Congestive Heart Failure: Fifty Years of Progress

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Volume 1 of *Circulation* provides an excellent snapshot of the understanding of the mechanisms and treatment of heart failure a half century ago. During that era, circulatory pathophysiology was at the center of investigative attention. For example, Tinsley Harrison and his group divided heart failure into “primary disorders of filling and primary disorders of emptying,” a forerunner of our current terms diastolic and systolic heart failure. The great Swedish clinical physiologist Gustav Nylin used 32P-labeled red blood cells for measuring cardiac output and cardiothoracic blood volume by the indicator-dilution method in normal subjects and in patients with heart failure. Andre Courmand’s group defined the pathophysiology of heart failure secondary to cor pulmonale, distinguished it from left ventricular failure, and compared the acute hemodynamic effects of digoxin in these 2 conditions. In a seminal paper, Raab and Lepeschkin extracted sympathin from the heart and established norepinephrine as the cardiac adrenergic neurotransmitter. In one of the earliest efforts to manage patients with chronic congestive heart failure on an outpatient basis, Vander Veer and colleagues demonstrated the effectiveness and tolerability of an oral form of the widely used parenteral diuretic mercuhydrin.

Myocardial Function

In the 1950s, the role of hypertrophy in the heart’s adaptation to hemodynamic overload was examined. After Laplace’s law was applied to the heart and permitted the calculation of wall stress in the human heart, it became clear that myocardial hypertrophy prevents excessive elevation of wall stress consequent to hemodynamic overload. In the 1960s, there was a lively debate about the mechanism of heart failure secondary to pressure overload. The question was framed as follows: “Does failure of the ventricle as a pump occur in the presence of (an) inadequate contractile mass while the contractile function of each unit (of myocardium) is normal or even supernormal, or does failure result as a consequence of a depression of contractility of the myocardium that is not compensated for by the increase in muscle mass?” The latter position was supported by the demonstration of contractile dysfunction in papillary muscles isolated from cats with heart failure secondary to pressure overload.

Subsequently, the contractile process in failing heart muscle has undergone ever closer scrutiny. A defect in sarcomere shortening has been found in myocytes isolated from multiple animal models, as well as from patients with advanced heart failure. Moreover, reversibility of this defect through “unloading” the failing heart by placing the patient on a ventricular assist device for several months has been demonstrated. This intriguing observation suggests that it may be possible, as a therapeutic strategy, to reverse a process that had long been considered to be irreversible and amenable only to palliative therapy. As a consequence, left ventricular assist devices currently used as “bridges to heart transplantation” may become “bridges to recovery.” Perhaps even more exciting is the recent realization that the intrinsic defects in myocardial contractile function present in some patients with chronic heart failure may be partially reversed by medical therapy. That is, treatment of patients with chronic systolic heart failure with ß-adrenergic blocking agents added to background therapy with ACE inhibitors improves systolic function and may reverse remodeling, leading to improved clinical outcomes, including prolonged survival and reduced hospitalizations. Thus, the view of chronic myocardial failure as an irreversible, end-stage process is being supplanted by the idea that it is possible to effect true biologically based improvement in the intrinsic defects of function and structure that afflict the chronically failing heart.

Abnormalities in Energy Metabolism

The cellular and molecular bases of heart failure have received considerable attention during the past half century and are under continuing active study. Although there is no single unifying pathogenetic theory, a number of biochemical abnormalities have been described in heart failure. There is agreement that the efficiency of the heart as a pump is reduced in the low-output, systolic heart failure that occurs in ischemic heart disease and dilated cardiomyopathy. The “external work” performed by the left ventricle is depressed, whereas its energy consumption is normal or almost so. Thus, the dilated, failing heart is energy-inefficient. Second, alterations in cardiac energy metabolism are frequently observed in systolic heart failure. Relative ischemia of the subendocardium occurs in ventricular hypertrophy and dilatation. High-energy phosphate stores, especially creatine phosphate (CrP), are reduced, not only in heart failure secondary to acute ischemia but in other forms as well.
TABLE 1. Signals and Signal Transduction Pathways That Mediate Pathological Hypertrophy in Model Systems

