Basic Science for Clinicians

Pathological Ventricular Remodeling
Mechanisms: Part 1 of 2

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Abstract—Despite declines in heart failure morbidity and mortality with current therapies, rehospitalization rates remain distressingly high, substantially affecting individuals, society, and the economy. As a result, the need for new therapeutic advances and novel medical devices is urgent. Disease-related left ventricular remodeling is a complex process involving cardiac myocyte growth and death, vascular rarefaction, fibrosis, inflammation, and electrophysiological remodeling. Because these events are highly interrelated, targeting a single molecule or process may not be sufficient. Here, we review molecular and cellular mechanisms governing pathological ventricular remodeling. (Circulation. 2013;128:388-400.)

Key Words: cardiac electrophysiology • fibrosis • inflammation • stem cells • ventricular remodeling

It is predicted that as our population ages, the direct medical costs of all cardiovascular diseases (including hypertension, coronary heart disease, stroke, and heart failure) will triple, reaching $818 billion in 2030.1 Prominent within this population of patients are the 5 million Americans who suffer from chronic heart failure, the final common pathway of many forms of heart disease and the most common discharge diagnosis in Medicare for several years running. This syndrome carries a mortality of ≈50% at 5 years, and its incidence and prevalence are expanding rapidly around the globe. Thus, not only is the problem of heart failure enormous and growing, it contributes importantly to runaway medical costs just as society is moving swiftly to contain those costs. As a result of these converging influences, we are at a crucial juncture where novel therapeutic approaches for heart failure are sorely needed. To accomplish this, a comprehensive understanding of biological processes leading to heart disease and disease-related ventricular remodeling is required.

In the setting of disease, the left ventricle (LV) manifests a robust plasticity response that has been called pathological remodeling.2-3 This process is the culmination of a complex series of transcriptional, signaling, structural, electrophysiological, and functional events occurring within the cardiac myocyte. In addition, other cellular elements within the ventricle participate, including fibroblasts (promoting fibrosis), vascular smooth muscle cells (promoting vascular stiffness), vascular endothelial cells (promoting endothelial dysfunction), and leukocytes (promoting inflammation; Figure). Current thinking holds that these events—the response of the heart to a variety of pathological insults—confers short-term benefit. However, left unchecked, these remodeling events are maladaptive and predispose to cardiovascular morbidity and mortality.

Current therapies, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aldosterone antagonists, and β-adrenergic receptor blockers (β-blockers), manifest significant efficacy in reducing morbidity and mortality in patients with chronic systolic heart failure.4 However, in many instances, disease progression continues unabated. Furthermore, less is known about the substantial proportion of disease when systolic performance of the LV is preserved. In addition, although novel disease targets are continually being discovered, most therapeutics do not demonstrate consistent efficacy in patients; indeed, many prove to be ineffective, even deleterious, before reaching phase III clinical trials. Here, we review many of the major molecular and cellular pathways governing LV remodeling in the 2 broad types of heart failure, heart failure with reduced (HFrEF) and heart failure with preserved (HFpEF) systolic function. In an accompanying article, we review relevant therapies.5

Classification of Heart Failure

Most current therapies and clinical trials to evaluate novel therapies target HFrEF, previously called systolic heart failure. However, it is estimated that 50% of heart failure patients have a preserved LV ejection fraction, or HFpEF.6 Initial studies attributed HFpEF to dysfunction of the myocardium during the filling phase of the cardiac cycle; diastolic stiffness, prolonged isovolumic LV relaxation, and slow LV filling were attributed to pathological dysfunction of the ventricular myocyte during diastole.7 However, it is clear that in some instances, the LV myocardium is an innocent bystander, manifesting dysfunctional filling caused by volume overload, insufficiency of perfusion, or inadequate filling times.8 In many instances, it is likely that perturbed diastolic relaxation9 and excessive volume resulting from extrinsic factors10 combine to perturb ventricular filling.

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Vascular stiffening and generalized systemic vascular dysfunction are observed in patients with HFpEF. Reduced aortic distensibility and increased end-systolic elastance lead to exaggerated fluctuations in blood pressure for the same change in afterload and preload. Indeed, therapeutic strategies that specifically target ventricular-arterial stiffening improve exercise tolerance in elderly, hypertensive individuals. In addition, impaired flow-mediated vasodilation has been observed, implicating endothelial dysfunction in HFpEF pathophysiology and suggesting the possibility of benefit with therapies targeting nitric oxide bioavailability. Pulmonary hypertension is also associated with HFpEF, and elevated pulmonary artery pressures predict mortality in HFpEF patients.

