UTSWMC Internal Medicine Grand Rounds

Growth and Death: Two Sides of the Same Coin in Chronic Heart Failure

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A. INTRODUCTION:

Cardiac failure due to a cardiomyopathy (myocardial failure) is generally regarded as an irreversible and progressive process characterized by ventricular enlargement, geometrical chamber alterations, eccentric hypertrophy, mechanical insufficiency, and depressed pump performance.[1] For years, we viewed chronic heart failure (CHF) purely as a "pump" problem. The weakened heart was incapable of delivering adequate blood and oxygen to the systemic metabolizing tissues.[2] Based on this hemodynamic paradigm, strategies for improving heart failure lead to the use of agents (vasodilators and inotropic agents) to pharmacologically improve hemodynamics. With the exception of isosorbide dinitrate-hydralazine [3] (and maybe amlodipine [4]), these strategies failed miserably.[3,5-9] While vasodilators and inotropic agents improved symptoms, hemodynamics, and functional ability [10-16], they either did not affect the natural history of heart failure or worsened it.[3,5-9] Additionally a common feature of the agents that pharmacologically increase myocardial performance is that they utilize components of ß-adrenergic pathways to increase contractility [17] or they indirectly activate neurohormonal/autocrine-paracrine compensatory mechanisms in response to vasodilation.[18,19] Thus, despite beneficial pharmacological properties, these medications all carried the potential to produce adverse effects on the biology of the heart.

In the latter part of the 1980s and early 1990s evidence began to emerge that certain other types of medical therapy might have a beneficial effect on the natural history of left ventricular dysfunction or myocardial failure, despite having initial hemodynamic effects that were either unimpressive [20-22] or even adverse.[23-26] These two types of therapies, angiotensin-converting enzyme inhibitors and ß-adrenergic blocking agents, have changed our thinking about the potential of medical treatment of heart failure. Data generated from both clinical trials and model systems indicate that both types of therapy may slow or even in some cases reverse the progression of pump dysfunction and pathological remodeling that characterizes the natural history of heart failure. *It is important to emphasize that the beneficial effects of these treatments are not pharmacologic, but rather are due to favorable effects on the biology of the failing heart.*[1] It appears that the favorable effect these agents have on the natural history of heart failure is due to a blockade of the deleterious growth and energetic effects of angiotensin II and norepinephrine on the heart. Heart failure should no longer be viewed purely as a hemodynamic illness, but an illness of abnormal growth and remodeling in the heart. In addition, the biological improvements produced by ACE inhibition and ß-adrenergic blockade in patients with myocardial failure means that the heart failure clinical syndrome need no longer be viewed as inexorably progressive processes.[1]

B. OVERVIEW OF HEART FAILURE COMPENSATORY MECHANISMS

Myocardial failure begins with an insult to pump function, such as a myocardial infarction, inflammation, severe hemodynamic overload from hypertensive or valvular disease, genetic causes, or idiopathic myocardial dysfunction. In response to as yet undefined signals that probably include arterial underfilling, tissue hypoperfusion and central venous congestion, compensatory mechanisms are activated to support the failing heart.[27,28] There are four physiologic adjustments the heart can use to stabilize or increase myocardial performance in the failing heart: 1) increase in heart rate [29] 2) increase in contractility 3) increase in preload [30,31] and 4) increase in the number of contractile elements. [32,33] These four adjustments are largely accomplished by an increase in activity of two interrelated neurohormonal/autocrine-paracrine systems, the adrenergic and renin-angiotensin systems.[27,28] These two neurohormonal systems cross-regulate each other such that activation of one results in increased activity of the other. Renin release from the kidney is a $ß_1$ adrenergic receptor mediated response [34], while angiotensin II facilitates presynaptic norepinephrine release.[35,36] Increase in heart rate and contractility is largely due to ß-adrenergic mechanisms mediated by increased cardiac neurotransmitter activity.[37,38] An increase in preload, which increases cardiac output via the Frank-Starling mechanism, [30,31] occurs by activation of both the renin-angiotensin and adrenergic systems. Angiotensin-II is a major mediator of aldosterone secretion, which through effects on the kidney causes salt and water retention.[27,39] Nonosmotic release of vasopressin (AVP) is accomplished by both ß-adrenergic [40] and angiotensin-II [41] receptor mechanisms in the neurohypophysis. Finally, both norepinephrine (via both α and ß-adrenergic receptor mechanisms) and angiotensin-II are powerful mediators of cardiac myocyte cell hypertrophy.[33,42-47] In addition, activation of both the adrenergic and renin-angiotensin systems causes vasoconstriction, which serves to stabilize central blood pressure, and redistribute cardiac output to the brain and the heart, which largely have autoregulatory control of flow. Although redistribution of fluid to these vital organs is obviously advantageous for the short term, the increase in peripheral resistance and left ventricular wall stress actually decreases myocardial performance, particularly in the presence of any degree of pump dysfunction. For this reason, as the adrenergic and renin-angiotensin systems are activated there is coactivation of several counterregulatory mechanisms such as atrial natriuretic peptides [48] and vasodilator prostaglandins [49] that serve to minimize the effect of α-adrenergic and angiotensin-II vasoconstriction.

C. PATHOLOGICAL REMODELING OF THE LEFT VENTRICLE DUE TO ACTIVATION OF THE ADRENERGIC, RENIN-ANGIOTENSIN, AND CYTOKINE SYSTEMS

Despite the short-term hemodynamic benefits of activation of the adrenergic nervous system and renin-angiotensin system (RAS), the long-term effects of these regulatory systems on ventricular function and remodeling are deleterious (**Figure 1**).