<table>
<thead>
<tr>
<th>Signal/Type</th>
<th>Signal Transduction System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stretch/wall stress (mechanical</td>
<td>Gq/PLC/PKC; sarcolemmal ion channels</td>
</tr>
<tr>
<td>deformation)</td>
<td></td>
</tr>
<tr>
<td>Angiotensin II (autocrine/paracrine</td>
<td>AT1 receptor–Gq/PLCβ, –TK pathways, –MAPK pathways, JAK/STAT pathways, other</td>
</tr>
<tr>
<td>or hormone)</td>
<td></td>
</tr>
<tr>
<td>Norepinephrine (neurotransmitter)</td>
<td>α-, β-Adrenergic pathways; oxidative stress pathways</td>
</tr>
<tr>
<td>Endothelin (paracrine)</td>
<td>ETa receptor–Gq/PLCβ pathway, calcineurin, and CAMK pathways</td>
</tr>
<tr>
<td>Ca2+ (intracellular signal)</td>
<td>CAM kinase pathway, calcineurin pathway</td>
</tr>
<tr>
<td>TNF-α (autocrine/paracrine)</td>
<td>TNF receptors, MAPK, PKC</td>
</tr>
<tr>
<td>IL-1β (paracrine)</td>
<td>IL-1 receptors, MAPK, TK pathways</td>
</tr>
<tr>
<td>Cardiotrophin-1 (autocrine/paracrine)</td>
<td>Gp 130 pathways</td>
</tr>
</tbody>
</table>

PLC indicates phospholipase C; AT1, angiotensin type 1; MAPK, mitogen-activated protein kinase; and PKC, protein kinase C.

CrP serves as a buffer maintaining high ATP concentrations and a high ATP/ADP ratio. It may also facilitate the transfer of high-energy phosphates from their source in the mitochondria to their principal sites of consumption at the myofibrils and in the sarcoplasmic reticulum. Mitochondrial abnormalities may reduce the availability of high-energy phosphate stores in failing myocardium, perhaps related to mitochondrial damage that is mediated by oxygen radicals or autoantibodies. Reductions in the activity of creatine kinase, the enzyme that catalyzes the transfer of high-energy phosphate stores from CrP to ADP to generate ATP, have been reported in many forms of heart failure. Reduced activity of this enzyme intensifies the energy deficit in heart failure. If severe enough, the resulting reduction in the free energy of ATP both slows the pump responsible for Ca2+ uptake by the sarcoplasmic reticulum required for myocardial relaxation and impairs myofilament cross-bridge cycling, which is the basis of cardiac contraction. These observations, first obtained in experimental models, have been extended to patients with dilated cardiomyopathy by use of 31P magnetic resonance spectroscopy. Importantly, a depressed CrP/ATP ratio in these patients has been found to be an independent, powerful predictor of early death.

Altered Expression or Function of Contractile Proteins

There is considerable evidence for changes in sarcomeric proteins in the failing human heart (Table 1). The data include changes in the gene expression and protein expression of myosin heavy chain isoforms and alterations in the expression of troponin T and in the isoform expression of myosin light chain-1. In each case, the altered gene and protein expression most likely represents an induction of a “fetal” pattern of gene expression, whereby certain contractile, calcium-handling, and counterregulatory proteins revert to the mRNA and protein expression pattern that characterizes the fetal stage of development. Although this paradigm was first observed in rodent myocardium, it is now abundantly clear that the same type of gene reprogramming also occurs in the failing, hypertrophied human heart. In the case of fetal expression patterns of thick- and thin-filament contractile proteins, some of the alterations (myosin heavy chain, troponin T) reduce, while at least one (myosin light chain-1) increases, myofibrillar ATPase activity and/or contractile function. The net effect appears to be a reduction in myofibrillar ATPase activity and contraction velocity, perhaps because the dominant changes are in myosin heavy chain isoforms. Although in animal models this reduction in velocity of shortening was originally interpreted as being an adaptive, energetically favorable change, the end result is an increase in wall stress and maladaptive neurohormonal/cytokine activation (see below) secondary to the reduction in stroke volume and increase in ventricular volume. Thus, activation of harmful hypertrophy signaling pathways may be the biggest outcome of a reversion to fetal gene expression.

A number of inherited cardiomyopathies may be related to mutations of genes encoding sarcomeric proteins. Familial hypertrophic cardiomyopathy, which causes impaired filling and diastolic heart failure (and less commonly and in late cases, a dilated phenotype with systolic heart failure), is caused by mutations in the genes encoding sarcomeric proteins. These include components of the thick filaments (cardiac β-myosin heavy chain and myosin light chains), components of the thin filaments (cardiac troponin T, troponin I, and α-tropomyosin), and cardiac myosin-binding protein C. All of these mutations probably produce abnormalities of force generation, which then incite a hypertrophic response. Dilated cardiomyopathy causing systolic heart failure may result from mutations in genes encoding actin, which appear to produce an abnormality of force generation or transmission similar to genetic defects in cytoskeletal proteins, which are also associated with dilated cardiomyopathy (see below).

