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Time and Technology Will Tell:

The Pathophysiologic Basis of Neurohormonal Modulation in Heart Failure

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Healers have been treating heart failure (HF) for millennia, but the central role of neurohormonal abnormalities in its pathogenesis and management was discovered only recently.¹ HF previously was understood almost entirely as the result of structural and functional abnormalities of the heart. In the eighteenth century, anatomists described gross enlargement of failing hearts removed at autopsy, and concluded rightly that hypertrophy was central to the pathobiology of HF. Technological advances in the early twentieth century permitted evaluation of the beating heart, and the field of cardiac physiology evolved. As a result, HF came to be conceived in mechanical terms: the fundamental insult in the failing heart was impaired contractility, and this abnormality was either exacerbated or alleviated by alterations in load. Structure and function reconciled well in animal physiology laboratories, because the hypertrophied and failing heart both resulted from and led to altered loading conditions.

The essential role of neurohormonal disturbances in human HF was recognized first in the 1970s and brought to prominence in the 1980s and 1990s.² In this conception of HF, circulating substances synthesized in the heart, kidneys, adrenal glands, and pituitary glands engendered the characteristic anatomic and physiologic abnormalities described by earlier researchers. HF was no longer simply a disease of the heart.

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Increased levels of aldosterone and vasopressin explained the chronically increased preload in the failing heart; norepinephrine and angiotensin (Ang) II induced pathologic hypertrophy and detrimental increases in afterload.

Randomized clinical trials (another important technological advance) reinforced the neurohormonal paradigm. In 1987, the CONSENSUS (Cooperative North Scandinavian Enalapril Survival Study) showed a 31% reduction in 1-year mortality in patients with end-stage HF treated with the angiotensin-converting enzyme (ACE) inhibitor, enalapril, confirming the importance of Ang II in the progression of HF.³ The use of beta-adrenergic receptor blockers (β -blockers) in HF was described first in 1981,⁴ although the first large mortality trial of β -blockers in HF was the MDC (Metoprolol in Dilated Cardiomyopathy) trial, published in 1993.⁵ MDC was followed in the next decade by the MERIT-HF (Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure), the US Carvedilol HF trials, CIBIS (Cardiac Insufficiency Bisoprolol Study) I and II, and COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival) trial, collectively proving that β -blockers improve survival in HF (reviewed in Ref.⁶).

In many respects, clinical trial data have provided the strongest endorsement of the neurohormonal paradigm. Drugs that alter hemodynamic parameters without blocking neurohormonal activation, including digoxin,⁷ non-potassium-sparing diuretics,⁸ and positive inotropes,⁹ have either neutral or negative effects on survival. In this respect, the contemporary use of neurohormonal modulators for HF pharmacotherapy offers an excellent example of reciprocity in translational science: elucidation of basic pathophysiology directs therapeutic targeting, and clinical trial results further inform the understanding of drug mechanism. This article discusses mechanisms of action for neurohormonal antagonists, with attention to both fundamental physiology and clinical trial outcomes.

THE SYMPATHETIC NERVOUS SYSTEM AND CARDIOVASCULAR PHYSIOLOGY

The sympathetic nervous system (SNS) is activated via arterial and venous baroreceptors and arterial chemoreceptors in response to decreases in perfusion pressure or oxygen delivery. In response, efferent fibers increase the release of norepinephrine (NE) (80%) or epinephrine (EPI) (20%) from synaptic varicosities in the myocardium and blood vessels, and stimulate the adrenal medulla to release NE (20%) and EPI (80%) into the blood. These hormones bind at least 9 different subtypes of adrenergic receptors (ARs) (3 beta-ARs [β 1, β 2, β 3], 3 alpha-1 ARs [α 1A, α 1B, α 1D], and 3 alpha-2 ARs [α 2A, α 2B, α 2C]) that are expressed variably by most cell types in the cardiovascular system and function primarily through G protein-coupled signaling cascades (Fig. 1).¹⁰

β 1-ARs predominate in the myocardium (70%–80% of total β -ARs), whereas β 2-ARs and β 3-ARs are less abundant (15%–18% and 2%–3% respectively) (see Fig. 1A).¹¹ The predominant β -AR in vascular tissue is β 2-AR, which mediates vasorelaxation (see Fig. 1B). Stimulation of β 1-ARs on cardiomyocytes activates stimulatory G protein (Gs) and protein kinase A (PKA), leading to increased contractility (via activation of L-type calcium channels and ryanodine receptors); heart rate (via stimulation of L-type calcium channels and

hyperpolarization-activated cyclic nucleotide-gated [HCN] channels); and rate of relaxation (via indirect stimulation of sarcoplasmic/endoplasmic reticulum calcium ATPase [SERCA] and Na/K-ATPase). Cardiomyocyte β 2-AR activation also increases inotropy, although these receptors are less abundant and have a lower affinity for NE. The β 2 is the predominant AR on cardiac fibroblasts, in which it likely plays important roles in HF pathobiology. β 3-ARs exert an exclusively negative inotropic effect through activation of nitric oxide.¹²

α 1-ARs are best known for their effects in vascular smooth muscle, where they promote vasoconstriction through activation of G_q , although myocardial α 1-ARs mediate broadly beneficial effects, including positive inotropy, physiologic cardiomyocyte hypertrophy, and protection from cell death.¹³ α 2-ARs are predominantly found in presynaptic terminals of adrenergic neurons and adrenal chromaffin cells, where they inhibit NE/EPI release via G_i -related signaling cascades that inhibit PKA activation.^{11,14} In this respect, α 2-ARs negatively regulate excess NE/EPI release and spillover in both central and peripheral adrenergic synapses.