Whether HFrEF and HFpEF are truly distinct disorders or rather represent a syndrome that exists across a spectrum is unknown. In addition, within each of the 2 broad categories of HFrEF and HFpEF, a wide variety of etiologies dictate pathogenesis. In other words, heart failure, a syndrome defined on clinical terms, derives from numerous different diseases: myocardial infarction, hypertension, cytokine or neuroendocrine dyscrasias, genetic disorders, and more. One prominent example in which personalized medicine has emerged to parse these elements is hypertrophic cardiomyopathy (HCM), in which distinct genetic variants have been identified that are informative in predicting phenotype and outcome. Classically, familial HCM is caused by mutations in sarcomeric genes that control cardiac myocyte myofilament movement and calcium handling. At least one third of patients presenting with HFpEF have normal extracellular matrix proteins (eg, collagen), suggesting that cardiomyocyte stiffness resulting from sarcomeric aberrations also contributes to pathogenesis. It is conceivable that genetic testing for familial HCM may aid in accurately diagnosing HFpEF early on.

Familial dilated cardiomyopathy (DCM) can manifest mendelian patterns of inheritance, and mutations in at least 50 genes have been identified and linked to familial DCM. These include sarcomeric genes such as those coding for proteins localized to the Z disk, nuclear membrane proteins, and proteins involved with connections to the plasma membrane. As with HCM, not all patients with DCM manifest the same phenotype. Importantly, some genetic variants, even within families, can cause either HCM or DCM, which renders diagnosis and risk prediction difficult on the basis of genetic testing. Recently, however, mutations in the gene coding for the giant sarcomeric protein titin (TTN) have been identified in 25% of patients with familial idiopathic DCM, whereas only 3 of 231 patients with HCM harbor these mutations. Mutations in this gene can also promote cardiomyocyte stiffness, which can contribute to HFpEF. Therefore, testing for mutations in TTN may aid in the differentiation of disease type and early diagnosis.

As research continues, more genetic mutations and polymorphisms will be identified, such as race-driven genetic predispositions that lead to cardiomyocyte stiffness or fibrosis. However, predicting disease on the basis of genotype is further complicated by the fact that modifying genes, epigenetic factors, and environmental influences contribute to the complexity of the disparate phenotypes.

HFpEF is observed commonly in older women with a history of hypertension. Difficulty treating HFpEF derives, at least in part, from its segregation with multiple comorbidities and a lack of standard definition. In fact, trials using angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and β-blockers have failed to demonstrate efficacy in patients with HFpEF. Aldosterone antagonists are currently being tested in a National Institutes of Health–funded trial called TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with Aldosterone Antagonist: www.clinicaltrials.gov; unique identifier: NCT00094302).

Although current therapies have decreased overall morbidity and mortality in patients with HFrEF, individual responses are not uniform. For example, some heart failure patients...
on angiotensin-converting enzyme inhibitor therapy harbor increased plasma angiotensin II levels, suggesting that angiotensin-converting enzyme inhibition is incomplete. Patients also respond variably to mineralocorticoid receptor antagonists. Inhibition of β-adrenergic signaling is standard of care for HFrEF patients. However, β-adrenergic receptor polymorphisms can render antagonist treatment ineffective. New therapies targeting β-receptor downstream effectors are being developed.

Hypertensive Ventricular Remodeling

High blood pressure is the single most important risk factor for heart failure; ≈75% of heart failure cases have antecedent hypertension. Because terminally differentiated cardiac myocytes are inefficient at reentering the cell cycle, these cells respond to pressure-overload stress by enlarging. This response, called hypertrophy, ultimately leads to ventricular wall thickening and stiffening.

On the basis of the Laplace law, ventricular wall stress is proportional to both ventricular pressure and cavity radius and inversely proportional to wall thickness. Thus, increases in wall thickness tend to diminish wall stress and to decrease oxygen demand; hence, they are adaptive. When the pressure stress is persistent, however, the myocardium slowly transitions to a state of decompensation and clinical heart failure. Our understanding of mechanisms underlying this transition from adaptive hypertrophy to maladaptive failure remains incomplete.

In recent years, a large number of preclinical studies have demonstrated that blunting load-induced hypertrophic growth of the LV is possible, even in the presence of persistent afterload stress, without compromising contractile performance. These studies, then, have uncovered a potentially new target of antiremodeling therapy, the hypertrophic phenotype itself. This strategy is based on the notion that although short-term hypertrophic remodeling may be adaptive, serving to normalize wall stress and oxygen demand, persistent, long-term activation of this response is detrimental. If true, suppressing pathological hypertrophy may be key to impeding the progression to heart failure.

Suggestive evidence in humans supports therapeutic targeting of the hypertrophic process.

Atrophic Remodeling

One goal of antihypertensive therapy is to slow, arrest, or possibly even reverse the progression of cardiomyocyte growth. Indeed, the cardiac myocyte is capable of significant shrinkage or atrophy. This shrinkage leads to reductions in LV mass and occurs under conditions of mechanical unloading (prolonged bed rest, mechanical support with an LV assist device, weightlessness during space travel) or increased catabolic state (eg, cancer). Atrophy is an energy-consuming process that involves changes in both anabolic and catabolic processes.