Abnormalities of Excitation-Contraction Coupling: Diastolic Heart Failure

Abnormalities of excitation-contraction coupling occur in many forms of heart failure. Calcium ions (Ca2+) play a central role in both cardiac contraction and relaxation, and a number of abnormalities of receptors, pumps, and proteins responsible for the transsarcolemmal and intracellular movements of Ca2+ have been described in the failing human heart. In end-stage human myocardial failure, the result of these changes appears to be a prolongation of the Ca2+ transient and an increase in diastolic Ca2+ concentration. These changes, probably caused by an impairment in the protein expression or function of sarcoplasmic reticular ATPase (SERCA-2a), would be expected to impair both diastolic and systolic function.

Diastolic dysfunction secondary to impaired myocardial relaxation and/or ventricular filling is associated with many cases of systolic dysfunction, but it is the primary cause of the clinical syndrome of heart failure in as many as one third of all cases. Impaired cardiac filling may be caused by structural abnormalities, eg, pericardial constriction or increased inter-
Cytoskeletal Abnormalities

The cardiac myocyte cytoskeleton is now known to be able to influence myocardial function dynamically, particularly in the setting of pressure overload, in which excessive microtubular polymerization has been shown to adversely affect systolic function. In addition, the concentrations of a number of cytoskeletal proteins, such as desmin, tubulin, vinculin, dystrophin, talin, and spectrin, appear to be increased in end-stage failing human hearts. Conversely, the sarcomeric skeletal proteins α-actinin, titin, and myomesin may be decreased in end-stage failing human hearts and in a single patient with an idiopathic dilated cardiomyopathy, a complete absence of metavinculin has been reported. These changes may interfere with normal myocyte function and cause or contribute to cell and chamber remodeling.

An impressively increasing number of cytoskeletal gene mutations have been shown to be the basis for dilated cardiomyopathy phenotypes. At the moment, the list in humans includes dystrophin, desmin, sarcomysins, and the nuclear-envelope proteins lamin A and C. The strain-specific model of heart failure/cardiomyopathy in the Syrian golden hamster has been shown to be due to a mutation in the δ-sarcoglycan gene. In animals, genetic ablation of the cytoskeleton-associated muscle LIM protein (MLP) produces a useful model of dilated cardiomyopathy. It has been reported that MLP expression is reduced in the failing left ventricular myocardium of patients with dilated and ischemic cardiomyopathy. Because MLP is important for the regulation of the cytoarchitecture of cardiac myocytes, reduced MLP content could be responsible for the impaired systolic function in ischemic or idiopathic dilated cardiomyopathy. Thus, mutations in various genes encoding cytoskeletal proteins appear to lead to the idiopathic dilated cardiomyopathy phenotype, suggesting that altered expression of this class of proteins might have a role in the development of acquired (secondary) dilated cardiomyopathies as well.

Alterations in β-Adrenergic Receptor Signal Transduction

An alteration in β-receptor signal transduction, downregulation of β1-adrenergic receptors, was one of the first candidates proposed for a molecular defect in the failing human heart. Multiple alterations in β-receptor signal transduction have been described in the failing human heart, and there is little doubt that they reduce cardiac reserve and contribute to decreased exercise responses in patients with chronic heart failure. As originally conceived, changes in β-receptor signal transduction were viewed as partially adaptive changes, serving the useful purpose of withdrawing the cardiac myocyte from harmful adrenergic stimulation. With the recent recognition that β-adrenergic receptors may possess intrinsic activity and exist in an activated state even in the absence of agonists, the idea has emerged that the loss of β-receptor signal transduction can directly reduce intrinsic myocardial function, that is, function in the absence of catecholamine agonists. However, at this point there is no evidence that this can occur in the failing human heart, inasmuch as dynamic changes in myocardial function can be dissociated from changes in intrinsic β-receptor signal transduction.

Ventricular Hypertrophy and Remodeling

Cardiac Myocyte Hypertrophy

Most types of myocardial failure are preceded by cell and chamber hypertrophy. The development of myocardial hypertrophy initially represents an important adaptive mechanism to hemodynamic stresses. The initial functional benefits of the hypertrophic response include an increase in the number of contractile elements, a lowering of wall stress through increased wall thickness in concentric hypertrophy, and increasing stroke volume by increasing end-diastolic volume in eccentric hypertrophy. The hypertrophic process is characterized by structural changes at the cardiac myocyte level that are translated into alterations in chamber size and geometry, collectively called remodeling. In addition to cardiac myocytes, other myocardial cells, such as fibroblasts, and increased production of extracellular matrix participate in the remodeling process. In pressure-overload hypertrophy, additional sarcomeres are assembled in parallel, leading to thicker myocytes, to a concentric pattern of ventricular hypertrophy, and initially to well-maintained systolic function. In contrast, in volume overload, additional sarcomeres are assembled in series, leading to longer myocytes, ventricular dilatation, and earlier dysfunction.