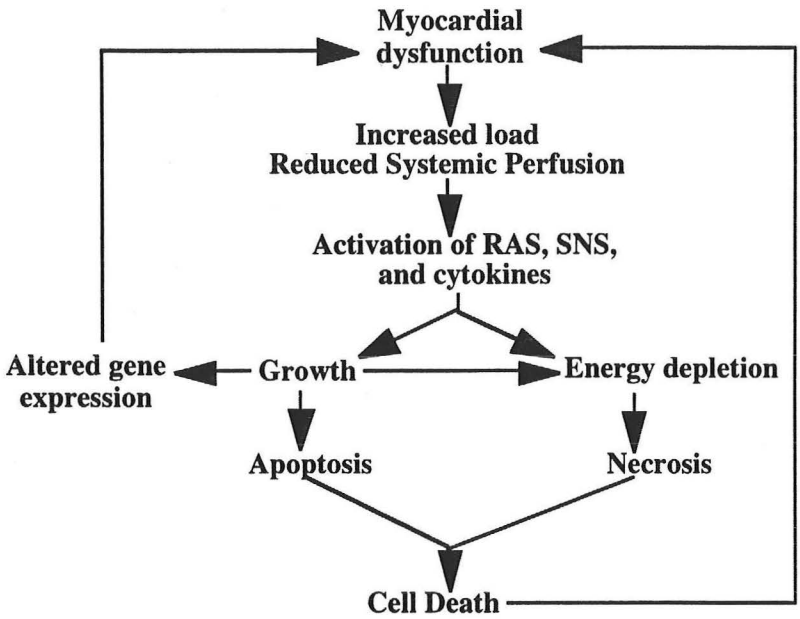


Figure 1: Relationship of neurohormonal activation and production of cardiac myocyte loss due to apoptosis and necrosis and altered gene expression. Cell loss and altered gene expression result in more myocardial dysfunction, and a vicious cycle is established (from reference 1).

Both growth alterations within the myocyte and interstitium and progressive cell death result in a deterioration in left ventricular function. The normal heart is small and elliptical in shape while the pathologically remodeled heart is large and spherical, a shape which is energetically and hemodynamically unfavorable.

Angiotensin II and norepinephrine as growth promoters-

Both angiotensin II and norepinephrine, as well as other cytokines and growth factors can elicit a growth response in the heart (Figure 2). Stretch of myocytes due to the altered load of heart failure results in paracrine/autocrine release of angiotensin II and receptor activation of phospholipase C and tyrosine kinase. This results in activation of protein kinase C by phospholipase C and activation of tumor suppressor genes p53 and p107.

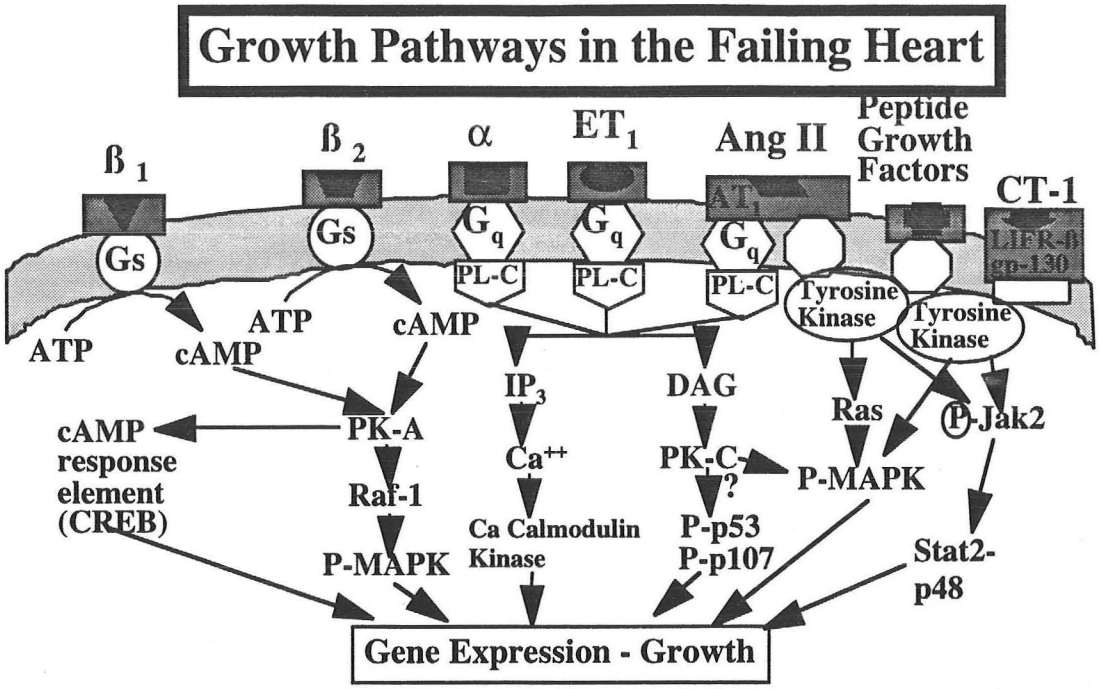
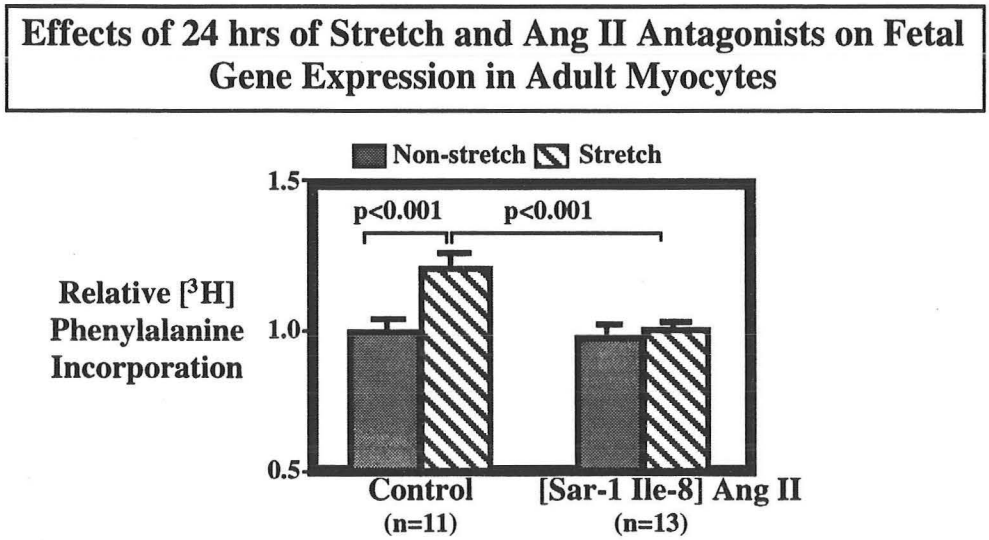


Figure 2: Proposed growth pathways within the myocyte.