Whether atrophy is associated with changes in cardiac function may depend on its magnitude, duration, and inciting factors. In a small number of patients with cachexia, significant loss of LV mass was not associated with specific cardiac abnormalities compared with noncachectic patients. However, short-term mechanical unloading in animals by heterotopic heart transplantation can reverse hypertrophy, whereas long-term unloading was associated with decreased function and increased fibrosis. Current investigations are ongoing to determine whether cardiac atrophy causes diastolic dysfunction during long-duration space flight.

Ventricular Remodeling in Ischemic Heart Disease

Coronary artery disease is a leading cause of HFrEF. In fact, most of our knowledge about LV remodeling is derived from patients and animal models of myocardial infarction. The extent of myocardial damage and its location within the LV directly affect the magnitude of LV remodeling. Underlying mechanisms derive directly from the infarction itself, including cell death and loss of contractile activity in the affected zone, as well as secondary ventricular dilation and remodeling in infarct-remote zones as a result of enhanced hemodynamic burden. Over time, a process called infarct expansion occurs wherein unremitting mechanical forces stretch the abnormally stressed tissue. The result is a dilated LV with abnormal levels of wall stress and distorted and ineffective contractile performance.

Reperfusion of the occluded, infarct-related artery is key to minimizing infarct size and maintaining ventricular performance. Significant advances in our understanding of the biology of ischemic heart disease, including the critical importance of restoration (percutaneous angioplasty) and maintenance (drug-eluting stents, antithrombotic agents) of arterial perfusion to the at-risk zone, have culminated in robust improvements in clinical outcomes. Although these advances have provided significant declines in mortality, the LV will inexcorably, over subsequent months and years, remodel in response to abnormally elevated load and demand, leading to ventricular dilation and ultimately dysfunction.

Remodeling of the LV after myocardial infarction has been divided into stages. After interruption of arterial perfusion from occlusion of a coronary vessel, death of cardiac myocytes immediately ensues. These cells die via necrosis, apoptosis, or possibly autophagy. Although cardiac stem cells have been identified in the adult heart and cardiac myocytes themselves are capable of reentering the cell cycle under only limited circumstances, myocyte proliferation does not contribute significantly to the response to infarct-related wave of cell death. In the next stage of infarct healing, dying cardiac myocytes release intracellular proteins into the circulation and trigger an inflammatory response. Inflammatory cells, including neutrophils, monocytes, macrophages, and lymphocytes, infiltrate the tissue. These immune cells remove dead myocytes and pave the way for healing. After resolution of the inflammatory response, cardiac fibroblasts proliferate and secrete extracellular matrix proteins such as collagen I to form a fibrotic scar that replaces dead myocytes. The resulting tightly cross-linked, fibrotic scar with significant tensile strength serves to prevent rupture. This remodeling of the LV continues progressively in response to increases in wall stress,
provoking cardiac myocyte hypertrophy in the infarct border zone, wall thinning, and chamber dilation. This global adverse remodeling response leads to increases in both LV end-diastolic and end-systolic volumes and reduced ejection fraction.53

**Contributing Cellular Events**

**Cardiac Myocyte Death**

**Biology**

Cardiac myocytes carry out the contractile function of the myocardium, and they are largely incapable of replication; hence, their survival is crucial. After myocardial injury, cardiac myocytes undergoing necrosis lyse, releasing intracellular contents, some of which can be detected in the blood and used as markers of injury (eg, creatine kinase, cardiac troponins). Apoptosis, an energy-dependent, programmed cell death response, does not entail release of intracellular contents and does not trigger an inflammatory response; it is reversible up to a point of no return. Emerging literature suggests that necrosis itself may be a programmed cellular process rather than uncontrolled disintegration of the cell.49 Furthermore, recent evidence suggests that necrosis and apoptosis are integrally linked and may be different faces of a single process (necroptosis).49

Often, dying cells manifest evidence of upregulated autophagy, an evolutionarily ancient process of ordered recycling of intracellular contents.50,51 Considerable debate has centered around whether this autophagic cascade reflects the response to stress, serving to promote cell survival, or represents a process that itself contributes to cell death.52 Consensus has emerged recently, however, that at least in some instances autophagic cell death (programmed cell death type II) exists,53 including in heart muscle.54 That said, divergent views exist.52 Regardless of whether autophagy can trigger cardiomyocyte death, considerable evidence supports a model in which cardiomyocyte autophagy can be adaptive or maladaptive, depending on the context.55–59

As a Therapeutic Target

Although all 3 types of cell death/intracellular remodeling occur within the heart, it is not entirely clear whether they are truly distinct and discrete events or represent a continuum of overlapping biochemical and molecular processes. Nevertheless, selective inhibitors targeting apoptosis (caspase inhibitors), necrosis (inhibitors of mitochondrial permeability transition pore opening), and necroptosis (necrostatin 1) have been used in the heart.60 Suppression of apoptosis decreases adverse remodeling and subsequent progression to heart failure in models of ischemia/reperfusion,61 myocardial infarction–induced heart failure,52 and nonischemic cardiomyopathy.52 However, optimal timing of therapy, targets for inhibition within apoptotic signaling cascades, precise mechanisms of inhibition, and even the cell types involved remain unresolved. Of note, several pharmacological therapies in current clinical use may suppress cell death. For example, angiotensin II and norepinephrine can trigger cardiomyocyte apoptosis, and their respective blockers antagonize these responses.64,65