As listed in Table 1, numerous signaling pathways have been shown to induce cardiac myocyte and myocardial chamber hypertrophy. Most, if not all, the signaling pathways listed in Table 1 produce pathological hypertrophy, that is, hypertrophy accompanied by contractile dysfunction and poor clinical outcomes. Increased hemodynamic stress (either pressure or volume overload) appears to be sensed by myocytes, leading to changes in myocardial gene expression. It has been proposed that mechanical deformation activates sarcomemmal ion channels and is also transmitted to the nuclear membrane by the cytoskeleton. Intracellular [Ca2+] is a regulator of myocyte hypertrophy, in part through a pathway involving calcineurin, a Ca2+-sensitive phosphatase, which can be blocked by cyclosporin A. This pathway and the calmodulin kinase pathway are both activated by increases in intracellular [Ca2+], and both may be involved in hypertrophic responses resulting from abnormalities in Ca2+ handling mechanisms or in response to neurohormonal-cytokine signaling.
ways), angiotensin II, endothelin 1, fibroblast growth factor, transforming growth factor-β1, the proinflammatory cytokines tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β), and G protein 130–signaling cytokines. These agonists transmit their signals through signal transduction proteins (such as ras, Gαq, and Gαi) to activate a family of enzymes (such as protein kinase C [PKC], mitogen-activated protein kinases, and Raf-1 kinases) that induce the fetal gene program. Activation of G-coupled isoforms of PKC stimulates hypertrophy, which can lead to a fibrotic cardiomyopathy.63,64 and PKC-β isoforms are upregulated in the failing human heart.65

The molecular signature of pathological hypertrophy is fetal gene induction, including changes in gene expression of contractile proteins and calcium handling that interfere with contractile function. Thus, hypertrophy is not simply a matter of a quantitative increase in contractile proteins and other key elements that initiate and regulate contraction, but rather, it is also associated with qualitative changes in gene expression that lead to an impairment of contractile function. A list of genes considered to be part of the human fetal program that is reinduced in hypertrophy is given in Table 2.

The precise mechanism(s) responsible for the transition from adaptive hypertrophy to maladaptive heart failure are elusive, but there are several candidate mechanisms. In addition to deficiencies in high-energy phosphate stores and defects in excitation-contraction coupling, excess formation of myocyte microtubules, which impairs sarcomere shortening, may be involved.42 On the basis of the work done in animal models60,61 and humans,24–28 induction of the contractile protein fetal gene program to the point where contractile function is severely impaired is a viable candidate, as is the development of Ca2+–handling abnormalities that are part of66,67 or separate from19 fetal gene induction. Attenuation, or in some cases even total loss, of β-adrenergic signal transduction as the major means of supporting decreased myocardial performance probably contributes to the transition as well.68 Other possibilities include ultrastructural disorganization of cytoskeletal proteins and the development of extensive interstitial myocardial fibrosis. Finally, apoptosis (see below) could be a key component of myocardial decompensation in certain settings.

### Relationship Between Myocardial Contractile Dysfunction and Hypertrophy/Remodeling

An extremely important concept that has emerged in recent years is the close connection between remodeling and contractile dysfunction. These are the 2 most important pathological processes in the failing heart, and as depicted in Figure 1, they are intimately interrelated. That is, if cardiac myocyte or myocardial contractile dysfunction is initially present, numerous hypertrophy signaling pathways that ultimately lead to remodeling will be activated. Conversely, if remodeling without contractile dysfunction is initially present, as has been demonstrated in some animal models,69 contractile dysfunction will follow. This may be due to any of several processes that include energetic stress,70 altered Ca2+ handling,71 and induction of the fetal gene program. Conversely, any type of therapy that interrupts this positive feedback cycle will attenuate or reverse the progression of myocardial function and remodeling.13

#### Extracellular Matrix

Hypertrophied and failing hearts usually exhibit considerable interstitial fibrosis, which stiffens the ventricles and impedes both contraction and relaxation. An increased expression of a number of extracellular matrix proteins, including several forms of collagen and fibronectin, has been described. Matrix metalloproteinases (MMPs) and their inhibitors (TIMPs) are intimately involved in the remodeling of the cardiac matrix. Enhanced expression of MMPs and reduced expression of TIMPs have been described in heart failure, and the application of an inhibitor has been shown to retard experimentally produced heart failure.72