Sadoshima et al. Cell 1993; 75: 977-984.

Figure 3: Effect of myocyte stretch on angiotensin II growth expression.

Tyrosine kinase results in activation of the Ras-MAP kinase and Jak-Stat pathways.[50] These ultimately produce Immediate-Early (IE) gene expression (especially *c-fos, c-jun, jun B, Egr-1, and c-myc*) which promotes growth.[45,51-53] Angiotensin-II can induce

protein synthesis [54] and produce cardiac myocytic hypertrophy in cultured cells [45], or overt hypertrophy at the organ level.[55-60] It is also mitogenic for cardiac fibroblasts, and stimulates collagen formation.[55,56]

Angiotensin may also provide a positive feedback regulation of the cardiac hypertrophic response by inducing the angiotensinogen gene and transforming growth factor $ß_1$ (TGF-ß) gene.[45,61] TGF-ß also has mitogenic potential and may induce hypertrophy.[62-64]

In response to adrenergic activity at the cell surface, the neurotransmitter norepinephrine is released and ß-adrenergic receptors are activated. Release of norepinephrine can be modulated locally by presynaptic α2 receptors (inhibitory) [65] and presynaptic angiotensin II and $ß_2$ receptors (facilitory).[35,36,66] Thus, ACE inhibitors will mildly reduce adrenergic activity in part by inhibiting norepinephrine release.[67] α-receptors on the cell surface will activate protein kinase C and inositol 1,4,5-triphosphate (IP_3). This will result in a growth response which may be mediated by tumor suppressor genes.[68,69] ß-receptors coupled to G-stimulatory proteins will transduce and amplify the agonist signal, promoting adenylate cyclase activity.[70] Once activated, adenylate cyclase produces an increase in cytoplasmic cAMP, which in turn activates intracellular protein kinase A and activates the cAMP response element (CREB).[33] Sarcolemmal and sarcoplasmic reticulum proteins are phosphorylated by these protein kinases and this results in an augmentation in intracellular calcium flux. Such an increase in intracellular calcium flux results in increased contractility and improved relaxation of the heart. Activation of the enhancer CREB produces a growth response. Norepinephrine has been shown to produce a hypertrophic response in culture via both α and ß-adrenergic mechanisms.[71,72]

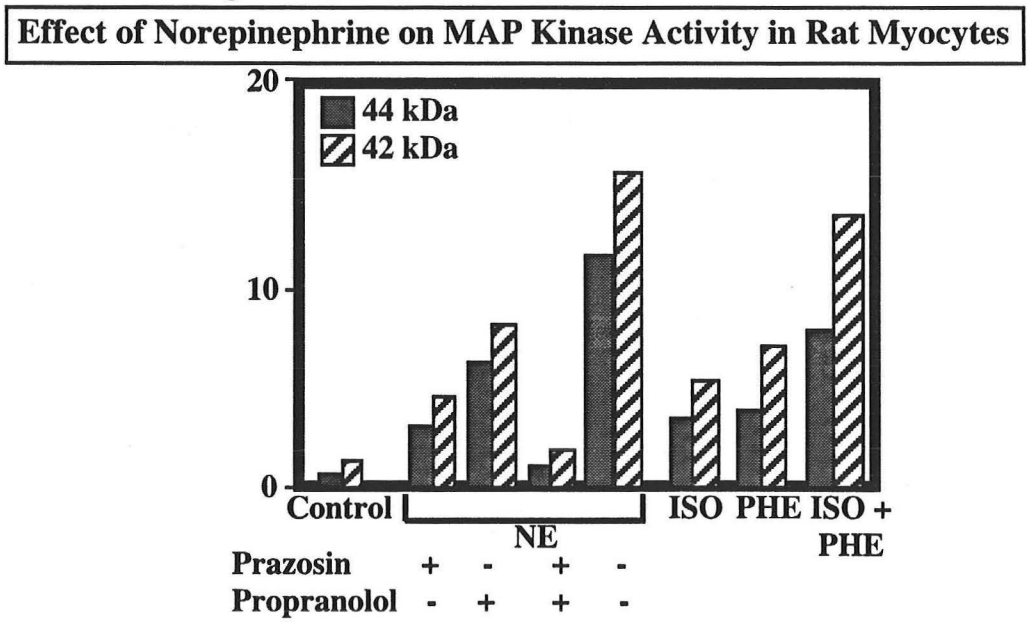


Figure 4: Effect of Norepinephrine on MAP kinase activity in rats (reference 72).

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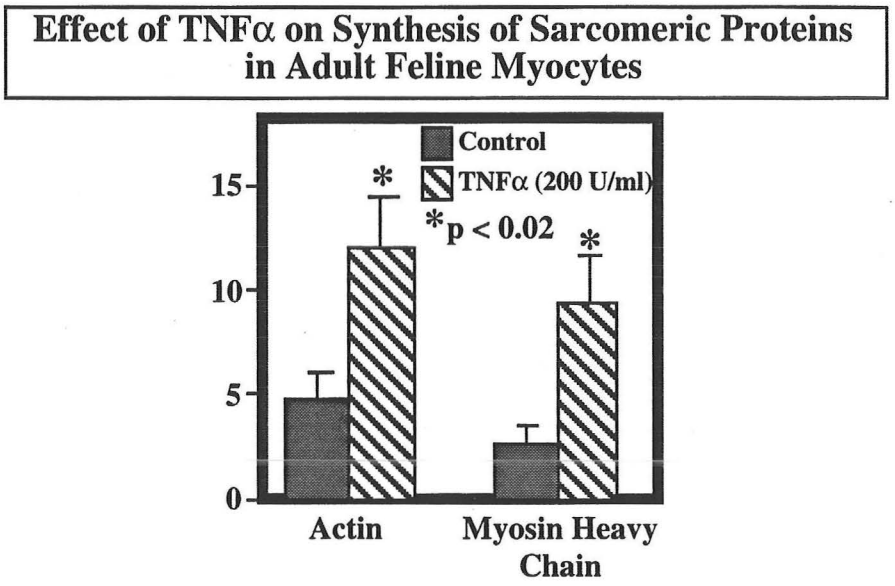
Other neurohormones may also be responsible for a growth response in the heart. These neurohormones include cytokines [42,73-77] (TNFα and cardiotrophin), endothelins[42,78] and insulin-like growth factor-1 (IGF-1).[79] TNFα at physiological concentrations has been shown to increase protein synthesis, especially the synthesis of sarcomeric contractile proteins actin and myosin heavy chain, in feline cardiac myocytes.[73] Cardiotrophin-1 is a unique cytokine which acts via the gp130 and leukemia inhibitory factor receptors to activate tyrosine kinase and induce a growth response in rat myocytes which is characterized by cell lengthening and production of sarcomeric units in series.[77]



Yokoyama T et al. Circulation 1997; 95: 1247-1252.