THE SNS AND HF PATHOPHYSIOLOGY

Chronic catecholamine excess is central to the pathobiology of HF, and the degree of activation is directly proportional to disease severity.^{15,16} SNS upregulation also extends to the central nervous system, where NE spillover and turnover is increased.^{17,18} In the periphery, SNS upregulation is organ specific: it is preferentially activated in cardiac tissue in mild to moderate HF, and only becomes activated in the kidney and other organ systems in severe HF.^{19,20}

Chronic activation of cardiac β -ARs leads to pathologic cardiac hypertrophy and fibrosis: the hallmarks of ventricular remodeling. Increased levels of both local and circulating catecholamines lead to cardiac hypertrophy by acting directly on the cardiomyocyte β 1-ARs²¹ or by stimulating the paracrine release of other hormones such as Ang II and endothelin-1 (ET-1).²² SNS activation also leads to direct stimulation of β 2-ARs on cardiac fibroblasts, leading to fibroblast proliferation and increased release of cytokines such as interleukin-6, and hormones such as Ang II and ET-1. These factors in turn lead to increased collagen deposition, fibrosis, pathologic differentiation of fibroblasts into myofibroblasts, and cardiomyocyte hypertrophy.²³ Furthermore, chronic β 1-AR hyperstimulation in animal models leads to necrotic and apoptotic cardiomyocyte death, implicating sustained SNS activity in another important cellular mechanism of HF.²⁴

Upregulation of the SNS can also cause ventricular arrhythmias²⁵ via direct effects on cardiomyocyte calcium handling mediated in part by catecholamine-induced ryanodine receptor dysfunction.²⁶ Chronic catecholamine surge can also promote both atrial and ventricular arrhythmias in HF indirectly through increased fibrosis and remodeling.²⁷

Chronic myocardial β 1-AR activation ultimately results in the depletion of NE from cardiac nerve terminals, and downregulation of myocardial β -ARs.²⁸ The desensitization and inactivation of membrane-bound β -ARs is performed by G protein-coupled receptor kinases (GRKs) that phosphorylate ARs, facilitating binding to beta-arrestins that uncouple the

receptor from G proteins and target it for internalization.¹⁰ The downregulation of both myocardial and presynaptic ARs results in decreased cardiac inotropic reserve, further disabling the failing heart. Inhibition of β 1-AR downregulation by blocking GRK2 activity improves cardiac function and myocyte survival,²⁹ providing further evidence that the diminution of β -AR signaling is at least partially responsible for the pathogenesis of HF.

Inhibitors of the SNS

The success of β -blocker therapy offers perhaps the clearest example of the critical role of neurohormones in HF. Physiologic studies in animals and humans conclusively show negative inotropy resulting from acute β -AR antagonism,^{30,31} and clinical guidelines historically contained a contra-indication for β -blocker use in patients with HF.³² Nevertheless, studies in cells and animals established the fundamental role of chronic NE exposure in the pathophysiology of HF (reviewed in Ref.³³), leading to the incremental translation to clinical trials and practice.

Three β -blockers currently are approved for use in HF: metoprolol succinate, carvedilol, and bisoprolol. These drugs were selected from randomized clinical trial evidence, although debate exists about whether the specific pharmacology of these agents confers superiority or whether β -blocker benefits arise purely from antagonism of the β 1-AR.^{34,35} No trial has convincingly tested head-to-head efficacy of multiple β -blockers in HF.³⁶

β -Blockers can be classified broadly based on selectivity for AR subtypes, vasodilating effects, and intrinsic sympathomimetic or sympatholytic properties (Table 1). First-generation β -blockers are not as well-tolerated in patients with HF, possibly as a result of blockade of vascular β 2 receptors, which may shunt catecholamines to α 1 receptors and cause vasoconstriction.³⁷ Second-generation β -blockers are considered cardioselective because of their selectivity for β 1-ARs.

Third-generation β -blockers generally are distinguished from first-generation agents by their vaso-dilating effects. Nebivolol causes vasodilation by stimulating nitric oxide release, possibly through β 3-AR activation. Bucindolol is a nonselective β -blocker with intrinsic sympatholytic activity and weak α 1-blocking properties. Carvedilol blocks β 1-ARs, β 2-ARs, and α 1-ARs, and is the most widely studied of these agents. Although the benefits of carvedilol have been attributed widely to afterload reduction resulting from α 1-AR antagonism, this effect dissipates within weeks.⁴¹ Thus, carvedilol's beneficial effects likely are caused primarily by β 1-blockade, although it also has adaptive effects on cellular metabolism, oxidative stress reduction, and protection from apoptotic cell death.^{45,46}

Mechanisms of β -Blocker Benefit in the Human Heart

Underlying mechanisms for the benefits of β -blockers in HF have not been elucidated completely, but likely are complex and multifactorial given the broadly pathologic effects of chronic catecholamine surge (Table 2).