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**TABLE 2. Fetal Gene Program Induction in Hypertrophied, Failing Human Ventricular Myocardium, Degree of Expression 0–4+**

<table>
<thead>
<tr>
<th>Gene Expressed</th>
<th>Adult Pattern</th>
<th>Fetal Pattern</th>
<th>Hypertrophy/Failure</th>
<th>Biologic Effect in Hypertrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-MyHC</td>
<td>++</td>
<td>0–+</td>
<td>0–+</td>
<td>↓ Contractile function</td>
</tr>
<tr>
<td>β-MyHC</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>↓ Contractile function</td>
</tr>
<tr>
<td>SERCA</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>↓ Contractile function</td>
</tr>
<tr>
<td>Natriuretic peptides (ANP, BNP)</td>
<td>0–+</td>
<td>+++</td>
<td>+++</td>
<td>↓ Cell growth</td>
</tr>
<tr>
<td>Skeletal actin</td>
<td>+</td>
<td>0–+</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Cardiac actin</td>
<td>+</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

MyHC indicates myosin heavy chain; SERCA, sarcoplasmic reticular ATPase; ANP, atrial natriuretic peptide; and BNP, brain natriuretic peptide.
Cardiac Myocyte Apoptosis

A recently emphasized and probably important component of the remodeling process and of the transition from adaptive hypertrophy to heart failure is cardiac myocyte apoptosis, or programmed cell death. This precisely orchestrated genetic program is stimulated by a variety of factors, including hypoxia; enhanced activity of G-coupled proteins through negative feedback; and cell injury of diverse causes, including O$_2^-$-derived free radicals; activation of certain sarcolemmal receptors (Fas receptors); and the action of a class of specific proteases, the caspases. The latter degrade target proteins in the nucleus, cytoskeleton, and mitochondria. Stretching of sarcomeres in vitro results in the release of angiotensin II from cardiac cells, which triggers myocyte apoptosis. ACE inhibition can prevent this form of cell death in vivo.

Pacing-induced heart failure has served as a useful experimental model for the study of idiopathic dilated cardiomyopathy. This form of heart failure has been found to be associated with enhanced expression of Bax, a gene that stimulates apoptosis, and with attenuation of the expression of a proto-oncogene, Bal-2, which protects against apoptosis. These changes in gene expression may be caused by the activation of the tumor suppressor gene p53. The myocardial apoptosis that occurs during aging and that is accelerated in overloaded cells increases the burden on surviving myocytes and hastens their death, thereby setting up a vicious circle. In experimental preparations, marked reductions in apoptosis have been found with $\beta$-adrenergic blockade, ACE inhibition, and blockade of the angiotensin II type I receptor. Although its role in less advanced forms of human myocardial failure is uncertain, cardiac myocyte apoptosis has been clearly demonstrated in end-stage failing human hearts. Thus, as shown in Figure 2, cell loss via apoptosis or necrosis joins altered expression of genes regulating contractility as 2 fundamental processes that can produce progressive myocardial dysfunction in the failing human heart.

Neurohormonal-Cytokine Changes

Studies in the early 1960s demonstrated the presence of increased concentrations of circulating norepinephrine and reduced cardiac content of norepinephrine in patients with heart failure. A large number of investigations on neurohormonal changes in heart failure followed. It is now clear that in conditions characterized by a reduction of cardiac output and/or an increase in wall stress, a number of neurohormonal systems, notably the adrenergic system, the renin-angiotensin-aldosterone system (RAAS), and the hypothalamic-neurohypophyseal system are activated. Also, there is release of endothelin from the vascular bed. The activation of these systems initially serves to maintain arterial pressure and thereby coronary and cerebral perfusion pressures. Blood volume is conserved in the presence of hypovolemia or is expanded in the case of heart failure; the latter enhances contraction of the acutely failing ventricle by allowing it to move up on its Starling curve.