Figure 5: Effect of TNFα on synthesis of sarcomeric proteins in adult feline myocytes (from reference 73).

The growth pattern of the failing myocyte is to develop additional contractile units in series.[80,81] This produces cell elongation and mild hypertrophy of the myocytes resulting in eccentric hypertrophy (increase in myocardial mass with only minimal or no increase in wall thickness) of the ventricle.[80-82] Myocyte cell volume may be increased by 100% in the remodeled human ventricle [81] due to individual cell hypertrophy. Nonmyocytes, particularly fibroblasts, also are major contributors to remodeling.[55,56] Interstitial fibrosis is increased in patients with eccentric myocyte hypertrophy, including subjects with ischemic and nonischemic dilated cardiomyopathies. Both the production and degradation of the collagen network are controlled by fibroblasts, which in the presence of remodeling and eccentric hypertrophy must produce additional extracellular matrix to maintain structural in-

tegrity of the ventricular wall.[55,56] However, the presence of increased interstitial collagen may account for reduced capillary density and increased oxygen diffusion distance, which may contribute to metabolic stress or even overt ischemia.[83-86] In addition, the increase in structural rigidity may impair the ability of myocytes to fully contract, thus reducing contractility.[55,56] Activation of fibroblasts and production of interstitial fibrosis is controlled to a large degree by the renin-angiotensin system.[55,56] This change in left ventricular geometry from a prolate ellipse to a larger, more spherical shape causes increased meridional wall stress [87,88], abnormal distribution of fiber shortening [87-89], functional mitral regurgitation [90], worsened exercise tolerance [91], and poorer long-term survival.[89]

D. DELETERIOUS EFFECTS OF NEUROHORMONAL ACTIVATION ON THE MYOCYTE

Toxic Effects of Neurohormones

Toxic Effect	Responsible Neurohormone
ß-receptor downregulation	SNS
Altered chamber geometry	SNS, RAS, Cytokines
Energy Depletion	SNS, RAS, Cytokines
Direct depression LV function	Cytokines
Production of fetal phenotype	SNS, RAS, Cytokines
Reduced cell viability	SNS, RAS, Cytokines

Figure 6: Toxic effects of neurohormones on myocytes

Downregulation of ß-receptors-

ß-adrenergic receptors are the most influential receptors in human myocardium.[70]

In non-failing hearts, the ratio of $ß_1$ to $ß_2$ receptors is approximately 80:20.[70,92] These receptors are "linked" to the cell by a family of homologous proteins known as guanine nucleotide-binding regulatory proteins, or G proteins. While a detailed description of the function of these proteins is beyond the scope of this discussion, the G proteins serve to amplify (100-fold) the effects of receptor activation.[70] Previous studies of heart failure have shown "downregulation" of the $ß_1$-adrenergic receptors on the myocardial cell surface while $ß_2$ receptors are relatively preserved.[70,92-94] In the failing ventricle, the ratio of $ß_1$

to β_2 receptors is approximately 60:40 (instead of 80:20).[92] The amount of downregulation is proportional to coronary sinus norepinephrine, a surrogate marker of adrenergic activity to the heart.[95] As the human heart does not possess spare ß-receptors,[93] "downregulation" or loss of these receptors at the cell surface theoretically results in less production of cAMP (intracellular second messenger) for any ß-agonist concentration at the cell surface. In addition to β_1 downregulation, the β_2 receptor is uncoupled from adenylate cyclase formation producing a subsensitive β_2 response to agonist.[70]

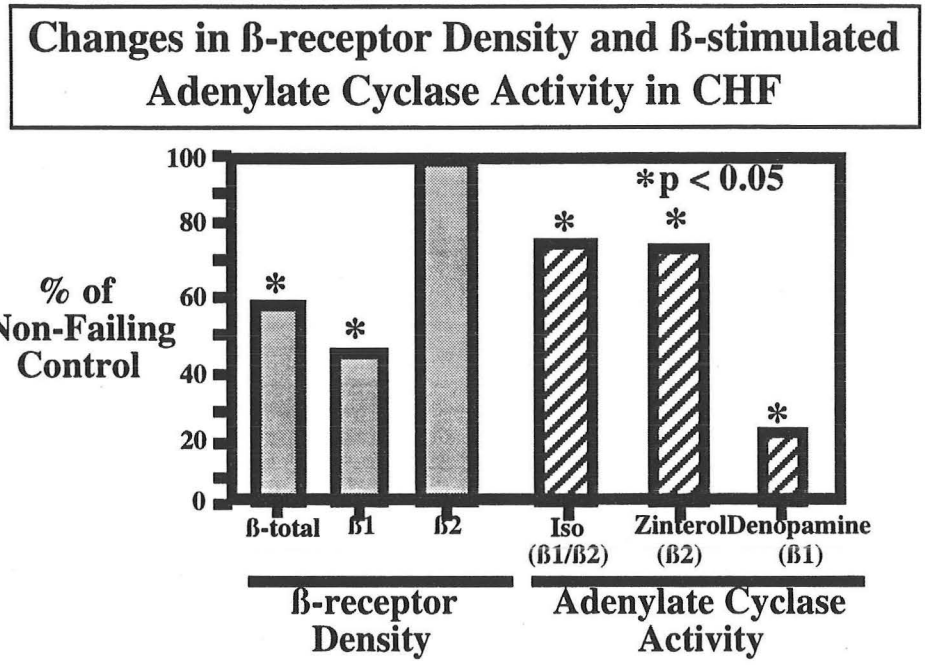


Figure 7: Changes in ß-receptor density and ß-stimulated adenylate cyclase activity in CHF.