**Cardiac Myocyte Hypertrophic Growth**

**Biology**

A central tenet in cardiac biology is the notion that most adult cardiac myocytes are terminally differentiated cells and therefore do not proliferate; rather, they respond to stress by growing, shrinking, or dying. Recent work has revealed that a fraction of cells within the ventricle are, in fact, capable of reentering the cell cycle and proliferating,66–68 although the size of this fraction is the subject of intense debate. Nevertheless, the preponderance of evidence indicates that the majority of cardiomyocytes are incapable of dividing and respond to stress by eliciting a hypertrophic growth response. As part of this process, a wide range of transcriptional and posttranslational events occur, including activation of a pattern of gene expression reminiscent of that observed during fetal development (fetal gene program).

Besides mechanical loading, cardiac myocytes respond to a variety of other growth cues, including cytokines, growth factors, catecholamines, vasoactive peptides, and hormones. Some evidence suggests that cell size is regulated by shared signaling pathways, whereas cell shape and sarcomeric organization are regulated by distinct pathways.68 If borne out by additional studies, this observation might facilitate precise definitions of cellular phenotype-specific regulatory mechanisms.

**As a Therapeutic Target**

Although no therapeutic agents target hypertrophic growth directly, some strategies in current use alter the hypertrophic response secondarily, including suppression of neurohormones (catecholamines, angiotensin II, aldosterone), calcium (eg, L-type Ca2+ channel blockers), or preload (eg, vasodilators or diuretics). However, efficacy of these strategies varies and depends on the pathway that is modulated. Furthermore, because there is redundancy among these pathways, downstream points of convergence may be more suitable to inhibit or reverse cardiac hypertrophy. Potential targets include oxidative stress, serine/threonine phosphatases, non-gated Ca2+ influx/Ca2+ signaling, downstream effectors of rapamycin or G-protein–coupled receptors, protein kinases, and chromatin remodeling agents (eg, histone deacetylases).69

Overlapping mechanisms exist in pathological (pressure overload) and physiological (exercise) hypertrophic growth, such as increased expression of genes responsible for cardiac myocyte structure, ion transport, and proteolysis.70 However, genes associated with metabolic processes and muscle contraction may be upregulated to a greater extent in response to exercise.70 Furthermore, capillary growth does not keep pace with myocyte growth in disease models, which, in concert with fibrotic change, limits oxygen delivery to the myocardium.71,72

**Cardiac Myocyte Hyperplasia**

**Biology**

Whereas growth of the adult heart has classically been held not to involve a significant hyperplastic response, recent evidence has demonstrated the existence of progenitor cells resident within the myocardium and cardiomyocytes capable of reentering the cell cycle, findings that contradict the traditional
idea that the heart is a strictly postmitotic organ. These dividing cells may participate in cardiac homeostasis at basal levels and potentially replace dying cardiac myocytes, albeit at low levels. Cardiac progenitors include cells characterized by the expression of cell surface markers, including c-Kit, Sca-1, or Islet-1, and cardiac side population cells. Self-adherent clusters of cells called cardiospheres have been developed from human biopsy specimens. The neonatal heart harbors cardiomyocytes capable of reentering the cell cycle, promoting wound repair.

Cardiac progenitors have been localized to the epicardial surface of the heart, where they contribute to coronary vasculature formation during embryogenesis. These epicardial cells are pluripotent and migrate into the myocardium, undergoing epithelial-to-mesenchymal transition, and circulating, collagen-secreting bone marrow–derived cells.

Fibrosis

Biology

A hallmark feature of ventricular remodeling is deposition of excessive extracellular matrix. This surplus extracellular matrix, which constitutes scar or fibrosis, promotes both contractile dysfunction and rhythm disturbances. As a result, cardiac fibrosis contributes to morbidity and mortality in many forms of heart disease. Indeed, the amount of fibrotic scar in the myocardium correlates strongly with the increased incidence of arrhythmias and sudden cardiac death.

Extracellular matrix deposition and fibrosis formation occur through the action of cardiac fibroblasts. In the setting of pathological stress, fibroblasts proliferate and differentiate into myofibroblasts, thereby gaining the capacity to contract and secrete collagen I, collagen III, and fibronectin. Proliferation and activation of these cells, the most abundant cell type in the myocardium, derive from a variety of sources, including resident fibroblasts, adult epicardial cells undergoing endothelial-to-mesenchymal transition, and circulating, collagen-secreting bone marrow–derived cells.

Scar formation after myocardial infarction arises from replacement fibrosis in which regions of myocyte dropout are replaced by scar. In contrast, fibrosis arising during hypertension-induced pressure overload and in remote regions after myocardial infarction is reactive (perivascular or interstitial), leading to decreased compliance and diminished oxygen diffusion capacity. Both individual myofibroblasts and collagenous septa within the LV facilitate and propagate the arrhythmic phenotype of the remodeled heart.

