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Mechanisms of Disease: detrimental adrenergic signaling in acute decompensated heart failure

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SUMMARY

Acute decompensated heart failure (ADHF) is responsible for more than 1 million hospital admissions each year in the US. Clinicians and scientists have developed therapeutic strategies that reduce mortality in patients with chronic heart failure (HF). Despite the widely appreciated magnitude of the ADHF problem, there is still a critical gap in our understanding of the cellular mechanisms involved and effective treatment strategies for hospitalized patients. Irrespective of the etiology, patients with ADHF present with similar symptoms (e.g. edema, altered hemodynamics and congestion) as multiple signaling pathways converge in a common phenotypic presentation. Investigations have shown that patients with ADHF have increased catecholamine levels, which cause chronic stimulation of β -adrenergic receptors. This overstimulation leads to chronic G-protein activation and perturbations in myocyte signaling, as the patient's heart attempts to adapt to progressive HF. Over time, these compensatory signaling mechanisms ultimately fail, and maladaptive signaling prevails with progressive worsening of symptoms. This Review summarizes some of the changes that occur during chronic adrenergic stimulation, and examines how downstream contractile dysfunction and myocyte death can alter the prognosis of patients with HF hospitalized for acute events.

Keywords

apoptosis; calcium; cardiac; necrosis; nitric oxide

INTRODUCTION

Heart failure (HF) is the most frequent hospital diagnosis in the US and the final common pathway for a variety of pathologic conditions.¹ Two key components of HF progression are structural and functional adaptations of cardiac myocytes. Initially, these changes in signal-transduction mechanisms are compensatory in light of increased cardiac demand; however, with time and as the disease progresses, they fail to correct the unfavorable changes and ultimately become maladaptive. β -Adrenergic-receptor (β AR) signaling has a key role in myocyte performance, and alterations in these signaling pathways are well-established disease pathways in HF.^{2,3}

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Competing interests

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Despite extensive guidelines for managing patients with chronic HF, few prospective randomized trials have studied patients with acute decompensated HF (ADHF); hence, there is no consensus on how these patients should be managed. The lack of effective treatment options is partly a consequence of the poor understanding we have of mechanisms in acute HF and the lack of prospective clinical trials demonstrating a change in mortality in ADHF with treatment. The 5-year mortality for HF is roughly 50%,¹ but recent data suggest that 1-year mortality in patients with HF who are admitted to hospital with ADHF could be as high as 33%.⁴ Conventionally, patients with ADHF can be divided into those who have a new diagnosis of HF, and those patients who have an acute decompensated event in the context of chronic HF. This Review focuses on the latter, larger group of HF patients who present with an acute decompensated event. The etiology of these patients is varied and a variety of circumstances can precipitate their hospitalization (Box 1).

In this Review, we attempt to present a nonpartisan view of ADHF highlighting β AR signaling as one of the final common pathways that may directly contribute to ADHF and the high mortality associated with this condition. We focus on the decreasing number of myocytes and altered excitation–contraction coupling (ECC) seen in patients with ADHF, as these two processes are likely to have a considerable impact upon the disease process and the patient's future constitution. We recognize, however, that these are not the only mechanisms that contribute to the disorder. Additional events that further exacerbate HF, such as fibrosis, pathological remodeling, dyssynchrony and hypertrophy, occur following the decrease in number of myocytes and worsening ECC associated with ADHF, leading to the progressive irreversibility of the disease.³ For demonstrative purposes only, we have selected the β AR to illustrate how its interactions with other signaling cascades can increase cell death through necrosis, apoptosis and perhaps autophagy (all three processes referred to as 'cell death', hereafter) and decrease contractile function (i.e. ECC; Figure 1). The mechanisms examined in this Review are not inclusive, nor is it the intent of the authors to imply that these mechanisms are more important than others not discussed.