While regulation of ß-receptors cannot explain the impaired resting ventricular function in heart failure [96], its importance exists during exercise.[1,97] Downregulation of ß-receptors impairs the response of the myocyte to norepinephrine spillover during times of stress or exercise. Thus, during exercise, the heart responds inadequately when metabolic need is high.

Alteration in myocardial phenotype-

While the process of hypertrophy increases the number of functioning contractile elements, alterations in gene expression involving calcium handling by the sarcoplasmic reticulum and changes in contractile proteins or their regulatory elements may produce an inefficient contractile element.[60-65] Some or all of these changes ultimately lead to progres-

sive left ventricular dysfunction, best understood as a continued decline in systolic function.

Systolic dysfunction of individual cardiac myocytes is by definition due to a change in gene expression. In rodent systems the constellation of alterations in gene expression that accompanies cardiac hypertrophy and its transition to myocardial dysfunction has been termed activation of a "fetal" program, as the changes recapitulate embryonic or neonatal patterns.[26,62] Because humans do not exhibit major changes in gene expression during development they do not exhibit the dramatic fetal program activation that characterizes hypertrophy or failure in rodent hearts.[62] However, there are certain changes in human hearts that resemble fetal activation. These include an up-regulation in gene expression of atrial natriuretic peptide [66,67] and down-regulation in the expression of SR-calcium ATPase [60-62] and a myosin heavy chain. [63,64] Angiotensin-II, [35-38], endothelins [35,65] and adrenergic stimulation [39,40] have been shown to be potent inducers of the fetal/hypertrophy gene program in model systems. In chronic heart failure, additional changes in gene expression that are not typically considered to be part of the fetal program occur, such as down-regulation in β_1 adrenergic receptors [68,69] and mRNA.[70] Taken together, these adjustments may decrease systolic performance and compromise myocardial reserve in times of stress, such as during exercise.[71]

Myocardial Phenotype

	Adult	Fetal	Hypertrophy /Failure
Cardiac α -actin	+++	+	+
Skeletal α -actin	+.	+++	+++
Smooth muscle α -actin	+	+++	+++
α -Myosin heavy chain	+++	+	+
ß -Myosin heavy chain	+	+++	+++
SR Ca^{++} ATPase	+++	+	+

Figure 8: Changes in calcium cycling and contractile proteins in the failing heart.

It appears that ß-adrenergic stimulation may play a major role in the development of myocyte dysfunction. In isolated cardiac myocytes exposure to norepinephrine causes myocyte toxicity, abnormal calcium handling, decreased macromolecular synthesis, and contractile dysfunction.[56] In humans, markedly elevated catecholamine levels accompanying

brain injury [72] or pheochromocytoma [73] cause intrinsic systolic dysfunction. Finally, the use of positive inotropic agents that act on the cyclic AMP contractility stimulating pathway appear to lead to depressed contractile function after they are withdrawn. [74,75] Therefore, changes in gene expression, which contribute to the slowing of contraction and disordered calcium handling, may be impacted by both the adrenergic and renin-angiotensin systems.

Acceleration of Cell Death-

The adult myocyte, when exposed to trophic signals such as angiotensin II, norepinephrine, endothelins, and cytokines (TNFα, cardiotrophin-1), not only stimulate altered growth patterns, but may accelerate cell death by two distinct processes: 1) cell necrosis and 2) apoptosis.

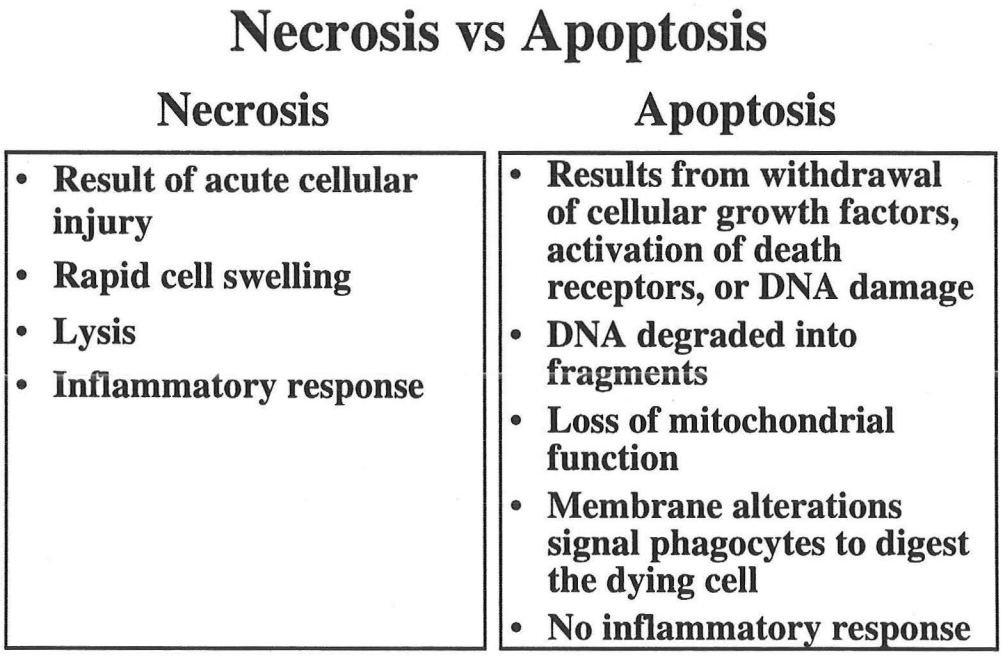


Figure 9: Different modes of cell death in heart failure.