As a Therapeutic Target

Cardiac fibrosis is an independent and predictive risk factor for heart failure in both ischemic and nonischemic cardiomyopathy. Recent work has demonstrated that cardiac fibrosis, long held to be irreversible, may regress under certain circumstances. Some evidence suggests that the modulation of cardiac fibrosis alters the arrhythmic phenotype in patients with heart disease. To date, no therapeutic strategy has been developed to specifically target fibrosis in the heart. Cardiac fibroblasts are unique and phenotypically distinct from fibroblasts isolated from other tissues (as reviewed elsewhere); they also display phenotypic heterogeneity within the heart itself. In addition, the precise phenotypes of fibroblasts from normal, injured, and failing hearts are ill defined, and mechanisms underlying the transition from normal wound healing to maladaptive fibrotic remodeling remain unresolved. Interestingly, the abundance of newly formed, thin collagen fibers increases in the remote region of infarcted heart but decreases with time in the infarct zone, suggesting collagen maturation in the infarct zone. Furthermore, neurohormonal inhibition leads to an increase in scar maturation while diminishing remote, reactive fibrosis. Because infarct-associated scar is necessary to prevent ventricular rupture, it may be advantageous to target new collagen fiber formation to allow scar maturation.

Regardless of these challenges, there is reason to believe that therapies focusing on cardiac fibrosis may prove salutary in the treatment of ventricular remodeling. Some therapies in current use may target, at least in part, cardiac fibroblasts. Specifically, angiotensin II provokes cardiac fibroblast proliferation and net accumulation of collagen in vitro and cardiac fibrosis in vivo. Interestingly, the expression of angiotensin II receptors in cardiac fibroblasts exceeds that in cardiac myocytes, and angiotensin receptor blockers appear to have antifibrotic actions. In patients with hypertensive heart disease, losartan reduced cardiac fibrosis and serum collagen markers. In addition, treatment with statins resulted in reduced fibrosis and reduced collagen synthesis. Small-molecule inhibitors of histone deacetylases attenuate fibrosis in a preclinical model of pressure overload via mechanisms involving transcriptional silencing of the gene coding for connective tissue growth factor (unpublished observations).

Inflammation

The immune system plays a significant role in ventricular remodeling, and its persistent activation may lead to long-term cardiac injury. Specifically, activation of a variety of inflammatory molecules and pathways, such as the complement system, T cells, and the formation of autoantibodies, have been reported in heart failure patients. Consequently, a number of strategies have been proposed to mitigate the harm caused by these inflammatory events; most have failed. In the 1970s, it became apparent that immunosuppression with glucocorticoids or nonsteroidal anti-inflammatory agents conferred risk in patients with ischemic heart disease. More recently, however, early results of studies seeking to decrease autoantibody titers are promising. High doses of intravenous immunoglobulin therapy to neutralize autoantibodies and the complement system improve heart failure symptoms, but long-term use is required. The few trials using immunoadsorption therapy in patients with DCM, in which autoantibodies are thought to play a role in pathogenesis, were promising. "Therapeutic plasma exchange, in which large amounts of plasma are removed from the circulation and replaced with 5% albumin, potassium chloride, and calcium gluconate and then terminally supplemented with immunoglobulins to replace the removed proteins, is being tested."
Vascular Remodeling

Biology

A wide range of cardiovascular diseases are marked by vascular remodeling. For example, both hypertension and immunosuppressive treatment are associated with vessel wall thickening. In preclinical models of myocardial infarction, hypertrophy in the border zone of the infarct is associated with diminished coronary flow reserve, increased media-to-lumen ratio, and increased medial thickness.

The development of significant coronary collateral circulation is a major mechanism of vascular remodeling. A recent meta-analysis reported diminished mortality risk in patients with high collateralization compared with those with low collateralization. Another study reported that although collaterals may be protective during early stages of infarct healing, after infarction is complete, their presence is not an independent predictor of clinical outcome. Some evidence suggests that promoting angiogenesis in the setting of pressure overload can protect the heart from injury.

As a Therapeutic Target

A large number of clinical trials of therapeutic neovascularization with gene or protein therapies have failed. This failure may stem, at least in part, from single, high-dose administration of therapy. For example, short-term exposure to vascular endothelial growth factor leads to leaky vessels that regress, whereas prolonged exposure promotes the formation of more stable vessels. To address this, novel polymers that degrade slowly and sustain release of growth factors have been used. However, it is unlikely that a single growth factor will be sufficient to promote neovascularization and to limit adverse remodeling. Therefore, the development of proangiogenic therapies will likely require combination therapy comprising multiple growth factors such as fibroblast growth factor-2, hepatocyte growth factor, monocyte chemoattractant protein-1, granulocyte macrophage colony-stimulation factor, platelet-derived growth factor-BB, and transforming growth factor-β. In addition, careful selection of end points in trial design and appropriate methods for evaluating those end points may increase the likelihood of success of future proangiogenic therapies. Mode and timing of delivery may also be important.

