Evolution and Pathophysiology of Chronic Systolic Heart Failure

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Understanding of the pathophysiology of chronic systolic heart failure evolved from a purely mechanical model to one in which a cascade of neurohormones and biologically active molecules are thought to be critical in the development, maintenance, and progression of the disease. Two important neurohormonal systems are the sympathetic nervous and renin-angiotensin-aldosterone systems. Initially, increases in norepinephrine concentrations from the sympathetic nervous system and in angiotensin II and aldosterone are beneficial in the short term to maintain cardiac output after an insult to the myocardium. However, long-term exposure to these neurohormones causes alterations of myocytes and interstitial make-up of the heart. These alterations in myocardium lead to progression of heart failure and, eventually, death.
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OUTLINE

An aging population and increased survival after myocardial infarction contribute to the prominent role of chronic heart failure in today's society. According to recent statistics, nearly 5 million persons in the United States have heart failure, with 400,000 new cases diagnosed every year.[1] It is estimated that the syndrome accounts for over 900,000 hospitalizations/year and is the most common diagnosis in hospital patients aged 65 years and older.[1] Significant mortality is associated with the disease. After a diagnosis, 5-year mortality is 50%; however, in any given patient, 1-year mortality may range from 5–50% depending on disease severity. The cost to treat heart failure is also staggering, estimated to be $17.8–56 billion annually, which does not take into account associated costs endured by caregivers.[1, 2] Since heart failure is so prevalent and devastating, vast amounts of time and energy have been devoted to understanding its pathophysiology. Much work has focused on the role of the sympathetic nervous and renin-angiotensin-aldosterone (RAA) systems.

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Evolution in Pathophysiologic Models

Understanding of the pathophysiology of heart failure evolved over the years as investigators pieced together the complex interplay of mechanical, biologic (endocrine, paracrine, autocrine), and functional alterations that occur. As our understanding increased, so did the complexity of the model to define the disease. Thirty to 40 years ago heart failure was looked at as a syndrome of salt and water retention that was due in part to abnormalities of renal blood flow. This cardiorenal model evolved into a cardiocirculatory model when hemodynamic measurements revealed a decrease in cardiac output and increase in peripheral vascular resistance.[3, 4] Based on these models, diuretics were administered to treat sodium and water

retention, and vasodilators and inotropic agents were administered to improve hemodynamics by increasing cardiac output and decreasing peripheral vascular resistance.

Although these models explain clinical manifestations and rationalize drug therapy, they do not adequately describe the devastating progression that occurs in treated patients with either asymptomatic or symptomatic heart failure. In attempt to describe disease progression in addition to renal and circulatory change, the neurohormonal model was put forward in the 1980s (Figure 1).[5–7] Heart failure begins with an insult or damage to the heart that results in a sustained decrease in cardiac function and output. This insult varies and may include coronary artery disease (ischemic dilated cardiomyopathy, which affects approximately two-thirds of patients), hypertension, and idiopathic causes (idiopathic dilated cardiomyopathy). A small number of patients may have other causes, such as ethanol abuse, drug-induced cardiomyopathy (doxorubicin), and viral infections.

After the insult and a sustained decrease in cardiac output, excessive neurohormonal activation occurs, specifically with the sympathetic and RAA systems, that causes sodium and water retention together with peripheral vasoconstriction. Initially, these neurohormones are compensatory and may maintain relatively normal cardiac output in the short term. However, long-term elevated concentrations of neurohormones result in toxicity, overcompensation, and eventually inability to maintain a normal cardiac function. With a sustained decrease in cardiac function, further neurohormonal activation, sodium and water retention, and peripheral vasoconstriction occur. A vicious cycle is created that leads to more symptoms, disease progression, and, eventually, death.

