent vagal fibers have a decreased response to elevations of atrial pressure. Both threshold and sensitivity to pressure changes are attenuated [65, 67]. The sensitivity of atrial receptors improves following reversal of experimental cardiac failure [68]. In chronic cardiac failure, despite persistent elevation of atrial and ventricular pressures, plasma renin and vasopressin are not suppressed. These data suggest that an alteration in cardiopulmonary control of sodium-retentive hormones may exist in cardiac failure. Altered cardiopulmonary baroreceptor function in cardiac failure may be secondary to decreased myocardial compliance or to structural changes within the baroreceptors. In addition, cardiac baroreceptors may be diminished by decreased contractile states. Arterial baroreceptor activities have been demonstrated in animal models of heart failure. Reductions in baroreflex sensitivity and/or increases in threshold reduce the reflex inhibition of sympathetic efferent activity. Thus, circulating levels of catecholamines, renin, and vasopressin may increase. As a result, activation of these neurohormonal systems may cause renal vasoconstriction and can contribute to sodium and water retention. The heart rate as well as systemic and regional vasoconstrictor responses to lower-body negative pressure or postural tilt are depressed or absent in patients with heart failure [69–72]. Furthermore, the increase in plasma catecholamines, plasma renin activity, and plasma vasopressin concentrations usually observed in normal subjects with orthostasis are impaired in patients with cardiac failure. The response of the endogenous vasodilating natriuretic hormones to changes in loading conditions of the cardiopulmonary receptors have not been well studied. The failure of head-out, total-body water immersion to induce natriuresis and diuresis in patients with chronic heart

**Table 2.** Effect of vasodilators on renal blood blow

| Vasodilator | Renal blood flow |
|---|---|
| ACE inhibitor | Increase (selective) |
| Hyralazine | Increase (nonselective) |
| Calcium channel blockers | Increase (nonselective) |
| Prazosin | No effect |
| Nitrates | No effect |

failure [57] suggests that the responses of ANF, $PGE_2$, and dopamine may be attenuated, or at least are insufficient to overcome the sodium retentive forces. Indeed, our preliminary data suggest that plasma ANF did not increase further during water immersion (unpublished data).

### *Renal response to vasodilatory drugs in cardiac failure*

As our understanding of the role of these neural and hormonal factors in cardiac failure has increased, development of more rational therapy has become possible. The last decade has seen the application of specific pharmacologic antagonists in the use of vasodilators in the management of congestive heart failure [10]. Angiotensin-converting enzyme inhibitors, which inhibit the production of angiotensin II, have become the gold standard of vasodilator therapy for congestive heart failure [23, 73]. Phentolamine and prazosin (alpha-adrenoreceptor antagonists) have been used to block vascular and renal effects of increased sympathetic nervous system activity. Nonselective vasodilators such as nitrates, hydralazine, and calcium antagonists also have been used for the treatment of patients with congestive heart failure. A critical determinant of the efficacy of vasodilators in the treatment of cardiac failure is the renal response to the vasodilator agent. Agents that increase renal blood flow and GFR should promote sodium excretion and enhance the effect of diuretics. Table 2 summarizes the effects of various vasodilators on renal blood flow. Angiotensin-converting enzyme inhibitors selectively increase renal blood flow in preference to other regional circulations [15, 22, 74]. Hydralazine and calcium antagonists increase renal blood flow nonselectively; that is, the increment of renal blood flow is directly proportional to the increase in cardiac output. Prazosin and nitrates have no effect on renal blood flow. The dominant role of the renin-angiotensin system in the pathogenesis of azotemia and sodium retention in congestive heart failure was suggested by the experimental studies of Ichikawa and coworkers [8]. Administration of angiotensin-converting enzyme inhibitor in rats with congestive heart failure resulted in an increase in $Q_A$, SNGFR, and a reduction in SNFF. These findings can best be explained by the demonstration that efferent arteriolar resistance fell substantially in response to the blockade of angiotensin II production (Fig. 5). Furthermore, the glomerular capillary ultrafiltration coefficient ($K_f$) rose significantly. The contribution of the renin-angiotensin system to renal dysfunction in patients with congestive heart failure is supported by reports that a significant correlation exists between serum creatinine and plasma renin activity [17, 75]. Patients with hyponatremia and elevated plasma renin activity have significantly higher BUN and plasma creatinine concentrations and lower renal blood flow and glomerular filtration rates [22]. Angiotensin-converting enzyme (ACE) inhibitor therapy may improve renal function in patients with severe cardiac failure and reduce the requirement for diuretic agents [15, 22, 74]. Furthermore, hyponatremia may revert to normal with the addition of an ACE inhibitor to the medical regimen [74, 76].