Box 1 Possible reasons for hospitalization of patients with an acute decompensated event in the context of chronic heart failure

- New-onset ischemia (macrovascular or microvascular)
- Increased wall strain or increased intracardiac filling pressures (can be secondary to diastolic or systolic ventricular dysfunction)
- Nonadherence (e.g. medications, fluid or diet)
- Tachyarrhythmia (e.g. recurrent atrial fibrillation, ventricular tachycardia)
- Uncontrolled hypertension
- NSAID usage
- Excessive ethanol consumption or illicit drug usage
- Endocrinopathies (e.g. diabetes, thyroid disease)
- Worsening valvular disease with chronic pathological remodeling
- Concurrent infection or upregulation of metabolic needs with a fixed cardiac output (e.g. urinary tract infection in a NYHA class IV patient)
- Gastrointestinal bleed
- Pregnancy
- Chemotherapy

- Constrictive disease and/or restrictive physiology
- Infiltrative cardiomyopathy with an inability to compensate
- Complications of hypertrophic cardiomyopathy
- Uncompensated pulmonary hypertension or right-sided ventricular function
- Progressively decreasing cardiac output ('cold and dry')

HYPOTHESIS

Irrespective of the stage at which adverse changes in cell signaling occur (whether they involve G-protein coupled receptors, tyrosine kinase receptors, cytokine signaling or the nitroso–redox balance), the majority of these unique initiators converge on a limited number of downstream pathways to produce similar clinical end points—decrement in left ventricular (LV) performance, LV remodeling and congestion with increased systemic vascular resistance and in more infirm patients, a decrement in cardiac output.⁵ The observed decrease in cardiac function is, in part, a consequence of decreased contractile function and accelerated cell death. We propose that with each episode of ADHF, cardiac cell function does not completely recover to the prehospitalized level. Although patients may seem to be recovered at hospital discharge, they will have progressive deleterious myocyte signaling with each acute decompensated event. We propose that this pathological signaling will continue to accelerate, irrespective of whether the outward phenotype suggests improved hemodynamics. We hypothesize that ADHF is part of the progressive pathophysiology of chronic HF, not just an inevitable consequence of the disease. In fact, the current standard of care could actually worsen a patient's long-term cardiac function, despite some perceived recovery in the short term (Table 1).

Maladaptive adrenergic signaling and increased cell death

Despite intensive investigation, the complete role of adrenergic signaling in HF development and the mechanism of action of β -blockers as a HF therapy have not yet been completely elucidated. Originally, it was hypothesized that β -blockers repopulated cell membranes with β ARs. This concept was partly based on the observation that the density of β ARs was reduced in patients with HF, and functional coupling of the remaining receptors with their G proteins was impaired. This concept has not been generally supported, however, as some of the most efficacious β -blockers, such as carvedilol, have not been shown to resensitize β ARs.⁶ Nevertheless, many β -blocker trials have demonstrated consistent improvement in HF with treatment, measured as improved LV function and attenuation in chamber size ('reverse-remodeling').^{7–9} These dichotomous results have led many investigators to conclude that the improvements seen in these clinical trials were mediated by more complicated and as yet poorly delineated, molecular and cellular signaling pathways.

β -Adrenergic receptor signaling

Aside from changes in myocyte cell size and tissue composition, an important component of LV remodeling during HF progression involves alteration of β -adrenergic signaling pathways. These pathways are important modulators of cardiac performance in normally functioning hearts and contribute to the equipoise between ECC and cell death. Catecholamines serve as endogenous agonists for both β_1 ARs and β_2 ARs, which when stimulated activate G_s proteins. Stimulation of G_s proteins increases cyclic AMP levels via activation of adenylyl cyclase. Of note, β_1 ARs use only G_s proteins, while β_2 ARs use two G proteins, G_i and G_s ; β_1 ARs have been implicated as being pathological in HF, whereas β_2 ARs have generally been perceived to be protective.^{10,11} This paradigm may or may not be true in chronic human HF. With progressive chronic HF and increased sympathetic tone, chronic increases in agonist exposure