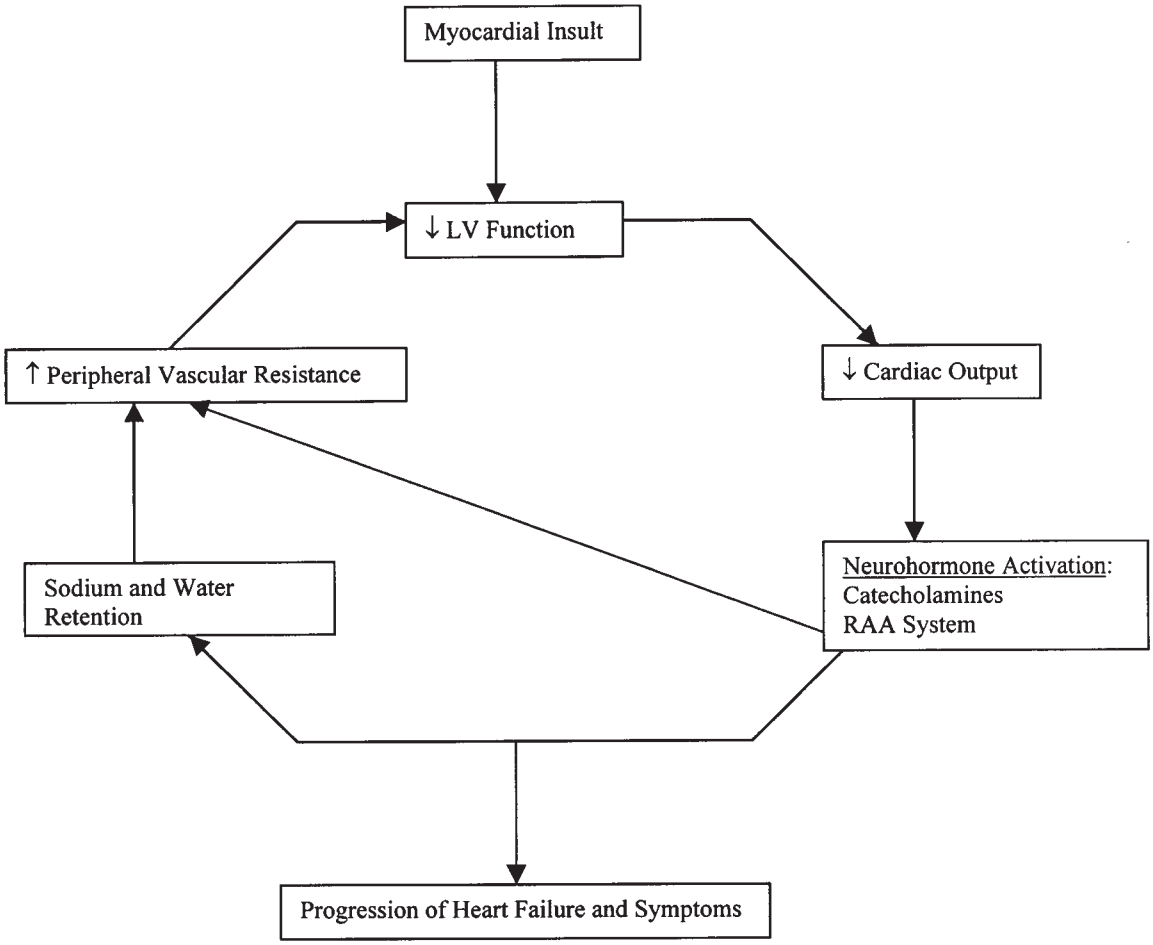

Figure 1. Pathophysiology of heart failure in the 1980s.

The neurohormonal model is still in vogue and is similar to what was proposed, but it now includes other neurohormones or biologically active molecules. The model appears to be applicable based on the following: experimental studies showed the ability of neurohormones to contribute to the development and progression of heart failure either in an intact or cellular model; clinical studies proved the benefit of neurohormonal antagonists; and regardless of the cause or type of heart failure, neurohormonal activation appeared to be similar.[3, 8–16] In addition to the contribution of biologically activated molecules such as endothelin, vasopressin, tumor necrosis factor-α, and counterregulatory neurohormones (atrial and brain natriuretic peptide), the model describes the role of left ventricular remodeling in disease progression.[10, 17–19]