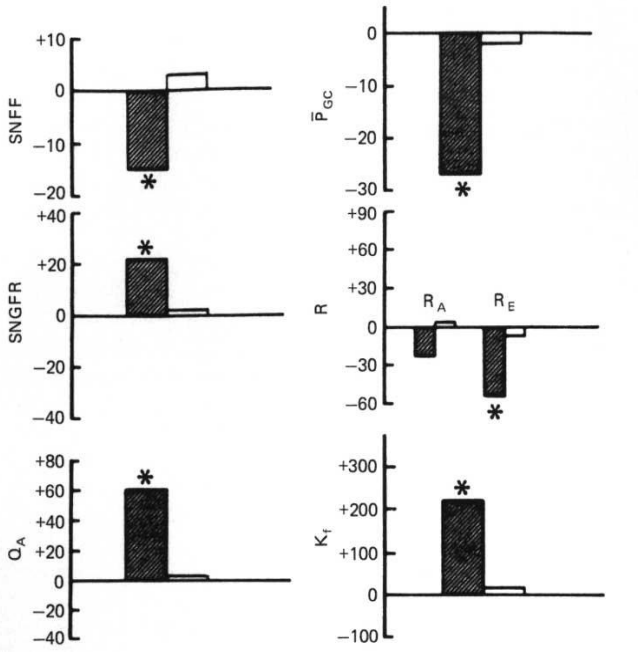


**Fig. 5.** *Effect of ACE inhibition on renal function of rat and man.* Changes in single-nephron filtration fraction (SNFF), single-nephron GFR (SNGFR), glomerular plasma flow rate ($Q_A$), mean glomerular capillary hydraulic pressure ($\bar{P}_{GC}$), afferent ($R_A$) and efferent ($R_E$) arteriolar resistance, and glomerular capillary ultrafiltration coefficent ($K_f$) in response to teprotide administration. Values are expressed as the mean percentage of changes from initial control levels. *Hatched bars* denote rats with myocardial infarction, *open bars* sham-operated control rats. The asterisk indicates a significant difference, with $P < 0.05$. (From Ref. 4.)

The renal effects of ACE inhibition in patients with cardiac failure have been debated. One can reasonably expect that ACE inhibition will improve or produce no effect on renal function in patients with mild to moderate cardiac impairment in whom the cardiac functional capacity is sufficient to sustain a significant increase in cardiac output necessary to maintain blood pressure and renal perfusion in the presence of systemic vasodilation. The renal response to ACE inhibition in patients with severe CHF is more complex, however. Pierpont and associates reported an increase in BUN and serum creatinine in 3 of 9 patients after 3 days of captopril therapy [77]. Faxon and colleagues saw an improvement in renal plasma flow without a change in the GFR after a single dose of captopril [78], whereas Mujais and colleagues reported that captopril reduced both renal plasma flow and GFR [79]. In contrast, studies with prolonged captopril administration have shown sustained improvement of both renal plasma flow and GFR [23, 74]. The

apparent discrepancies might be due to differences in study design. For example, in studies of captopril's short-term effects, a single captopril dose was not titrated to blood pressure or to the hemodynamic response [78, 79]; furthermore, diuretic agents were withheld in these studies. On the other hand, in studies in which captopril doses were titrated and the GFR and renal plasma flow were studied during chronic therapy, sustained improvement of renal plasma flow and GFR were reported [23, 74, 80]. As Pierpont and associates showed, the initial deterioration of renal function with acute captopril administration might be related to an excessive decrease in renal perfusion pressure, complicated by blockade of angiotensin-mediated autoregulation of GFR [77]. The mean blood pressure of these patients with severe congestive heart failure is often very near the autoregulatory break point. Thus, a further fall in blood pressure can result in a substantial decrease in renal plasma flow and GFR.