leads to a decrease in the density of β_1 ARs, while the density of β_2 ARs actually increases as the patient's condition worsens.¹² This change in receptor density might change signaling preferences, as well as the efficacy or mechanism of action of specific β -blockers. Biased agonists may utilize different G-protein signaling pathways preferentially to maximize the effect of a given drug class.¹³ Despite downregulation of β_1 ARs in HF (the AR most implicated in worsening HF), empirical evidence has shown that the overall condition of patients with ADHF usually worsens, suggesting that β_2 AR and α_1 AR signaling could have a greater role in the progression of HF than previously appreciated. Perhaps the key to success with the next generation of β -blockers will lie with their ability to favorably alter the G_i – G_s protein balance and subsequent downstream signaling. Some newer therapies might actually circumvent the β ARs or use G-protein-independent pathways to selectively activate more favorable signaling.^{13,14} Of note, clinical trials have demonstrated that time-dependent administration of selective and nonselective β -blockers leads to chronic ventricular reverse-remodeling and an attenuation in mortality not attributable to hemodynamic changes alone.^{6,8,9} Data also suggest that chronic administration (i.e. at least 3–6 months, preferably years) of β -blockers is essential for functional changes and a survival benefit to be seen.¹⁵

Following receptor activation, second-messenger-dependent protein kinases, including cyclic-AMP-dependent protein kinase (PKA), phosphorylate serine and threonine residues within the cytoplasmic loops and C-terminal-tail domains of the β ARs. Phosphorylation of these sites is sufficient to impair receptor–G-protein coupling.¹⁶ An additional mechanism for desensitizing the receptor, which does not require agonist activation, involves G-protein receptor kinases (GRKs) and β -arrestin, a regulatory protein that initiates and attenuates various signaling pathways. One of the principle functions of GRKs in adrenergic signaling is to increase receptor affinity for β -arrestin through serine/threonine phosphorylation.^{17,18} Following GRK-mediated phosphorylation of the receptor, it is the binding of β -arrestin to the AR complex that leads to receptor desensitization and internalization. Irrespective of the HF model, chronic downstream adrenergic activation leads to an upregulation of GRKs, protein phosphatases, G_i protein and PKA expression, which is usually paralleled by a decrement in G_s expression and a reduction in sarcoplasmic reticulum calcium (Ca^{2+}) levels and an increase in cytosolic Ca^{2+} concentration.³ Mediated through PKA and calcium/calmodulin-dependent protein kinase II (CaMKII) mechanisms, chronic β -adrenergic stimulation increases apoptosis by increasing sarcoplasmic reticulum stress, deregulating mitogen-activated protein kinases, and unbalancing or making phosphoinositide 3-kinase–protein kinase B (AKT) signaling ineffective by inducing changes in the location and phosphorylation of AKT, thus, altering its protective mechanisms (Figure 2).^{19,20} These intracellular events lead to an observable change in the functional capacity of the failing heart with an observed decrement in myocyte contractile function and a decrease in the total number of myocytes.

Myocardial tissue changes and cell death

A hallmark feature of HF progression in both animal models and humans is the time-dependent adaptation of myocardium that leads to changes in cardiac myocyte performance and subsequent changes in myocardial tissue composition.²¹ For example, ventricular chamber dilation, myocyte hypertrophy and interstitial fibrosis are all well-recognized features of HF.²² Elevated sympathetic nervous system activity is also common, as the body attempts to maintain cardiac output and systemic perfusion. Each of these changes can be considered as adaptations for acute increases in cardiac demand, but it is likely that they also contribute to progressive pump failure and are considered deleterious over the long term.²³ Recent studies have shown evidence of myocyte ‘drop out’ during HF progression, suggesting that myocyte populations continuously decline in the failing myocardium, increasing the demand on those remaining.^{24,25} These findings are consistent with increasing levels of cell death as a result of progressive detrimental molecular signaling and not as a consequence of hemodynamic

dysregulation.²⁶ During pathological remodeling, an absolute reduction in the total number of myocytes contributes to the outward phenotype. This cell loss leads to decreased wall thickness, increased wall strain and dyssynchrony, all of which add to subsequent additional cell loss and progressive maladaptive physiology as the patient's ventricular function continues to decline.²⁷