Left ventricular remodeling occurs due to alterations in hemodynamics (increase preload) and load-independent changes in myocyte biology and chamber geometry (Figure 2). At

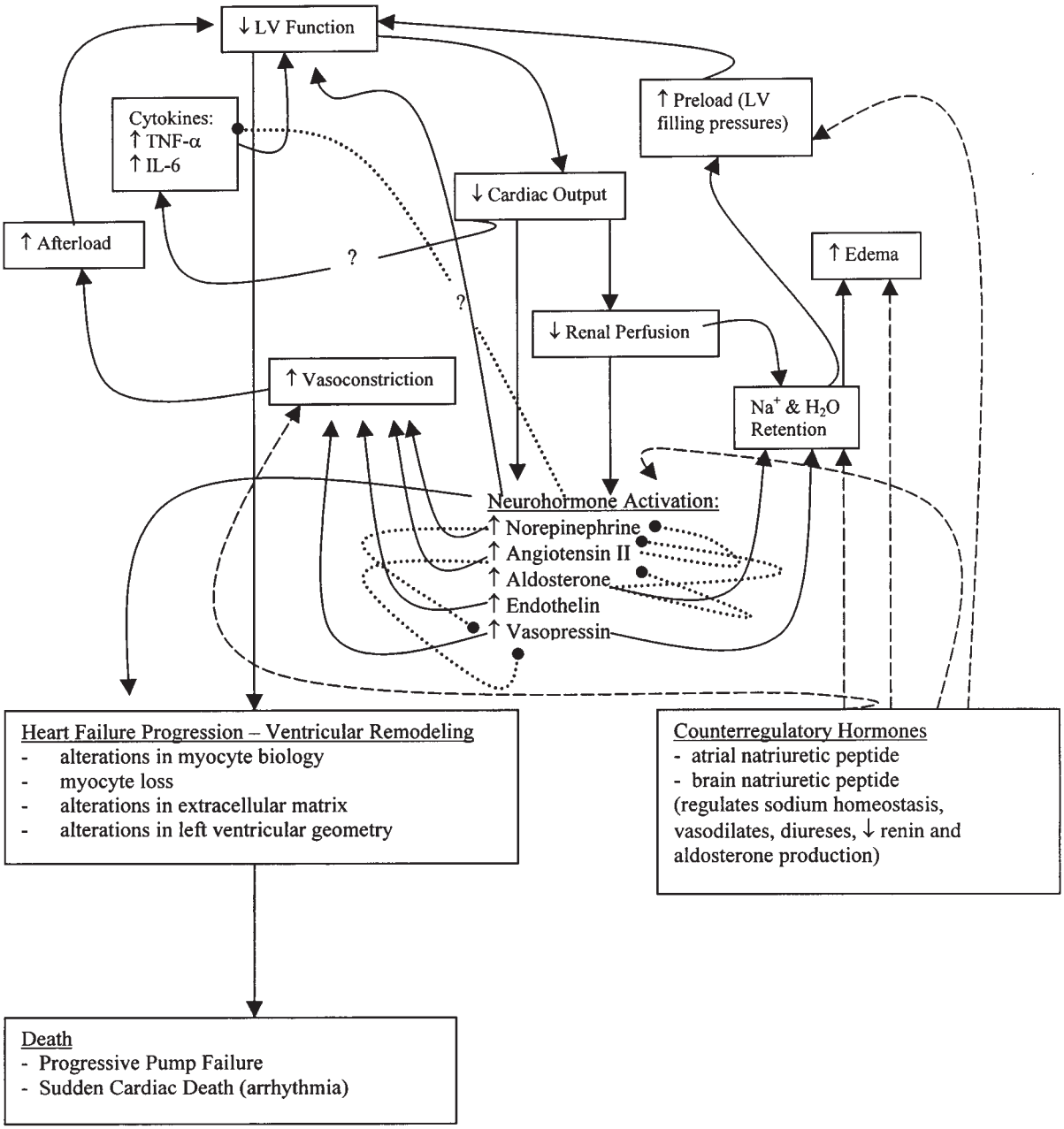

Figure 2. Pathophysiology of chronic systolic heart failure today. Direct effect = ——>; counterregulatory effect = – – –>; induce production or increase effect of a biologically active molecule = ·····•.