Hemodynamics

Acute blockade of myocardial β_1 -ARs has negative inotropic and chronotropic effects. Chronic β -blocker use improves cardiac performance in patients with HF, possibly because negative chronotropy increases filling time.⁶⁶ Heart rate reduction has been used as an index of β -blocker efficacy and a meta-analysis of 23 randomized clinical trials indicates that heart rate reduction is a more powerful predictor of benefit than β -blocker dose. For every heart rate decrease of 5 beats per minute in the pooled β -blocker groups there was an 18% reduction in risk of death.⁴⁷ The early success of the specific HCN channel blocker ivabradine,⁶⁷ which slows heart rate without modulating the SNS, may corroborate the primary importance of negative chronotropy in HF therapy.

Chronic β -blocker use does not decrease contractile function in patients with HF. Invasive hemodynamic studies show improved stroke volume and cardiac index, at rest and peak exercise, after chronic carvedilol treatment.⁶⁸ A meta-analysis of 21 randomized clinical trials found an absolute increase in ejection fraction of 4% in patients with HF treated with β -blocker relative to placebo,³⁴ and a separate analysis of 18 trials reported a 29% relative increase in ejection fraction.²⁵ Ex vivo experiments on failing human heart tissue suggest that β -blocker use improves inotropic response to β -AR agonists and restores aspects of physiologic cardiomyocyte calcium handling⁶⁹ and responsiveness.⁷⁰ β -Blockers also improve the diastolic performance of the hypertrophied human heart.⁷¹

Reverse remodeling

Numerous clinical trials show the favorable effect of chronic β -blocker use on ventricular remodeling. In a MERIT-HF substudy, left ventricular (LV) end-diastolic volume index decreased by 17% and LV mass index decreased by almost 10% after 6 months of metoprolol.⁴⁸ Metoprolol also decreased LV end-diastolic index by 10% to 15% in patients with asymptomatic LV dysfunction in the REVERT (Reversal of Ventricular Remodeling with Toprol-XL) study.⁴⁹ Both CAPRICORN⁵⁰ and the Australia–New Zealand HF Research Collaborative Group⁵¹ showed similar improvements with carvedilol.

β -Blockers decrease fibrosis in animal models of HF^{72,73} and reduce circulating markers of fibrosis in humans,⁷⁴ although direct effects are not readily demonstrable in human hearts, perhaps because the β_2 -AR is the predominant AR on cardiac fibroblasts.

Antiarrhythmic effects

Sudden cardiac death is the primary cause of mortality in patients with New York Heart Association class I - III HF, and the well-established antiarrhythmic effects of β -blockers also contribute to their survival benefit. Although sudden cardiac death was not reduced in all trials of β -blockade in HF, a reduction was seen in the BHAT (Beta-Blocker Heart Attack Trial),⁷⁵ CAPRICORN,⁷⁶ CI-BIS II,³⁸ and MERIT-HF.³⁹ A recent meta-analysis of 30 trials (24,779 patients) of β -blockers in HF found a 31% reduction in the risk of sudden cardiac death (odds ratio, 0.69; 95% confidence interval, 0.62–0.77) with a number needed to treat of 43 patients to prevent 1 sudden cardiac death per year.⁵² β -Blocker use also substantially decreases the risk of both appropriate⁵³ and inappropriate defibrillator therapies.⁵⁴

Molecular changes in human heart

Chronic β -blocker use in HF mitigates the characteristic decrease in myocardial β -AR abundance, although it is unclear whether this effect is essential for clinical or physiologic benefit.^{66,77} β -Blocker use also abrogates the pathologic changes in gene expression in the failing heart: α -myosin heavy chain abundance increases, β -myosin heavy chain decreases, and sarcoplasmic reticulum Ca^{2+} ATPase levels are restored.⁷⁷

Digoxin and the SNS

In the past, the usefulness of digoxin in HF has been attributed to its positive inotropic effects. However, these effects are only present at high serum digoxin concentrations (>1 ng/mL), at which an increased risk of mortality has also been observed.⁷⁸ It has been proposed that the benefits of digoxin at lower concentrations result in part from neurohormonal modulation. Among its many pharmacologic actions, digoxin decreases circulating norepinephrine and renin levels^{79,80} and has a favorable impact on natriuretic peptide release.⁸¹

Risks of sympatholysis in HF

Although the essential role of catecholamine excess in the pathophysiology of HF is beyond dispute, direct sympatholytic therapies have been associated with poorer outcomes. In a study of patients with chronic HF, a sustained-release preparation of moxonidine, an imidazoline receptor agonist that reduces sympathetic outflow, improved ventricular performance but led to an increase in serious adverse events.⁸² These risks were confirmed in a larger trial, which was terminated early because of a nearly 2-fold increase in death among those randomized to moxonidine.⁸³ The intrinsic sympatholytic properties of bucindolol may help explain why outcomes in the BEST (Beta-Blocker Evaluation in Survival Trial) were less favorable than those of other β -blocker clinical trials.⁴⁴