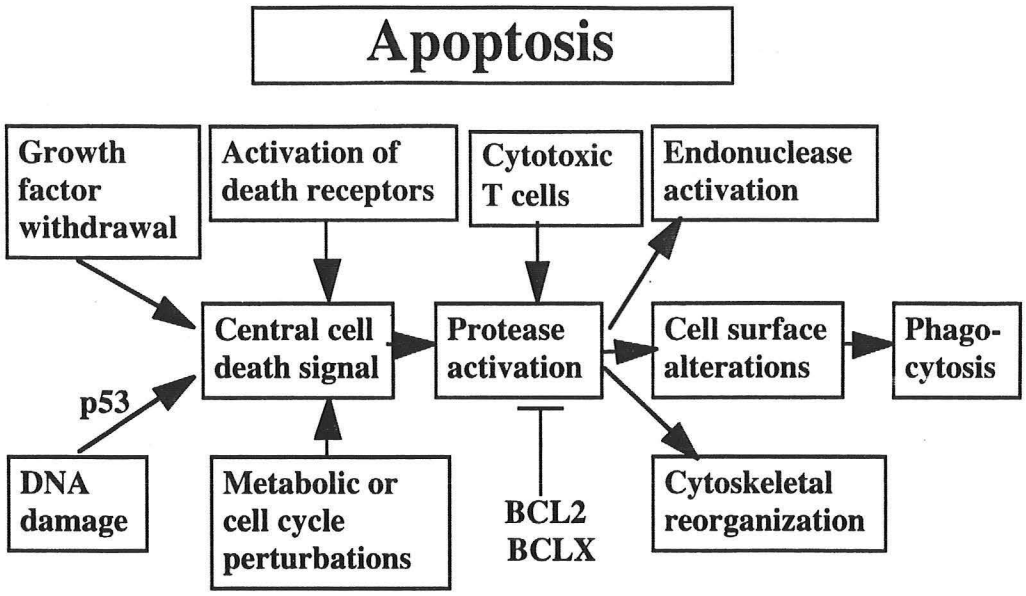


Figure 10: Mechanism of myocyte death due to apoptosis (from reference 102).

Cell necrosis, which is an inflammatory process, may occur by two hypothetical mechanisms: 1) Chamber remodeling leads to a larger, more spherical ventricle with elevated wall stress and left ventricular end-diastolic pressure. At the same time, the reduction in systolic performance leads to reduced stroke volume and aortic diastolic (and coronary perfusion) pressure. The reduction in coronary perfusion pressure and elevation in left ventricular end-diastolic pressure results in reduced epicardial-endocardial pressure gradient, leading to reduced endocardial blood flow. In addition, as interstitial remodeling may lead to increased interstitial collagen, reduced capillary density, and increased oxygen diffusion distance, these factors may contribute to metabolic stress or even overt ischemia within the remodeled ventricle.[83-86] Thus, overt ischemia may result leading to cell necrosis. 2) Cell necrosis may also occur as a direct result of exposure to elevated levels of angiotensin II [98,99], norepinephrine [100,101], or other toxins.

Apoptosis is a non-inflammatory process of programmed cell self-destruction.[102] Within a cell type, control of cell number is determined by a balance between cell proliferation and cell death. Excessive cell proliferation may lead to malignancy whereas excessive cell death may lead to organ dysfunction or death. Apoptosis, the process of programmed cell death, is characterized by condensation of cytoplasm, loss of plasma membrane microvilli, segmentation of the nucleus, and extensive degradation of chromosomal DNA into oligomers of about 180 bp caused by activation of endogenous endonucleases.[102-107] The control of apoptosis within the cell is controlled by a delicate

balance of factors which either inhibit or induce it. Factors which produce apoptosis include: cytokines, TGFß, growth factor withdrawal, calcium, DNA damaging agents (viral, chemotherapeutic, radiation, toxins), oncogenes (myc, fos, rel, E1A), tumor suppressors (p53), and free radicals. Inhibitors of apoptosis include growth factors, estrogen, androgens, viral genes, bcl-x, bcl-2 gene expression, tumor promoters.[102] Apoptosis has been reported in heart failure models in animals [108] and recently was reported in human heart failure.[109]

Apoptosis likely occurs as a response to prolonged growth stimulation in the adult terminally differentiated myocyte. The adult myocyte, unable to divide [110], shifts from a program of cell maintenance to production of muscle-specific gene products. While a clear link between neurohormonal activation and apoptosis has not been established, it is known that the intermediates responsible for apoptosis (including p53 [111]) appear to be up-regulated in the failing heart and may be further up-regulated by angiotensin-II.[68] Additionally, the cytokine TNFα, which is increased in chronic heart failure [112] and mediates biologic effects in the failing human heart [113], is a potent stimulus for growth [114-116] and apoptosis induction [114,117] in model systems. Cell loss from apoptosis and cell necrosis results in a progressive loss of myocytes and contractile units, leading to progressive ventricular dysfunction.

E. ALTERATIONS IN REMODELING WITH NEUROHORMONAL ANTAGONISTS

Attenuation of the remodeling and myopathic process by inhibition of the renin-angiotensin system-

Studies in animals have demonstrated that angiotensin is produced in the heart and is released in a paracrine/autocrine fashion in response to myocyte stretch.[51,118,119] Several investigators have demonstrated that the use of an ACE inhibitor can result in regression of hypertrophy in the pressure overload animal model [57,58] and can interfere with normal postnatal growth of the left ventricle.[59] ACE inhibitors can also retard the progressive remodeling process and ventricular dilatation in rats post infarct and this may be integrally related to survival.[120,121]

Recent work in a pacing-tachycardia dog model of heart failure has shown that an ACE inhibitor can attenuate the myocyte lengthening, reduction in velocity of shortening, and reduction in left ventricular ejection fraction that is associated with ventricular remodeling in this model.[122] This study highlights the close relation between myocyte function, chamber function, and chamber architecture and emphasizes the benefit of an ACE inhibitor on all

these levels. Other studies in canine heart failure models have demonstrated a slowing or reversal of the remodeling process with ACE inhibitor therapy.[123,124] Thus, angiotensin-II appears to play a critical role in the development of left ventricular hypertrophy, myocyte dysfunction, and chamber architecture and ACE inhibitors are able to regress or prevent the development of these changes in several animal models.