Chronic captopril therapy with dosage adjustments, as in our studies, can avoid an excessive and precipitous reduction in renal perfusion pressure and can optimize renal hemodynamic changes. Indeed, in our experience [23, 74], GFR increased by 38% and renal plasma flow by 48% after one week of captopril therapy. Recently Packer and coworkers compared the effect of two different angiotensin-converting enzyme inhibitors on renal function in patients with cardiac failure and reported that enalapril therapy increased serum creatinine and plasma potassium and reduced creatinine clearance [81]. In contrast, captopril improved creatinine clearance and reduced body weight, but it had no effect on serum creatinine or plasma potassium. These discrepant renal effects can be explained by the duration of actions of these two drugs. Enalapril, which has a prolonged duration of action, may produce sustained renal hypotension in contrast to the effect of captopril, and thus causes a net reduction in creatinine clearance.

We examined whether an ACE inhibitor alone (without diuretics) has a significant diuretic effect in patients with congestive heart failure or whether furosemide is needed for this response [74]. We studied 14 patients receiving a diet containing 40 mEq of sodium daily. Significant weight loss did not occur despite the improved renal plasma flow and GFR in patients treated with captopril alone for 5 days. However, when captopril was given with furosemide, body weight and edema were both reduced significantly. Furthermore, the diuresis and natriuresis were achieved without inducing azotemia and with a modest dose of the diuretic agent (40 to 80 mg/day). In our experience, the renal effects of ACE inhibitors seemed to reflect primarily an enhancement of the renal response to furosemide.

Another area of debate concerns the ACE inhibitor's effect on hyponatremia in patients with cardiac failure. We have reported that hyponatremia was corrected with the addition of captopril to the medical regimen [23, 74]. Pierpont and associates [77] and Maslowski and colleagues [82], on the other hand, reported that serum sodium concentration decreased after 3 and 6 days of captopril therapy. However, the protocol used by these authors, in which diuretic agents were withheld when captopril was administered, differed from that in our study. Our data show that captopril itself has little effect on serum sodium concentration. Captopril and furosemide in combination, however, corrected hyponatremia in patients with severe cardiac failure (Fig. 6).

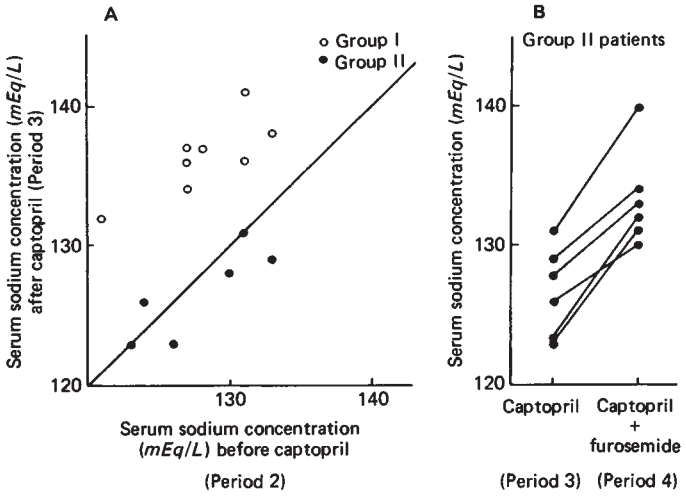


**Fig. 6. A** *Comparison of serum sodium concentration in two groups of hypernatremic patients with CHF.* After a control period with captopril or furosemide (period 1), the first group of patients received furosemide (period 2) and then captopril plus furosemide (period 3). The second group did not receive furosemide during period 2 and received captopril alone during period 3. (Adapted from Ref. 74.) **B** *Response of serum sodium concentration of the same patients in the second group* (captopril alone, period 3) *when furosemide was added to captopril* (period 4). (Adapted, with permission, from: Dzau VJ, Mollenberg NK: Renal response to captopril in severe heart failure. *Ann Intern Med* 100:777–782, 1984.)