first it occurs to maintain stroke volume and contractility by enlarging the ventricle and increasing myocardial and interstitial mass. At the cellular level, remodeling may occur by several mechanisms, including myocyte hypertrophy, interstitial growth, and myocyte slippage. Over time these changes become maladaptive, leading to increased wall stress and oxygen demand, together with fibrosis and decreased contractility. Further discussion relating to cellular and molecular changes that occur during heart failure is available elsewhere.[3, 20, 21]

The current model, as can be expected, is not complete and continues to evolve. Critical pieces of information, such as specific roles and interplay among biologically active molecules, genetic determinations, and how the transition from asymptomatic to symptomatic heart failure occurs, are missing. Fortunately, however, the sympathetic nervous and RAA systems have clarified many important aspects of the pathophysiology of the syndrome.

Sympathetic Nervous System

The significance of the sympathetic nervous system, specifically norepinephrine, in heart failure probably has been known for at least 25 years. Classic data from the 1980s showing that norepinephrine concentrations were elevated and were a prognostic indicator for mortality further focused research efforts on the system.[22, 23] This led to therapy with β-adrenergic receptor antagonists, which once were thought to be harmful in the treatment of heart failure.

Initially, an increase in norepinephrine concentrations may have beneficial short-term effects by increasing heart rate, contractility, and blood pressure, which maintain normal cardiac output after an insult to the myocardium. However, long-term effects have direct adverse effects on the heart that are mediated by excess activation of the cardiac adrenergic receptor pathway.[24–29] In support of these data, transgenic animal models in which β- and α-adrenergic receptors are overexpressed developed cardiomyopathies and cardiac hypertrophy. In these models, the β_1-receptor may be the most important in causing overt heart failure.[29, 30]

Activation of the sympathetic adrenergic system occurs early in the syndrome, beginning with cardiac followed by systemic adrenergic activation.[31, 32] Sustained adrenergic activation results in alterations in the cardiac adrenergic receptor profile and in desensitization of signal transduction through β-adrenergic receptors, which results in decreases in myocardial reserve and exercise capacity. In a nonfailing heart the β_1-:β_2-receptor ratio is approximately 80:20. In the failing heart, downregulation of the β_1-receptor alters the ratio to approximately 60:40.[33, 34] In addition to changes in the β-adrenergic pathway, upregulation of α_1-receptors causes a further change in the overall cardiac adrenergic receptor profile.[35, 36]

Desensitization or reduction of β-receptor signal transduction due to excess activation by norepinephrine may occur through several mechanisms. One is downregulation of β_1-receptors; another is uncoupling of the β-receptor from its effector site, adenylyl cyclase.[37–39] Both β_1- and β_2-receptors are coupled to adenylyl cyclase through the stimulatory G protein. Adenylyl cyclase converts adenosine triphosphate to cyclic adenosine monophosphate (cAMP), which acts on protein kinase A, which leads to phosphorylation of cellular proteins, resulting in an increase in intracellular calcium from, in part, sarcoplasmic reticulum. The increase in intracellular calcium causes myocardial inotropic and chronotropic response. Therefore, uncoupling of the β-receptor to adenylyl cyclase leads to myocardial dysfunction. Uncoupling of the β_2-adrenergic receptor occurs in ischemic and idiopathic dilated cardiomyopathy, and uncoupling of β_1-adrenergic receptor in ischemic dilated cardiomyopathy.[24, 37]

Another mechanism for abnormal signal transduction is upregulation of β-adrenergic receptor kinase (βARK-1).[40–43] Increased βARK-1 activity leads to receptor phosphorylation and may contribute to receptor uncoupling. An increase in G-inhibitory (G_i) protein activity causes signal transduction abnormalities, probably through receptor uncoupling.[44–47] These and other mechanisms may account for 50–60% loss in total signal transducing potential, resulting in decreased myocardial function.[24]