One conceivable explanation for the apparent risk associated with sympatholysis is the abrogation of adaptive effects of myocardial α 1-AR activation. Evidence from human studies suggests that the relative increase in α 1-AR expression observed in advanced HF may be a compensatory response to preserve myocardial function in the setting of β 1-AR downregulation and dysfunction.⁸⁴ These cardioprotective effects may explain why therapies that inhibit α 1-ARs have been linked to adverse outcomes in patients with HF. An arm of ALLHAT that randomized patients to the α 1-blocker doxazosin was stopped early for a 2-fold increase in incident HF.⁸⁵

THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM AND CARDIOVASCULAR PHYSIOLOGY

The renin-angiotensin-aldosterone system (RAAS) consists of a protease cascade that is activated by renin release from the juxtaglomerular cells of renal afferent arterioles. Renin is secreted in response to decreased renal perfusion pressure, decreased salt delivery to the distal convoluted tubule, increased renal sympathetic nerve activity, or changes in circulating natriuretic peptides. Renin catalyzes the cleavage of angiotensinogen, a circulating protein produced by the liver. The resulting peptide, angiotensin I (Ang I), is then

cleaved by ACE, to generate Ang II, which is among the most potent endogenous vasoconstrictors. Ang II binds to 2 G protein-coupled receptors, angiotensin II receptor, type I (AT1) and AT2. AT1 is the primary receptor expressed on vascular smooth muscle, endothelium, myocardium, neurons, and fibroblasts, whereas AT2 is primarily expressed early in development and its effects are less well understood in adults.^{86,87}

The other potent effector hormone of RAAS, aldosterone, is a steroid hormone released primarily from the adrenal cortex in response to increased Ang II and plasma $[K^+]$. Aldosterone binds to the intracellular mineralocorticoid receptor (MR) leading to increased salt and water reabsorption, increased blood volume, and alterations in ion-channel expression.⁸⁸

In the past, RAAS-associated hormones were considered to be renally controlled endocrine hormones that exerted effects widely throughout the body. However, it is now well understood that tissues such as the heart, blood vessels, lungs, and brain have an intrinsic RAAS that functions in an autocrine/paracrine manner.⁸⁹ In the heart, local stress, cellular damage, and stretch can each lead to an upregulation of locally produced RAAS components including ACE, Ang II, and aldosterone.^{90,91} It is now thought that cardiac-generated RAAS components play a major role in the progression of HF.⁹²

THE RAAS AND HF PATHOPHYSIOLOGY

Circulating and intrinsic Ang II and aldosterone are increased in HF, and contribute to HF pathophysiology through both extracardiac and direct cardiac effects.^{92,93} In vascular tissue, Ang II and aldosterone mediate increased vasoconstriction, unfavorable vascular remodeling, and endothelial dysfunction (Fig. 2B).^{94,95} Ang II and aldosterone promote sodium and water reabsorption in the proximal and distal convoluted tubules respectively. RAAS hormones also have important direct effects on myocardial cells.⁹⁶ Ang II induces cardiomyocyte hypertrophy and cardiac fibroblast proliferation through activation of AT1 receptors,⁹⁷ promoting cardiac hypertrophy independent of effects on blood pressure.⁹⁸ Aldosterone also promotes cardiac fibrosis through activation of mineralocorticoid receptors on cardiac fibroblasts (see Fig. 2A).

In addition to the directly deleterious effects of Ang II and aldosterone, RAAS also interacts with other neurohormonal signals that contribute to the pathobiology of HF. For example, local Ang II production leads to increased NE release from sympathetic nerve terminals in the heart.⁹⁹ Ang II also has effects on the central nervous system, causing a central activation of sympathetic nerves that target the cardiovascular system.¹⁰⁰ Central inhibition of AT1 receptors leads to a decrease in sympathetic nerve activity in the heart.¹⁰¹

In addition to these well-known RAAS constituents, several other RAAS enzymes contribute to cardiovascular regulation. ACE2, neprilysin (also known as neutral endopeptidase),⁸⁷ prolylendo-peptidases, and prolylcarboxypeptidases break down Ang I and II, ultimately leading to the generation of a peptide known as Ang(1–7).⁸⁷ Ang(1–7) acts on its own receptor, MasR, counteracting the effects of Ang II by causing vasodilation, decreased fibrosis, decreased oxidative stress, and decreased hypertrophy.¹⁰² In addition to cleaving Ang I, ACE also is the main enzyme that breaks down the vasodilator bradykinin.

It has been proposed that one of the key mechanisms of ACE inhibitors in the treatment of HF is increasing bradykinin levels, directly leading to vasodilation and decreased afterload.¹⁰³ However, increased bradykinin is also responsible for several of the side effects of ACE inhibitor treatment such as angioedema and dry cough.¹⁰⁴

Inhibitors of the RAAS

Inhibitors of RAAS used in the management of HF include ACE inhibitors, angiotensin receptor blockers (ARBs), and aldosterone receptor antagonists. ACE inhibitors prevent the conversion of Ang I to Ang II, whereas ARBs competitively inhibit the effect of Ang II on AT1 receptors in heart, kidney, and vascular tissue. Aldosterone receptor antagonists competitively inhibit the binding of aldosterone to mineralocorticoid receptors in the heart, kidney, and peripheral vasculature. The benefits of ACE inhibitors, ARBs, and aldosterone receptor antagonists in HF are considered class-wide effects, because clinical trials of multiple agents from each drug class show benefit. Higher doses of ACE inhibitors and ARBs confer greater reductions in hospitalizations compared with lower doses,^{105,106} but head-to-head comparisons between the two classes have been inconclusive.