The mechanism of hyponatremia in patients with severe congestive heart failure is unclear and probably multifactorial, as I alluded to earlier [83–86]. Decreased effective arterial volume and renal perfusion in congestive heart failure can lead to water retention due to (*1*) decreases in distal delivery of sodium and filtrate resulting in impairment of free-water excretion; (*2*) increased thirst or increased antidiuretic hormone release in response to nonosmotic stimuli; and (*3*) a water-excreting defect induced by diuretic agents. Our data show that diuretic agents were not primarily responsible for hyponatremia in those patients, because discontinuation of furosemide did not affect serum sodium concentration [74]. Excessive water intake was not principally responsible for hyponatremia in the patients in this study because total fluid intake was similar to that in the normonatremic patients. A contribution of antidiuretic hormone to the hyponatremia cannot be excluded and is quite likely the major cause of the observed water-excreting defect.

Enhanced proximal tubular reabsorption of sodium occurs with edema. More than 20 years ago, Cirksena, Dirks, and Berliner demonstrated enhanced proximal tubular reabsorption of sodium by performing micropuncture studies in dogs with caval constriction [87]. This conclusion is supported by evidence based on clearance and micropuncture techniques in dogs with cardiac failure due to an arteriovenous fistula [88]. These observations are supported by two lines of investigation in humans. In patients with congestive heart failure, the natriuresis associated with distal tubular blockade induced by diuretic agents led to the conclusion that proximal tubular reab-

sorption was increased [89]. In patients with congestive heart failure or hepatic cirrhosis, moreover, administration of an osmotic diuretic agent led to increased free-water clearance; this observation could be accounted for only on the basis of increased delivery of sodium from the proximal tubule to the loop of Henle [90, 91]. The loop of Henle may also contribute to this sodium reabsorption. Haas and coworkers have shown that this is the likeliest site of sodium reabsorption during mineralocorticoid escape [92]. Because patients with congestive heart failure usually have severe secondary aldosteronism, sodium retention can be enhanced by the action of the mineralocorticoid.

We have confirmed that in the presence of a stable perfusion pressure, captopril can induce an increase in renal plasma flow in patients with advanced congestive heart failure. The consequent increase in peritubular capillary hydraulic pressure, accompanied with maintained or increased glomerular filtration rate all would tend to lead to increased delivery of sodium to the loop of Henle, the locus of furosemide's action, and in this way would enhance the action of furosemide. Another possibility is that the increased cortical blood flow could have led to increased delivery of furosemide to the kidney and to its site of action in the loop. Angiotensin converting enzyme inhibition also blocks aldosterone production and thus might enhance the natriuretic action and counteract the kaliuretic effect of furosemide. A more remote possibility is that the combination of ACE inhibitors and furosemide leads to a more substantial improvement in cardiac hemodynamics and pulmonary congestion, and results in the suppression of plasma antidiuretic hormone levels responsible for hyponatremia. Finally, Carvounis and colleagues showed that captopril decreased vasopressin-stimulated water flow in the toad bladder [93]. Such a mechanism may be operative, when combined with furosemide, in the correction of hyponatremia in patients with congestive heart failure.

In summary, ACE inhibition may improve renal plasma flow and GFR in patients with congestive heart failure if sustained hypotension is avoided. Significant diuresis and natriuresis can be achieved without inducing azotemia by using a combination of furosemide and captopril. Diuresis and correction of hyponatremia occur in patients treated with captopril and furosemide but not with captopril alone. Angiotensin-converting enzyme inhibition enhances the renal effect of furosemide. On the basis of our study [74], we recommend titration of the dose of the ACE inhibitor to minimize hypotension. We also recommend the concurrent use of furosemide, especially for those in whom azotemia and hyponatremia are present.