Apoptosis

Several investigators have suggested that apoptotic signaling is increased 232-fold in patients with progressive HF compared with matched controls.^{27,28} We believe the rate of apoptosis is also increased in patients with ADHF. The majority of apoptotic signaling cascades coalesce with the activation of a group of constitutively active proteases called caspases that are activated by proteolytic cleavage or dimerization. When activated, caspases coordinate signaling cascades that ultimately lead to myocyte death. Caspase activation can occur through two interwoven pathways within myocytes and fibroblasts. The extrinsic pathway is associated with increasing inflammatory response and cytokine signaling, and is known to be upregulated in some types of ADHF. The activation of this pathway usually requires agonists to bind to cell-surface receptors ('death receptors') such as the Fas and tumor necrosis factor (TNF) receptors, which then interact with adaptor molecules, transducing the signal. This receptor signaling then activates pro-caspase-8, which subsequently acts upon BH3-interacting domain death agonist (BID) and caspase-3. In turn, caspase-3 activates caspase-7 and, thereafter, both act as 'executioner' or effector caspases by translocating to the nucleus and degrading essential components. Some data suggest that nonspecific β -blockers decrease TNF-induced apoptosis in human cells.²⁹

The other 'intrinsic' apoptotic pathway is mediated through perturbations in Ca^{2+} signaling and mitochondrial and sarcoplasmic reticulum stress. Eloquent, early studies in humans demonstrated aggressive apoptosis and upregulation of proteases in specific cardiomyopathies. Through a variety of signaling mechanisms, cytochrome c translocates from the mitochondria to the cytosol. Once in the cytosol, cytochrome c binds to apoptosis protease activating factor 1 (APAF-1) and pro-caspase-9, forming the apoptosome. This protein complex then cleaves pro-caspase-9 releasing active caspase-9, which subsequently activates caspase-3, leading to DNA fragmentation and cell death.^{23,28,30–33}

CONTRACTILITY IN ACUTE DECOMPENSATED HEART FAILURE

New data suggest that apoptotic signaling is not as simple as first thought—that the apoptotic cascade was either active (cell death) or inactive (no cell death).³⁴ It is now recognized that apoptotic signaling cascades can decrease contractile function before cell death by cleaving contractile proteins.^{35,36} In this regard, overexpression of caspase-3 can directly reduce LV contractile function.³⁶ In addition, caspase inhibition has been shown to improve contractile function by attenuating contractile protein loss.³⁷ A decreased contractile state with activated apoptotic signaling could be an intermediate state of 'cell death' in which cells can progress towards death, continue to be dysfunctional or, in the correct environment, recover. In transgenic animals, overexpression of caspase-8 revealed a direct correlation between expression of this protein and increased myocyte death.²⁴ In addition, even at low levels of caspase-8 expression, significant failure was induced in the animal model of chronic HF.²⁴ Similar lines of investigation have indicated that activating apoptosis intermediates also results in development of severe cardiomyopathies and contributes to decreased contractile function.^{35,36} Of note, altered Ca^{2+} handling can lead to apoptosis, but also contribute to contractile dysfunction.^{37,38} The caspase cascade and Ca^{2+} mishandling are examples of how apoptosis and contractile dysfunction intersect.