Mechanisms of RAAS Blockade Benefit in Human HF

The benefits of RAAS antagonists initially were thought to result from their favorable effects on loading conditions as mediated by activity in the kidney and peripheral vasculature, but salutary direct myocardial effects are now recognized (see Table 2).

Hemodynamics

Decreased activation of vascular AT1 receptors by circulating Ang II produces vasodilation and thus decreases cardiac afterload. In addition, less salt and water are retained as a result of decreased downstream aldosterone release, thereby reducing preload. In one randomized hemodynamic trial, fasinopril decreased pulmonary capillary wedge pressure (preload) and systemic vascular resistance (afterload) acutely. After 10 weeks of therapy, preload and afterload were durably reduced and cardiac index was increased compared with placebo.⁵⁶ Aldosterone receptor antagonists cause a mild decrease in preload acutely through their potassium-sparing diuretic effects. However, a clinically meaningful diuretic effect is less commonly observed at the low doses used in HF and is unlikely to explain the magnitude of benefit observed in clinical trials.

Reverse remodeling

ACE inhibitors and ARBs have uniformly favorable effects on cardiac remodeling in HF. In the SOLVD (Studies of Left Ventricular Dysfunction) trial, 1 year of enalapril resulted in a 10% decrease in both LV end-diastolic and end-systolic volumes.⁵⁷ Similar results were reported with post-MI treatment with captopril in SAVE (Survival and Ventricular Enlargement) trial.¹⁰⁷ Losartan led to greater regression of LV hypertrophy than atenolol in the LIFE (Losartan Intervention For Endpoint) trial,⁵⁸ and treatment with valsartan led to decreased ventricular volume and increased ejection fraction in Val-HeFT (Valsartan Heart Failure Trial).⁵⁵

Aldosterone receptor antagonists reduced circulating markers of collagen turnover in both RALES (Randomized Aldactone Evaluation Study) and EPHEsus (Eplerenone Post-AMI Heart Failure Efficacy and Survival Trial), suggesting that inhibition of cardiac fibrosis contributes to the benefit associated with both spironolactone and eplerenone.^{62,63} However, aldosterone receptor antagonists do not consistently confer beneficial remodeling in clinical trials.⁶¹

Antiarrhythmic effects

In contrast with β -blockers, there is no clear signal that ACE inhibitors or ARBs reduce arrhythmias or sudden cardiac death in patients with HF.¹⁰⁸ For example, in CONSENSUS there was a 50% relative risk reduction in death caused by progressive HF, but no change in sudden cardiac death after treatment with enalapril.³ Aldosterone blockade reduces the risk of both atrial and ventricular arrhythmias, which may partly explain the reductions in sudden cardiac death observed in clinical trials.^{64,65} This antiarrhythmic effect may be caused by maintenance of physiologic serum potassium concentrations in the setting of aggressive loop diuretic therapy or it may be an epiphenomenon of reverse remodeling and decreased fibrosis.

Other effects

Animal studies reveal that ACE inhibitors have antiatherogenic effects resulting from inhibition of vascular smooth muscle cell proliferation and restoration of endothelial function.⁵⁹ Results from clinical trials substantiate these findings. ACE inhibitors improved post-MI outcomes in both SAVE and SOLVD and a large meta-analysis confirmed a 20% to 25% reduction in risk of acute coronary syndrome in patients with HF who received an ACE inhibitor.⁶⁰ ACE inhibitors also delay progression of renal dysfunction, which is a harbinger of poor outcome in HF.¹⁰⁹

ACE (aldosterone) escape

The efficacy of RAAS antagonists can diminish over time through an effect known as aldosterone or ACE escape, whereby a maladaptive increase in RAAS components is observed after chronic treatment with RAAS antagonists.¹¹⁰ ACE escape occurs in approximately 10% of patients within 6 months and 50% of patients within 12 months of starting treatment.¹¹¹ There are several potential physiologic explanations for this phenomenon. Prolonged inhibition of ACE or AT1 leads to increased levels of renin and Ang I because of the loss of negative feedback by Ang II. In the setting of ACE inhibition, several other enzymes such as chymase and cathepsin also cleave circulating and local Ang I to Ang II, leading to aldosterone production (escape).¹⁰⁴

Further, a receptor for renin and prorenin (inactive renin) has recently been discovered. Binding of (pro)renin to the (pro)renin receptor (PRR) leads to increased fibrosis and release of cytokines and prohypertrophic growth factors. PRR also serves an enzymatic function, generating active renin from inactive (pro)renin.¹¹²

Multiple clinical trials have investigated the possibility that dual RAAS antagonist therapy could abrogate ACE escape and improve outcomes in HF. Combined treatment with ACE

inhibitor and ARB produced incremental improvements in cardiovascular mortality and hospitalizations but was also associated with an increase in adverse events.^{113,114} Meta-analysis of 4 published clinical trials of RAAS combination therapy found a 2-fold increased risk of worsening renal function and a nearly 5-fold higher risk of hyperkalemia,¹¹⁵ likely caused by pronounced decreases in circulating aldosterone levels.