 Whereas activation of these systems is clearly adaptive over the short term in acute heart failure and hypovolemic shock, it became clear in the 1980s that persistent activation is maladaptive in chronic heart failure. Thus, continued activation of the adrenergic system increases ventricular afterload and therefore the hemodynamic burden placed on the failing ventricle. At the same time, activation of this system contributes to an increase in heart rate and myocardial energy costs; it may cause hypertrophy, ischemia, and tachyarrhythmias and damage myocytes further, perhaps through myocardial Ca$^{2+}$ overload or apoptosis. At the myocardial level, there is ample evidence of overactivity of adrenergic drive. The original observation in failing human hearts was that cardiac content of the adrenergic neurotransmitter norepinephrine was reduced or depleted. We now know that this tissue-store depletion is the result of sustained increased release and decreased reuptake of neurotransmitter, resulting in a constant exposure to levels of norepinephrine that are almost certainly cardiotoxic. Chronic $\beta$-adrenergic stimulation has been shown to induce expression of the proinflammatory cytokines TNF- $\alpha$, IL-1, and IL-6, which may impair cardiac contraction, promote chamber enlargement, and thus play a significant role in the development of a dilated cardiomyopathy phenotype. The reaction of the heart to this maladaptive signaling is easily measured; in explanted, severely failing human hearts, the density of $\beta_1$-adrenergic receptors, the G protein coupling of both $\beta_1$- and $\beta_2$-receptors, $\beta$-adrenergic stimulation of the activity of the enzyme adenyl cyclase, and in some studies the intracellular concentration of cAMP are all reduced. Phosphorylation of $\beta_1$-receptors by the $\beta$-adrenergic receptor kinase-1, an enzyme that is increased in heart failure, has been shown to be an important mechanism for desensitization of these receptors. Activation of $\beta_1$-receptors through a cAMP-dependent kinase, PKA, causes the phosphorylation of phospholamban, a protein that in its unphosphorylated state inhibits the uptake (and release) of Ca$^{2+}$ by the SERCA-2a. Phosphorylation of phospholamban enhances the uptake of Ca$^{2+}$ from the cyto-
plasm. Loss of the \( \beta \)-adrenergic mechanism in heart failure leaves phospholamban in the unphosphorylated state, thereby impairing \( Ca^{2+} \) movements and interfering with cardiac contraction and relaxation. In addition, genetic variants of \( \beta \)-adrenergic receptors may be associated with rapid progression of heart failure. 

In the severely failing heart, acute blockade of \( \beta \)-adrenergic receptors can remove hemodynamically important \( \beta \)-adrenergic support and may thereby intensify heart failure. Gradual escalation of the dose of orally administered \( \beta \)-adrenergic blockers, however, has been shown to be of substantial clinical benefit, and \( \beta \)-blocker therapy is now recommended for all but the most advanced cases of symptomatic chronic systolic heart failure. The myocardial functional effects of chronic \( \beta \)-blockade are in fact diametrically opposite to the acute effects, because long-term (\( \geq 3 \) months) blockade is associated with improved intrinsic systolic function and decreased ventricular volumes. These salutary effects on myocardial function and structure are most likely responsible for the majority of the clinical benefits produced by \( \beta \)-blockers and, which include a substantial reduction in mortality and a reduction in heart failure–related hospitalizations in chronic heart failure. 

Heart failure is also characterized by elevated circulating and tissue concentrations of angiotensin II, a vasoconstrictor that increases ventricular afterload and causes myocyte hypertrophy, apoptosis, interstitial fibrosis, cardiac and vascular remodeling, and the secretion of aldosterone. The latter also plays an important role in cardiac remodeling, the proliferation of fibroblasts, and the deposition of collagen. These changes increase the passive stiffness of the ventricles and the arterial bed, interfere with ventricular filling, and reduce arterial compliance. Elevated concentrations of circulating aldosterone are predictive of adverse outcome in heart failure patients. Inhibitors of the RAAS, ie, ACE inhibitors, angiotensin receptor blockers, and aldosterone inhibitors, have all been found to exert salutary effects in the treatment of heart failure. Indeed, ACE inhibitors are now considered to be a cornerstone in the management of most forms of heart failure and many forms of cardiac hypertrophy.

There is increasing evidence of cross talk between the adrenergic system and the RAAS. Thus, in patients with heart failure, ACE inhibition has been found to reduce the enhanced peripheral sympathetic nerve impulse traffic and cardiac adrenergic drive, and the beneficial effects of ACE inhibitors appear to be especially prominent in patients with adrenergic activation. Aldosterone reduces the neuronal reuptake of norepinephrine and thereby enhances cardiac arrhythmias. Heart failure patients who are already receiving an ACE inhibitor and a diuretic and who have normal renal function receive a substantial mortality benefit from the administration of spironolactone. Eplerenone, a new specific aldosterone antagonist that does not have the adverse effects of spironolactone, such as gynecomastia, is now being tested.

Arginine vasopressin (AVP) is synthesized in the hypothalamus and then stored and released from the neurohypophysis; its release is enhanced by osmolar stimuli as well as elevated concentrations of norepinephrine and angiotensin II. Increased release of AVP in heart failure causes vasoconstriction (through binding to \( V_1 \) receptors), water retention, and dilutional hyponatremia. Multiple signaling molecules, including angiotensin II, norepinephrine, AVP, and IL-1, all stimulate the production of endothelin, which, by activating endothelin A receptors, constricts vascular smooth muscle. The concentration of circulating endothelin is an important predictor of outcome in heart failure, and endothelin growth pathways are likely to be important determinants of pathological remodeling. 