Excitation–contraction coupling

The initiating event in ECC is firing of the action potential, which leads to Ca^{2+} influx via the L-type Ca^{2+} current ($I_{\text{Ca-L}}$). This Ca^{2+} influx, also known as the trigger Ca^{2+} , activates the Ca^{2+} release channels found on the sarcoplasmic reticulum—the ryanodine receptors—causing a graded release of Ca^{2+} from the sarcoplasmic reticulum, a process termed Ca^{2+} -induced Ca^{2+} release. The myofilaments are, in turn, activated by this increase in Ca^{2+} concentration such that there is a direct, though nonlinear, relationship between free Ca^{2+} concentration and contraction. The Ca^{2+} sensitivity of the myofilaments can also be altered (e.g. by β -adrenergic stimulation) to further regulate contraction and relaxation. After activation, the Ca^{2+} concentration returns to diastolic levels via uptake by the sarcoplasmic/endoplasmic reticulum calcium ATPase/phospholamban (SERCA/PLB) complex and the Na^+ – Ca^{2+} exchanger (NCX), a process that also contributes to the action potential waveform.³⁹

The cardiac dysfunction in HF can be observed at the cellular level as a blunted force-frequency response.⁴⁰ Much of this dysfunction is due to changes in the expression of certain proteins such as transient outward potassium channels, inward rectifier potassium channels, NCX, ryanodine receptors and SERCA, among others.³⁹ These protein expression changes lead to increased action potential duration, reduced Ca^{2+} transient and shortening amplitude, and slowed rates of cytosolic Ca^{2+} decline and relaxation.⁴¹ Clinically, medications that further attenuate Ca^{2+} handling (e.g. calcium-channel blockers) increase mortality in patients who already have decreased ventricular function.

Calcium/calmodulin-dependent protein kinase II

The δ isoform of CaMKII is the predominant isoform found within myocytes. CaMKII is a serine/threonine kinase that is activated by Ca^{2+} and calmodulin. Within myocytes, the Ca^{2+} transient leads to oscillations of Ca^{2+} –calmodulin concentration,⁴² which can activate CaMKII on a beat-per-beat basis. In addition, autophosphorylation of CaMKII keeps calmodulin bound to the kinase to retain activity even after Ca^{2+} levels decrease. Intriguingly, independent of its effects on Ca^{2+} handling, sustained β AR stimulation can increase CaMKII activity directly.⁴³ While CaMKII can modulate many proteins involved in ECC, its major action is the regulation of ryanodine receptors.⁴⁴ CaMKII-mediated phosphorylation of ryanodine receptors increases diastolic Ca^{2+} leak from the sarcoplasmic reticulum, which is disadvantageous as it reduces sarcoplasmic reticulum Ca^{2+} load, a main determinant of contractility,⁴⁵ and increases the propensity for arrhythmias.⁴⁶ Interestingly, the leak associated with increased β AR stimulation is attributable to increased activity of CaMKII and not PKA.⁴³ Importantly, increasing Ca^{2+} flux via ryanodine receptors alone is not sufficient to cause arrhythmogenic Ca^{2+} waves. Another stimulus is, therefore, needed to keep sarcoplasmic reticulum Ca^{2+} content at a level sufficient for Ca^{2+} wave production.⁴⁷ We believe that in ADHF, continued β AR stimulation activates CaMKII, causing diastolic Ca^{2+} leak from the sarcoplasmic reticulum via ryanodine receptor phosphorylation, and that PKA activation maintains sarcoplasmic reticulum Ca^{2+} at a level sufficiently high for the production of arrhythmogenic Ca^{2+} waves. In addition to alterations in Ca^{2+} handling, CaMKII can also phosphorylate ion channels. For example, CaMKII can phosphorylate Na^+ channels, enhancing the late (persistent) Na^+ current, which leads to a prolonged QT interval and increased Na^+ concentration.⁴⁸ These effects lead to monomorphic and polymorphic ventricular tachycardia and arrhythmias, which can be further exacerbated by hypokalemia and hypomagnesemia in patients with ADHF. Sustained CaMKII activation seen in ADHF could, therefore, lead to electrophysiological changes that make the patient more prone to sudden cardiac death (Figure 3).⁴⁹