The compensatory increase in renin release in the setting of ACE inhibitor and/or ARB therapy has also prompted trials of direct renin inhibitors (DRIs) in patients with HF. It was postulated that renin inhibition would augment downstream RAAS blockade and provide additive benefits when combined with ACE inhibitor or ARB therapy. Although the DRI aliskiren reduces plasma renin activity, there is no evidence of a clinical benefit in HF. In ASTRONAUT (Aliskiren Trial on Acute Heart Failure Outcomes), a large randomized controlled clinical trial of patients on optimal HF therapy (including other RAAS antagonists), aliskiren failed to reduce a composite of cardiovascular death or hospitalizations and was associated with hypotension, renal dysfunction, and hyperkalemia.¹¹⁶ ATMOSPHERE (Aliskiren Trial of Minimizing Outcomes for Patients with Heart Failure), a trial comparing aliskiren with enalapril in patients with HF is underway.¹¹⁷

NATRIURETIC PEPTIDES AND CARDIOVASCULAR PHYSIOLOGY

The natriuretic peptides (atrial natriuretic peptide [ANP], B-type natriuretic peptide [BNP], and C-type natriuretic peptide [CNP]) collectively produce adaptive effects in HF and oppose the actions of the effector hormones of the SNS and RAAS. ANP is released by cells in the atrial wall in response to stretch or increases in plasma Ang II, ET-1, and vasopressin.¹¹⁸ BNP is released primarily from the left ventricle, although atrial cells also release BNP at a much lower concentration than ANP.¹¹⁹ CNP is released by endothelial cells in response to increased cytokines and other hormones such as acetylcholine.¹²⁰ ANP, BNP, and CNP bind to 2 transmembrane-bound guanylyl cyclases (GCs), GC-A and GC-B, to increase intracellular cyclic guanosine monophosphate (cGMP) and elicit wide-ranging physiologic effects including vasodilation, increased salt and water excretion, decreased renin release, dampened SNS activity, decreased cardiac fibrosis, and blunted cardiomyocyte hypertrophy.^{121–125}

Targeting Natriuretic Peptides for HF Therapy

Nesiritide is a recombinant form of BNP that binds GC receptors on vascular endothelium and in the kidney. Nesiritide mimics the salutary effects of endogenous BNP on cardiovascular hemodynamics and renal physiology, but does not reduce symptoms to a significantly greater extent than diuretics and vasodilators.¹²⁶ In large clinical trials, nesiritide did not improve survival, although early concerns over increased mortality and worsening renal function have subsided.

BNP has a short plasma half-life because of its removal by cellular reuptake, the natriuretic peptide clearance receptor (GC-C), and breakdown by neprilysin, the same enzyme that generates Ang(1–7) from Ang I.¹²⁷ Neprilysin inhibitors have been developed in an attempt to increase the half-life of circulating BNP for therapeutic benefit, although they typically

also have been designed to antagonize RAAS in order to counter the unfavorable effects of decreased Ang(1–7) levels. Omapatrilat, a vasopeptide inhibitor of both neprilysin and ACE, exerted favorable hemodynamic effects, but was associated with a more than 3-fold increase in angioedema compared with an ACE inhibitor, likely caused by its inhibition of both bradykinin and substance P degradation.¹²⁸ The focus has since shifted to compounds that both inhibit neprilysin and block Ang II receptors. A study comparing enalapril and LCZ696, a dual neprilysin inhibitor and ARB, in chronic HF is underway.¹²⁹

VASOPRESSIN IN HF PATHOPHYSIOLOGY AND PHARMACOTHERAPY

Vasopressin (arginine vasopressin [AVP]) is released in response to increased osmolarity, Ang II, or SNS stimulation, and is chronically increased in HF.¹³⁰ AVP is secreted primarily from the posterior pituitary, but local vasopressin production may also contribute to the progression of HF.¹³¹ Vasopressin stimulates the activity of 3 G protein–coupled receptors, V1_a, V1_b, and V2. V1_a, expressed on vascular smooth muscle and ventricular myocardium, couples to G_q, increasing intracellular calcium and causing vasoconstriction, positive inotropy, and hypertrophy.¹³² The V2 receptor mediates free water reabsorption in the kidney. Excess stimulation can lead to hypervolemic hyponatremia in patients with HF.

Recognition that AVP secretion is upregulated in HF prompted investigations of vasopressin receptor antagonists (VRAs) as another novel therapeutic strategy. Despite aggressive diuretic therapy, many patients with HF continue to retain excess free water and hyponatremia is common. However, whether hyponatremia represents a target of pharmacologic therapy or a surrogate marker for the severity of disease remains an area of controversy. VRAs competitively inhibit V₂ receptors in renal collecting ducts, thereby preventing the reabsorption of free water. Tolvaptan, an oral VRA, is selective for V₂ receptors, whereas intravenous conivaptan also inhibits V_{1A} receptors. In EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan), tolvaptan conferred improvements in some HF symptoms, but did not improve survival.¹³³ Although tolvaptan partially corrects hyponatremia, the effect is not durable after discontinuation of therapy.¹³⁴ The reasons for the modest clinical impact of this physiologically rational therapeutic approach are unclear.