### *Neurohormonal levels and prognosis in clinical cardiac failure*

Despite advances in the understanding of the pathophysiology of cardiac failure, the prognosis for patients with congestive heart failure remains poor [94, 95]. Recent data demonstrated that plasma hormonal levels and serum sodium concentration can predict the survival of patients with congestive heart failure [95, 96]. Cohn and coworkers reported that patients with plasma norepinephrine levels greater than 800 pg/ml have a significantly worse prognosis than do those with plasma norepinephrine levels of 400 to 800 pg/ml [95]. Patients whose plasma norepinephrine levels are nearly normal, that is, less than 400 pg/ml, have relatively the best prognosis. Lee and Packer observed that hyponatremic patients with CHF have a significantly shorter survival time than do normonatremic patients with cardiac failure (Fig. 7A) [96]. These independent observations are clearly related; a relationship has been described between hyponatremia and elevated plasma vasoconstricting-sodium retentive hormones in patients with poorly compensated heart failure [19–21]. Lee and Packer reported further that administration of an ACE inhibitor significantly improved the survival of hyponatremic patients with CHF, whereas administration of non-ACE inhibitor vasodilators did not influence the prognosis of patients with hyponatremia (Fig. 7B) [96]. Thus, blockade of the actions of vasoconstricting-sodium retentive hormones might influence the course of cardiac failure. Recently, the Veterans Administration Heart Failure Study reported that the combination of hydralazine and isosorbide nitrate reduced the cumulative mortality of CHF patients, whereas prazosin had no effect [97]. Unfortunately this study did not examine the effect of ACE inhibitors. One retrospective analysis of all controlled studies involving vasodilator therapy, including ACE inhibition, in cardiac failure reported that neither nitrates, prazosin, nor hydralazine alone had any impact on mortality rates in patients with cardiac failure who were receiving digitalis and diuretics [98]. In contrast, patients receiving ACE inhibitors had a significantly lower mortality rate than did patients receiving a placebo. The beneficial effect of ACE inhibition in cardiac failure might be due to the blockade of angiotensin II, reduction in sympathetic activity, and activation of endogenous prostaglandins [99]. These effects can reduce both afterload and preload as well as improve renal function. The failure of hydralazine or prazosin to improve survival might be due to activation of neurohormonal mechanisms during the chronic administration of these vasodilators [15]. Indeed, a recent double-blind comparison of captopril and prazosin demonstrated that prazosin treatment activated plasma norepinephrine and renin-angiotensin levels [100]. Chronic administration of prazosin resulted in an increase in body weight and an attenuation of vasodilatory effects over time. In contrast, administration of an ACE inhibitor blocked angiotensin II production, did not affect plasma norepinephrine levels, improved renal function, and reduced body weight [100]. In a similar study, Lilly and coworkers demonstrated that hydralazine markedly increased plasma norepinephrine levels, whereas captopril did not [101]. Patients who were treated with hydralazine had a higher mortality rate as compared with those who received captopril. Increased plasma catecholamine may predispose these patients to ventricular arrhythmias and sudden death. On the other hand, ACE inhibitors have been shown to reduce the frequency of ventricular arrhythmias in these patients [102]. Thus, neurohormonal compensatory activation during vasodilator therapy may determine survival as well as drug response.

In summary, circulatory and renal adaptive mechanisms are activated during cardiac failure. These compensatory changes contribute to the pathophysiology of the syndrome of cardiac failure, form the rational basis for vasodilator therapy, determine long-term drug responsiveness, and probably influence survival in these patients.