Reactive oxygen species

Studies have shown that chronic activation of the β AR pathway can lead to increased production of reactive oxygen species (ROS). This effect is most probably mediated via downregulation of copper–zinc-superoxide dismutase.⁵⁰ Moreover, during acute decompensated episodes there is an inflammatory response caused by an increase in diastolic wall stress because of pressure and volume overload. This increase in wall stress leads to the production of the inflammatory cytokines TNF, interleukin 1 and interleukin 6.⁵¹ Another possible cause of cytokine production is mesenteric venous congestion or bowel-wall edema, or hypoperfusion, which lead to intestinal bacterial translocation, endotoxin release, and subsequently an immune response.⁵² Indeed, a study demonstrated a transient increase in cytokine production in patients admitted for ADHF that peaked 12 h after admission and steadily decreased until steady-state was achieved 2 weeks after admission.⁵³ An increase in cytokine levels also leads to increased production of ROS.⁵⁴ We, therefore, believe that ROS production is greatly increased during ADHF.

Many studies have shown that direct exposure to ROS will lead to contractile dysfunction.^{55,56} This negative inotropic effect of ROS occurs via modulation of sarcoplasmic reticulum function, membrane currents, myofilaments and direct G-protein signaling. ROS can decrease SERCA activity, reducing Ca^{2+} uptake and sarcoplasmic reticulum Ca^{2+} load.⁵⁷ An increase in cellular ROS concentration can also increase NCX activity.⁵⁸ This increase in NCX activity when coupled with an increase in cytosolic Na^+ can lead to an increase in reverse-mode NCX. Consistent with this hypothesis, inhibition of reverse-mode NCX inhibits the increase in diastolic force that normally occurs after ROS exposure.⁵⁶ In addition, raised ROS levels lead to an increase in ryanodine receptor open probability (as with CaMKII).⁵⁹ The threshold stimulating Ca^{2+} leak from the sarcoplasmic reticulum can, thus, be reduced via ROS-mediated (and CaMKII) modulation of ryanodine receptor activity.

The Na^+ channel is also affected by changes in ROS concentration. ROS-induced activation of the late Na^+ current leads to prolonged action potential duration, increased cellular Na^+ concentration and early afterdepolarizations.⁶⁰ Effects related to both Na^+ and Ca^{2+} channel changes occur early in ROS-induced dysfunction, and the alterations in Ca^{2+} handling outlined previously are responsible for the early cellular injury. The late phase of injury is most probably caused by myofilament changes; it is hypothesized that the increase in Ca^{2+} activates calpain, leading to the degradation of the troponin complex, which influences myofilament sensitivity.⁵⁶ ROS (H_2O_2 in particular) can also decrease G_s protein activity, leading to decreased adenylyl cyclase activation following β AR stimulation.⁵⁵ The net effects of increased ROS concentration are, thus, a shift in the Ca^{2+} pool location, from the sarcoplasmic reticulum to the cytosol, a decrease in Ca^{2+} -induced Ca^{2+} release, an increase in Na^+ concentration (which ultimately leads to increased diastolic tension), reduced developed tension, a decreased β AR responsive, and ultimately the development of arrhythmias (Figure 3).

Reactive nitrogen species

Nitric oxide (NO) and related congeners are signaling molecules that modulate cardiac contractility. Cardiac myocytes express three isoforms of NO synthase. Neuronal NO synthase (nNOS or NOS1) and endothelial NO synthase (eNOS or NOS3) are constitutively expressed and produce low amounts of NO, while inducible NO synthase (iNOS or NOS2) is not normally expressed in cardiac myocytes. NOS2 expression is induced during an inflammatory response, common in patients with HF,⁶¹ and once expressed, produces much higher levels of NO than do NOS1 and NOS3.⁶² Sustained β AR stimulation can upregulate NOS2 expression and the formation of reactive nitrogen species (e.g. peroxynitrite).⁶³ Interestingly, cyclic AMP can stabilize NOS2 mRNA, resulting in even greater NOS2 concentrations.⁶⁴ We believe that NOS2 expression is increased substantially during ADHF as a result of the activated