SUMMARY

The depth to which disease mechanism is understood is often dictated by extant technologies. In that respect, the conception of HF was informed successively by gross anatomy, organ-level physiology, and cellular physiology. As outlined in this review, recent advances have enabled an expansion in knowledge of the cellular and subcellular mechanisms that underlie the characteristic neurohormonal disturbances in HF. How will today's emerging technologies influence understanding of HF? Will massively parallel sequencing technologies inform clinicians that HF fundamentally is a disease of genetic and epigenetic modifications?^{135,136} Will the next generation of HF therapies target DNA methylation? Epigenetic reader proteins?¹³⁷ Noncoding RNAs or microRNAs?¹³⁸ As always, only time will tell.

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KEY POINTS

- Neurohormonal abnormalities are central to the pathobiology of heart failure and antagonism of their systemic effects is the basis of contemporary heart failure pharmacotherapy.
- β -Blockers likely confer benefit through induction of reverse remodeling, reduction of sudden cardiac death, and restoration of adaptive adrenergic signaling.
- Antagonists of the renin-angiotensin-aldosterone system have beneficial activities in cells of the heart in addition to their effects in the kidneys and peripheral vasculature.
- All agents that improve survival in heart failure target neurohormones, but not all neurohormonal modulators improve survival.

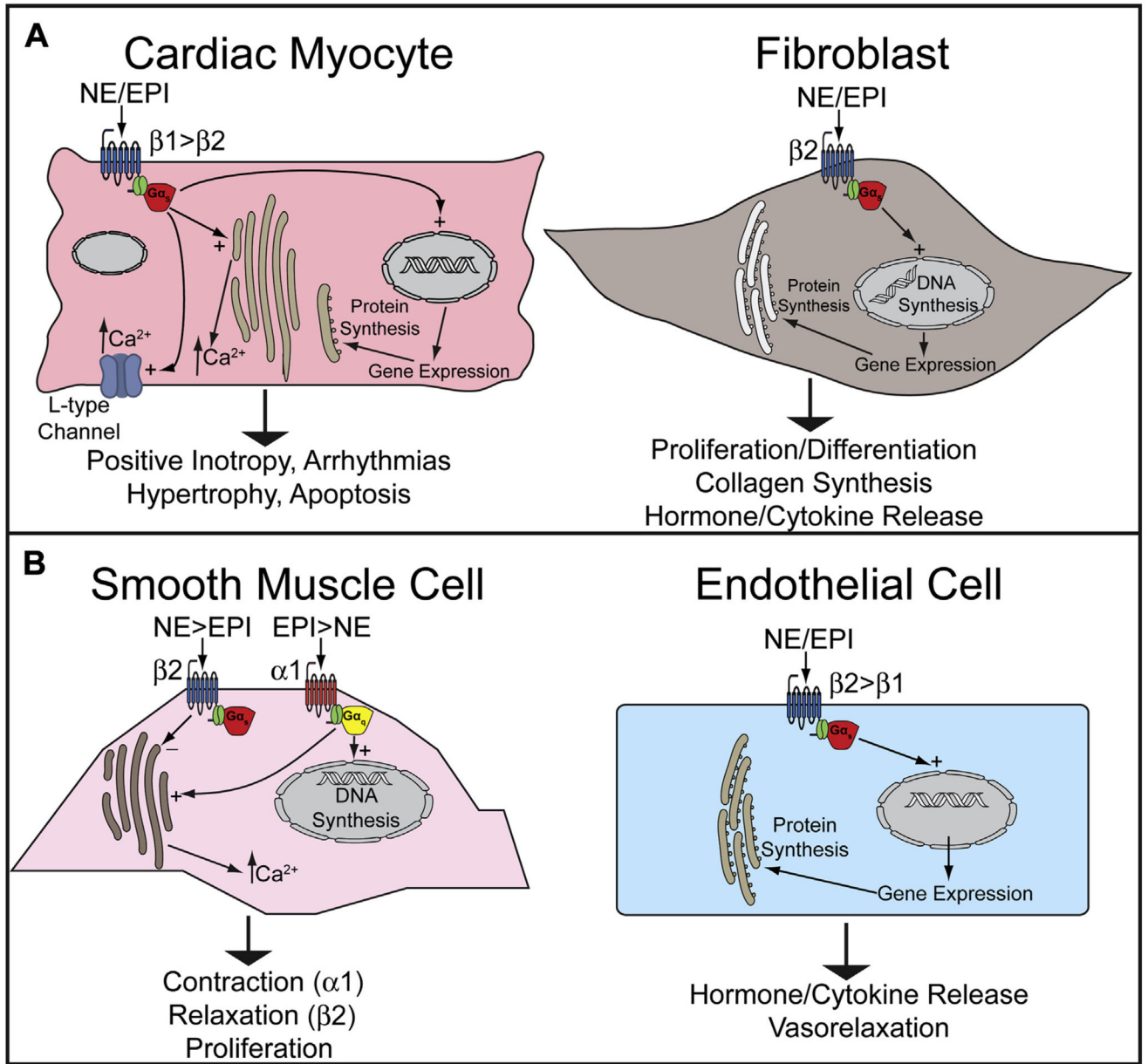


Fig. 1. SNS effector hormones and adrenergic receptor subtypes in cells of the (A) heart and (B) peripheral vasculature.