Because some of these growth factors tend to promote salvage of ischemic myocardium, early treatment may prove beneficial. Conversely, a study using a mouse model of cardiac-specific induction and inactivation of a vascular endothelial growth factor–sequestering soluble receptor reported that vascular endothelial growth factor activity even at late stages of heart remodeling was sufficient to rescue function. This study also suggested that a point of no return may still exist because augmenting neovascularization at late time points did not reverse fibrosis or myocyte hypertrophy.

Metabolic Remodeling

Biology

Patients with diabetes mellitus and obesity are at increased risk of developing coronary artery disease, hypertension, and heart failure. Under normal physiological conditions, the metabolic demands of the heart are met by metabolism of fatty acids and glucose, and, to a lesser extent, lactate and ketone bodies.

With the onset of insulin resistance and obesity-driven type II diabetes mellitus, the uptake of metabolic substrates into cardiomyocytes becomes dysfunctional; fatty acid utilization is increased at the expense of glucose, which contributes to myopathy characterized by ventricular dilation, cardiomyocyte hypertrophy and death, interstitial fibrosis, and perturbations of diastolic relaxation. In animal models of obesity, triglycerides accumulate in the heart, coupled with impaired mitochondrial function, to oxidize the increased lipid load. Several molecular and cellular mechanisms have been implicated in diabetic cardiomyopathy, including disordered activation of forkhead transcription factors, mammalian target of rapamycin, microRNAs, mitochondrial dysfunction, the unfolded protein response, proteasome activation, and autophagy.

The term obesity paradox has been coined to describe the association between obesity and improvements in heart failure outcomes; among patients with similar heart failure severity, obese patients manifest improved survival compared with normal-weight patients, and higher body mass indexes are associated with lower mortality risk. Whether this association relates to mechanism is unknown, but conceivably it may be attributed to depression of the neurohumoral system or to an increase in nutritional or metabolic reserve. For example, the adipokine leptin, which regulates appetite and energy balance, has direct cardioprotective effects against ischemia/reperfusion injury.

The obesity paradox was tested in an animal model in which insulin-insensitive rats were fed a high-fat diet and compared with insulin-insensitive lean rats, allowing measurement of an effect of obesity in isolation. Obese rats manifested relative ischemia/reperfusion tolerance associated with activation of reperfusion injury salvage kinase and nitric oxide synthase signaling pathways.

The myocardium itself can have direct effects on metabolism within other organs. For example, natriuretic peptides such as atrial natriuretic factor and B-type natriuretic peptide are secreted from cardiomyocytes in response to stress. These peptides, circulating levels of which are elevated in heart failure, have lipolytic effects on adipose tissue, which are specific to primates. Recently, it was reported that cardiomyocyte-specific expression of MED13, a transcriptional regulator, or pharmacological inhibition of miR-208a, antagonizes high-fat diet–induced obesity and improves insulin sensitivity and glucose tolerance.

As a Therapeutic Target

Therapy that specifically targets cardiomyopathy caused by obesity and diabetes mellitus does not currently exist. However, some strategies targeting weight loss manifest benefit to the heart. Weight loss from lifestyle changes or bariatric surgery is associated with decreases in LV dimensions, wall thickness, mass, and left atrial dimensions. Removal of subcutaneous fat by liposuction does not elicit beneficial metabolic changes. In addition, whereas both orlistat (a gastrointestinal lipase inhibitor) and sibutramine (a monoamine reuptake inhibitor) lead to weight loss and glycemic homeostasis, they have no significant effects on cardiac structure or dimensions.
Recently, a proteasome inhibitor, MG-132, was shown to manifest antioxidative and anti-inflammatory functions in an animal model of diabetic cardiomyopathy. In addition, inhibition of phosphodiesterase-5 with tadalafl attenuated inflammation, improved fasting glucose and triglyceride levels, decreased body weight, and reduced infarct size in an ischemia/reperfusion injury model in obese, diabetic mice. Synthetic mimetics of natriuretic peptides have been approved for the treatment of acute heart failure, although the largest study so far of nesiritide, a recombinant form of human B-type natriuretic peptide, failed to detect improvements in mortality or rehospitalization.

Electrophysiological Remodeling

Patients with LV hypertrophy are at significantly increased risk of malignant arrhythmias, accounting for a substantial component of the mortality associated with cardiac hypertrophy. Indeed, arrhythmia, especially ventricular tachyarrhythmia, is a major cause of death in patients with LV heart failure. Sustained ventricular tachycardia or ventricular fibrillation can occur immediately after myocardial infarction, during the remodeling process, or late after injury.

In recent years, electrical remodeling, a term that encompasses alterations in multiple electrogenic transport processes within the cardiac myocyte, has emerged as an important pathophysiologic mechanism in many types of cardiac pathology. Yet, our understanding of mechanisms underlying the myriad facets of electrical remodeling is limited. As a result, means of treating hypertrophy-associated arrhythmias remain disappointingly ineffective. In addition, there is substantial evidence that alterations in transmembrane Ca\(^{2+}\) fluxes, a central feature of electrical remodeling, contribute to the pathogenesis of hypertrophy and failure by abnormally activating Ca\(^{2+}\)-responsive signaling pathways.