In addition to desensitization of signal transduction, sustained adrenergic activation has a direct adverse biologic effect on cardiac myocytes that contributes to myocardial dysfunction. Alteration in myocyte function, specifically cell loss, may occur by either necrosis or apoptosis.[9, 48–52] Data from cultured cardiac myocytes indicate that at norepinephrine concentrations seen clinically, necrosis occurs.[48] In addition to a direct effect, ischemia due to increase oxygen demand and a decrease in

oxygen delivery may contribute to cell necrosis. Apoptosis appears to be mediated mainly through the β_1-receptor.[53, 54] Recent data suggest that stimulation of the β_2-receptor and activation of G_i proteins and mitogen-activated protein kinase actually may have antiapoptotic effects.[54–56] A decrease in myocyte function due to alteration in gene expression also may occur. This includes alterations in calcium handling by the myocyte, such as decreased expression of sarcoplasmic reticulum Ca^{2+}-adenosine triphosphatase, a protein that is necessary for excitation-contraction coupling.[57] Other effects may include fetal gene expression, activation of fibroblast growth factor, myocyte hypertrophy, and changes in the proteins responsible for β-adrenergic signal transduction.[58–62] These factors are also important in contributing to left ventricular remodeling that occurs in patients with systolic failure.

Overall, alteration in both signal transduction and the biology of myocytes due to activation of the sympathetic nervous system contributes to the myocardial dysfunction that is observed in patients with chronic systolic heart failure and leads to symptoms and progression of heart failure.

RAA System

The RAA system is activated in patients with heart failure. Similar to the sympathetic nervous system, initial activation may be important to maintain cardiac output in a damaged heart by increasing preload through sodium retention and volume expansion. Perfusion also may be maintained by vasoconstriction. However, long-term effects of prolonged activation of the RAA system are deleterious through excessive hemodynamic alterations and direct effects on myocardium. These effects are mediated in part by production and formation of renin, angiotensin II (ATII), and aldosterone. Renin, which is produced in the juxtaglomerular cells of the kidneys, is increased by three main factors: decreased blood flow to the kidneys, decreased serum sodium, and increased sympathetic tone.[63] Renin then converts circulating angiotensinogen to angiotensin I (ATI), which is inactive. Angiotensin I is converted to ATII by either angiotensin-converting enzyme (ACE) or a non-ACE pathway (Figure 3). In this so-called alternative or independent pathway, chymase and cathepsin G may convert ATI to ATII; other molecules such as elastase, tonin, and tissue plasminogen activator may directly convert angiotensinogen to ATII.[64–71] This alternative pathway may account for significant production (> 50%) of ATII.[72,73] The ACE also effects the kallikrein-kinin system by inactivating bradykinin, a potentially important vasodilatory activator. Neutral endopeptidase also inactivates bradykinin and natriuretic peptides. In addition to circulating angiotensinogen and ACE, both molecules may be produced by a variety of tissues, resulting in local production of ATII, which may have important autocrine and paracrine actions that may contribute significantly to the pathophysiology of heart failure.[74–77]

Angiotensin II

Effects of ATII are mediated by the activation of specific angiotensin receptors, AT_1 and AT_2.[78, 79] Both receptors have high affinity for ATII but are functionally distinct. They are located throughout the body including the kidneys, brain, endothelium, and heart.[80–83] Binding of ATII to AT_1 and AT_2 receptors may produce biologic effects that may be important to the pathophysiology of heart failure. The AT_1 receptor-signaling pathway interacts with both adenylate cyclase and the G protein system. Stimulation of the AT_1 receptor causes activation of several phospholipases, leading to an increase in inositol 1,4,5 triphosphate, which stimulates intracellular calcium release and vasoconstriction.[84–88] In addition, AT_1 stimulation leads to a decrease in cAMP by G_i, which may contribute to vasoconstriction observed with ATII.[83, 87] Activation of the AT_1 receptor causes an increase in the L-type calcium channel opening, resulting in an increase in intracellular calcium that may be a stimulus for aldosterone production in adrenal cells.[87, 89] Through this receptor, ATII also activates Janus kinases (JAK), signal transducers, and activators of transcription, which may cause activation of early growth-response genes, resulting in proliferative effects (myocardial hypertrophy).[90–93] In addition, the AT_1 pathway may activate a number of proto-oncogens that ultimately regulate genes involved with cell growth and extracellular matrix proteins.[87, 94–97] This process is important for myocardial hypertrophy and alteration in the collagen make-up of the heart.