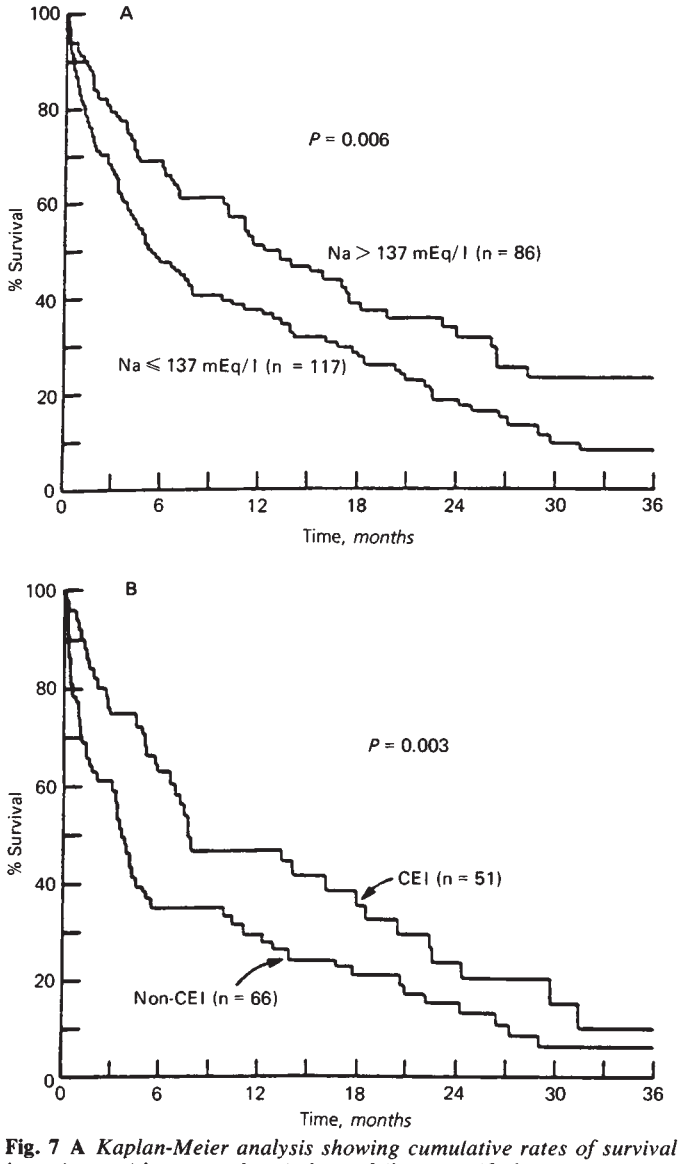


**Fig. 7** **A** *Kaplan-Meier analysis showing cumulative rates of survival in patients with severe chronic heart failure stratified into two groups based on pretreatment serum sodium concentration* (> 137 versus ≤ 137 mEq/liter). Hyponatremic patients fared significantly worse than did patients with a normal serum sodium concentration ($P$ = .006, Wilcoxon Breslow). **B** *Kaplan-Meier analysis of cumulative rates of survival in patients with cardiac failure and hyponatremia* (pretreatment serum sodium concentration ≤ 137 mEq/liter) *stratified into two groups based on treatment.* Patients treated with converting-enzyme inhibitors (CEI) had a significantly more favorable long-term prognosis than did patients who received drugs that did not interfere with the renin-angiotensin system (Non-CEI) ($P$ = < .003, Wilcoxon-Breslow). (From Ref. 97.)

### Questions and answers

DR. NICOLAOS E. MADIAS (*Chief, Division of Nephrology, New England Medical Center Hospitals*): Is the hemodynamic and clinical response to converting enzyme inhibition related to basal renal function in patients with congestive heart failure?

DR. DZAU: The acute hemodynamic response to converting enzyme inhibition is not influenced directly by basal renal function but by plasma renin activity. We and others have reported that the magnitude of the decline in systemic blood pressure and left ventricular filling pressure to converting enzyme inhibition correlated inversely with serum sodium concentration [19, 21]. In this context, an indirect relationship exists between acute hemodynamic response and renal function; we observed that patients with elevated PRA and hyponatremia in general have elevated BUN and serum creatinine levels.

DR. RONALD PERRONE (*Division of Nephrology, New England Medical Center Hospitals*): Can one generally predict who does well or poorly when given a converting enzyme inhibitor?

DR. DZAU: As I said earlier, the acute hemodynamic response including symptomatic hypotension can be predicted by the baseline serum sodium concentration [21]. Patients with hyponatremia are more prone to develop symptomatic hypotension in response to an ACE inhibitor than are normonatremic patients. As a group, hyponatremic patients have poor hemodynamic compensation, and ACE inhibition appears to increase survival in these patients [96].

DR. PERRONE: Are the hyponatremia data obtained on random patients with random salt and water intake, and are there any rigorious studies of free-water clearance and balance?

DR. DZAU: A large part of our data is derived from metabolic balance studies performed in the Clinical Research Center in patients who are not taking diuretics [19, 23, 24, 74]. However, the rest of our data [17] as well as the large experiences of other investigators [20, 21] are based on patients with a random-sodium diet and free access to water who are receiving diuretics. Thus it appears that the relationship of hyponatremia and plasma renin activity holds true regardless of the study conditions.

DR. MICHAEL MADAIO (*Division of Nephrology, New England Medical Center Hospitals*): What is the explanation for the increased systemic vascular resistance following indomethacin administration in patients with congestive heart failure and hyponatremia?

DR. DZAU: Patients with hyponatremia have elevated plasma levels of vasoconstrictive hormones such as angiotensin and catecholamines. The effects of these hormones on the vasculature are modulated by increased tissue production of vasodilatory prostaglandins. Indomethacin inhibits cyclooxygenase activity and blocks the synthesis of prostaglandins $I_2$ and $E_2$. This inhibitory action causes "unopposed" vasoconstriction.