The benefits of blocking neurohormonal activation in heart failure extend to endothelin and AVP. Blockade of receptors to these agonists has been shown to be efficacious in patients and experimental models of heart failure. Although these agents have not yet been approved for clinical use, they represent a promising area for future development.

Vascular endothelium also produces the potent vasodilator nitric oxide (NO), but the response to this substance is reduced in heart failure, contributing to the vasoconstrictor characteristic of this condition.

Proinflammatory Cytokines

In addition to neurohormonal activation, a number of proinflammatory cytokines, including TNF-\( \alpha \) and IL-1\( \beta \), are over-expressed in the failing heart. TNF-\( \alpha \) is also increased in the systemic circulation. TNF-\( \alpha \) is produced as a consequence of volume overload and evokes both systemic and local (cardiac) inflammatory responses. The former include the cachexia and skeletal muscle myopathy characteristic of heart failure, and the latter cause myocardial inflammation, cell proliferation, and apoptosis, thereby causing or intensifying heart failure. Transgenic mice that overexpress TNF-\( \alpha \) exhibit myocarditis, heart failure, and shortened survival. TNF-\( \alpha \) also activates transcription factors as well as enzymes involved in signal transduction and induces a number of genes, including the fetal gene program and those that encode growth factors, receptors, and heat-shock proteins. Release in the heart of TNF-\( \alpha \) and other cytokines may activate inducible NO synthase, an enzyme that enhances the production of NO, a substance that may impair myocardial function. The infusion of soluble receptors for TNF-\( \alpha \) blocks its action on the heart and improves the depressed ventricular function in rats infused with the cytokine. Early studies with this receptor in patients with heart failure are promising. Myocardial TNF-\( \alpha \) content has been shown to be reduced by chronic ventricular unloading with a left ventricular assist device, and this may play a role in the reversal of myocardial failure referred to earlier.

Figure 3 displays, in simplified form, current ideas of the interplay between cardiac function and neurohormonal cytokine systems. The impairment of cardiac function caused by myocardial injury activates these systems, many of which confer a beneficial response in acute heart failure. However, their chronic activation causes additional myocardial injury and depresses cardiac function further. By causing myocyte hypertrophy and apoptosis, as well as remodeling and fibrosis of the ventricles, they set up a series of vicious circles. Fortunately, many of these maladaptive processes can now be blocked, thereby preventing or interrupting these circles.
Indeed, blockade of the activated neurohormonal systems with \( \beta \)-adrenergic blockers, ACE inhibitors, angiotensin type I receptor blockers, and aldosterone antagonists is a key component of the contemporary management of heart failure.

The vasodilator peptides, such as atrial natriuretic peptide and brain natriuretic peptide, which are elaborated by dilated atria and ventricles, are also overexpressed in chronic heart failure, but in contrast to the aforementioned neurohormonal systems, they exert a counterregulatory or beneficial effect. By acting on specific receptors in vascular smooth muscle and the kidneys, they cause vasodilation, enhanced sodium excretion, and reduced secretion of renin and aldosterone. Drugs that prevent metabolism of these peptides, so-called neutral-endopeptidase inhibitors, especially when they are combined with an ACE inhibitor in a single molecule, so-called vasopeptidase inhibitors, appear to be promising.\(^{112} \)

**Ischemic Heart Failure**

It has been known for more than a century that myocardial ischemia can cause acute heart failure and that chronic ischemic heart disease can cause chronic heart failure. However, it has become appreciated only relatively recently that when severe, prolonged myocardial ischemia is relieved, the recovery of cardiac function is not immediate, but may require hours,\(^{113} \) days, or even weeks; this phenomenon has been called myocardial stunning.\(^{114} \) Repetitive episodes of ischemia caused by increases in myocardial oxygen requirements in the presence of a fixed oxygen supply can cause chronic stunning, which is characterized by persistent impairment of cardiac function. In myocardial hibernation, a process closely related to chronic stunning, myocardial function is downregulated to match a chronic reduction in coronary blood flow.\(^{115} \) Whatever the responsible mechanism(s), chronic stunning and hibernation are characterized by viable myocardium that fails to contract normally, and when this contractile defect involves a large enough portion of the left ventricle, it may cause heart failure. Coronary revascularization has been shown to restore function in the chronically ischemic myocardium and thereby reduce heart failure and prolong survival.\(^{116} \) Indeed, the restoration of function of chronically ischemic myocardium by revascularization has emerged as an important approach to reversing heart failure.