Overall, the consequences of AT_1 activation by ATII is significant with regard to the pathophysiology of heart failure. They include vasoconstriction of blood vessels, release of

aldosterone and catecholamines from adrenal glands, release of vasopressin from the pituitary (leading to sodium and water retention), catecholamine release from the presynaptic terminal, myocardial hypertrophy, and alteration in the extracellular matrix of the heart. These effects may lead to symptoms and, most significant, progression of heart failure.

The role of the AT_2 receptor is less well known but appears to modulate or have the opposite effects of the AT_1 receptor. Angiotensin II stimulation of the AT_2 receptor may result in vasodilation by increasing nitric oxide.[98] Activation of the receptor may lead to antiproliferative effects and may cause apoptosis.[99–103] Theoretically, this may be beneficial in heart failure by counteracting negative effects that occur by ATII activation of the AT_1 receptor.

Aldosterone

Aldosterone may play a significant role in the pathophysiology of heart failure that goes beyond sodium and water retention. Circulating or plasma concentrations of aldosterone are produced in the adrenals. Angiotensin II stimulation of the AT_1 receptor increases aldosterone secretion, although other mechanisms also may do this, such as plasma potassium, adrenocorticotropic hormone, and endothelin, and decreased metabolic clearance.[104–108] These mechanisms may become important when ATII concentrations are suppressed by drug therapy with ACE inhibitors. This may account in part for the observation that aldosterone levels are suppressed only transiently but not over the long term after ACE inhibitor therapy.[109–111] This finding is referred to as aldosterone escape. Local