In humans, it is clear that in the presence of systolic dysfunction ACE inhibitors reduce mortality and retard the progression of the heart failure clinical syndrome both in chronic heart failure [125,126] and after myocardial infarction.[127-130] After a myocardial infarction there is a progressive increase in left ventricular systolic and diastolic volumes and an increase in the sphericity of the left ventricle between three weeks and one year. [131-133] This change in geometry occurs at a time when infarct expansion has already occurred and thus represents ventricular remodeling. These late geometrical changes can be prevented or retarded by ACE inhibitor therapy.[131-133] In patients with chronic heart failure, ACE inhibitors retard progressive increases in left ventricular volumes and mass.[134-136]

Effects of ACE Inhibitors on Survival in Patients with CHF

	Mortality		
Trial	**ACEI**	**Controls**	**RR (95% CI)**
Chronic CHF			
Consensus I	**50 / 127 (39%)**	**68 / 126 (54%)**	**0.56 (0.34-0.91)**
SOLVD (Treatment)	**452 / 1285 (35%)**	**510 / 1284 (40%)**	**0.82 (0.70-0.97)**
SOLVD (Prevention)	**313 / 2111 (15%)**	**334 / 2117 (16%)**	**0.92 (0.79-1.08)**
Post MI			
SAVE	**228 / 1115 (20%)**	**275 / 1116 (25%)**	**0.81 (0.68-0.97)**
AIRE	**170 / 1004 (17%)**	**222 / 982 (23%)**	**0.73 (0.60-0.89)**
TRACE	**304 / 876 (35%)**	**369 / 873 (42%)**	**0.78 (0.67-0.91)**
SMILE	**38 / 772 (5%)**	**51 / 784 (6.5%)**	**0.75 (0.40-1.11)**
Totals	**1555 / 7290 (21%)**	**1829 / 7282 (25%)**	

Figure 11: Effect of ACE inhibitors on survival in patients with LV dysfunction.

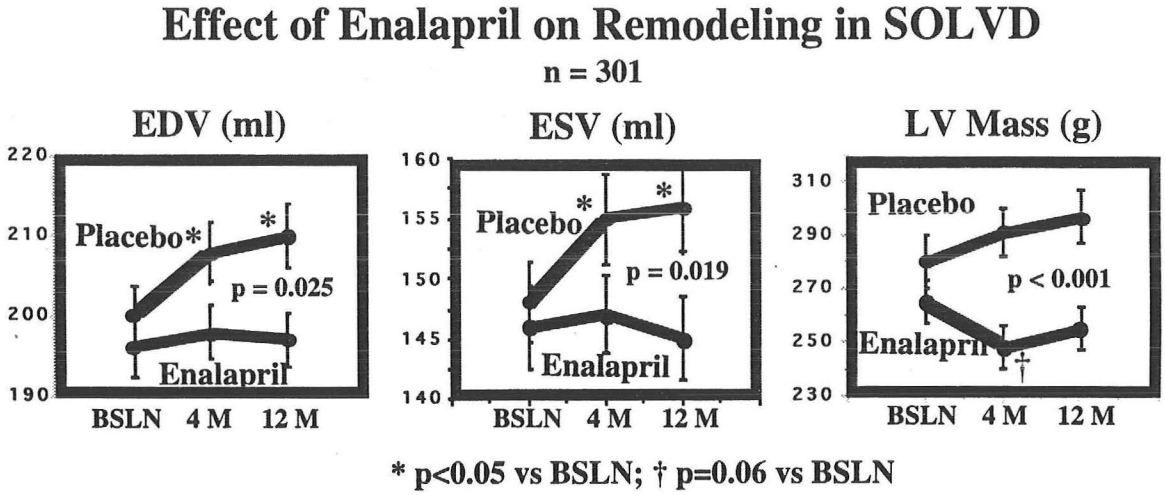


Figure 12: Effect of enalapril on ventricular remodeling in heart failure (from reference 135).

However, there is no evidence from clinical investigations that ACE inhibitor therapy can lead to substantial reversal of the remodeling process or to improved intrinsic myocyte function. Rather, the available data indicate that in established dilated cardiomyopathies administration of ACE inhibitors retard progression to increased LV mass and a more spherical geometry. Although ACE inhibitors diminish the effects of the renin-angiotensin system on the myocyte and despite the fact that ACE inhibitors initially reduce adrenergic activity [67,137], plasma norepinephrine increases over time.[137] These data suggest that progressive sympathetic nervous system activation occurs even in the presence of ACE inhibitors and enforce the need for a concomitant adjunctive anti-adrenergic strategy to block the long-term sequelae of norepinephrine on the heart. The use of a ß-blocking agent will also result in further deactivation of the renin-angiotensin system, even in the presence of an ACE inhibitor.[138]

Reversal of the remodeling and myopathic process by ß-adrenergic blockade-

It is clear from animal and human studies that ß-adrenergic blockade results in improvement in myocyte and chamber function in heart failure. Gwathmey and co-workers have examined the effect of ß-blocker therapy in the furazolidone-treated turkey model, which resembles human dilated cardiomyopathy with regard to mechanical dysfunction, morphology, and biochemical alterations.[139-141] In these studies administration of ß-blockers resulted in improvement in ejection fraction, reduction of ventricular volumes, an increase in developed pressure, and normalization of the force-frequency relationship which is altered in heart failure.[139-142]

Carabello and associates have examined the effect of ß-adrenergic blockade in a canine model of chronic mitral regurgitation.[143] They found that treatment with atenolol resulted in restoration of ventricular (chamber) and myocyte contractile function. Thus, the fundamental improvement in contractility was not a pharmacologic effect but was the result of biological improvement within the myocyte itself.