inflammatory-mediated mechanisms and sustained β AR stimulation. Studies have shown that once expressed, NOS2 diminishes the cellular response to β AR stimulation via alterations in Ca^{2+} handling.^{62,65,66} Overexpression of NOS2 and the resulting elevated production of NO and ROS will in turn lead to the formation of peroxynitrite. We have found that the peroxynitrite donor 3-morpholininosyndomine (SIN-1) decreases the β AR response, predominantly through activation of protein phosphatases that decrease the level of PLB phosphorylation.⁶⁷ This pathway might prove to be central in the β AR hyporesponsiveness observed in ADHF. Interestingly, failing human myocytes treated with an NOS2 inhibitor had a near-normal response to β AR stimulation,⁶⁶ indicating that NOS2 signaling could also have a role in β AR receptor desensitization, possibly via altered palmitoylation.⁶⁸

NOS1 and NOS3 signaling might also be involved in the pathogenesis of ADHF. NOS1 and NOS3 signaling are in fact dissimilar, targeting different ECC proteins and leading to diverse functional effects.⁶¹ NOS1 and NOS3 provide some degree of protection for patients with HF;^{69,70} however, as HF develops the expression of NOS3 decreases,⁷¹ resulting in a negation of its protective role. Interestingly, in the failing heart, NOS1 translocates from the sarcoplasmic reticulum to the caveolae.⁷¹ We believe that this translocation is due to the loss of NOS3—with decreased NOS3 expression, NOS1 takes up a functional role similar to that of NOS3 in order to maintain protection and decrease the detrimental effects of sustained β AR stimulation. In fact, a study has shown that translocation of NOS1 leads to a reduced β AR response.⁷² With the increased NO production via NOS2, we envision that the protective roles of NOS1 and NOS3 are further diminished in HF. Specifically, the compartmentalized and tightly regulated NO production via NOS1 and NOS3 seen in the normal heart will be lost with the high NO concentration resulting from increased NOS2 expression (Figure 3). This altered NOS1 and NOS3 signaling may also enhance GRK-mediated desensitization of the β AR receptors.⁷³

It is important to note that the nitroso–redox balance—the equilibrium between NO and ROS concentrations—is tightly regulated in normal hearts and altered in HF.⁷⁴ The altered spatial and temporal production of NO and ROS leads to peroxynitrite formation, which has profound functional effects on the response to β AR stimulation.

CONCLUSIONS

During pathological remodeling, it is now known that an absolute reduction in the total number of myocytes contributes to HF progression.^{27,28} Furthermore, apoptotic signaling cascades may decrease contractile function before cell death by cleaving contractile proteins.^{34,35} Additional changes in intracellular Ca^{2+} handling have a profound effect in ADHF. The decrease in internal sarcoplasmic reticulum Ca^{2+} levels^{40,75} and concordant increase in cytosolic Ca^{2+} concentration leads to a decrease in contractile function and an increase in apoptotic signaling. The result is fewer myocytes, and a decrease in contractile function of the remaining myocytes. In addition, progressive nitroso–redox biology activates mitochondrial apoptotic machinery, while simultaneously having a deleterious effect on ECC.⁶⁶ A switch in β AR signaling is a key feature of progressive HF. In order for patients to truly recover, there must be a change in the chronic deleterious signaling mechanisms in the remaining myocytes. Our data suggest that fibrosis is not significantly reversed with physiologic or functional recovery, nor does the number of myocytes increase significantly.⁷⁶ That clinicians and basic scientists will be able to retread these maladaptive signaling pathways is unlikely. As such, innovative ways to ‘reverse’ signaling in sick hearts is required. Future therapies targeted towards cell death and altered ECC present hope for improved reverse remodeling and better patient outcomes.