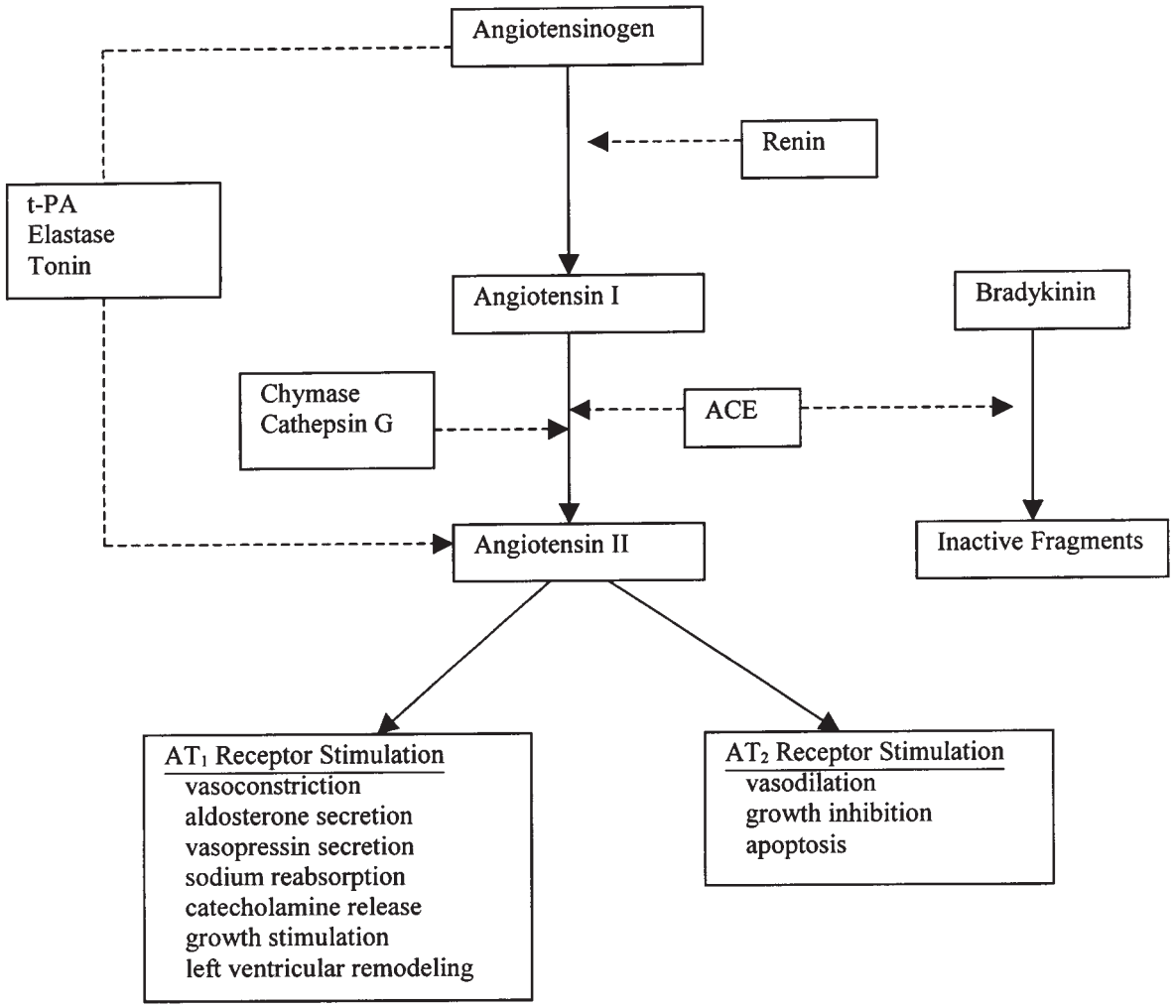

Figure 3. The renin-angiotensin-aldosterone system. ACE = angiotensin-converting enzyme.

synthesis of aldosterone may have important autocrine and paracrine effects on cardiovascular tissue because concentrations may be higher there than circulating aldosterone concentrations.[112–114]

Increased aldosterone concentrations may contribute significantly to the pathophysiology of heart failure and appear to be a prognostic indicator. Post hoc analysis from the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) showed that plasma levels elevated at baseline were associated with increased mortality ($p<0.01$) in patients with symptomatic New York Heart Association class IV disease.[115]

For several reasons, aldosterone may be important in the prognosis and pathophysiology of heart failure. It can promote sodium and water retention while increasing magnesium and potassium excretion.[116] Sodium and water retention can contribute to the symptoms of heart failure, and electrolyte loss may promote arrhythmia formation. Aldosterone also prevents uptake of norepinephrine by myocardium, which may be arrhythmogenic especially in the setting of low magnesium and potassium levels.[110, 116] It may reduce parasympathetic activity in part by directly decreasing baroreceptor discharge from the carotid sinus.[117–119] Reduced parasympathetic activity may be associated with increased mortality.[120, 121] Another mechanism by which aldosterone may contribute to the pathophysiology of heart failure is to stimulate collagen production, resulting in myocardial fibrosis that may contribute to left ventricular remodeling and dysfunction.[122–124] Aldosterone may cause vascular damage and decrease blood vessel compliance that may contribute to ischemia, which may promote arrhythmia formation and potentially heart failure progression.[125, 126] Animal data suggest that it may increase ATII binding and increase ATII hypertrophic response.[127] Overall, similar to ATII, and by several mechanisms, aldosterone significantly alters hemodynamics and has a direct effect on myocardium.

Conclusion

The pathophysiology of heart failure is complex and cannot be defined in simple terms. Based on information from animal and human studies, both the sympathetic nervous and RAA systems at many different levels contribute significantly to disease maintenance and progression. Therapies targeted at the pathophysiology of heart failure, or more specifically at these neurohormonal systems, are effective. They may not only significantly decrease morbidity and mortality but attenuate and, on some levels, actually reverse disease progression. As our understanding of heart failure continues to evolve, the approach to treatment will lead to new therapies including other neurohormonal antagonists and perhaps even gene therapy specifically design to arrest and reverse this devastating syndrome.

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