Mechanisms underlying ventricular arrhythmia are multifactorial, but they derive, at least in part, from disordered electrical currents arising from prolongation of ventricular action potentials. The resulting delay in the recovery of excitability, a consistent feature of ventricular hypertrophy, predisposes to early and late afterdepolarizations. Superimposition of myocardial fibrosis, with altered electrotonic coupling between cells, slowed conduction, and dispersion of refractoriness, exacerbates the proarrhythmic phenotype.

Lengthening of ventricular cardiomyocyte action potential duration is commonly observed in both cardiac hypertrophy and failure, a phenotype that contrasts with the action potential shortening in the stressed (fibrillating) atrium. In the setting of excessive afterload, action potential duration increases more in subepicardial myocytes than in subendocardial myocytes. In a canine model of pacing-induced heart failure, action potential duration increased significantly more in mid-myocardial cells than in subepicardial cells.

Action potential prolongation is caused by a wide range of changes in myocyte ion channels and electrogenic ion transporters (reviewed elsewhere). Briefly, loss of voltage-gated Na\(^+\) channel inactivation leading to a late inward sodium current is increased in failing cardiomyocytes. In addition, downregulation of outward K\(^+\) currents, upregulation of inward Ca\(^{2+}\) currents, and changes in Ca\(^{2+}\) current inactivation all contribute. Indeed, in many models of heart failure, diminished outward, repolarizing current secondary to downregulated K\(^+\) channel levels (particularly I\(_{\text{Kr}}\)) is observed.

In contrast to heart failure, upregulated inward Ca\(^{2+}\) current contributes to action potential prolongation in ventricular hypertrophy, particularly in models of modest hypertrophy. In fact, the density of L-type Ca\(^{2+}\) current (I\(_{\text{Ca,L}}\)) may be inversely correlated with disease progression, being increased in mild to moderate hypertrophy and decreased in severe hypertrophy and failure. Importantly, entry of small amounts of Ca\(^{2+}\) from the extracellular space triggers release of much larger amounts of Ca\(^{2+}\) from intracellular stores, amplifying even modest changes in inward Ca\(^{2+}\) flux. In addition, in many species, membrane impedance is relatively high during phase 2 of the action potential, so changes in I\(_{\text{Ca,L}}\) have significant effects on action potential morphology and duration.

The Na\(^+\)-Ca\(^{2+}\) exchanger, which catalyzes the bidirectional exchange of 3 Na\(^+\) ions for a single Ca\(^{2+}\) ion, is a major mechanism of Ca\(^{2+}\) elimination during diastole. Because 1 net positive charge moves per reaction cycle, Na\(^+\)-Ca\(^{2+}\) exchanger generates a transmembrane current that approaches half the magnitude of I\(_{\text{Ca,L}}\). Alterations in Na\(^+\)-Ca\(^{2+}\) exchanger activation in heart disease can contribute to late afterdepolarizations and triggered ventricular activity.

Normal electrical conduction depends on cell-cell connections through gap junctions such as connexin 43, and these connections can be disorganized in the failing heart, disrupting normal impulse conduction. Furthermore, in the failing heart, phosphorylation of the ryanodine receptor by Ca\(^{2+}\)/calmodulin-dependent protein kinase II results in calcium leakage from sarcoplasmic reticulum with concurrent downregulated expression of the sarcoplasmic/endoplasmic reticulum Ca\(^{2+}\)-ATPase 2a and reduced Ca\(^{2+}\) uptake into the sarcoplasmic reticulum. The resulting depletion of sarcoplasmic reticulum Ca\(^{2+}\) stores, coupled with elevations in cytoplasmic Ca\(^{2+}\), potentiates the development of ventricular arrhythmia.

Aging

Processes involved in maladaptive ventricular remodeling are age dependent, and most patients with heart disease are older. Indeed, a caveat to translating preclinical results into the human context is that most animal studies are performed with young animals. Mortality resulting from myocardial infarction increases with age, a fact not explained by larger infarcts. Aging in mice is associated with an attenuated inflammatory response and decreased macrophage-mediated phagocytosis of dead cells. In addition, aged mice have decreased numbers of myofibroblasts and perturbed extracellular matrix deposition, resulting in malformed scar. Cell death is also affected by age-related accumulation of mitochondrial damage and DNA mutations. Cumulative organelle damage with age may also increase the need for clearance by autophagy, a process that declines with age. Cardiomyocyte hypertrophy is more pronounced in aged heart, contributing to cardiac dysfunction, and the intrinsic capacity of the heart to regenerate diminishes with aging.
Environmental Exposures
Cumulative environmental exposures alter disease risk, therapeu-
tic responsiveness, biomarker expression, and cellular pheno-
types in the heart. This can begin as early as during fetal
development. Epidemiological data suggest that an adverse
intrauterine environment increases the risk of cardiovascular
disease in adulthood.169 For example, prenatal hypoxia leads
to altered expression of proteins such as protein kinase Cε,
heat shock protein 70, and endothelial nitric oxide synthase.169
However, these environmental exposures are not always mim-
icked reliably in preclinical studies using laboratory animals.
Even when nongenetically modified laboratory rodents are fed
a high-fat diet to induce obesity and cardiac dysfunction, they
do not develop atherosclerotic plaques as seen in humans. In
chimpanzees, heart disease is mediated primarily by aberrant
myocardial fibrosis, not by vascular atherosclerotic plaque,
despite high levels of cholesterol and low-density lipoprotein.170