Two other canine studies of heart failure have found that ß-adrenergic blockade halts the progression or even reverses the process of chamber remodeling and growth.[123,124]

Over 15 placebo controlled studies involving more than 2000 patients with chronic heart failure from systolic dysfunction have examined the effect of ß-adrenergic blockade on ventricular function. [96,144-163] In every study of more than one month duration, left ventricular ejection fraction has been consistently shown to increase with ß-blocker therapy.[96,144-163] No negative studies of more than one month duration exist. Most importantly, three human studies [154,157,164] and one animal [143] study using four different ß-blocking agents have shown that the improvement in ventricular function is due to increased systolic ventricular performance. Improved performance appears to be due to enhanced contractility.[143]

Controlled Trials of ß-blockers

Trial	Nos.	Pre LVEF	Post LVEF	↑Exercise	↓Symptoms
Engelmeier et al (144)	8	.13±.06	.18±.05	Yes	Yes
Ikram et al* (145)	15	.47±.13	.44±.15	No	-----
Currie et al* (146)	10	-----	-----	No	-----
Gilbert et al (147)	23	.26±.07	.35±.11	No	Yes
Pollock et al (148)	12	.19±.07	.23±.08	Yes	Yes
Woodley et al (149)					
all patients	29	.23±.08	.29±.11	No	Yes
IDC	13	.26±.06	.35±.10	No	Yes
ISCDC	16	.21±.08	.23±.09	No	Yes
Metra et al (150)	40	.20±.07	.30±.12	Yes	Yes
Olsen et al (151)	54	.20±.06	.31±.12	Yes	Yes
MDC (152)	380	.14±.03	.31±.16	Yes	Yes
Bristow et al (153)	139	.24±.07	.30±.12	No	No
Wisenbaugh (154)	24	.23±.08	.33±.12	No	-----
Paolisso et al (155)	10	-----	-----	Yes	Yes
Krum et al (156)	49	.17±.07	.24±.11	Yes	Yes
Eichhorn et al (157)	24	.22±.10	.33±.13	-----	Yes
Fisher et al (158)	50	.22±.08	.29±.11	Yes	Yes
ANZ (159)	415	.28±.09	.34±.13	No	No
PRECISE (160)	278	.22±.07	.30±??	No	Yes
MOCHA (161)	345	.23±.08	0.31±??†	No	Yes

IDC = Idiopathic dilated cardiomyopathy; ISCDC = Ischemic dilated cardiomyopathy.
*Denotes trial of only 1 month duration; † denotes only highest dose of carvedilol.

Figure 13: Controlled trials of ß-blockade

To underscore that the effects of ß-blocking agents are not directly related to their pharmacologic properties, a recent study demonstrated that after one day of therapy with metoprolol left ventricular ejection fraction was depressed compared to baseline, but by one month was back to baseline.[165] Improvement in left ventricular function occurred between 1 and 3 months of therapy. These data support the biological changes (as opposed to pharmacological effects) which occur as a result of ß-blocker therapy. There appears to be continued improvement in left ventricular function between 3 and 6 months.[157] Despite consistent improvement in left ventricular function by 3-6 months of therapy [96,144-163], left ventricular architecture does not change until much later.[165] By 12-18 months, ß-blocking agents have started to reduce left ventricular mass and remodel the shape of the heart into a more normal elliptical shape.[165,166]

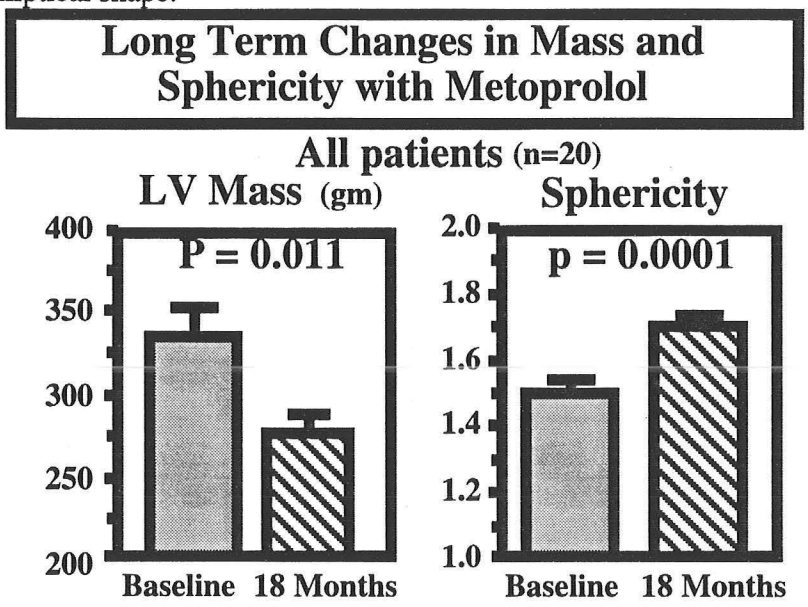


Figure 14: Changes in LV Mass and shape with metoprolol therapy (reference 165).

E. CLINICAL IMPLICATIONS

Heart failure has long been considered to have a progressive downhill course leading inexorably to an early demise. The downhill course often occurs silently, in the absence of any obvious cardiac insults. The reason for this is a combination of cell loss (necrosis and/or apoptosis), myocyte dysfunction (altered phenotype), impaired energetics, and pathological remodeling of the chamber. These events result in a progressive reduction in left ventricular systolic and diastolic function.[167] Impaired left ventricular systolic function as reflected by decreased LVEF is a powerful predictor of adverse outcome in subjects with

chronic heart failure. [168,169] Thus, improved clinical outcome should result from strategies that reduce the biologic signals responsible for myocyte growth, dysfunction and loss, and chamber remodeling. In the case of ACE inhibitors, their relatively minor effects consisting of an attenuation of the remodeling process, translate into modest reduction (15%–30%) in mortality.[125-127] The addition of ß-adrenergic blockade on top of ACE inhibition may result in a further reduction in mortality of 20-65%.[170,171] Moreover, since carvedilol and bucindolol produce a dose related improvement in left ventricular function and a dose related reduction in mortality [153,171], it is likely that the mortality reduction seen with carvedilol was related to improvement in myocardial biologic function. Because of the therapeutic potential of biologic modification of the failing heart by third generation ß-blocking agents, the NIH and VA cooperative clinical trials programs are jointly sponsoring a large mortality trial with bucindolol (the BEST trial) [172], which also is examining specific mechanisms by which this type of treatment alters myocardial gene expression. It is likely that additional treatments to inhibit the renin-angiotensin and adrenergic systems will be developed, and other critical pathways involved in adverse biologic processes in the failing heart will be identified and lead to additional therapeutic strategy.

Our ability to alter the biology of the failing heart through ß-blocker therapy strongly suggests that in the future treatment of heart failure will involve identifying the adverse biological processes that result in pump failure, and then developing treatments that neutralize or normalize those adverse processes. In time, it may be possible for the clinician to view the treatment of heart failure largely as a matter of improving the biological function of the myocardium.

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