KEY POINTS

- Acute decompensated heart failure (ADHF) is a large clinical problem, yet little is known about the basic mechanisms associated with disease progression; the final common pathway in ADHF is increased adrenergic signaling, independent of ADHF etiology
- Long-term (or maladaptive) adrenergic signaling in ADHF will lead to activation of calcium/calmodulin-dependent protein kinase, increased cytokine levels, nitroso–redox imbalance, and a shift in Ca^{2+} pools from the sarcoplasmic reticulum to the cytosol
- Maladaptive adrenergic signaling leads to caspase activation, cytochrome c translocation and progressive cell death, leading in turn to progressive worsening of heart function
- Maladaptive adrenergic signaling alters cardiac excitation–contraction coupling, which leads to decreased contractility and an increased propensity for arrhythmias
- Therapeutic targeting of these two common pathways (cell death and altered excitation–contraction coupling) of ADHF may improve patient recovery

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Figure 1.

Altered adrenergic signaling following an acute episode of ADHF initiates a maladaptive cellular response. Although hemodynamics are usually improved before discharge, mortality subsequent to hospital discharge is increased. ^aSee Box 1. ^bSee reference ⁴. Abbreviation: ECC, excitation–contraction coupling.

Figure 2.

Chronic βAR stimulation perturbs normal signaling (increasing PKA, CaMKII, and diastolic Ca²⁺ levels, and making PI3K/AKT signaling ineffective) leading to many maladaptive mechanisms including mitochondrial swelling and cytochrome c release. The release of cytochrome c ultimately activates the caspases, resulting in increased apoptosis and decreased contractile function. With persistent decompensated heart failure there is progressive decrease in myocyte contractile function, while the total number of myocytes decreases secondary to apoptosis, adrenergic-mediated necrosis and autophagy. Blue lines represent direct βAR activation, while green lines represent G-protein-independent signaling. Abbreviations: AKT, protein kinase B; βAR, β-adrenergic receptor; Ca²⁺, calcium ions; CaMKII, calcium/calmodulin-dependent protein kinase II; cAMP, cyclic AMP; GRK, G-protein receptor kinases; IP₃R, inositol triphosphate receptor; PI3K, phosphoinositide 3-kinase; PKA, cyclic-AMP-dependent protein kinase; PLB, phospholamban; RGS, regulator of G-protein signaling; RyR, ryanodine receptor; SR, sarcoplasmic reticulum.

Figure 3.

Possible mechanisms of reduced contractility in acute decompensated heart failure. Chronic β AR stimulation activates CaMKII, NOS2 expression and increased ROS production. In addition, NOS1 and NOS3 expression and localization might be altered. The ensuing difference in spatial and temporal nitric oxide production, coupled with increased ROS production, results in RNS formation and altered nitroso-redox balance. Stimulation (blue) or inhibition (red) of targeted excitation-contraction coupling proteins will result in contractile dysfunction and increased diastolic Ca^{2+} concentration. Abbreviations: β AR, β -adrenergic receptor; Ca^{2+} , calcium ions; CaMKII, calcium/calmodulin-dependent protein kinase II; GRK, G-protein receptor kinase; Na^+ , sodium ions; NCX, Na^+ - Ca^{2+} exchanger; NOS1, neuronal nitric oxide synthase; NOS2, inducible nitric oxide synthase; NOS3, endothelial nitric oxide synthase; PLB, phospholamban; RNS, reactive nitrogen species; ROS, reactive oxygen species; RyR, ryanodine receptor; SR, sarcoplasmic reticulum.

Table 1

Medical therapies commonly used to treat patients with acute decompensated heart failure.

Drug class	Short-term effect (i.e. 1–3 days)	Intermediate-term effect (i.e. 4–14 days)	Long-term effect (i.e. >14 days)
ACE inhibitors	±	++	+++
Digoxin	±	+	½+
Loop diuretics	++	+	–
Aldosterone antagonist	±	+	++
Morphine sulfate	++	+	+
Vasodilators	+++	++	++
Inotropes	++	– –	– – –
β-Blockers	±	+	+++
Arterial dilators	±	+	+

Abbreviations: +, favorable effect; –, detrimental effect; ±, favorable and detrimental effects; ACE, angiotensin-converting enzyme.