Recently, sialic acid N-glycolyneuraminic acid, a molecule
not synthesized in humans but found in red meat and milk
products, was identified in the endothelium of human ath-
ersclerotic plaque.171 This sugar, foreign to humans but not
other mammals, promotes the generation of antibodies and
inflammation and is associated with carcinoma progression in
humans.172 In a recent epidemiological study of major dietary
sources, high red meat intake was associated with coronary
heart disease.173 These data raise the possibility that this sugar
could be used as a biomarker for patient stratification and therapeu-
tic effectiveness, as well as being a therapeutic target
itself (eg, generation of neutralizing antibodies). Recent evi-
dence implicates intestinal microbiota in the link between red
meat consumption and cardiovascular risk174 because bacte-
rial metabolism of red meat–derived L-carnitine can promote
atherogenesis.175

Sex Differences
Coronary artery disease, the leading cause of HFrEF, occurs
more commonly in men than women.6,176 In contrast, HFpEF
affects women more commonly than men by a proportion of
2:1. Underlying mechanisms remain unclear, although sex
differences have been described in cardiac structure, LV
diastolic function, ventricular-arterial stiffness, and aging.177
Males, both human and animal models, tend to develop eccen-
tric LV remodeling in response to stress, whereas females
develop concentric remodeling.177 In addition, women dis-
play enhanced regression of LV hypertrophy after aortic valve
replacement compared with men, suggesting enhanced sus-
cceptibility to afterload stress in women.178 Cardiac structural
differences have also been demonstrated in regard to con-
centric LV remodeling and systolic hypertension, which are
enhanced in aging women.179,180 This may be exacerbated by
the comorbidities of aging such as obesity, diabetes mellitus,
and physical inactivity, which may occur more frequently in
women than men.181,182

One possible mechanism underlying sexual dimorphism
in heart disease involves mutations in mitochondrial DNA.
Mitochondrial DNA encodes proteins associated with oxida-
tive phosphorylation and is inherited from the mother’s egg.
Therefore, mutations in mitochondrial DNA would be passed
on only by women, which can lead to family cohorts in which
the offspring of female members are at risk for disease but
the offspring of male members are not. Some mitochondrial
DNA mutations or seemingly neutral mitochondrial DNA
polymorphisms may not be pathogenic in offspring immedi-
ately but rather lead to an inability to adapt to aging or envi-
ronmental exposures, triggering emergence of pathology later
in life. In fact, mitochondria harboring mutant DNA may
selectively proliferate in response to a defect in the respiratory
electron transport chain, rendering these mutant mitochondria
more prevalent in postmitotic cells such as cardiac myocytes.
Sex-specific hormones also affect mitochondria. Ubiquinol-
cytochrome-c reductase, a component of complex III within
the respiratory electron transport chain, is reduced in the
absence of ovarian hormones.183

Unlike the Y chromosome, the X chromosome is enriched in
genes essential for development and viability. X-chromosome
silencing occurs to inactivate 1 of the 2 X chromosomes in
female cells. Originally, it was thought that silencing is main-
tained throughout the individual’s life span; however, it has
been shown more recently that loss of X-chromosome silenc-
ing can occur with aging.184 Furthermore, ≈15% of X-linked
genes escape inactivation in a manner that differs across
regions of the X chromosome.185 Genomic imprinting of com-
plex traits can also depend on sex.186

Conclusions
Heart failure is exploding in incidence and prevalence around
the world. Defined by clinical criteria, this syndrome derives
from a wide range of underlying disease etiologies and is
marked by a diverse spectrum of structural, functional, electro-
physiological, cellular, and molecular events. At one level, it
comes as little surprise that only a small number of therapeutic
strategies have emerged with efficacy, given these complexi-
ties. The effects of genetic, neurohumoral, environmental, and
age-related influences—and more—combine to dictate patho-
genesis and clinical outcome. Ultimately, these complexities
must be elucidated in the context of the individual patient to
optimize therapeutic success. That the myocardium comprises
a host of cell types, each manifesting unique transcriptional,
signaling, remodeling, proliferative, and death responses,
underscores the seemingly insurmountable complexity of
the challenge we face. However, the unequivocal successes
achieved already and the expanding scope of the problem will
continue to drive progress in this fascinating field.

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None.
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