DR. JORDAN J. COHEN (*Chairman, Department of Medicine, Michael Reese Hospital and Medical Center, Chicago, Illinois*): In relation to the other mechanisms you described, how important is the sympathetic innervation of the kidney in congestive heart failure?

DR. DZAU: I think the role of the sympathetic nervous system is well established. It is activated in "decompensated" patients with congestive heart failure, and it contributes to vasoconstriction and sodium retention.

DR. RICHARD KOPELMAN (*Division of General Internal Medicine, New England Medical Center Hospitals*): Does enalapril also stimulate prostaglandin synthesis?

DR. DZAU: This is an area of some controversy. Given et al

reported that enalapril did not increase plasma $PGE_2$ metabolite levels in normal volunteers [103]. Zusman reported that captopril but not enalapril produced an increase in $PGE_2$ synthesis by cultured renal medullary interstitial cells [104]. However, Oparil and coworkers reported increased urinary 6-keto-$PGF_{1\alpha}$ excretion in patients with low-renin, essential hypertension who were treated with enalapril [105].

DR. MADIAS: You alluded to the discrepant renal effect of captopril and enalapril in patients with cardiac failure [81]. Are differences in the mechanism of action rather than in duration more important? Is chronic treatment with captopril characterized by periodic escape from converting-enzyme inhibition?

DR. DZAU: This is an excellent question. Several mechanisms might account for the differences in renal functional response to captopril and enalapril: (*1*) differences between the two drugs in the duration of blood pressure reduction and serum ACE inhibition, (*2*) differences in renal prostaglandin production that might influence renal hemodynamics, and (*3*) differences in the profile of tissue ACE inhibition. Indeed, evidence suggests that enalapril produces a more prolonged and complete inhibition of renal and cardiac ACE than does captopril [106].

DR. JOHN T. HARRINGTON (*Chief, Department of Medicine, Newton-Wellesley Hospital, Newton, Massachusetts*): Are there experimental studies which show that captopril decreases proximal tubular sodium reabsorption?

DR. DZAU: I am not aware of any.

DR. COHEN: Are the renin-aldosterone-angiotensin and neurohormonal systems maladaptive in congestive heart failure?

DR. DZAU: The renin-angiotensin system is an adaptive system that maintains cardiovascular homeostasis in organisms with normal cardiac function during states of dehydration, hemorrhage, and volume contraction [25]. In severe CHF, the system is maladaptive. In severe heart failure, the neurohormonal systems are activated to support blood pressure. The intense vasoconstriction can reduce regional blood flow, however. With the increase in systemic vascular resistance, the impedance to ventricular ejection is also greatly increased and, as a consequence, the forward output is decreased.

DR. COHEN: You appear to be describing a positive-feedback system. Why doesn't the system fall apart when it gets into this mode?

DR. DZAU: Indeed, the fundamental hypothesis in severe cardiac failure is that it *is* a vicious cycle of impaired cardiac output and increased vasoconstriction and that, if untreated, there is ultimate cardiovascular collapse. In fact, the physiologic and pharmacologic basis of vasodilator therapy is the elimination of this positive feedback.

DR. MADIAS: Recent data have provided evidence that activation of the vascular tissue renin-angiotensin system might contribute to the increased vascular tone in chronic two-kidney, one-clip hypertension [108]. Are there any similar data in experimental models of congestive heart failure?

DR. DZAU: No, none of which I am aware.

DR. COHEN: The ultimate inhibitor of the renin-angiotensin system is bilateral nephrectomy. Are there any data on the response of the failing heart in patients who have no kidneys?

DR. DZAU: I know of no clinical or laboratory data on bilateral nephrectomy in cardiac failure.

DR. GEETHA NARAYAN (*Clinical Director, Tri-City Dialysis Center, Medford, Massachusetts*): In the presence of a stable perfusion pressure, how does converting enzyme inhibition increase glomerular filtration rate in cardiac failure?

DR. DZAU: In advanced congestive heart failure, intense angiotensin-mediated renal arterial, as well as afferent and efferent arteriolar, constriction may be seen. Furthermore, glomerular surface area also is reduced because of angiotensin-mediated mesangial contraction. In the presence of a stable perfusion pressure, angiotension converting enzyme inhibition may, therefore, increase GFR via renal arterial and afferent arteriolar dilation as well as via increased glomerular surface area.

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