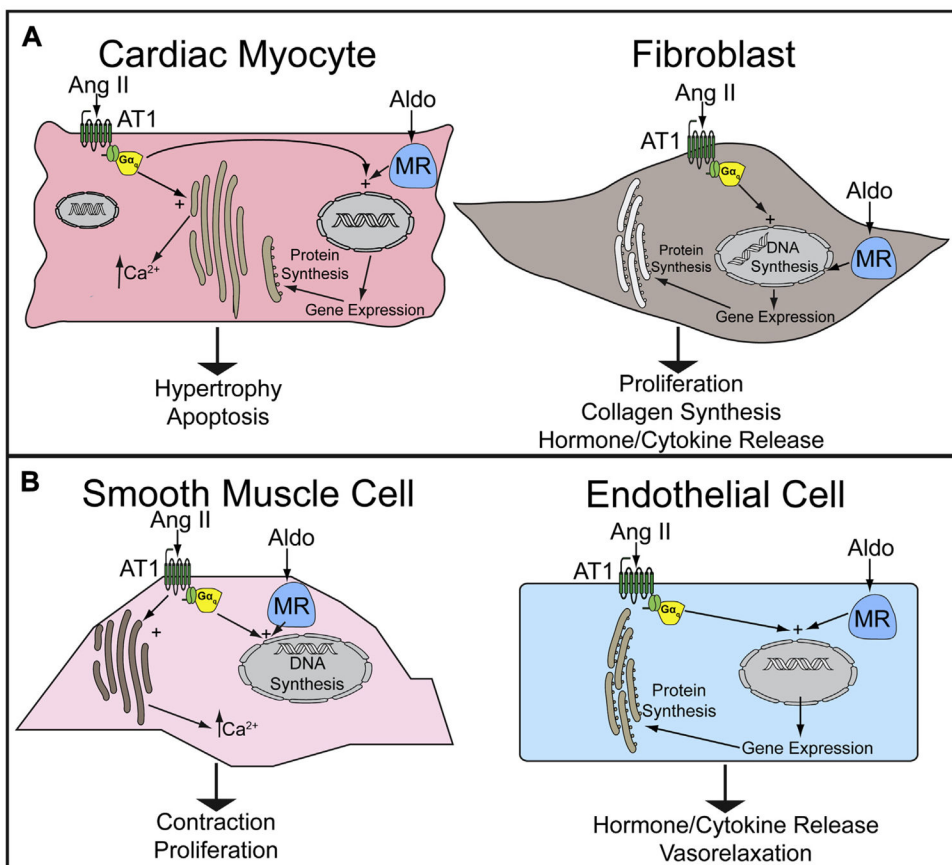


Fig. 2. RAAS effector hormones and receptors in cells of the (A) heart and (B) peripheral vasculature. Aldo, aldosterone.

Table 1

Classification and effects of β -blockers used in HF clinical trials

β -Blocker	β 1 Block	β 2 Block	α 1 Block	Vascular Effects	Survival Benefit
First Generation					
Propranolol	+	+	-	None or vasoconstriction ³⁷	No
Second Generation					
Bisoprolol	+	-	-	None	Yes ³⁸
Metoprolol	+	-	-	None	Yes ³⁹
Third Generation					
Carvedilol	+	+	+	Acute: vasodilation ⁴⁰ Chronic: none ⁴¹	Yes ⁴²
Nebivolol	+	-	-	Vasodilation	No ⁴³
Bucindolol	+	+	+(weak)	Vasodilation	No ⁴⁴

Table 2

Beneficial effects of neurohormonal antagonists in clinical trials of HF pharmacotherapy

Drug Class	Hemodynamic Effects	Remodeling Effects	Vascular Effects	Antiarrhythmic Effects
β -Blocker	\uparrow EF ^{25,34} \downarrow Heart rate ⁴⁷	\downarrow Volume ⁴⁸⁻⁵¹	Minimal	\downarrow Arrhythmias \downarrow SCD ⁵² \downarrow ICD shocks ^{53,54}
ACE inhibitor or ARB	\uparrow EF ⁵⁵ \downarrow Afterload ⁵⁶ \downarrow Preload ⁵⁶	\downarrow Volume ^{55,57} \downarrow Hypertrophy ⁵⁸	\downarrow Atheroma ⁵⁹ \downarrow ACS ⁶⁰ \uparrow Compliance	None
Aldosterone receptor antagonist	\uparrow EF	\pm Volume ⁶¹ \downarrow Fibrosis ^{62,63}	\uparrow Endothelial function	\downarrow Arrhythmias ^{64,65} \downarrow SCD ^{64,65}

Abbreviations: ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; EF, ejection fraction; ICD, implantable cardioverter defibrillator; SCD, sudden cardiac death.