**Conclusions**

During the past half century, both the causes and treatment of heart failure have changed considerably. Hypertensive and valvular heart diseases were the most frequent causes of heart failure in the United States and other Western nations in 1950. Now, ischemic heart disease, hypertensive heart disease, and idiopathic dilated cardiomyopathy are dominant. The treatment of heart failure in 1950 consisted of bed rest, a diet restricted in sodium, the inotropic agent digitalis, and parenterally administered diuretics. Today, physical activity is encouraged, and drugs that block neurohormonal activation are widely used. Powerful oral diuretics are available, and for end-stage heart failure, left ventricular assist devices and transplantation may be lifesaving. Digitalis is still used in systolic heart failure, but it plays a secondary role except when atrial fibrillation is present. Ventricular fibrillation, a leading cause of death in heart failure, can now be prevented in many cases with an internal cardioverter-defibrillator.

Despite the enormous advances in the understanding and treatment of heart failure that have taken place during the 50 years since the birth of *Circulation* and that have been so well described in this journal, this condition remains a serious, and in fact, a growing problem in the United States and worldwide. It has been estimated that there are 4.6 million patients in the United States with heart failure and perhaps an equal number with asymptomatic left ventricular dysfunction who are at high risk of developing heart failure. This condition is the primary discharge diagnosis in almost 1 million patients from US hospitals annually, and an estimated 550,000 new cases occur each year. Prognosis is poor, with median survival after onset only 1.7 years in men and 3.2 years in women.\(^{117} \) Heart failure is a condition that affects principally the elderly, and with the progressive aging of the population, it is virtually certain that the prevalence of heart failure will continue to grow during the next decade both in developed and in developing nations.

What accounts for the seeming paradox of the greatly improved management of virtually all forms of heart disease that lead to heart failure and the increasing occurrence of heart failure? Many forms of heart disease that can now be successfully treated are not really cured. For example, the treatment of severe hypertension may avert premature death from a cerebrovascular hemorrhage. However, antihypertensive therapy often converts severe to mild hypertension; the latter, acting over many years, can cause left ventricular hypertrophy and ultimately lead to heart failure. Similarly, the prolongation of survival after acute myocardial infarction by acute reperfusion may be associated with substantial myocardial damage that subsequently causes heart failure via the remodeling process or with subsequent ischemic damage. Progressive myocyte loss is a feature of aging,\(^{118} \) and when
additional cardiac damage, be it secondary to chronic hemo-
dynamic overload or ischemia, is superimposed on an aging
heart with a dwindling number of myocytes, the burden on
the remaining myocytes increases and the likelihood of heart
failure rises. Finally, on the basis of estimates of the propor-
tion of eligible patients with heart failure, only a minority are
receiving both ACE inhibitors and β-blocking agents, the 2
major classes of agents for which databases from multiple
clinical trials have consistently and unequivocally demon-
strated reductions in mortality and delayed progression of the
heart failure syndrome. In other words, although much
progress has been made in heart failure clinical trials (a 46% 
reduction in mortality in the last 10 years), this has not been
translated optimally into clinical practice. The reasons for this
are complex, but this mismatch between the ideal and the
actual must be corrected if the heart failure problem is to be
solved.

Future scientific progress in heart failure is likely to take 4
principal directions. Most important of all will be the preven-
tion of atherosclerotic heart disease, the most common cause
of heart failure. Prevention is likely to commence much
earlier in life, when genetic analysis makes it possible to
identify persons with a high likelihood of developing a risk
factor for atherosclerosis later in life. A second type of
advance will be the extension of current efforts to inhibit the
activated neurohormonal-cytokine systems in heart failure.
As discussed above, blockade of endothelin, of AVP, of
cytokines, including TNF-α, and of the breakdown of natri-
uretic peptides all appear to be promising. Third, both cardiac
unloading with long-term ventricular assistance and replace-
ment of the heart with a totally implanted mechanical device
or xenotransplant have the potential to prolong life greatly in
patients with heart failure. Further on the horizon, new agents
designed to modulate novel therapeutic targets and/or gene
therapy may become useful as we learn more about the
molecular defects in various types of myocardial failure.
Therefore, we predict with confidence that in 2025, when the
American Heart Association celebrates 75 years of publica-
tion of its flagship journal, Circulation, understanding of the
mechanisms responsible for heart failure will have increased
enormously, therapy will be greatly enhanced, and the pre-
valence of the condition will have peaked and be on the
decline.

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